Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-344454

54. **TÍTULO** Derivados Biciclicos Para usar en el tratamiento de Afecciones Asociadas con el Receptor de Andrógeno

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** AStraZeneca AB

DOMICILIO S-SE 151 85 Södertälje. Suecia

74. **APODERADO** J. IAN RAISBECK

22. **BOGOTÁ, D.C.,** Junio de 2010

(FORMA P-10)

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-074454- -00000-0000
Fecha: 2010-06-21 16:56:23 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 882

PETITORIO - FORMULARIO U
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000093**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** ASTRAZENECA AB **Dirección:** S-SE-151 85 Södertälje **Nacionalidad o Domicilio:** Suecia **Lugar de Constitución:** Suecia **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** J. IAN RAISBECK **Dirección:** Diagonal 34 No. 5-28 Bogotá **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [x] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79.376.996 **TP** 135.799
INVENTOR (ES) (72)	**Nombre: 1)** Robert Hugh BRADBURY; 2)Neil James HALES; 3) Alfred Arthur RABOW; **Dirección: 1 Y 3)** AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK 10 4TG; **2)** AstraZeneca Intellectual Property, S-SE-151 Södertälje; **Nacionalidad o Domicilio:** 1 y 2) Britanica; 3) Estadounidense	

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2008/051206 Fecha Diciembre 18, 2008

Publicación Internacional No. WO 2009/081197 Fecha Julio 2, 2009

(6) **Título (54)** **DERIVADOS BICICLICOS PARA USAR EN ELTRATAMIENTO DE AFECCIONES ASOCIADAS CON EL RECEPTOR DE ANDRÓGENO**

Clasificación Internacional (51) C07D 471/04, C07D 487/04, C07D 519/00, A61K 31/4196, A61K 31/437, A61K 31/5025, A61P 35/00 31/4965, A61P 3/00

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

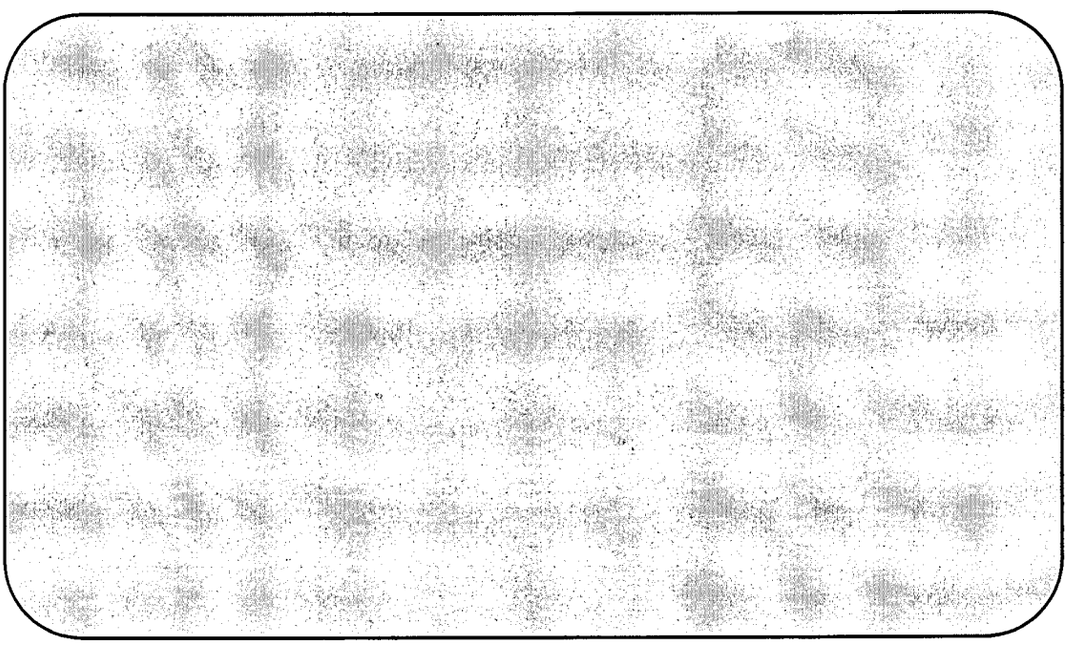
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Diciembre 21, 2007	61/015,755
US	Septiembre 11, 2008	61/096,090
US	Octubre 23, 2008	61/107,804
US		

(9) **Comprobante de pago No.** 10- **Fecha** Junio de 2010

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple. Ver expediente No. 08-129.814
- [ ] 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). (IPRP)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional. Formulario PCT/IB/306.
- [x] Otros. Búsqueda Internacional.

(11) **FIGURA CARACTERÍSTICA:**



(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK

FIRMA: _____

C.C. 79.376.996 Btá T.P. 135.799

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

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 49,662
FECHA : JUNIO 21 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-074454- -00000-0000
Fecha: 2010-06-21 16:56:23 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 882

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEY	CONSIGNACION	BANCO DE BOGOTA	062754387	174688286	21/06/2010	7,858,000.00

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

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

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Traducción oficial de un documento cuyo original está en inglés

No. 11426

El Ministerio de Relaciones Exteriores en Estocolmo certifica por el presente documento que Mrs. Anna-Karin Östin, de la Oficina de Registro de Compañías de Suecia, Sundsvall, ha expedido y firmado la anterior certificación en su calidad oficial.

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

Hay un sello firmado de la Embajada de Sudán en Estocolmo.

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Certificación Notarial

Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anders Burén, debidamente autorizado para firmar en nombre de Astrazeneca AB ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

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

Apostilla adjunta:

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

1. País:	Suecia
	El presente documento público
2. Ha sido firmado por:	Anne-Marie Bonde
3. Actuando en calidad de:	Notario Público
4. Lleva el sello / estampilla de:	Notario Público de Estocolmo.
	Certificado
5. En:	Estocolmo
6. El:	Día 26 de Octubre de 2007
7. Por:	Björn Sandin, Notario Público
8. Bajo el No.	4071
9. Sello / estampilla:	Björn Sandin, Notario Público de Estocolmo.
10. Firma:	(Firmado)

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Min. Rel."

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 10-054

OCT 2007

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

G

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country :** Sweden

   This public document

2. **has been signed by** Anne-Marie Bonde

3. **acting in the capacity of** Notary Public

4. **bears the seal/stamp of**

   Notary Public in Stockholm

Certified

5. **at** Stockholm **6. the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4071

9. **Seal/stamp:** **10. Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olart
J. Ian Raisbec
Ana María Frie
Juan Guillermo Mour
Natalia Castr

Zayde Chahí
Simón Salina
Alexander Agudel
Camilo A. Rodrígue
Lina Mosquer
Catalina Barbastefan

Of Couns
Guillermo Chahí
Graciela Mel
Jacqueline Chaparr
Cruz E. de Moncalean

Power of Attorney

The undersigned,

AstraZeneca AB

domiciled in

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

AstraZeneca AB

domiciliado en

Vastra Malarehamnen 9 S-151 85 Södertälje, Sweden

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: Anders Burén
Authorized Signatory

Date/Fecha: 24 OCTUBRE 2022

City,Country/Ciudad,País: Södertälje, Sweden

World Trade Center - Torre A, Calle 100 No. 8A – 37, Piso 4, Bogotá D.C., Colombia
Tel + 57 1 601-7700, Fax + 57 1 601-7799, office@olarteraisbeck.com, www.olarteraisbeck.com

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

2. That the grantor has executed the foregoing document as DULY AUTHORISED SIGNATORY of ASTRAZENECA AB

3. That ASTRAZENECA AB having its principal place of business located in SODERTALJE, SWEDEN is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB

2. AUTHORISATION IN FAVOUR OF SIGNATORY

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

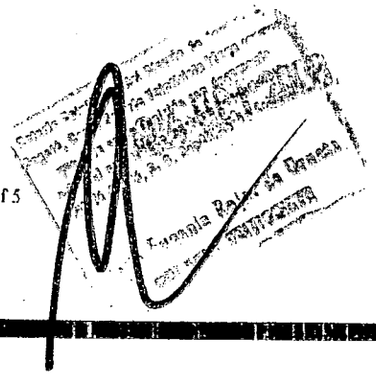
4. Que
con sede principal ubicada en

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

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

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

NOTARY PUBLIC (Signature):
Name and Particulars (e.g. Notary's name, Jurisdiction, Date of Licence Expiration)
SEAL (optional)





Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

851 81 Sund... Tel. 060-18 40 00 – Fax: 060 129840.
bolagsverket@bolagsverket (Ilegible)

Certificado de Existencia

Yo, Anna-Karin Östin, de Bolagsverket, la Oficina de Registro de Compañías de Suecia, certifico por medio del presente documento que

AstraZeneca AB

Registro No. 556011-7482

es una compañía debidamente constituida según las leyes de Suecia, vigente y con existencia corporativa legal hasta donde muestran los registros de esta oficina en la fecha que se indica más adelante.

En testimonio de lo anterior, he puesto mi firma y estampado el sello oficial de Bolagsverket en Sundsvall, este día 8 de Agosto del año 2007.

(Firmado) Anna-Karin Östin.

Hay un sello de Bolagsverket

Bolagsverket, la Oficina de registro de Compañías de Suecia, es el Registrador Oficial de las Compañías Limitadas y otras formas de empresas comerciales en Suecia. Antes de que se expida un Certificado de existencia, los registros radicados en esta oficina se examinan para tener la seguridad de que la compañía en cuestión llena los siguientes requerimientos:

- La compañía tiene una Junta Directiva competente.
- La compañía tiene un Auditor titulado calificado.

24 OCT 2007

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 276 - 1993 Miami

- La compañía ha llenado sus obligaciones con respecto a la radicación correcta de su informe anual.
- La compañía no es el sujeto de acciones legales de división de compañías, terminación o bancarrota.
- La compañía no ha sido disuelta como resultado de una fusión y no ha salido del registro por ninguna otra razón.

El Certificado está firmado por un funcionario autorizado para expedir estos y similares documentos en nombre de Bolagsverket, la Oficina de Registro de Compañías de Suecia.

Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Certificación Notarial

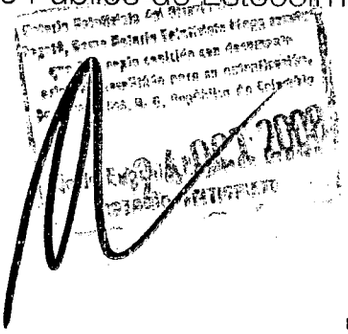
Yo, la suscrita Anne-Marie Bonde, Notario Público de la ciudad de Estocolmo, certifico por medio del presente que Anna-Karin Östin, debidamente autorizada para firmar en nombre de la Oficina de Registro de Compañías de Suecia, ha expedido y firmado el anterior documento en original, del cual la presente es una copia auténtica.

Derechos: 340 coronas. Estocolmo, 26 de Octubre de 2007.

Ex oficio:

(Firmado) Sello: "Anne-Marie Bonde – Notario Público de Estocolmo".

Apostilla adjunta:



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

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

1. País:	Suecia
	El presente documento público
2. Ha sido firmado por:	Anne-Marie Bonde
3. Actuando en calidad de:	Notario Público
4. Lleva el sello / estampilla de:	Notario Público de Estocolmo.
	Certificado
5. En:	Estocolmo
6. El:	Día 26 de Octubre de 2007
7. Por:	Björn Sandin, Notario Público
8. Bajo el No.	4070
9. Sello / estampilla:	Björn Sandin, Notario Público de Estocolmo.
10. Firma:	(Firmado)

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Cert.Bolagsverket"

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 10-053

María Eugenia Rojas de Orozco
PRIMERA INSTANCIA

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

12

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. **Country :** Sweden

   This public document

2. **has been signed by** Anne-Marie Bonde

3. **acting in the capacity of** Notary Public

4. **bears the seal/stamp of**

   Notary Public in Stockholm

Certified

5. **at** Stockholm

6. **the** 26.10.2007

7. **by** Björn Sandin

   Notary Public

8. **No** 4070

9. **Seal/stamp:**

10. **Signature:**

NOTARIUS PUBLICUS I STOCKHOLM
BJÖRN SANDIN

13

Bolagsverket

851 81 Sundsvall
Besökare: Badhusparken
Tel: 060-18 40 00 • Fax: 060-12 98 40
bolagsverket@bolagsverket.se • bolagsverket.se

Certificate of Good Standing

I, Anna-Karin Östin, of Bolagsverket, the Swedish Companies Registration Office, do hereby certify that

AstraZeneca AB
registration number: **556011-7482**

is a duly incorporated company under the laws of Sweden and is in good standing and has a legal corporate existence as far as the records of this office show as of the date stated below.

In testimony hereof, I have hereunto set my hand and the official seal of Bolagsverket at Sundsvall, this 8th day of August in the year of two thousand and seven.

Anna-Karin Östin

Bolagsverket, the Swedish Companies Registration Office, is the official registrar of limited companies and other forms of business enterprise in Sweden. Before a Certificate of Good Standing is issued, the records kept by this office are examined to ensure that the following requirements are fulfilled for the company in question:

- the company has a registered competent board of directors
- the company has a registered qualified auditor
- the company has fulfilled its obligations regarding the correct filing of its annual report
- the company is not the subject of company division, winding up or bankruptcy proceedings
- the company has not been dissolved as the result of a merger and has not been struck off the register for any other reason.

The Certificate is signed by an official authorized to issue these and similar documents on behalf of Bolagsverket, the Swedish Companies Registration Office.

14

1142b

The Ministry for Foreign Affairs in Stockholm, hereby certifies that

Mr. Anna-Karin Bäck

Swedish Companies Registration Office, Sundsvall

has issued and signed the foregoing attestation in ~~his~~ her official capacity

For Stockholm this 14th day of August 2007

Agneta Lodelius

EMBASSY OF THE REPUBLIC OF THE SUDAN STOCKHOLM

SIGNATURE OF Agneta Lodelius

AND STAMP OF : Sc. MFA

SIGNATURE : Mohamed Hussein

DATE : 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM ANNE-MARIE UGGLA

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 July 2009 (02.07.2009)

PCT

(10) International Publication Number
WO 2009/081197 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/437* (2006.01)
C07D 487/04 (2006.01) *A61K 31/5025* (2006.01)
C07D 519/00 (2006.01) *A61P 35/00* (2006.01)
A61K 31/4196 (2006.01)

(21) International Application Number:
PCT/GB2008/051206

(22) International Filing Date:
18 December 2008 (18.12.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/015,755	21 December 2007 (21.12.2007)	US
61/096,090	11 September 2008 (11.09.2008)	US
61/107,804	23 October 2008 (23.10.2008)	US

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BRADBURY, Robert, Hugh** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **HALES, Neil, James** [GB/GB]; AstraZeneca Intellectual Property, S-SE-151 85 Södertälje (SE). **RABOW, Alfred, Arthur** [US/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

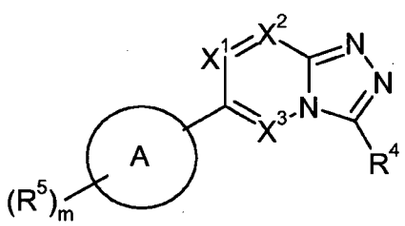
(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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

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(54) Title: BICYCLIC DERIVATIVES FOR USE IN THE TREATMENT OF ANDROGEN RECEPTOR ASSOCIATED CONDITIONS



(I)

(57) Abstract: The invention concerns bicyclic compounds of Formula (I), wherein the integers X^1, X^2, X^3, Ring A, R^4, R^5 and m are as defined in the description. The present invention also relates to processes for the preparation of such compounds, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use in the prevention or treatment of androgen-receptor associated conditions.

WO 2009/081197 A1

BICYCLIC DERIVATIVES FOR USE IN THE TREATMENT OF ANDROGEN RECEPTOR ASSOCIATED CONDITIONS

This invention relates to new bicyclic derivatives and, more particularly, to bicyclic derivatives that act as ligands of the androgen receptor (AR). This invention also relates to methods for the preparation of such bicyclic derivatives, and novel intermediates in the preparation thereof, to pharmaceutical compositions containing such bicyclic derivatives, to the use of such bicyclic derivatives in the preparation of medicines, and to the use of such bicyclic derivatives in the treatment of androgen-receptor associated condition such as prostate cancer.

Prostate cancer is the second most common cause of death from cancer amongst men in developed countries. Four percent of deaths amongst men over 55 can be attributed to prostate cancer. Although the death rate is relatively low, it is currently increasing yearly at a rate of about 14%. The proportion of men for whom prostate cancer is likely to be diagnosed has risen by 30% in recent years, an increase which is attributable largely to better diagnostic methods and to a general increase in the age of the population, rather than to any increased incidence of new disease (E.J. Small, D.M. Reese, Curr. Opinion. Oncology, 2000,12,265-272).

The early stages of prostate cancer tumour growth are androgen–dependent. Provided that the tumour is confined to the prostate itself, it can usually be treated by surgical removal, radiation therapy and/or by chemotherapy. In more advanced cases in which the tumour is no longer confined to the prostate, but has formed metastatic tumours elsewhere in the body, the tumour may be treated palliatively by reducing blood testosterone levels. Such a reduction in blood testosterone levels may be achieved by surgical castration (orchidectomy) or medicinally by treatment with antiandrogens (Casodex, cyproterone acetate, flutamide), LHRH-Agonists (Zoladex, Buserelin), LHRH antagonists (Cetrorelix), or 5α-reductase inhibitors (Finasteride). Since adrenal androgen synthesis is unaffected by surgical castration, a recent trend has been to combine surgical and medicinal treatment. This treatment has only temporary success since after an interval of up to 2 years renewed growth of the tumour normally occurs and this renewed tumour growth is usually not hormonally dependent (L.J. Denis and K. Griffith, Seminars in Surg. Onc., 2000, 18, 52-74). Despite extensive research on this topic during the past 50 years

there is still no effective treatment for the advanced stages of prostate cancer. For patients with advanced prostate cancer the 5-year survival rate is under 15%.

There is evidence that the androgen receptor plays an important role in the development and growth of prostate cancer not only in the early hormone-dependent stages but also in the advanced hormone-independent stages.

The androgen receptor belongs to the family of steroid hormone receptors, which function as transcription factors. The binding of an androgen to the androgen receptor results in the stabilisation of the receptor and protects it form undergoing a rapid proteolytic degradation. The complex of androgen and androgen receptor is transported into the nucleus, where it regulates the expression of androgen responsive genes by binding to their androgen response DNA elements in the promoter region of such androgen responsive genes (D.J. Lamb et al. Vitam. Horm. 2001, 62,199-230).

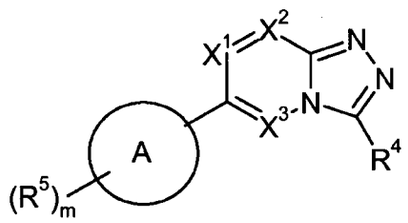
Investigation of prostate tumours shows that in 30% of advanced cases an amplification of the androgen receptor gene locus had occurred; in other cases a range of mutations of the androgen receptor were found in various domains of the androgen receptor and that lead to androgen receptors with altered properties. Such mutated receptors can have a higher than normal affinity for androgens, can be constitutively active, can have altered ligand specificity resulting in activation by other steroid hormones or even by antiandrogens, can be activated by interaction with molecules from other growth promoting signal transduction pathways, can alter interactions with other co-factors, or can activate other target genes (J.P. Elo, T. Visakorpi, Ann. Med. 2001,33,130-141).

The identification of antiandrogens that would inhibit not only the natural form of the androgen receptor but also its mutated forms and thereby so alter the receptor molecule that it became unstable would be very useful in the treatment of prostate tumours at various stages of growth. Such compounds could inhibit a recurrence of tumour growth or at least prolong the disease free interval. In the case of oestrogen receptors, such ligands have been identified that destabilise the receptor and lead to a reduction in the receptor content both in vitro and in vivo (S. Dauvois et al., Proc Natl. Acad. Sci. USA, 1992, 89,4037-41; R.A. McClelland et al. Eur. J. Cancer, 1996, 32A, 413-416).

Non-steroidal antiandrogens have been described in US5411981 (phenylimidazolidine derivatives), in WO97/00071 (specifically substituted

phenyldimethyl hydantoins and their imino- and thio-derivatives), in WO00/37430 (phenylalanines, phenylhydantoins, and phenylureas), in WO01/58855 (aminopropanilides), and in EP1122242 (substituted cyanophenylpiperazines).

A series of bicyclic derivatives capable of inducing cellular down-regulaton of the androgen receptor is described herein. According to a first aspect of the present invention there is therefore provided the use of a compound of Formula (I) for the treatment of an androgen receptor associated condition;



(I)

wherein

X^1 is selected from –N– and –C(R^1)–;

X^2 is selected from –N– and –C(R^2)–;

X^3 is selected from –N– and –C(R^3)–;

Wherein at least one of X^1, X^2 and X^3 is not –N-;

Ring A is selected from a mono or bicyclic heterocyclic ring and a carbocyclic ring;

R^1, R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, halo and cyano wherein an alkyl chain in R^1, R^2 and R^3 is optionally substituted by up to three halo groups;

R^4 is selected from hydrogen, hydroxy, halo, cyano, amino, N-C_{1-6}alkylamino, N,N-di-C_{1-6}alkylamino, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_n$- wherein n is an integer from 0-2 and a C_{3-4}carbocyclic ring, wherein a alkyl, alkenyl or alkynyl chain within R^4 can optionally be substituted with up to 5 groups selected from cyano, halo, amino, C_{1-6}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-6}alkylthio and when R^4 comprises an alkyl chain the chain can be perfluorinated;

R^5 is selected from oxo or the group –L^1-J-L^2-K

wherein

L^1 and L^2 are independently selected from a direct bond, C_{1-6}alkylene, C_{2-6}alkenylene C_{2-6}alkynylene, C_{1-6}alkylidene, wherein an alkyl, alkenyl, alkynyl or

alkylidenyl chain within L^1 and L^2 can optionally be substituted with up to 3 groups selected from R^7 and wherein L^1 and L^2 can also be selected from one of the following groups or an alkyl, alkenyl, alkynyl or alkylidenyl chain into which is inserted one of the following groups, said groups independently selected from: -O-, -C(O)-, -C(O)-O-, -O-C(O)-, - $N(R^6)$-, -$N(R^6)$-C(O)-; -C(O)-$N(R^6)$-, -$N(R^6)$-C(O)-O-, -O-C(O)-$N(R^6)$-, -C(O)-$N(R^6)$-O-; -O-$N(R^6)$-C(O)-, -$N(R^6)$-C(O)-$N(R^6)$-, -$S(O)_{0-2}$-, -O-$S(O_2)$-, S-(O_2) -O-, -$N(R^6)$-$S(O)_2$- and -$S(O)_2$-$N(R^6)$-;

J is selected from a direct bond, C_{1-4}alkylene, aryl, heterocyclyl and heteroaryl wherein J is optionally substituted by up to five groups selected from R^8;

K is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, a carbocyclic ring, aryl, heterocyclyl and heteroaryl wherein K is optionally substituted by up to five groups selected from R^8;

R^6 is selected from hydrogen and C_{1-6}alkyl;

R^7 is selected from hydroxy, carboxy, carbamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-4}alkyloxyC_{1-4}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl-$S(O)_n$- wherein n is an integer from 0 to 2, aminosulphonyl, carbamoyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, N-C_{1-4}alkylaminocarbonyl, N,N-di-C_{1-4}alkylaminocarbonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di-C_{1-4}alkylaminosulphonyl, oxo, C_{1-6}alkyl(C_{1-6}alkoxy)oxophosphinyl, diC_{1-6}alkyloxophosphinyl, aryl, carbocyclyl, heterocyclyl, heteroaryl wherein R^7 is optionally substituted by up to three groups selected from hydroxy, halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy and a carbocyclic ring and an N,N-di-C_{1-4}alkylamino group within R^7 is optionally cyclized to form a ring;

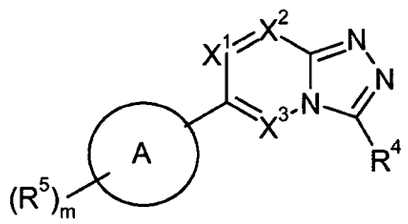
R^8 is selected from hydroxy, oxo, cyano, halo, nitro, hydroxy, carboxy, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, cyanoC_{1-6}alkoxy, C_{1-6}alkenyloxy, C_{1-6}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl-$S(O)_n$– wherein n is an integer from 0 to 2, amino, C_{1-6}alkylsulphonyloxy, carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di-C_{1-4}alkylaminosulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino, carbamoyl, N-C_{1-4}alkylaminocarbonyl, N,N-di-C_{1-4}alkylaminocarbonyl, aryl, carbocyclyl, heterocyclyl and heteroaryl wherein an alkyl chain or ring in R^8 is optionally substituted by up to five groups selected from halo, amino, hydroxy, carboxy, C_{1-4}alkoxy, N-C_{1-4}alkylamino,

N,N-di-C_{1-4}alkylamino, carbamoyl, N-C_{1-4}alkylaminocarbonyl, N,N-di-C_{1-4}alkylaminocarbonyl and oxo and an N,N-di-C_{1-4}alkylamino group within R^8 is optionally cyclized to form a ring; and

m is an integer from 1 to 4;

or a pharmaceutically acceptable salt thereof.

According to a second aspect of the present invention there is provided the use of a compound of Formula (Ia) as a medicament;



(Ia)

wherein X^1, X^2, X^3 , Ring A, R^1, R^2, R^3, R^4 and R^5 are as defined above in the definition of a compound of Formula (I)

with the proviso that

(i) when m is 1 then $(R^5)_m$ cannot be hydroxy, oxo or C_{1-6}alkyl and when m is 2 then $(R^5)_m$ cannot be dihydroxy;

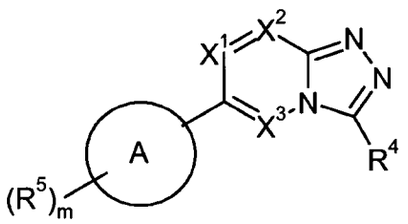
(ii) $-L^1$-J-L^2-K cannot be trifluorophenylpiperidin-1-yl when the piperidine group is substituted by amino or C_{1-4}alkylcarbonylamino;

(iii) When Ring A is pyrrolidin-1-yl, m is 2 and $(R^5)_m$ is substituted piperidine-1-ylcarbonyl and substituted phenyl or substituted piperidine-1-ylcarbonyl and substituted pyridyl then the phenyl or pyridyl ring cannot be substituted by fluoro, chloro, cyano, trifluoromethyl or methoxy.

(iv) when Ring A is indoline and m is 1 then R^5 cannot be unsubstituted or substituted pyrrolidinylcarbonyl or unsubstituted or substituted piperidinylcarbonyl.

or a pharmaceutically acceptable salt thereof.

According to a third aspect of the present invention there is provided a compound of Formula (Ib);



(Ib)

wherein X^1, X^2, X^3 , Ring A, R^1, R^2, R^3, R^4 and R^5 are as defined above in the definition of a compound of Formula (I)

the proviso that

(i) when m is 1 then $(R^5)_m$ cannot be hydroxy, C_{1-6}alkyl, oxo, acetyl, carbamoyl, ethoxycarbonyl, methylsulphonyl, methylsulphonylamino, isopropylaminocarbonylmethyl or isobutylaminocarbonylmethyl and when m is 2 $(R^5)_m$ cannot be dihydroxy and cannot be cyano and amino;

(ii) when R^4 is trifluoromethyl or methyl and Ring A is piperazin-1-yl substituted at the 4 position by phenyl, benzyl phenethyl, phenylsulphonyl, phenylcarbonyl or anilinocarbonyl then the phenyl ring cannot be unsubstituted or substituted by 2-methyl, 2,3-dimethyl, 2,4-dimethyl, 2,6-dimethyl, 2-methoxy, 4-methoxy, 3-chloro, 4-chloro, 3-fluoro, 4-fluoro, 2,6-difluoro, 3-trifluoromethyl, 2-nitro, 4-nitro or 2,3,5,6-tetrafluoro-4-trifluoromethyl;

(iii) when R^4 is trifluoromethyl or methyl and Ring A is piperazinyl substituted by $-L^1$-J-L^2-K at the 4-position and m is 1 then $-L^1$-J-L^2-K cannot be unsubstituted α-carbamoylbenzyl, α-phenylbenzyl,unsubstituted pyrrolidin-1-ylcarbonyl, unsubstituted morpholinocarbonylmethyl, unsubstituted thien-3-ylmethyl, unsubstituted thiazol-2-yl, unsubstituted pyridin-2-yl, unsubstituted pyridin-4-ylmethyl, unsbustituted pyrazin-2-yl, unsbustituted pyrimidin-2-yl, unsubstitued tetrazolo[1,5-b]pyridazin-6-yl, unsubstituted quinolin-8-ylmethyl, unsubstituted 1,3-benzodioxol-5ylmethyl, 2,6-difluorophenylsulphonyl, 5-chlorothien-2-ylsulphonyl, 2-methylthiazol-4-ylmethyl, 2-(4-methoxyphenyl)thiazol-4-ylmethyl;

(iv) $-L^1$-J-L^2-K cannot be trifluorophenylpiperidin-1-yl when the piperidine group is substituted by amino or C_{1-4}alkylcarbonylamino; and

(v) When Ring A is pyrrolidin-1-yl, m is 2 and $(R^5)_m$ is substituted piperidine-1-ylcarbonyl and substituted phenyl or substituted piperidine-1-ylcarbonyl and

substituted pyridyl then the phenyl or pyridyl ring cannot be substituted by fluoro, chloro, cyano, trifluoromethyl or methoxy;

(vi) when Ring A is indoline and m is 1 then R^5 cannot be unsubstituted or substituted pyrrolidinylcarbonyl or unsubstituted or substituted piperidinylcarbonyl.

(vii) when R^4 is trifluoromethyl or methyl and Ring A is piperidinyl substituted by $-L^1$-J-L^2-K at the 4-position and m is 1 then $-L^1$-J-L^2-K cannot be mono or disubstituted carbamoyl;

(viii) The following compounds are excluded:

6-[2-(2,4-dimethoxyphenyl)-1-pyrrolidinyl]-3-(trifluoromethyl)-1,2,4-Triazolo[4,3-b]pyridazine;

6-[4-(7-ethyl-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]-3-(trifluoromethyl)-1,2,4-Triazolo[4,3-b]pyridazine,

6-[4-(1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]-3-(trifluoromethyl)-1,2,4-Triazolo[4,3-b]pyridazine;

6,7,8,9-tetrahydro-3-[1-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-b]pyridazin-6-yl]-3-piperidinyl]- 5H-1,2,4-triazolo[4,3-a]azepine;

6-[4-[2-(3,5-dimethoxyphenyl)ethyl]-1-piperidinyl]-3-(trifluoromethyl)- 1,2,4-triazolo[4,3-b]pyridazine;

2-thienyl[4-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-b]pyridazin-6-yl]-1-piperazinyl]-methanone;

N-cyclopentyl-N-methyl-1-(3-methyl-1,2,4-triazolo[4,3-b]pyridazin-6-yl)- 4-piperidinamine;

6-[4-(2-benzoxazolyl)-1-piperidinyl]-3-(trifluoromethyl)- 1,2,4-triazolo[4,3-b]pyridazine

6-(3-phenylpyrolidin-1yl)-1,2,4-triazolo[4,3-b]pyridazine; and

1-[[2,3-dihydro-1-(3-methyl-1,2,4-triazolo[4,3-b]pyridazin-6-yl)-1H-indol-2-yl]carbonyl]-3-methyl- piperidine;

or a salt thereof.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Examples of suitable methods for separating the enantiomers of a racemic compound include chromatography using a suitable chiral stationary phase; or conversion of a racemic mixture into diastereomeric derivatives, separation of the mixture of diastereomeric derivatives into two single diastereomers, and regeneration of a separate single enantiomer from each separate single diastereomer.

Examples of suitable methods for separating a mixture of diastereomers include fractional crystallisation, normal-phase chromatography, or reverse-phase chromatography.

It is to be understood that certain compounds of Formula (I) defined above may exhibit the phenomenon of tautomerism. In particular, tautomerism may affect any heterocyclic groups that bear 1 or 2 oxo substituents. It is to be understood that the present invention includes in its definition any such tautomeric form, or a mixture thereof, which possesses the above-mentioned activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings or named in the Examples.

It is to be understood that certain compounds of Formula (I) above may exist in unsolvated forms as well as solvated forms, such as, for example, hydrated forms. It is to be understood that the present invention encompasses all such solvated forms that possess androgen receptor ligand activity.

It is also to be understood that certain compounds of the Formula (I) may exhibit polymorphism, and that the present invention encompasses all such forms which possess androgen receptor ligand activity.

In this specification the generic term "alkyl", unless specifically specified otherwise, includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, and references to individual branched-chain

alkyl groups such as "isopropyl" are specific for the branched-chain version only. The same principle also applies to generic terms "alkenyl" and "alkynyl", unless specified otherwise.

The term "fluoroC_{1-6}alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length which may be straight-chained or branched wherein at least one of the hydrogen atoms have been replaced by fluorine. For example, "fluoroC_{1-6}alkyl" includes, but is not limited to, fluoromethyl, fluoroethyl, fluoropropyl, fluoroisopropyl, fluorobutyl, fluoroisobutyl, fluoro-tert-butyl, fluoropentyl, fluoroisopentyl, fluorohexyl, fluoroisohexyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, nonafluorobutyl, undecafluoropentyl and tridecafluorohexyl. The term "fluoroC_{1-4}alkyl" should be construed accordingly.

The term "C_{1-6} alkoxy" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to oxygen. For example, "C_{1-6} alkoxy" includes, but is not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

The term "C_{2-6}alkanoyl" is intended to mean a saturated carbon chain of 1 to 5 carbon atoms in length which may be straight-chained or branched, linked to carbonyl. For example, "C_{2-6}alkanoyl" includes, but is not limited to, ethanoyl, propanoyl, butanoyl, pentanoyl and hexanoyl.

The term "C_{1-6}alkoxyC_{1-6}alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked via oxygen to another saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, "C_{1-6}alkoxyC_{1-6}alkyl" includes, but is not limited to, methoxyethyl, methoxypropyl, ethoxypropyl, propoxyethyl and butoxypropyl.

The term "hydroxyC_{1-6}alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, comprising a single hydroxyl group. For example "hydroxyC_{1-6}alkyl" includes, but is not limited to, hydroxymethyl, hydroxyethyl, 2-hydroxypropyl , 3-hydroxypropyl, 1-hydroxyisopropyl, 4-hydroxybutyl, hydroxypentyl, hydroxyhexyl and hydroxyisohexyl.

The term "C_{1-6}alkylsulphanyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulphur. For example, "C_{1-6}alkylsulphanyl" includes, but is not limited to, methylsulphanyl,

ethylsulphanyl, propylsulphanyl, isopropylsulphanyl, butylsulphanyl, isobutylsulphanyl, *tert*-butylsulphanyl, pentylsulphanyl and hexylsulphanyl.

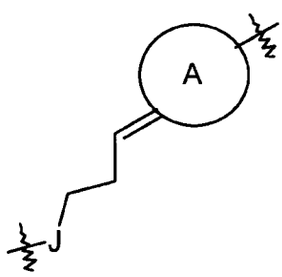
The term "C_{1-6}alkylsulphinyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulphoxide. For example, "C_{1-6}alkylsulphinyl" includes, but is not limited to, methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl, butylsulphinyl, isobutylsulphinyl, *tert*-butylsulphinyl, pethylsulphinyl and hexylsulphinyl.

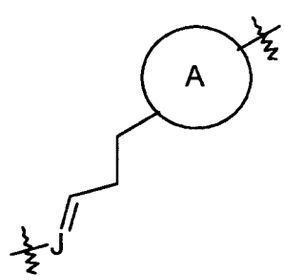
The term "C_{1-6}alkylsulphonyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulphur doioxide. For example, "C_{1-6}alkylsulphonyl" includes, but is not limited to, methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl, butylsulphonyl, isobutylsulphonyl, *tert*-butylsulphonyl, pentylsulphonyl and hexylsulphonyl.

The term "N-C_{1-4}alkylamino" is intended to mean a saturated carbon chain of 1 to 4 carbon atoms in length, which may be straight-chained or branched, linked to a secondary amino group. For example, "N-C_{1-4}alkylamino" includes, but is not limited to, methylamino, ethylamino, propylamino and butylamino.

The term "N,N-di-C_{1-4}alkylamino" is intended to mean a saturated carbon chain of 1 to 4 carbon atoms in length, which may be straight-chained or branched, linked to a tertiary amino group, which is in turn linked to a further saturated carbon chain of the same length. For example, "N,N-di-C_{1-4}alkylamino" includes, but is not limited to, N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino and N,N-dibutylamino.

The term alkylidene is used to denote an alkylidene chain which can be in either orientation within the molecule, thus for example where L^1 is propylidene this would cover the following two structures:





The term "halo" is used herein to denote fluoro, chloro, bromo and iodo.

The term "haloC_{1-4}alkyl" is intended to mean a saturated carbon chain of 1 to 4 carbon atoms in length which may be straight-chained or branched wherein at least one of the hydrogen atoms have been replaced by a halo atom. For example, "haloC_{1-4}alkyl" includes, but is not limited to, difluoromethyl, trifluoromethyl, chloro(difluoro)methyl, difluoroethyl and difluoropropyl.

The term "aryl" refers to phenyl or naphthyl.

The term "carbamoyl" refers to the group $-C(O)NH_2$.

Unless stated otherwise, the term "heteroaryl" refers to a 4-10 membered aromatic mono or, bicyclic ring containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. In one embodiment the term "heteroaryl" refers to a 5-10 membered aromatic mono or bicyclic ring containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. In another embodiment the term "heteroaryl" refers to a 5 or 6 membered aromatic monocyclic ring containing up to 4 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered heteroaryl rings include pyrrole, furan, imidazole, triazole, tetrazole, pyrazine, pyrazole, pyrimidine, pyridazine, pyridine, pyrrole, isoxazole, oxazole, 1,2,4 oxadiazole, isothiazole, thiazole, thiadiazole, 1,2,4-triazole and thiophene. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuran, benzimidazole, benzthiophene, benzthiazole, benzisothiazole, benzoxazole, benzisoxazole, 1,3-benzodioxole, indole, pyridoimidazole, pyrimidoimidazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or $S(O_2)$ group.

Unless stated otherwise, the term "heterocyclyl" refers to a 4-10 membered saturated or partially saturated mono or bicyclic ring containing up to 5 heteroatoms

selected from nitrogen, oxygen or sulphur linked via ring carbon atoms or ring nitrogen atoms. Examples of 'heterocyclyl' include tetrahydrofuranyl, 2,3-dihydro-4H-pyranyl, tetrahydro-2*H*-pyranyl, pyrrolinyl, pyrrolidinyl, 1,3-thiazolidine, morpholinyl, oxetanyl, piperidinyl, piperazinyl, dihydropyridinyl, dihydropyrimidinyl and azepane. Particular examples of 'heterocyclyl' include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or $S(O_2)$ group.

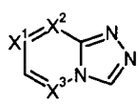
The term "carbocyclyl" or carbocyclic ring refers to a totally saturated or partially saturated mono, bicyclic 3-10 membered carbon ring. Examples of carbocyclic rings are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[4,2,0]octane or 2,3-dihydroindene.

Particular novel compounds of the invention include, for example, compounds of Formula (I), or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated, each of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, J, K, L^1, L^2 and m have any of the meanings defined hereinbefore or in paragraphs (1) to (56) hereinafter:-

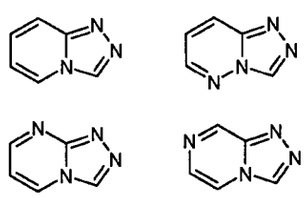
(1) X^1 and X^2 and X^3 are all -C(H)-;

(2) X^1 is $-C(R^1)-$, X^2 is $-C(R^2)-$ and X^3 is $-C(R^3)-$;

(3) The ring



is selected from one of the following



;

(4) X^1 is $-C(R^1)-$, X^2 is $-C(R^2)-$ and X^3 is –N-;

(5) X^1 and X^2 are both C(H) and X^3 is –N-;

(6) Ring A is selected from pyrrolidinyl, , piperidinyl, 1,2-dihydropyridyl, 1,2,5,6-tetrahydropyridyl, morpholinyl, thiomorpholinyl, oxazepanyl, thiazepanyl, azepanyl, 1,2,5,6-1H-tetrahydroazepinyl, piperazinyl, diazepanyl, tetrahydroimidazolyl, octahydro-1H-indolyl, octahydro-2H-isoindolyl,

azabicyclo[2.2.1]heptanyl, azabicyclo[3.3.0]octanyl, azabicyclo[3.2.1]octanyl, triazaspirodecanyl, octahydropyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-c]pyrrolyl, diazabicyclo[3.2.1]octanyl and diazabicycloheptanyl;

(7) In another embodiment Ring A is selected from tetrahydrofuranyl, tetrahydropyranyl, and 5,6-dihydro-2H-pyranyl;

(8) Ring A is selected from piperidinyl, pyrrolidinyl, piperazinyl and diazepanyl;

(9) Ring A is selected from piperidinyl, piperazinyl, diazepanyl, 1,3,8-triazaspiro[4.5]decan-4-onyl, 1,3,4,6,7,8,9,9a-octahydropyrido[1,2-a]pyrazinyl, ,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, 3,8-diazabicyclo[3.2.1]octanyl and 2,5-diazabicyclo[2.2.1]heptanyl.

(10) Ring A is selected from piperidinyl, piperazinyl, 3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, and diazepanyl;

(11) Ring A is selected from piperazinyl and 3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl;

(12) R^1 is C_{1-4}alkyl and R^2 is C_{1-4}alkyl;

(13) R^1 is hydrogen and R^2 is C_{1-4}alkyl;

(14) R^1 is C_{1-4}alkyl and R^2 is hydrogen;

(15) R^1 is selected from methyl and ethyl;

(16) R^1 is selected from hydrogen and methyl;

(17) R^2 is selected from hydrogen and methyl;

(18) R^3 is selected from hydrogen and methyl;

(19) R^3 is hydrogen;

(20) R^4 is selected from halo, C_{1-6}alkyl optionally substituted by up to 5 halo substituents, C_{1-6}alkylS(O)n- where in n is an integer from 0 to 2 and amino;

(21) R^4 is selected from halo, C_{1-4}alkyl optionally substituted by up to 5 halo substituents, C_{1-4}alkylthio and amino;

(22) R^4 is selected from chloro, difluoromethyl, trifluoromethyl, 1,1,2,2-tetrafluoroethyl, methylthio or amino;

(23) R^5 is the group $-L^1$-J-L^2-K;

(24) R^5 is the group $-L^1$-K;

(25) R^5 is the group $-L^1$-J-K;

(26) R^5 is the group –K;

(27) R^5 is the group $-L^1-L^2-K$;

(28) L^1 and L^2 are independently selected from a direct bond, C_{1-6}alkylene wherein an alkyl chain within L^1 and L^2 can optionally be substituted with up to 3 groups selected from R^7 and wherein L^1 and L^2 can also be selected from one of the following groups or an alkyl chain into which is inserted one of the following groups, said groups independently selected from: -O-, -C(O)-, -C(O)-O-, -O-C(O)-, -$N(R^6)$-, -$N(R^6)$-C(O)-; -C(O)-$N(R^6)$-, -$N(R^6)$-C(O)-O-, -O-C(O)-$N(R^6)$-, -C(O)-$N(R^6)$-O-; -O-$N(R^6)$-C(O)-, -$N(R^6)$-C(O)-$N(R^6)$-, -$S(O)_{0-2}$-, -O-$S(O_2)$-, S-(O_2) -O-, -$N(R^6)$-$S(O)_2$- and -$S(O)_2$-$N(R^6)$-;

(29) L^1 and L^2 are independently selected from a direct bond, C_{1-6}alkylene wherein an alkyl chain within L^1 and L^2 can optionally be substituted with up to 3 groups selected from R^7 and wherein L^1 and L^2 can also be selected from one of the following groups or an alkyl chain into which is inserted one of the following groups, said groups independently selected from: -O-, -C(O)- and -$S(O)_{0-2}$-;

(30) L^1 and L^2 are independently selected from a direct bond, C_{1-4}alkylene, -O-, -C(O)-, -OC(O)-, -C(O)O-, -$N(R^6)$-, -$N(R^6)$C(O)-, -C(O)$N(R^6)$-, -$N(R^6)$C(O)O-, -$S(O)_n$- wherein n is an integer from 0 to 2, -$OS(O)_2$-, -$S(O)_2N(R^5)$- and -$N(R^5)S(O)_2$-;

(31) L^1 and L^2 are independently selected from a direct bond, C_{1-4}alkylene, -O-, -C(O)-, -C(O)O-, -$N(R^6)$-, -$N(R^6)$C(O)-, -C(O)$N(R^6)$-, -$N(R^6)$C(O)O-, -S-, -$S(O)_2$-, -$OS(O)_2$-, -$S(O)_2N(R^6)$- and -$N(R^6)S(O)_2$-;

(32) L^1 and L^2 are independently selected from a direct bond, C_{1-2}alkylene, -O-, -$S(O)_2N(R^6)$- and -$N(R^6)S(O)_2$-;

(33) L^1 is independently selected from a direct bond, C_{1-2}alkylene, -O-, -$S(O)_2N(R^6)$- and -$N(R^6)S(O)_2$- and L^2 is a direct bond;

(34) L^1 is selected from a direct bond, C_{1-4}alkylene, -C(O)-, -C(O)O-, -C(O)$N(R^6)$-, -$S(O)_2$- and $-S(O)_2N(R^6)$-;

(35) L^2 is selected from a direct bond, -O-, -C(O)O-, -$N(R^6)$-, -$N(R^6)$C(O)-, -C(O)$N(R^6)$-, -$N(R^6)$C(O)O-,-S-, -$S(O)_2$-, -$OS(O)_2$-, - $(R^6)S(O)_2$-;

(36) L^2 is a direct bond;

(37) J is selected from a direct bond, aryl and heteroaryl ring wherein J is optionally substituted by up to five groups selected from R^8;

(38) J is selected from a direct bond, phenyl, imidazolyl and pyridyl;

(39) J is a direct bond;

(40) K is selected from aryl and heteroaryl ring wherein K is optionally substituted by up to five groups selected from R^8;

(41) K is selected from C_{1-6}alkyl, C_{2-6}ethenyl, cyclohexyl, phenyl, naphthyl, , furanyl, pyrrolidinyl, pyrrolyl, morpholinyl, piperaziyl, thienyl, thiazolyl, thiadiazolyl, pyrazolyl, piperidinyl, pyridyl, 2,3-dihydropyridyl, pyrazinyl, pyrimidinyl, quinolinyl, quinoxalinyl, benzothiophenyl, 1-benzofuranyl, 2,3-dihydro-1-benzofuranyl, 1,2,3,4-tetrahydroquinolinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, 1,3-benzoxazolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzothiazolyl and benzimidazolyl;

(42) K is selected from methyl, ethyl, propyl, butyl, ethenyl, prop-2-enyl, cyclohexyl, phenyl, naphthyl, , furanyl, pyrrolidinyl, pyrrolyl, morpholinyl, piperazinyl, thienyl, thiazolyl, thiadiazolyl, pyrazolyl, piperidinyl, pyridyl, 2,3-dihydropyridyl, pyrazinyl, pyrimidinyl, quinolinyl, quinoxalinyl, benzothiophenyl, 1-benzofuranyl, 2,3-dihydro-1-benzofuranyl, 1,2,3,4-tetrahydroquinolinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, 1,3-benzoxazolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzothiazolyl and benzimidazolyl;

(43) K is selected from phenyl, naphthyl, , furanyl, pyrrolyl, , thienyl, thiazolyl, thiadiazolyl, pyrazolyl, piperidinyl, pyridyl, pyrazinyl, pyrimidinyl, quinolinyl, quinoxalinyl, benzothiophenyl, 1-benzofuranyl, 1,2,3,4-tetrahydroquinolinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, 1,3-benzoxazolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzothiazolyl and benzimidazolyl;

(44) R^6 is selected from hydrogen and C_{1-4}alkyl;

(45) R^6 is selected from hydrogen, methyl;

(46) R^7 is selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl and phenyl;

(47) R^7 is selected from phenyl;

(48) R^8 is selected from oxo, cyano, halo, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, C_{1-6}alkyl-$S(O)_n$– wherein n is an integer from 0 to 2, C_{1-6}alkylsulphonyloxy, carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di-C_{1-4}alkylaminosulphonyl, N-C_{1-4}alkylaminocarbonyl, N,N-di-C_{1-4}alkylaminocarbonyl, aryl, carbocyclyl, heterocyclyl and heteroaryl

wherein an alkyl chain or ring in R^8 is optionally substituted by up to five groups selected from halo, carboxy, C_{1-4}alkoxy, N,N-di-C_{1-4}alkylamino, carbamoyl, N-C_{1-4}alkylaminocarbonyl, N,N-di-C_{1-4}alkylaminocarbonyl and oxo and an N,N-di-C_{1-4}alkylamino group within R^8 is optionally cyclized to form a ring;

(49) R^8 is selected from C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, hydroxy, carbamoyl, cyano, halo, nitro, amino,. N-C_{1-4}alkylamino, N,N-diC_{1-4}alkylamino and oxo wherein an alkyl, chain in R^8 is optionally substituted by up to 5 halo groups;

(50) R^8 is selected from C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, hydroxy, carbamoyl, cyano, halo, nitro, amino,. N,N-diC_{1-4}alkylamino and oxo wherein an alkyl, chain in R^8 is optionally substituted by up to 5 halo groups;

(51) R^8 is selected from methyl, propyl, isopropyl, 2-methylpropyl, t-butyl, ethynyl, trifluoromethyl, methoxy, ethoxy, butoxy, difluoromethoxy, trifluoromethoxy, ethoxycarbonyl, hydroxy, carbamoyl, cyano, chloro, bromo, fluoro, amino, dimethylamino; diethylamino andoxo;

(52) m is an integer from 0 to 3;

(53) m is 1;

(54) m is 2;

(55) m is 3;

(56) m is 4;

Particular novel compounds of the invention include any one of the following:

6-[4-(4-nitrophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-(4-phenethylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-(1-benzothiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine

6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile

6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile

6-[4-(thiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-(1H-indol-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]isoquinoline

6-[4-[(4-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

6-[4-[(3-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

3-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile

6-[4-[(4-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-(1H-indol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-(3-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-methylsulfanylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[[3-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4,5-dimethylfuran-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile

3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile

6-[4-[(4-methoxyphenyl)-phenylmethyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethylsulfanyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

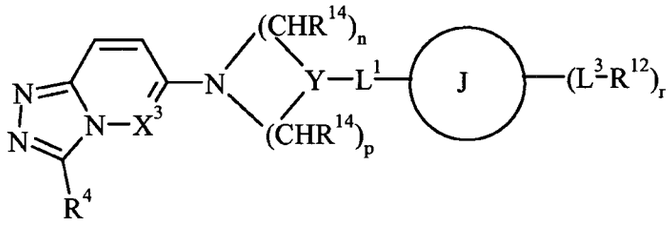
6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[4,4-bis(4-fluorophenyl)butyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[2-[(3-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

or pharmaceutically acceptable salts thereof.

According to a fourth aspect of the present invention there is provided a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use as a medicament:



(Ic)

wherein

X^3 represents CH or N;

R^4 represents haloC_{1-4}alkyl;

Y represents CH, COH or N;

R^{14}, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

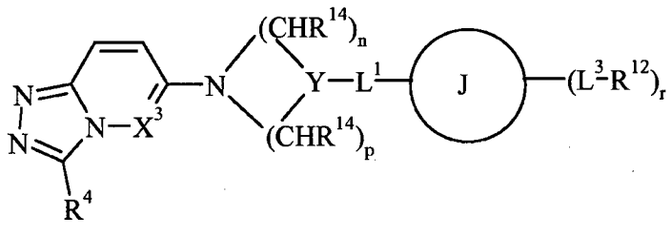
a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

According to a fifth aspect of the present invention there is provided a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer:



(Ic)

wherein

X^3 represents CH or N;

R^4 represents haloC_{1-4}alkyl;

Y represents CH, COH or N;

R^{14}, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-,

-S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring comprising 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system comprising 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

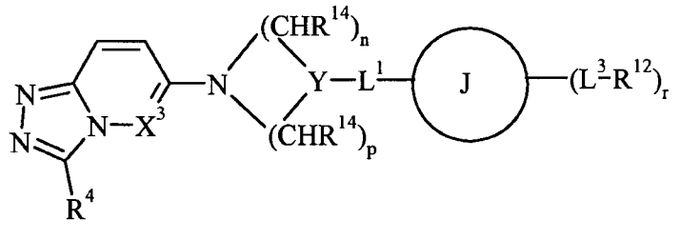
a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl,

N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

According to a sixth aspect of the present invention there is provided a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

wherein

X^3 represents CH or N;

R^4 represents haloC_{1-4}alkyl;

Y represents CH, COH or N;

R^{14}, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl or thiadiazolyl; or

a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

L^3 represents a direct bond, -$(CR^9R^{10})_t$-, -C(O)N(R^{11})-$(CH_2)_q$-, -C(O)N(R^{11})-$(CH_2)_q$-S$(O)_2$-, -NR^{11}C(O)-$(CH_2)_q$-, -C(O)-$(CH_2)_q$-, -O-$(CH_2)_q$-, -O-$(CH_2)_q$-NR^{11}-$(CH_2)_q$-, –O-$(CH_2)_q$-C(O)NR^{11}-$(CH_2)_q$-, -S-, -S(O)- or –$S(O)_2$-;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or –C(O)N$R^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl;

r represents 1, 2 or 3 when J represents aryl;

r represents 0 when J represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

r represents 0, 1, 2 or 3 when J represents furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl, thiadiazolyl, or a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

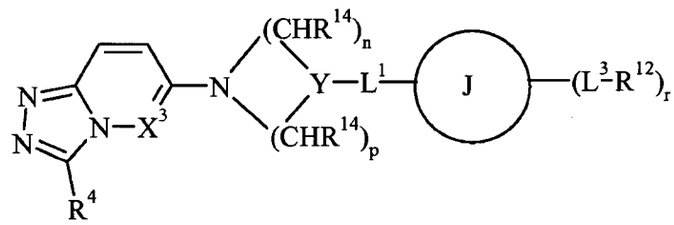
with the proviso that the compound of Formula (Ic) is other than:

4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;

6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-fluorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(imidazo[1,2-*a*]pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(3,4-dimethoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-{4-[2-(3,5-dimethoxyphenyl)ethyl]piperidin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(4-methoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(3-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(4-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(2-methylbenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
6-[4-(4-fluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;
or
6-{4-[(2,6-difluorophenyl)sulfonyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.

According to one embodiment of the sixth aspect of the present invention there is provided a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

wherein

X^3 represents CH or N;

R^4 represents difluoromethyl, trifluoromethyl or chloro(difluoro)methyl;

Y represents CH, COH or N;

R^{14}, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ or $-N(R^{11})-(CH_2)_q-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q represents 0, 1, 2 or 3;

t represents 1 or 2;

v represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl; or

a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;

L^3 represents a direct bond, $-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-$, $-O-(CH_2)_q-C(O)NR^{11}-$, -S-, -S(O)- or $-S(O)_2-$;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy,

hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl;

r represents 1, 2 or 3 when J represents aryl;

r represents 0 when J represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

r represents 0, 1, 2 or 3 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;

with the proviso that the compound of Formula (Ic) is other than:

4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;

6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-fluorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(imidazo[1,2-*a*]pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3,4-dimethoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-{4-[2-(3,5-dimethoxyphenyl)ethyl]piperidin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-methoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-methylbenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

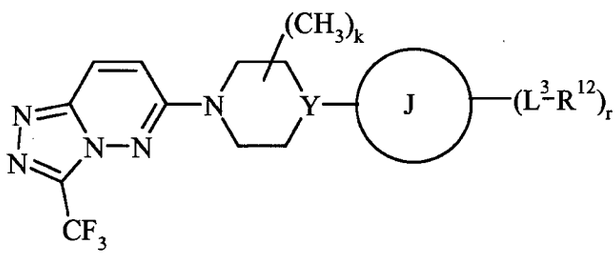
6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine; or

6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.

According to a further embodiment of the sixth aspect of the present invention there is provided a compound of Formula (If), or a pharmaceutically acceptable salt thereof:



(If)

wherein

Y represents CH, COH or N;

k represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl or thiadiazolyl; or

a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl;

r represents 1, 2 or 3 when J represents aryl;

r represents 0 when J represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

r represents 0, 1, 2 or 3 when J represents furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl, thiadiazolyl, or a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

with the proviso that the compound of Formula (If) is other than:

4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;

6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

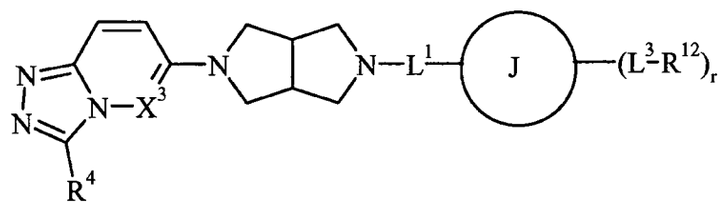
6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

or

6-[4-(4-fluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.

According to a seventh aspect of the present invention there is provided a compound of Formula (Id), or a pharmaceutically acceptable salt thereof:



(Id)

wherein

X^3 represents CH or N;

R^4 represents haloC_{1-4}alkyl;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

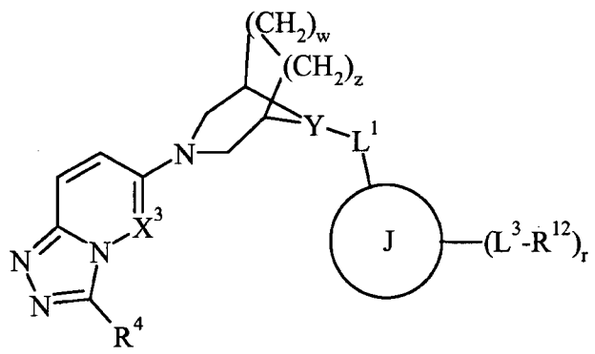
R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

According to an eigth aspect of the present invention there is provided a compound of Formula (Id) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to a ninth aspect of the present invention there is provided a compound of Formula (Id) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer.

According to a tenth aspect of the present invention there is provided a compound of Formula (Ie), or a pharmaceutically acceptable salt thereof:



(Ie)

wherein

X^3 represents CH or N;

R^4 represents haloC_{1-4}alkyl;

Y represents CH, COH or N;

w and z independently represent 0 or 1;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

According to an eleventh aspect of the present invention there is provided a compound of Formula (Ie) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to a twelfth aspect of the present invention there is provided a compound of Formula (Ie) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer.

In further embodiments of the fourth, fifth, sixth, seventh, eigth, ninth, tenth, eleventh and twelfth aspects of the present invention, each of the following definitions of J, L^1, L^3, n, p, r, w, z, R^4, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, X^3 and Y in paragraphs (1) to (61) hereinafter may be used individually or in combination with one or more of the other following definitions to limit the broadest definitions of Formulae (Ic), (Id), (Ie) or (If).

(1) X^3 represents N;

(2) X^3 represents CH;

(3) R^4 represents difluoromethyl, trifluoromethyl, chloro(difluoro)methyl, difluoroethyl or difluoropropyl;

(4) R^4 represents difluoromethyl, trifluoromethyl or chloro(difluoro)methyl;

(5) R^4 represents difluoromethyl

(6) R^4 represents trifluoromethyl;

(7) R^4 represents chloro(difluoro)methyl;

(8) R^{14} represents hydrogen;

(9) n and p both represent 2;

(10) n and p both represent 1;

(11) Y represents CH or COH;

(12) Y represents CH

(13) Y represents COH;

(14) Y represents N;

(15) L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ or $-N(R^{11})-(CH_2)_q-$;

(16) L^1 represents a direct bond, $-CH_2-$, $-CH(CH_3)-$ or $-O-$;

(17) L^1 represents a direct bond;

(18) L^1 represents $-CH_2-$;

(19) J represents phenyl, pyridinyl, indolyl, indazolyl or pyrrolopyridinyl;

(20) J represents phenyl;

(21) J represents pyridinyl;

(22) J represents pyridin-3-yl;

(23) L^3 represents a direct bond;

(24) L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$ or $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$;

(25) L^3 represents $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$ or $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$;

(26) L^3 represents $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$ or $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$;

(27) L^3 represents $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$ or $-O-(CH_2)_q-$;

(28) L^3 represents a direct bond, $-C(O)N(R^{11})-(CH_2)_q-$ or $-O-(CH_2)_q-$;

(29) L^3 represents $-C(O)N(R^{11})-(CH_2)_q-$ or $-O-(CH_2)_q-$;

(30) L^3 represents $-O-(CH_2)_q-$;

(31) L^3 represents $-O-CH_2-CH_2-$;

(32) R^9 and R^{10} both represent hydrogen;

(33) R^{11} represents hydrogen;

(34) R^{11} represents methyl;

(35) q represents 0, 1 or 2;

(36) R^{12} represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, cyano, hydroxy, imidazolyl, pyrrolidinyl, piperidinyl, methylsulphonyl, morpholinyl, pyrazolyl or phenyl;

(37) R^{12} represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, hydroxy, imidazolyl, pyrrolidinyl, piperidinyl, methylsulphonyl, morpholinyl, pyrazolyl or phenyl;

(38) R^{12} represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, cyano, hydroxy, methylsulphonyl, dimethylamino, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or pyrazolyl;

(39) R^{12} represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, hydroxy, methylsulphonyl, dimethylamino, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or pyrazolyl;

(40) R^{12} represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, cyano or hydroxy;

(41) R^{12} represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl or hydroxy;

(42) R^{12} represents pyrrolidinyl, piperidinyl, methylsulphonyl, morpholinyl or pyrazolyl;

(43) R^{12} represents pyrazolyl;

(44) R^{12} represents pyrazol-5-yl;

(45) R^{12} represents 1-methyl-1H-pyrazol-5-yl;

(46) r represents 1 or 2 when J represents aryl;

(47) r represents 1 when J represents aryl;

(48) r represents 0 or 1 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;

(49) r represents 1 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;

(50) r represents 0 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl,

pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;

(51) r represents 1 when J represents pyrazolyl;

(52) L^3 represents -O-CH_2-CH_2-, R^{12} represents 1-methyl-1H-pyrazol-5-yl and r represents 1;

(53) R^{13} represents methyl, methoxy, oxo, hydroxy, cyano, acetyl or methylsulphonyl;

(54) R^{13} represents methyl, methoxy, oxo, hydroxy, acetyl or methylsulphonyl;

(55) R^{13} represents methyl, oxo or hydroxy;

(56) R^{13} represents methyl;

(57) k represents 0;

(58) k represents 1;

(59) k represents 2;

(60) w and z both represent 1;

(61) w and z both represent 0.

Particular novel compounds of Formula (Ic) include, but are not limited to, the following compounds:

4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile;

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine;

4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

3-(difluoromethyl)-6-{4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl}[1,2,4]triazolo[4,3-b]pyridazine;

4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

N-(2-methoxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

N-(2-hydroxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-(4-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}piperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

N-(2-methoxyethyl)-N-methyl-3-({1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}oxy)benzamide;

2-morpholin-4-yl-N-(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}phenyl)acetamide;

6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-{4-[2-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-{4-[(6-methylpyridin-3-yl)methyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

1-[(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}phenyl)carbonyl]piperidin-4-ol;

N-methyl-N-[2-(methylsulfonyl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-[3-(4-methoxyphenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine; and

4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

and pharmaceutically acceptable salts thereof.

Crystalline forms of particular novel compounds of Formula (Ic), and a particular salt thereof, have also been identified.

According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a 2θ value of about 9.18°, 15.51°, 16.01°, 18.94° or 24.59° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ..

According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of about 9.18°, 15.51°, 16.01°, 18.94° and 24.59° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of 8.30, 9.18, 9.96, 10.41, 14.35, 15.02, 15.51, 16.01, 17.03, 18.46, 18.94, 19.18, 19.82, 20.35, 20.61, 21.80, 22.65, 23.38, 24.15, 24.59, 25.43, 26.12, 26.35, 26.59, 27.43, 29.38, 31.83 and 37.33° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 1 when measured using CuKa radiation.

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a 2θ value of about 12.34°, 15.78°, 20.42°, 23.75° or 24.73° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ..

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of about 12.34°, 15.78°, 20.42°, 23.75° and 24.73°

when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of 6.28, 7.92, 9.65, 12.34, 12.69, 14.92, 15.78, 16.89, 18.78, 19.28, 20.42, 20.99, 21.57, 22.49, 23.31, 23.75, 24.34, 24.73, 25.38, 26.93, 28.14, 29.08, 31.16, 31.86, 32.50, 33.14, 34.79, 36.34, 36.78, 38.01 and 38.64° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 2 when measured using CuKa radiation.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a 2θ value of about 4.90°, 13.47°, 15.93°, 16.64° or 22.83° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ..

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of about 4.90°, 13.47°, 15.93°, 16.64° and 22.83° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of 4.90, 9.784, 11.50, 11.94, 12.97, 13.47, 14.72, 15.93, 16.64, 17.36, 18.32, 18.67, 19.195, 19.67, 20.26, 20.58, 20.87,

21.33, 21.64, 22.83, 23.7, 24, 24.40, 25.99, 26.75, 27.15, 28.10, 28.55, 29.02, 29.46, 29.74, 30.12, 30.65, 31.37, 31.85, 33.66, 34.28, 35.85, 36.42, 37.62 and 38.53° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 3 when measured using CuKa radiation.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a 2θ value of about 6.90°, 15.38°, 21.55°, 24.48° or 27.56° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of about 6.90°, 15.38°, 21.55°, 24.48° and 27.56° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of 6.90, 9.6, 10.78, 12.82, 13.16, 13.85, 14.44, 15.38, 16.44, 17.46, 18.25, 18.92, 19.27, 20.18, 21.03, 21.55, 22.36, 22.63, 23.55, 23.76, 24.48, 25.2, 25.76, 26.47, 27.56, 27.83, 28.21, 29.10, 29.93, 30.59, 31.20, 32.49, 33.33, 34.04, 34.62, 36.18, 36.54, 37.45, 38.17 and 39.32° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray

powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 4 when measured using CuKa radiation.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern with at least one specific peak at a 2θ value of about 11.72°, 16.46°, 17.58° or 21.89° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern with specific peaks at 2θ values of about 11.72°, 16.46°, 17.58° and 21.89° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern with specific peaks at 2θ values of 4.51, 5.90, 11.72, 12.22, 13.23, 16.46, 17.58, 19.74, 20.26, 21.18, 21.89, 23.86, 24.17, 25.83, 26.75, 28.78, 30.54 and 31.51° when measured using CuKa radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 5 when measured using CuKa radiation.

Reference herein to a compound of Formula (I) should be understood to refer equally to a compound of Formula (Ic), (Id), (Ie) and (If).

A suitable pharmaceutically-acceptable salt of a compound of the Formula (I) is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the

Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. A further suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, a salt formed within the human or animal body after administration of a compound of the Formula I.

A suitable pharmaceutically-acceptable solvate of a compound of the Formula I is, for example, a hydrate such as a hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate or an alternative quantity thereof.

The compounds of the invention may be administered in the form of a pro-drug, that is a compound that is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the Formula I and *in vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the Formula I.

Accordingly, the present invention includes those compounds of the Formula I as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the Formula I that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the Formula I may be a synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

Various forms of pro-drug have been described, for example in the following documents :-

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);

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

g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volume 14; and

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the Formula (I) containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C_{1-6}alkyl esters such as methyl, ethyl and *tert*-butyl, C_{1-6}alkoxymethyl esters such as methoxymethyl esters, C_{1-6}alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, C_{3-8}cycloalkylcarbonyloxy- C_{1-6}alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and C_{1-6}alkoxycarbonyloxy- C_{1-6}alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof.

An *in vivo* cleavable ester or ether of a compound of the Formula (I) containing a hydroxy group is, for example, a pharmaceutically-acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically-acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically-acceptable ester forming groups for a hydroxy group include

C_{1-10}alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C_{1-10}alkoxycarbonyl groups such as ethoxycarbonyl, *N,N*-[di-C_{1-4}alkyl]carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-C_{1-4}alkylpiperazin-1-ylmethyl. Suitable pharmaceutically-acceptable ether forming groups for a hydroxy group include α-acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C_{1-4}alkylamine such as methylamine, a di-C_{1-4}alkylamine such as dimethylamine, *N*-ethyl-*N*-methylamine or diethylamine, a C_{1-4}alkoxy-C_{2-4}alkylamine such as 2-methoxyethylamine, a phenyl-C_{1-4}alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically-acceptable amides from an amino group include, for example an amide formed with C_{1-10}alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, *N*-alkylaminomethyl, *N,N*-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C_{1-4})alkylpiperazin-1-ylmethyl.

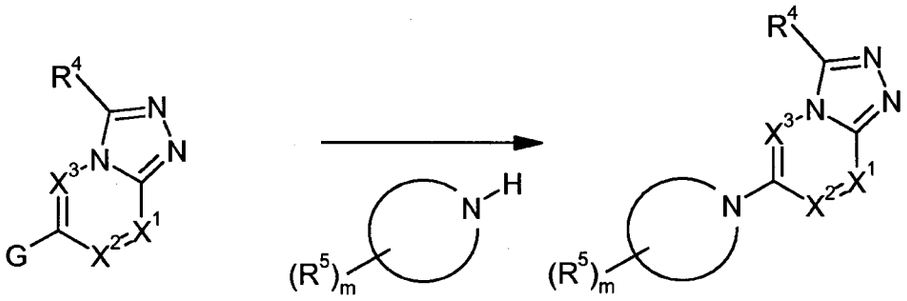
The in vivo effects of a compound of the Formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the Formula (I). As stated hereinbefore, the in vivo effects of a compound of the Formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

An example of a metabolite of a compound of the Formula (I) is 3-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]pyridine 1-oxide which is a metabolite of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol.

The compounds of Formula (I) can be prepared by a process comprising a step selected from (1) to (10) as follows, these processes are provided as a further feature of the invention:-

Preparation of Compounds of Formula (I)

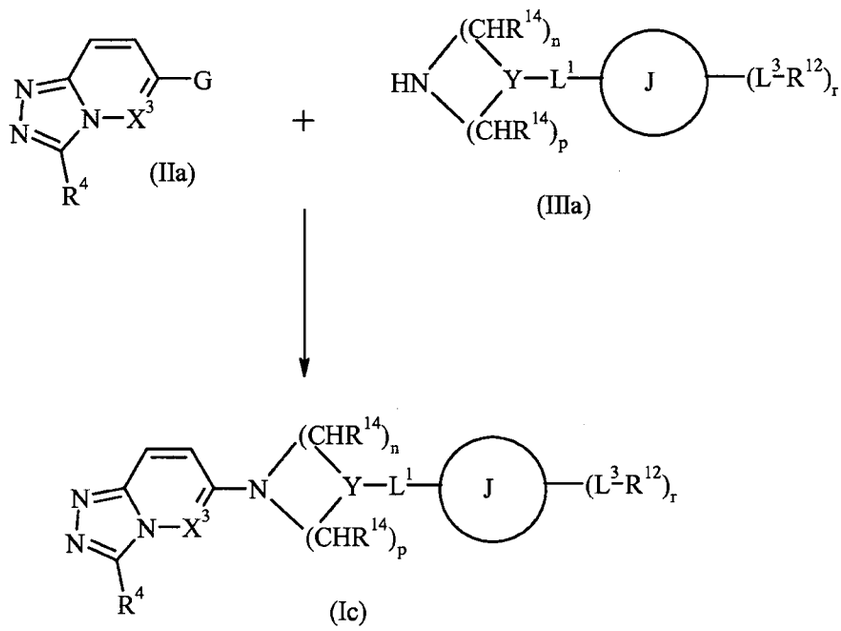
1. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formula (II), wherein G is a leaving group such as halogen, alkane sulfonyloxy, or arylsulfonyloxy and R^4, X^1, X^2, and X^3 are as defined above, with a monocyclic or bicyclic amine of Formula (III), wherein R^5 and m are as defined above.



(II) (III)

The reaction may be carried out by combining the components in an inert solvent such as ethanol, xylene, or N-methylpyrrolidone at temperatures between 25°C and 250°C, preferably between 50°C and 150°C. The reaction may be advantageously catalysed by bases such as organic bases, for instance diisopropylethylamine or by low-valent transition metal catalysts such as Pd(0), for instance bis(dibenzylideneacetone) palladium(0). The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

In one embodiment of the invention, there is provided a process for the preparation of compounds of Formula (Ic) which comprises reacting a compound of Formula (IIa), wherein G is a suitable leaving group such as halogen, for example chloro, and R^4 and X^3 are as defined hereinbefore in relation to Fromula (Ic), with an amine of Formula (IIIa), wherein J, Y, L^1, L^3, R^{12}, R^{14}, n, p and r are as defined hereinbefore in relation to Formula (Ic):



and thereafter, if necessary:

(i) converting a functional group of one compound of the invention into another functional group;

(ii) introducing a new functional group into one compound of the invention;

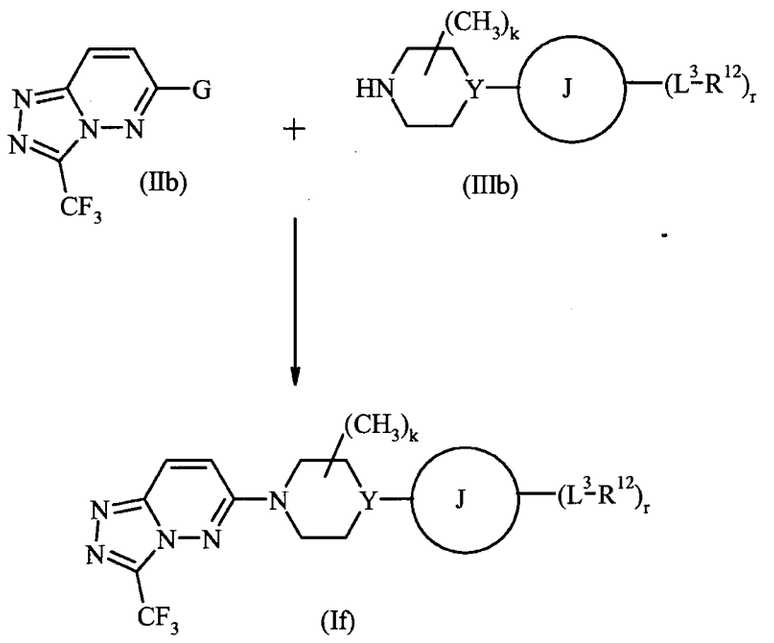
(iii) removing any protecting groups;

(iv) for compounds of the invention in the form of a single enantiomer separating a racemic compound of the invention into separate enantiomers;

(v) preparing a pharmaceutically acceptable salt thereof; and/or

(vi) preparing a crystalline form thereof.

In a further embodiment of the invention, there is provided a process for the preparation of compounds of Formula (If) which comprises reacting a compound of Formula (IIb), wherein G represents halogen, with an amine of Formula (IIIb), wherein Y, J, L^3, R^{12}, k and r are as defined hereinbefore in relation to Formula (If):



and thereafter, if necessary:

(i) converting a functional group of one compound of the invention into another functional group;

(ii) introducing a new functional group into one compound of the invention;

(iii) removing any protecting groups;

(iv) for compounds of the invention in the form of a single enantiomer separating a racemic compound of the invention into separate enantiomers;

(v) preparing a pharmaceutically acceptable salt thereof; and/or

(vi) preparing a crystalline form thereof.

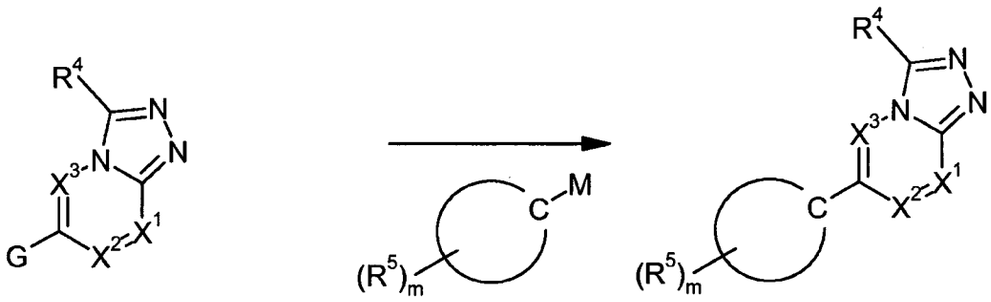
The above reactions may be carried out by combining the components of formula (IIa) and (IIIa) or (IIb) and (IIIb) in a suitable solvent, for example dimethylformamide or dimethylacetamide, at a suitable temperature, for example between 25°C and 250°C, more particularly between 50°C and 150°C, in the presence of a suitable base, for example diisopropylethylamine. The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

Compounds of formula (II), (IIa) or (IIb) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance as described in in W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Part 1 and Part 2, *Systems with Bridgehead Nitrogen*, Interscience,

1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; and *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman and R.F. Cookson, Wiley, 1979 and references therein.

Amines of formula (III), (IIIa) or (IIIb) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance J.R. Malpass, *Aliphatic and Cyclic Amines* in *Comprehensive Organic Chemistry*, Volume 2, p3, D. Barton and D. Ollis Eds, Pergamon, 1979, J.M.J.Gladych and D. Hartley, *Polyfunctional Amines* in *Comprehensive Organic Chemistry*, Volume 2, p61, D. Barton and D. Ollis Eds, Pergamon, 1979; *Houben-Weyl Methods of Organic Chemistry*, Vol E 23 e *Cyclic Compounds I* (1999) to Vol E 23 j *Cyclic Compounds VI* (2000) and references therein and modified as required by functional group transformations well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance *Comprehensive Functional Group Transformations,* A.R. Katritzky, O. Meth-Cohn, and C.W. Rees Eds., Pergamon, 1995, and references therein.

2. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formula (II), wherein G is a leaving group such as iodide, bromide, chloride, alkane sulfonyloxy, or arylsulfonyloxy and R^4, X^1, X^2, and X^3 are as defined above, with a monocyclic or bicyclic organometallic compound such as an organozinc compound of formula (IV) wherein R^5 and m are as defined above and M is a suitable metal such as Zn-W wherein W is one or more inert ligand or ligands, such as bromide or iodide.



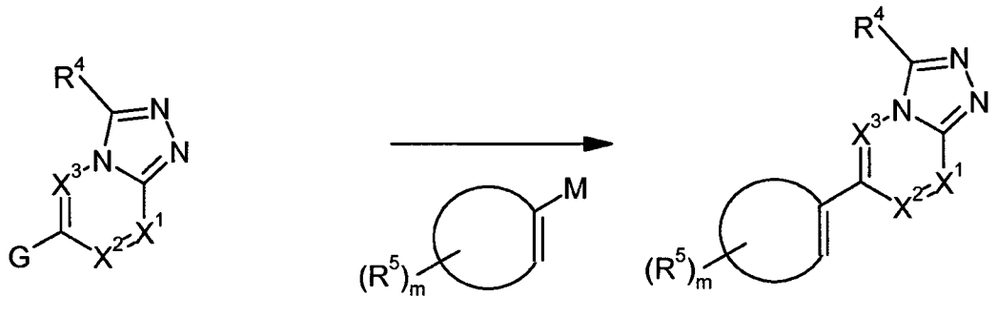
(II) (IV)

The reaction may be advantageously catalysed by low-valent transition metal catalysts such as Pd(0), for instance bisdiphenylphosphinoferrocene)palladium(II) dichloride (dppf). The reaction may be carried out by combining the components in an inert solvent such as

xylene or tetrahydrofuran at temperatures between 0°C and 150°C, preferably between 25°C and 100°C. The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

Organometallic reagents of formula (IV) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance E. Nakamura, *Organozinc Chemistry* p590 in *Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002 and references therein.

3. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formula (II), wherein G is a leaving group such as iodide, bromide, chloride, alkane sulfonyloxy, or arylsulfonyloxy and R^4, X^1, X^2, and X^3 are as defined above, with a monocyclic or bicyclic organometallic compound such as an organoborane compound of formula (V) wherein M is an organometallic residue such as $B(OH)_2$ and wherein R^5 and m are as defined above.



(II) (V)

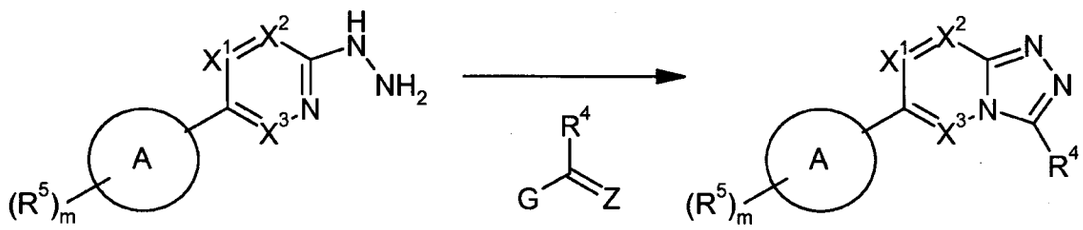
Alternatively, M is a leaving group such as iodide, bromide, chloride, alkane sulfonyloxy, or arylsulfonyloxy and R^4, X^1, X^2, and X^3 are as defined above and G is an organometallic compound such as an organostannane and wherein R^5 and m are as defined above.

The reaction may be advantageously catalysed by low-valent transition metal catalysts such as Pd(0), for instance bis(dibenzylideneacetone)palladium/triphenylarsine. The reaction may be carried out by combining the components in an inert solvent such as xylene or tetrahydrofuran or N-methylpyrrolidone at temperatures between 0°C and 150°C, preferably between 25°C and 100°C. The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

For further details of such coupling reactions see for instance *Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002, and references therein.

Organometallic reagents of formula (V) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance *Comprehensive Organometallic Chemistry*, G. Wilkinson and F.G.A. Stone, Eds., Pergamon, 1982, and *Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002, and references therein

4. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formaula VI with an acylating agent, such as a carboxylic acid or a reactive derivative thereof wherein R^4, X^1, X^2, and X^3, R^5, and m are as defined above. Suitable acylating reagents RC(Z)G are for instance carboxylic acid derivatives wherein G = is selected from Cl, O-C(=O)R, O-Alkyl, S-Alkyl and Z is selected from O, S, N-Alkyl or N-Aryl, or wherein Z and G taken together with the carbon atom to which they are attached form a nitrile or an orthoester or an orthoamide.



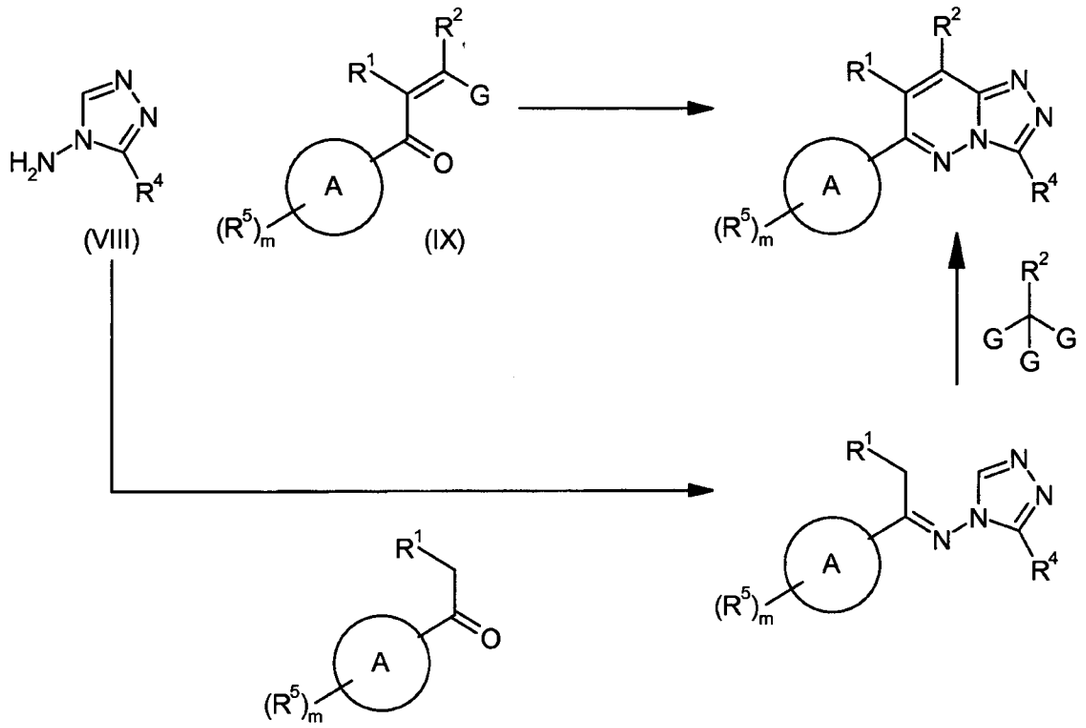
(VI) (VII)

The reaction may be carried out by combining the components in the absence of a solvent or in an inert solvent such as ortho-dichlorobenzene at temperatures between 25°C and 250°C, preferably between 50°C and 150°C. The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

Compounds of formula (VI) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance as described in in W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Part 1 and Part 2, *Systems with Bridgehead Nitrogen*, Interscience, 1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; and *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman and R.F. Cookson, Wiley, 1979 and references therein.

5. A process for the manufacture of compounds of Formula (I) wherein X^1 and X^2 are $C(R^1)$ and $C(R^2)$ respectively and X^3 is nitrogen comprises reacting an N-amino-1,2,4-triazole (VIII) wherein R^4 is as defined above with an unsaturated ketone or unsaturated

ester (IX) wherein G is a leaving group such as alkoxy or dialkylamino and R^1, R^2, R^5. and m are as defined above

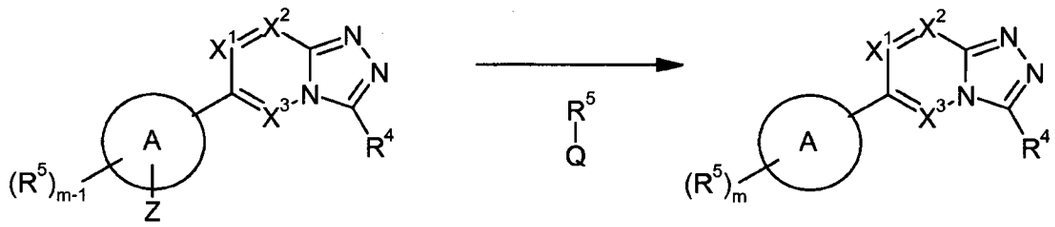


The reaction may be carried out in one or two steps as shown and the last step takes place in a solvent such as acetic acid at temperatures between between 25°C and 250°C, preferably between 50°C and 150°C for instance according to the procedure of D.F. Lieberman and J.D. Albright, *J. Het. Chem.*, **1988**, 827.

Other useful and related processes for the manufacture of compounds of Formula (I) or for the preparation of starting materials for the manufacture of compounds of Formula (I) are disclosed in the literature for instance in W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Part 1 and Part 2, *Systems with Bridgehead Nitrogen*, Interscience, 1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; and *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman and R.F. Cookson, Wiley, 1979 and references therein.

6. A process for the manufacture of compounds of Formula (I) comprises introducing a group R^5 by reacting a compound of formula (X) wherein Z is a replaceable group such as a hydrogen of a primary or secondary amine, or Z is a leaving group such as halogen or alkyl or aryl sulfonyloxy, or Z is a counterion such as sodium(I) or magnesium(II) with a

compound of formula (XI) wherein R^5 is as defined above and Q is a replaceable group such as a hydrogen of a primary or secondary amine, or Q is a leaving group such as halogen or alkyl or aryl sulfonyloxy, or Q is a counterion such as sodium(I) or magnesium(II).



(X) (XI)

Examples of reactions of this type include alkylations, acylations, and sulfonylations. Alternatively, if Z is the hydrogen of a secondary amine, preferably a cyclic secondary amine and R^5-Q is an aldehyde, the mth group R^5 may be introduced by reductive amination, for instance by reducing the mixture of aldehyde and secondary amine with sodium cyanoborohydride.

7. A process for the manufacture of compounds of Formula (I) comprises converting a functional group of one compound of the invention into another functional group using standard chemical reactions well-known to those skilled in the art to produce another compound of the invention. Such methods are described for instance in *Comprehensive Organic Chemistry*, Volume 2, p3, D. Barton and D. Ollis Eds, Pergamon, 1979, *Comprehensive Functional Group Transformations,* A.R. Katritzky, O. Meth-Cohn, and C.W. Rees Eds., Pergamon, 1995, and by various authors in *Houben-Weyl, Methods of Organic Chemistry*, Verlag Chemie, various years, and references therein.

8. A process for the manufacture of compounds of the invention comprises introducing a new functional group into one compound of the invention using standard chemical reactions well-known to those skilled in the art to produce another compound of the invention. Such methods are described for instance in *Comprehensive Organic Chemistry*, Volume 2, p3, D. Barton and D. Ollis Eds, Pergamon, 1979, *Comprehensive Functional Group Transformations,* A.R. Katritzky, O. Meth-Cohn, and C.W. Rees Eds., Pergamon, 1995, and by various authors in *Houben-Weyl, Methods of Organic Chemistry*, Verlag Chemie, various years, and references therein.

9. A process for the manufacture of compounds of the invention in the form of a single enantiomer comprises separating a racemic compound of the invention into separate enantiomers.

Examples of suitable methods for separating the enantiomers of a racemic compound include chromatography using a suitable chiral stationary phase; or conversion of a racemic mixture into diastereomeric derivatives, separation of the mixture of diastereomeric derivatives into two single diastereomers, and regeneration of a separate single enantiomer from each separate single diastereomer; or selective chemical reaction of one of the enantiomers of a racemic compound (kinetic resolution) using a diastereoselective reaction catalysed by a microbiological agent or an enzyme.

Examples of suitable methods for separating a mixture of diastereomers include fractional crystallisation, normal-phase chromatography or reverse-phase chromatography.

Examples of suitable diastereomeric derivatives where R^5 contains an hydroxy- or amino-group include esters formed by acylation of R^5 using an activated derivative of a single enantiomer of a carboxylic acid. An example of a suitable carboxylic acid is camphanic acid.

Examples of suitable diastereomeric derivatives where R^5 contains a carboxylic acid include esters or amides formed by acylation of a single enantiomer of an alcohol or amine using an activated derivative of a compound of Formula (I) wherein at least one of R^5 contains a carboxylic acid. An example of a suitable amine is 1-phenylethylamine and an example of a suitable alcohol is menthol.

Examples of suitable agents to carry out a kinetic resolution of a racenic mixture of compounds of the invention include Hog Liver Esterase and Baker's Yeast.

10. A process for the manufacture of a compound of the invention in the form of a single enantiomer comprises carrying out one of the processes described in the preceding sections using chiral intermediates in resolved form.

It will be appreciated by a person skilled in the art that it may be necessary/desirable to protect any sensitive groups in the compounds in some of the processes/ reactions mentioned herein. The instances where protection is necessary or desirable, and suitable methods for providing such protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see P.G.M. Wuts and T.W. Green, *Protective Groups in Organic Synthesis*,

4th Edition, John Wiley and Sons, 2002). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

Any protecting groups utilised in the processes described herein may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as trifluoroacetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl or heteroaroyl group, for example picolinoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable acid such as hydrochloric, sulphuric, or phosphoric acid or trifluoroacetic acid or a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting

group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Biological Assays

The ability of compounds to reduce Androgen Receptor (AR) numbers was assessed in a cell based immuno-fluorescence assay using the LNCaP prostate epithelial cell line.

a) LNCaP Androgen Receptor down-regulation cell assay

This immunofluorescence end point assay measures the ability of a test compound to down-regulate and reduce measured levels of the AR in the LNCaP prostate carcinoma cell line (LNCaP clone FGC (CRL-1740) obtained from the American Type Culture Collection (ATCC)).

LNCaP cells were cultured in Growth Medium (phenol red free Roswell Park Memorial Institute (RPMI) 1640 (Invitrogen Code no. 11835-063) containing 2mM L-Glutamine (Invitrogen Code no. 25030-024) and 1%(v/v) Penicillin/Streptomycin (10000

units/ml Penicillin and 10000 μg/ml of Streptomycin utilising penicillin G (sodium salt) and streptomycin sulphate: prepared in normal saline, Invitrogen Code no. 15140122) and 10%(v/v) foetal bovine serum (FBS)) in a 5% CO_2 air incubator at 37°C. Cells for assay were harvested from T175 stock flasks by washing once in PBS (phosphate buffered saline, pH 7.4) (Invitrogen Code no. 14190-094) and harvested using 5mls of 1 x Trypsin / ethylaminediaminetetraacetic acid (EDTA) (10 x Trypsin-EDTA, 5.0 g/L Trypsin, 2.0 g/L of EDTA•4Na and 8.5 g/L of NaCl, without Phenol Red, Invitrogen Code no. 15400-054) diluted in PBS solution. A 5ml volume of Growth Medium was added to each flask (as above except that 5% (v/v) charcoal stripped FBS (HyClone Code no. SH30068.03) was included instead of 10% (v/v) FBS). Cells were syringed at least twice using a sterile 18G x 1.5" (1.2 x 40mm) broad gauge needle and cell density was measured using a haemocytometer. Cells were further diluted in Growth Medium plus 5% (v/v) charcoal stripped FBS and seeded at a density of $6.5x10^3$ cells per well (in 90ul) into transparent, black, tissue culture treated 96 well plates (Packard, No. 6005182).

Test data reported herein was generated using two different compounds preparation and dosing methods. In method (1) a 10mM compound stock solution in 100% (v/v) DMSO was serially diluted in 4-fold steps in 100% (v/v) DMSO using a Thermo Scientific Matrix SerialMate. The diluted compounds were then further diluted 1 in 30 in assay media using a Thermo Scientific Matrix PlateMate and a 10μl aliquot of this dilution was dosed to cells manually using a multi-channel pipette. In method (2) starting with a 10mM compound stock solution, the Labcyte Echo 550 was used to generate a compound concentration response set diluted in 30μl of assay media. The Echo 550 is a liquid handler that uses acoustic technology to perform direct microplate-to-microplate transfers of DMSO compound solutions. The system can be programmed to transfer volumes as low as 2.5 nL in multiple increments between microplates and in so doing generates a serial dilution of compound which is then back-filled to normalise the DMSO concentration across the dilution range. A 10μl volume of diluted compound is then dosed to cells using a Thermo Scientific Matrix PlateMate.

Plates were incubated overnight at 37°C, 5% CO_2. Wells were then dosed with compound prepared by one of the 2 methods above and further incubated for 20-22 hours at 37°C, 5% CO_2. Plates were fixed by the addition of 20 μl of 10% (v/v) formaldehyde solution (in PBS) to each well (final formaldehyde conc.= 1.67%(v/v)) and left at room

temperature for 10 mins. This fixative solution was removed and cells were washed with 250µl of PBS/0.05% (v/v) Tween 20 (PBST) using an automated plate washer. This process was then repeated twice more.

Immunostaining was performed at room temperature. Cells were permeabilised by the addition of 35 µl of PBS containing 0.5% Tween 20 and incubated for 1 hour at room temperature. Permeabilisation solution was removed and cells were washed with 250µl of PBST using an automated plate washer. This process was then repeated twice more. 35 µl of Blocking Solution (PBST containing 3%(w/v) Marvel dried skimmed milk (Nestle)) was added to each well and plates were incubated at room temperature for a minimum of 1 hour. Following removal of the Blocking Solution with a plate washer, 35µl of mouse anti-human AR monoclonal antibody (clone AR441) (immunogen – synthetic peptide corresponding to amino acids 229-315 of the human AR coupled to keyhole limpet hemocyanin, DAKO, Code No. M3562), diluted 1:500 in Blocking Solution, was added to each well and incubated for 1 hour. Then this primary antibody solution was removed from the wells followed by 3 x 100µl PBST washes using a plate washer. Then 35µl of Alexa-Fluor 488 goat anti-mouse IgG secondary antibody (Invitrogen, Code No. A-11001), diluted 1:500 in Blocking Solution, was added to each well. Henceforth, wherever possible, plates were protected from light exposure. The plates were incubated for 1 hour and then the secondary antibody solution was removed from the wells followed by 3 x 100ul PBST washes using a plate washer. Then 50µl of PBST was added to each well and plates were covered with a black plate seal and stored at 4°C before being read. Plates were read within six hours of completing the immunostaining.

The Green Fluorescent AR-associated signal in each well was measured using an Acumen Explorer HTS Reader (TTP Labtech Ltd., Cambridge). AR-associated fluorescence emission can be detected at 530nm following excitation at 488nm. The instrument is a laser-scanning fluorescence microplate cytometer which samples the well at regular intervals and uses threshold algorithms to identify all fluorescent intensities above the solution background without the need to generate and analyse an image. These fluorescent objects can be quantified and provide a measure of the AR levels in cells. Fluorescence dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Down-

regulation of AR levels was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give a 50% reduction of the AR signal.

The following table discloses biological data for compounds of the present invention using the aforementioned down-regulation assay.

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$	Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$	Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
1	3.4	21	0.27	41	28
2	8.3	22	1.4	42	12.0
3	11	23	0.45	43	1.5
4	2.5	24	>26	44	1.3
5	1.6	25	1.1	45	1.4
6	7.5	26	1.0	46	1.3
7	18	27	1.2	47	1.5
8	1.7	28	2.8	48	1.5
9	1.7	29	4.2	49	3.2
10	14	30	0.38	50	1.4
11	2.5	31	2.1	51	8.4
12	4.3	32	1.6	52	1.3
13	8.4	33	0.68	53	7.9
14	0.69	34	20	54	6.7
15	2.5	35	3.0	55	8.8
16	0.77	36	0.99	56	2.1
17	2.5	37	1.4	57	4.3
18	1.2	38	1.2	58	3.1
19	0.52	39	5.0	59	2.7
20	1.8	40	3.3	60	0.61

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
61	7.4
62	0.72
63	1.5
64	2.5
65	0.76
66	0.33
67	1.0
68	1.20
69	1.4
70	0.64
71	1.4
72	1.0
73	12
74	5.6
75	2.3
76	2.3
77	1.4
78	1.20
79	2.4
80	16
81	7.2
82	1.6
83	2.5
84	1.8
85	1.6

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
86	1.2
87	5.2
88	1.5
89	23
90	3.2
91	1.2
92	12
93	1.3
94	0.93
95	0.67
96	>1.3
97	0.36
98	2.3
99	2.9
100	1.8
101	1.7
102	2.9
103	6.2
104	9.5
105	3.2
106	4.4
107	7.2
108	2.3
109	7.2
110	1.3

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
111	0.77
112	4.7
113	7.1
114	6.5
115	2.5
116	1.1
117	1.7
118	0.30
119	2.2
120	1.7
121	4.8
122	4.3
123	4.1
124	1.7
125	1.9
126	2.0
127	1.5
128	2.3
129	0.99
130	1.8
131	4.1
132	2.6
133	1.3
134	1.8
135	4.9

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
136	1.2
137	1.5
138	13
139	2.0
140	7.1
141	9.7
142	5.1
143	8.8
144	4.9
145	1.2
146	7.3
147	2.5
148	3.4
149	7.9
150	7.6
151	3.1
152	6.7
153	7.9
154	1.6
155	18
156	11
157	2.4
158	3.0
159	1.4
160	6.6

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
161	1.4
162	1.0
163	3.6
164	1.7
165	1.7
166	0.93
167	2.4
168	1.6
169	0.92
170	0.61
171	0.62
172	0.81
173	1.2
174	0.94
175	0.68
176	0.85
177	0.77
178	0.88
179	0.59
180	1.2
181	2.1
182	1.2
183	1.2
184	14
185	0.68

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
186	2.8
187	4.7
188	2.2
189	1.1
190	0.79
191	2.1
192	8.7
193	2.0
194	2.4
195	4.0
196	1.5
197	0.82
198	1.2
199	1.9
200	1.3
201	1.7
202	11
203	1.7
204	1.5
205	0.53
206	2.0
207	7.6
208	13
209	12
210	1.8

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
211	8.2
212	3.7
213	4.5
214	15
215	7.4
216	6.8
217	3.7
218	>7.3
219	3.5
220	3.6
221	3.1
222	2.6
223	4.7
224	12
225	9.2
226	11
227	13
228	15
229	1.9
230	2.1
231	2.1
232	3.6
233	1.5
234	2
235	1.9

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
236	5.3
237	5.3
238	5
239	2.8
240	3
241	13
242	7.4
243	3.7
244	15
245	17
246	23
247	12
248	1.7
249	6.3
250	4.9
251	9.3
252	8.9
253	3.7
254	1.3
255	1.8
256	7.4
257	9
258	6.4
259	4.8
260	5.6

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
261	7.9
262	25
263	11
264	0.95
265	3.8
266	0.63
267	0.85
268	0.91
269	2
270	10
271	1.8
272	1.8
273	10
274	6.1
275	6
276	15
277	2
278	0.65
279	13
280	0.78
281	0.8
282	2.4
283	0.78
284	0.98
285	2.7

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
286	8.5
287	2
288	3.3
289	2.7
290	5.8
291	>9.7
292	7
293	11
294	9.5
295	3.4
296	2.1
297	15
298	5.7
299	0.84
300	1
301	1.8
302	1.1
303	5.8
304	1.8
305	4
306	1.3
307	3.4
308	1.4
309	1.6
310	3.2

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
311	5
312	2.6
313	1.8
314	4.6
315	2
316	12
317	4.1
318	3.7
319	11
320	8.6
321	8
322	9.6
323	>8.1
324	5.9
325	>1.2
326	2
327	1
328	0.75
329	3.6
330	3.7
331	16
332	16
333	2.7
334	1.1
335	1.5

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
336	2.4
337	1.5
338	8.5
339	0.77
340	1.5
341	1.3
342	2.1
343	1.7
344	0.29
345	1.1
346	8.5
347	0.97
348	1
349	1.7
350	0.74
351	1.9
352	0.57
353	0.69
354	2.7
355	0.72
356	2.2
357	2.1
358	6.7
359	2.6
360	1

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$	Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$	Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
361	4.7	386	2.4	411	2.2
362	1	387	1.1	412	9.1
363	22	388	1.6	413	1.9
364	16	389	1.5	414	>10
365	19	390	1.7	415	1.4
366	>33	391	2.7	416	2.7
367	4.1	392	4.5	417	4.6
368	3.4	393	1.9	418	>14
369	8.7	394	5.6	419	4
370	11	395	10	420	5.9
371	6.2	396	1.8	421	4
372	1.3	397	3.9	422	4.2
373	4	398	1.9	423	7.4
374	0.93	399	3.7	424	2.2
375	11	400	1.8	425	3.6
376	3	401	1.6	426	2.2
377	5.9	402	2.8	427	4.3
378	11	403	4.8	428	15
379	18	404	2.7	429	2.6
380	4.2	405	3	430	1.7
381	2.1	406	6.3	431	1.5
382	1.8	407	5.7	432	1.2
383	1.3	408	1.7	433	0.9
384	2.9	409	3.9	434	0.83
385	2.1	410	2.1	435	0.98

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
436	0.75
437	0.53
438	1.6
439	0.48
440	2.3
441	0.22
442	0.44
443	1.5
444	1.2
445	1.6
446	0.7
447	16
448	6.3
449	4.8
450	8.2
451	9.7
452	16
453	5.7
454	9.2
455	10
456	21
457	11
458	21
459	15
460	5.1

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
461	13
462	7.7
463	0.98
464	1.4
465	4
466	>19
467	4.9
468	>11
469	1.8
470	4.6
471	2
472	3.9
473	3.2
474	0.96
475	>15
476	3.5
477	6.3
478	1.3
479	17
480	9.6
481	6.6
482	1.8
483	>30
484	>14
485	10

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
486	>13
487	16
488	3.1
489	3.6
490	5.9
491	7.2
492	>30
493	18
494	0.43
495	0.35
496	11
497	2.8
498	2.4
499	1.7
500	>18
501	1.2
502	2.2
503	4.3
504	1.9
505	>19
506	9.8
507	0.53
508	2.2
509	1.8
510	3.7

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
511	10
512	0.87
513	0.24
514	0.87
515	1.4
516	1.4
517	1.5
518	11
519	1.2
520	1.4
521	5.4
522	3.9
523	1
524	3.2
525	5.2
526	2.5
527	0.67
528	2.2
529	1.9
530	1.6
531	1.8
532	0.98
533	2.3
534	2.3
535	1.9

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
536	1.4
537	3
538	2.3
539	1.5
540	1.5
541	4
542	2.6
543	3.2
544	2.9
545	3.6
546	1.7
547	1.2
548	2.2
549	1.6
550	7.2
551	4
552	7.8
553	2.6
554	4.9
555	1.4
556	4.4
557	3.1
558	2.6
559	2
560	8.8

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
561	2.9
562	2
563	1.3
564	6.7
565	3.5
566	16
567	>16
568	3.3
569	2.7
570	4.5
571	0.96
572	3.4
573	10
574	4
575	2.5
576	5
577	5
578	2.5
579	4.1
580	2
581	3.3
582	2.4
583	4.1
584	2.8
585	1.5

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
586	2.1
587	>17
588	5.3
589	4.8
590	22
591	20
592	9.6
593	7.2
594	22
595	6.8
596	4.2
597	2.9
598	4.2
599	5.8
600	0.85
601	2.2
602	1.6
603	3.5
604	1.7
605	5
606	2.7
607	7.4
608	2.7
609	6.6
610	3.2

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
611	1.6
612	>13
613	3.3
614	>12
615	0.88
616	1.7
617	4.3
618	>4
619	4.5
620	>13
621	2.3
622	7.4
623	0.89
624	3.1
625	1.4
626	1.1
627	1.7
628	2.7
629	1.3
630	2.4
631	1.1
632	1.2
633	1.9
634	1.1
635	2.9

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
636	20
637	1.8
638	0.9
639	1.2
640	0.92
641	1.4
642	1.4
643	6
644	1.5
645	2.3
646	6.1
647	1.7
648	2.1
649	2.3
650	3.1
651	1.9
652	3.1
653	1
654	2.6
655	1.1
656	1.1
657	3.2
658	0.94
659	1
660	0.63

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
661	0.65
662	5.4
663	2.7
664	3.6
665	0.82
666	0.94
667	1
668	1.1
669	0.6
670	0.67
671	1.6
672	0.58
673	0.73
674	1.1
675	1.5
676	0.56
677	4.5
678	15
679	0.58
680	0.6
681	1.3
682	0.58
683	0.49
684	0.69
685	5.7

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
686	4.2
687	3.8
688	6.6
689	4.1
690	17
691	>28
692	4.2
693	2.3
694	3.2
695	3.3
696	4.2
697	>22
698	5.6
699	2.1
700	7.1
701	14
702	>12
703	5.5
704	4.2
705	5.3
706	2.9
707	7.9
708	6.2
709	1.7
710	2.1

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
711	2.5
712	3
713	0.81
714	>9.9
715	1.2
716	0.81
717	2.9
718	3.6
719	3.5
720	2.7
721	2.9
722	4.1
723	0.9
724	0.69
725	1.2
726	1.4
727	1.2
728	1.5
729	0.92
730	0.72
731	1.1
732	1.1
733	0.6
734	2.5
735	1.9

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
736	0.4
737	0.74
738	3.3
739	3.2
740	2
741	2.2
742	17
743	14
744	9.6
745	3.4
746	3.3
747	23
748	5.6
749	>22
750	2.6
751	6.3
752	18
753	2.1
754	2.5
755	2.2
756	3.2
757	>12
758	1.3
759	3.9
760	>3.1

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
761	1.5
762	1.2
763	>9.8
764	2.5
765	8.8
766	>17
767	>12
768	4.7
769	11
770	6.3
771	3.1
772	14
773	3.1
774	8
775	6.8
776	6.9
777	4.6
778	2.6
779	0.54
780	0.51
781	0.82
782	2
783	0.84
784	2.2
785	1.7

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
786	8.4
787	1.3
788	2.2
789	2.1
790	2
791	0.96
792	16
793	1.6
794	1.1
795	2.4
796	0.63
797	2.4
798	1
799	1.6
800	1.1
801	1.3
802	1.2
803	7
804	1.3
805	1
806	2.3
807	7.5
808	1
809	
810	1.9

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
811	1.2
812	2.1
813	6.8
814	1.8
815	>17
816	9.3
817	5.6
818	3.8
819	>18
820	4
821	2
822	1.7
823	4.7
824	1.9
825	1.9
826	1.4
827	1
828	9.5

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
829	13
830	0.85
831	3.1
832	1.4
833	>12
834	4.4
835	20
837	1.6
838	7.6
839	1.1
840	2.6
841	2.9
842	1.1
843	0.93
844	0.78
845	0.9
846	0.27
847	3.1

Example Number	Androgen Receptor Down-regulation Assay (a) $IC_{50}/\mu M$
848	3.5
849	0.68
850	0.56
851	0.92
852	0.29
853	1.3
854	Not tested
855	0.44
856	2.2
857	>33
858	>33
859	>33
860	0.8
861	Not tested
862	Not tested
863	Not tested
864	Not tested

b) Androgen Receptor – Ligand binding domain competitive binding assay

The ability of compounds to bind to isolated Androgen Receptor Ligand binding domain (AR-LBD) was assessed in competition assays using either a Fluorescence Polarisation (FP) or a LanthaScreen™ Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) detection end-point.

For the FP test, an assay test kit was purchased from Invitrogen and used to measure compound binding to the isolated rat AR-LBD which shares 100% sequence identity to the human AR-LBD. The Invitrogen PolarScreen™ Androgen Receptor Competitor Assay Red (Product Code No. PV4293), is a fluorescence polarisation (FP) – based competition assay which measures if test compound can displace a fluorescently-labelled tracer compound. If the test compound binds to the AR-LBD it will prevent the formation of the receptor/tracer complex, which will result in a low polarisation value. If the test compound does not bind the receptor, it will have no effect on formation of the receptor/tracer complex, and the measured polarisation value of the tracer will remain high. The assay was performed as essentially described in the Invitrogen method with the exception that the final assay volume was 12μl and this required an appropriate low volume black 384 well microtitre plate. Compounds were dosed directly from a compound source microplate containing serially diluted compound (4 wells containing 10mM, 0.1mM, 1μM and 10nM final compound respectively) to an assay microplate using the Labcyte Echo 550. The Echo 550 is a liquid handler that uses acoustic technology to perform direct microplate-to-microplate transfers of DMSO compound solutions and the system can be programmed to transfer multiple small nL volumes of compound from the different source plate wells to give the desired serial dilution of compound in the assay which is then back-filled to normalise the DMSO concentration across the dilution range. FP dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Competitive AR binding was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give a 50% reduction in tracer compound binding to AR-LBD.

The following table discloses various biological data for a representative selection of compounds of the present invention using the aforementioned FP ligand binding assay.

Example Number	Androgen Receptor FP Ligand-Binding Assay IC_{50}/μM
4	20.18
41	19.55

Example Number	Androgen Receptor FP Ligand-Binding Assay $IC_{50}/\mu M$
166	6.085
174	16.3
183	14.37
Other Examples within the range Example 1 - Example 215 show Androgen Receptor Ligand-Binding IC50 greater than 20μM	

For LanthaScreen™ TR-FRET, a suitable fluorophore (Product code PV4294) and rat GST-tagged AR-LBD were purchased from Invitrogen and used to measure compound binding. The assay principle is that AR-LBD is added to a fluorescent ligand to form a receptor/fluorophore complex. A terbium-labelled anti-GST antibody is used to indirectly label the receptor by binding to a GST tag, and competitive binding is detected by a test compounds' ability to displace the fluorescent ligand resulting in a loss of TR-FRET signal between the Tb-anti-GST antibody and the tracer. The assay was performed as follows with all reagent additions carried out using the Thermo Scientific Matrix PlateMate :-

1. Acoustic dispense 120nl of the test compound into a black low volume 384 well assay plates.
2. Dispense 6μl of the 2x Fluorophore reagent into each well of the assay plate
3. Dispense 6μl of the 2x AR-LBD/Tb-anti-GST Ab into each well of the assay plate
4. Cover the assay plate to protect the reagents from light and evaporation, and incubate at room temperature for 1 hour.
5. Excite at 340nM and measure the fluorescent emission signal of each well at 495nm and 570nm using the BMG PheraSTAR.

Compounds were dosed directly from a compound source microplate containing serially diluted compound (4 wells containing 10mM, 0.1mM, 1μM and 10nM final compound respectively) to an assay microplate using the Labcyte Echo 550. The Echo 550 is a liquid handler that uses acoustic technology to perform direct microplate-to-microplate transfers of DMSO compound solutions and the system can be programmed to transfer multiple small nL volumes of compound from the different source plate wells to give the desired serial dilution of compound in the assay which is then back-filled to normalise the

DMSO concentration across the dilution range. In total 120nL of compound plus DMSO is added to each well and compounds were tested in a 12-point concentration response format over a final compound concentration range of 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001, 0.0001μM, respectively. TR-FRET dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Competitive AR binding was expressed as an IC_{50} value. This was determined by calculation of the concentration of compound that was required to give a 50% reduction in tracer compound binding to AR-LBD.

Table of Results – LanthaScreen™ AR Binding Assay

Example Number	511	513
IC_{50} (μM)	>100 (n=2)	1.3 (n=2)

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier. The composition may be in a form suitable for oral administration, for example as a tablet or capsule; for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream; or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients. For pre-clinical *in vivo* applications simple formulations and suspensions may be used. For example, 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol may be formulated as a simple aqueous suspensions in 1%w/v Polysorbate 80 or 0.67%w/v PVP (Polyvinylpyrrolidone)/0.33%w/v Aerosol AOT (sodium 1,2-bis(2-ethylhexoxycarbonyl)ethanesulphonate). Formulations of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine may be prepared as suspensions with reduced particle size (mean particle size less than 1 micro-meter) as follows. The required amount of compound is vortexed and/or magnetically stirred in vehicle (water containing

1%w/v Pluronic F127) in order to break down any large aggregates, wet the compound and displace any air from the surface. The resultant slurry is transferred to a zirconia milling pot containing about one third of 0.6-0.8mm diameter zirconia milling beads. Additional zirconia milling beads are added to the pot until the level of slurry and beads is approximately equal and the top of the pot closed. The pot is then sealed with a teflon ring and zirconia lid and placed on a suitable mill, for example, a Fritsch P7 planetary micromill. The pot is rotatated in the mill for 4 x 30 minute cycles at a rotation speed of 800rpm with 15 minutes cooling period between each cycle. At the end of the 4 cycles the pot is allowed to cool to room temperature. The milled suspension is removed from the pot using a suitable pipette and transferred to a suitable vessel. Finally the milled suspension is made to volume with vehicle (water containing 1%w/v Pluronic F127) to produce the suspension at the required concentration.

The compound of Formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg/m^2 body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol could be administered to a human patient at a dose of 500 to 1500 mg BID (twice a day), more particularly about 1000 mg BID, and 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine could be administered to a human patient at a dose of 165 to 660 mg BID, more particularly about 430 mg BID. The predicted human doses for 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol and 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine are based on a standard human weighing 70 kg and BID doses are per dose (*i.e.* half the total daily dose).

For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry

(Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, or pharmaceutical compositions containing them, are effective modulators of the androgen-receptor.

Accordingly, the compounds of the present invention are expected to be potentially useful agents in the treatment of diseases or medical conditions mediated alone or in part by the androgen receptor. Compounds of the invention may induce down-regulation of the androgen receptor and/or be selective agonists, partial agonists, antagonists or partial antagonists of the androgen receptor.

The compound of the invention are useful in the treatment of androgen receptor-associated conditions. An "androgen receptor-associated condition," as used herein, denotes a condition or disorder which can be treated by modulating the function or activity of an androgen receptor in a subject, wherein treatment comprises prevention, partial alleviation or cure of the condition or disorder. Modulation may occur locally, for example, within certain tissues of the subject, or more extensively throughout a subject being treated for such a condition or disorder.

In one embodiment, compounds of the present invention can be administered to animals, for example humans, for the treatment of a variety of conditions and disorders, including, but not limited to the treatment of androgen-sensitive diseases or disorders whose progress or onset is aided by activation of the androgen receptor or androgen receptor modulators. Examples of particular androgen-sensitive diseases or disorders include, but are not limited to, androgen-sensitive cancers such as prostate cancer and other cancers composed of malignant tumor cells containing the androgen receptor, such as is the case for breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers; cancers of the skin, pancreas, endometrium, lung and colon; osteosarcoma; hypercalcemia of malignancy; metastatic bone disease; and androgen senstive disorders such as benign prostatic hyperplasia and prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, endometriosis, polycystic ovarian syndrome, treatment of spermatogenesis, conteracting preeclampsia, eclampsia of pregnancy and preterm labor, treatment of premenstrual syndrome, treatment of vaginal dryness, sexual perversion, virilisation, and the like. Compounds of the invention may also be used to improve ovulation in a domestic animal.

In another embodiment, compounds of the present invention can be administered to animals, for example humans, for the treatment of a variety of conditions and disorders, including, but not limited to maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or age-related functional decline ("ARFD") in the elderly (e.g., sarcopenia); treatment of catabolic side effects of glucocorticoids; prevention and/or treatment of reduced bone mass, density or growth (e.g., osteoporosis and osteopenia); treatment of chronic fatigue syndrome (CFS) ; chronic myalgia; treatment of acute fatigue syndrome and muscle loss following elective surgery (e.g., post-surgical rehabilitation); accelerating of wound healing; accelerating bone fracture repair (such as accelerating the recovery of hip fracture patients); accelerating healing of complicated fractures, e.g. distraction osteogenesis; in joint replacement; prevention of post-surgical adhesion formation; acceleration of tooth repair or growth; maintenance of sensory function (e.g., hearing, sight, olefaction and taste); treatment of periodontal disease; treatment of wasting secondary to fractures and wasting in connection with chronic obstructive pulmonary disease (COPD), chronic liver disease, AIDS, weightlessness, cancer cachexia, burn and trauma recovery, chronic catabolic state (e.g., coma), eating disorders (e.g., anorexia) and chemotherapy; treatment of cardiomyopathy; treatment of thrombocytopenia; treatment of growth retardation in connection with Crohn's disease; treatment of short bowel syndrome; treatment of irritable bowel syndrome; treatment of inflammatory bowel disease; treatment of Crohn's disease and ulcerative colitis; treatment of complications associated with transplantation; treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treatment of anorexia (e.g., associated with cachexia or aging); treatment of hypercortisolism and Cushing's syndrome; Paget's disease; treatment of osteoarthritis; induction of pulsatile growth hormone release; treatment of osteochondrodysplasias; treatment of depression, nervousness, irritability and stress; treatment of reduced mental energy and low self-esteem (e.g., motivation/assertiveness); improvement of cognitive function (e.g., the treatment of dementia, including Alzheimer's disease and short term memory loss); treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g., associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure;

protection against ventricular-24 dysfunction or prevention of reperfusion events; treatment of adults in chronic dialysis; reversal or slowing of the catabolic state of aging; attenuation or reversal of protein catabolic responses following trauma (e.g., reversal of the catabolic state associated with surgery, congestive heart failure, cardiac myopathy, burns, cancer, COPD etc.); reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis; treatment of immunosuppressed patients; treatment of wasting in connection with multiple sclerosis or other neurodegenerative disorders; promotion of myelin repair; maintenance of skin thickness; treatment of metabolic homeostasis and renal homeostasis (e.g., in the frail elderly); stimulation of osteoblasts, bone remodeling and cartilage growth; regulation of food intake; treatment of insulin resistance, including NIDDM, in mammals (e.g., humans); treatment of insulin resistance in the heart; improvement of sleep quality and correction of the relative hyposomatotropism of senescence due to high increase in REM sleep and a decrease in REM latency; treatment of hypothermia; treatment of congestive heart failure; treatment of lipodystrophy (e.g., in patients taking HIV or AIDS therapies such as protease inhibitors); treatment of muscular atrophy (e.g., due to physical inactivity, bed rest or reduced weight-bearing conditions); treatment of musculoskeletal impairment (e.g., in the elderly); improvement of the overall pulmonary function; treatment of sleep disorders; and the treatment of the catabolic state of prolonged critical illness, ; age related decreased testosterone levels in men, male menopause, hypogonadism, male hormone replacement, male and female sexual dysfunction (e.g., erectile dysfunction, decreased sex drive, sexual well-being, decreased libido), urinary incontinence, male and female contraception, hair loss, and the enhancement of bone and muscle performance/strength.

The term treatment is also intended to include prophylactic treatment.

In addition, the conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome as detailed in Johannsson J. Clin. Endocrinol. Metab., 82, 727-34 (1997), may be treated employing the compounds of the invention.

In one embodiment the the androgen-receptor associated conditions include prostate cancer, benign prostatic hyperplasia and prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, polycystic ovarian syndrome, sexual perversion, virilisation, and the like. Compounds of the invention may also be used to improve ovulation in a domestic

animal.

Accordingly, the present invention relates to a method of treating any one of the aforementioned androgen-receptor associated condition in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further aspect the present invention relates to the use of compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of any one of the aforementioned androgen-receptor associated condition.

According to another aspect of the present invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt or pro-drug thereof, as defined hereinbefore for use in the treatment of any one of the aforementioned androgen-receptor associated condition.

According to another aspect of the present invention there is provided a compound of the Formula (Ia), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

According to a further aspect of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt or pro-drug thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-androgenic effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-androgenic effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

The term "anti-androgenic effect" is used herein to mean the inhibition and/or down regulation of androgen receptors.

According to a further aspect of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cell-proliferation effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to an additional feature of this aspect of the invention there is provided a method of treating androgen-sensitive cancers in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of androgen-sensitive cancers.

According to a further feature of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of androgen-sensitive cancers.

According to an additional feature of this aspect of the invention there is provided a method of treating prostate cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore. In one embodiment of this aspect of the invention, the prostate cancer is hormone resistant.

According to a further feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of prostate cancer, more particularly hormone resistant prostate cancer.

According to a further feature of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of prostate cancer, more particularly hormone resistant prostate cancer.

Hormone resistant prostate cancer (HRPC) arises when the prostate cancer progresses to the hormone-independent stage of the disease.

According to an additional feature of this aspect of the invention there is provided a method of treating any one of the following conditions: benign prostatic hyperplasia, prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, polycystic ovarian syndrome, sexual perversion, or virilisation; in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of any one of the following conditions: benign prostatic hyperplasia, prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, polycystic ovarian syndrome, sexual perversion, or virilisation.

According to a further feature of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of any one of the following conditions: benign prostatic hyperplasia, prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, polycystic ovarian syndrome, sexual perversion, or virilisation.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The androgen receptor ligands of the present invention may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment, in addition to the androgen receptor ligand

treatment defined hereinbefore, may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

(i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinase inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and iodoxyfene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin™], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbitux, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors

of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(ix) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(x) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) - (x) herein above, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of an androgen sensitive disorder.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer, such as prostate cancer.

According to another feature of the invention there is provided the use of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above, in the manufacture of a medicament for use in the treatment of an androgen senstive disorder in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above, in the manufacture of a medicament for use in the treatment of cancer, such as prostate cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above for use in treatment of an androgen-sensitive disorder in a warm-blooded animal, such as man.

According to another feature of the invention there is provided a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above for use in treatment of cancer, such as prostate cancer in a warm-blooded animal, such as man.

Therefore in an additional feature of the invention, there is provided a method of treating an androgen-sensitive disorder in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above.

Therefore in an additional feature of the invention, there is provided a method of treating cancer, such as prostate cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above.

According to a further aspect of the present invention there is provided a kit comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above.

According to a further aspect of the present invention there is provided a kit comprising:

a) a compound of Formula (I) or a pharmaceutically acceptable salt thereof in a first unit dosage form;

b) an anti-tumour agent selected from one listed under (i) – (ix) herein above; in a second unit dosage form; and

c) container means for containing said first and second dosage forms.

In particular, the compounds of the invention may be used for the treatment of various hormone dependent cancers including without limitation prostate cancer in combination with one or more of the following agents: gonadotrophin agonists (GnRH) (LH-RH agonists); inhibitors of gonadotrophin secretion; 5-alpha reductase inhibitors; antiprogestins; antiestrogens; aromatase inhibitors; progestins; estrogens; cytostatic agents; cytotoxic agents; inhibitors of cell growth signalling pathways, including without limitation kinase inhibitors such as VEGF kinase inhibitors; antibodies including without limitation antibodies directed at cell-growth signalling factors such as EGF antibodies; antisense oligonucleotides; immunological modifiers such as interferons, interleukins, growth hormones, and other cytokines; and other hormonal therapies.

The compounds of the invention man also be used for the treatment of various hormone dependent diseases and disorders, such as prostate cancer in combination with one or more of the following agents: antibiotics; anti-inflammatory agents; potassium channel openers; synthetic thyroid hormone replacements; protein kinase C inhibitors (PKC inhibitors); and immunophilin inhibitors or antagonists.

According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of the Formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

In addition to their use in therapeutic medicine, the compounds of Formula (I) and their pharmaceutically acceptable salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The invention will now be illustrated in the following Examples in which, generally:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18 to 25°C;

(ii) organic solutions were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600 to 4000 Pascals; 4.5 to 30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and / or analytical LC-MS, and reaction times where given are for illustration only.

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 500 MHz using perdeuterio dimethyl sulfoxide (DMSO-d_6) as solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) Mass spectra (MS) and LC-MS data were generated on an LC-MS system where the HPLC component comprised generally either an Agilent 1100, Waters Alliance HT (2790 & 2795) equipment or an HP1100 pump and Diode Array with CTC autosampler and was run on a Phenomenex Gemini C18 5µm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture), or basic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in acetonitrile mixture); and the MS component comprised generally a Waters ZQ mass spectrometer scanning over an appropriate mass range. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram

from 220-300nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is the (M+H)+ for positive ion mode and (M-H)- for negative ion mod;

(x) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;

(xi) any microwave reactions were carried out in either a Biotage Optimizer EXP, or a CEM Explorer microwave;

(xii) preparative high performance liquid chromatography (HPLC) was performed on a Gilson instrument using the following conditions:-

Column: C18 reversed-phase silica, for example, Waters 'Xbridge', 5 μm silica, 19 x 100 mm, or 30 x 100 mm, using decreasingly polar solvent mixtures as eluent (decreasing ratio of Solvent A to Solvent B)

Solvent A: Water with 1% ammonium hydroxide

Solvent B: Acetonitrile

Flow rate: 28 ml / min or 61 ml / min

Gradient: Tailored to suit each compound – generally 7-10 min in length

Wavelength: 254 nm

(xiii) Strong cation exchange (SCX) chromatography was performed on pre-packed cartridges (for example, ISOLUTE SCX-2 propyl sulfonic acid-based cartridges supplied by International Sorbent Technology), using a basic eluent (for example, 2M ammonia in methanol);

(xiv) the following abbreviations have been used herein, where necessary:-

DMF	*N*,*N*-dimethylformamide
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMSO	dimethylsulphoxide
THF	tetrahydrofuran
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
DCCI	1,3-Dicyclohexylcarbodiimide
PYBOP	Benzotriazole-1-yl-oxy-trispyrrolidinonophosphonium hexafluorophosphate

DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DTAD	Di-tert-butyl azodicarboxylate
DIPEA	N,N-Diisopropylethylamine
MeOH	Methanol
TFA	Trifluoroacetic acid
m-CPBA	m-Chloroperoxybenzoic acid
AcOH	Acetic acid
DMA	*N,N*-Dimethylacetamide
EtOAc	Ethyl acetate
EtOH	Ethanol
MeCN	Acetonitile
MTBE	Methyl tert-butyl ether
CAS	Chemical Abstracts Service

X-Ray Powder Diffraction (XRPD)

The X-ray powder diffraction patterns of the crystal forms were determined by mounting a sample of the crystalline material on Siemens single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40 kV and 40 mA with a wavelength of 1.5418 Angstroms using a Bruker D5000 powder X-ray diffractometer (Bruker AXS, Banner Lane Coventry CV4 9GH). The collimated X-ray source was passed through an automatic variable divergence slit set at V20 and the reflected radiation directed through a 2 mm antiscatter slit and a 0.2 mm detector slit. The sample was exposed for 1 second per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in continuous scan theta-theta mode. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a Dell Optiplex 686 NT 4.0 Workstation operating with Diffrac+ software.

The skilled person is aware that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment, sample preparation or machine used). In particular, it is

generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions and sample preparation. For example, the skilled person will realize that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realize that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence a person skilled in the art will appreciate that the diffraction pattern data presented herein is not to be construed as absolute (for further information see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996). Therefore, it shall be understood that the crystalline form is not limited to the crystals that provide X-ray powder diffraction patterns identical to the X-ray powder diffraction patterns shown in Figures A to D and any crystals providing X-ray powder diffraction patterns substantially the same as that shown in Figures A to D fall within the scope of the present invention. A person skilled in the art of X-ray powder diffraction is able to judge the substantial identity of X-ray powder diffraction patterns.

Differential Scanning Calorimetry (DSC)

DSC was recorded using a Thermal Analysis Q1000 system. Typically less than 5mg of material, contained in an aluminium pan fitted with a sealed lid, was heated over the temperature range 25°C to 300°C at a constant heating rate of 10°C per minute. A nitrogen purge gas was used with flow rate 50ml per minute.

General Synthetic Method 1

General procedure for the reaction of a 6-chloro-3-(fluorinated-alkyl)-[1,2,4]-triazolo[4,3-b]pyridazine with a cyclic amine

A solution of the cyclic amine (1.47 mmol; 3 equivalents) in ethanol (1 mL) was added to the 6-chloro-3-(fluorinated-alkyl)-[1,2,4]-triazolo[4,3-b]pyridazine (0.49 mmol) (see below for preparation of novel starting materials) and the reaction was heated and shaken at 70°C overnight. The reaction mixture was evaporated to dryness and purified by hplc using an Waters X Bridge C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 5% aqueous ammonia) and acetonitrile to give the corresponding 6-cyclicamino-3-(fluorinated-alkyl)-[1,2,4]-triazolo[4,3-b]pyridazine.

6-Chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine used as starting material for General Synthetic Method 1 was prepared according to the following procedure:

6-Chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine

A mixture of 3-chloropyridazin-6-yl hydrazine (5.0g ,34.72 mmol) and difluoroacetic acid (21.93 mL; ca. 347 mmol) was heated at 100 °C for 3 hours and then evaporated to dryness. The involatile residue was dissolved in ethyl acetate (200 mL) and washed sequentially with saturated aqueous sodium carbonate and then saturated brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated to give 6-chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine (6.0 g, 84.7%) as a white solid that was used without further purification.

^{1}H NMR (300.13 MHz, DMSO-d_6) δ 7.68 (1H, t), 7.72 (1H, t, J_{HF} = 51.2 Hz), 8.59 - 8.62 (1H, m); m/z 205.38 $(M+1)^+$.

6-Chloro-3-(3,3,3-trifluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine used as starting material for General Synthetic Method 1 was prepared according to the following procedure:

6-Chloro-3-(3,3,3-trifluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine

A mixture of 3-chloropyridazin-6-yl hydrazine (5.0 g, 34.72 mmol) and trifluoropropionic acid (44.4 g, 347 mmol) was heated at 100 °C for 3 hours and then evaporated to dryness. The involatile residue was extracted with boiling ethyl acetate (200 mL), the hot ethyl acetate extract was filtered and allowed to cool to room temperature, and the product was isolated by filtration to give 6-chloro-3-(3,3,3-trifluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine (2.0 g, 24 %) as an off-white solid that was used without further purification.

^{1}H NMR (300.13 MHz, DMSO-d_6) δ 4.37 - 4.40 (2H, m), 7.56 - 7.59 (1H, m), 8.51 - 8.54 (1H, m); m/z 237.42 $(M+1)^+$.

6-Chloro-3-(2,2,3,3-tetrafluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine used as starting material for General Synthetic Method 1 was prepared according to the following procedure:

6-Chloro-3-(2,2,3,3-tetrafluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine

A mixture of 3-chloropyridazin-6-yl hydrazine (5.0 g, 34.72 mmol) and tetrafluoropropionic acid (32.5 mL; ca. 347 mmol) was heated at 100 °C for 3 hours and

then evaporated to dryness. The involatile residue was dissolved in ethyl acetate (200 mL) and washed sequentially with saturated aqueous sodium carbonate and then saturated brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated to give 6-chloro-3-(2,2,3,3-tetrafluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine (4.2 g, 48.8%) as a white solid that was used without further purification.

^1H NMR (300.13 MHz, DMSO-d_6) δ 7.21 (1H, t), 7.73 - 7.77 (1H, m), 8.65 - 8.68 (1H, m); m/z 255.28 $(M+1)^+$.

General Synthetic Method 2

General procedure for the reaction of a 6-chloro-3-(heteroatom)-[1,2,4]-triazolo[4,3-b]pyridazine with a cyclic amine

A solution of the cyclic amine (1.10 mmol; 3 equivalents) in ethanol (2 mL) was added to the 6-chloro-3-(heteroatom)-[1,2,4]-triazolo[4,3-b]pyridazine (0.37 mmol) (see below for preparation of novel starting materials) and the reaction was heated and shaken at 70°C overnight. The reaction mixture was evaporated to dryness and purified by hplc using a Waters X Bridge C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 5% aqueous ammonia) and acetonitrile to give the corresponding 6-(cyclicamino)-3-(heteroatom)-[1,2,4]-triazolo[4,3-b]pyridazine.

General Synthetic Method 3

General procedure for the reaction of a 6-chloro-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine with a cyclic amine

A solution of the cyclic amine (0.55 mmol) in ethanol (1 mL) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.050 g, 0.22 mmol) and the mixture was heated at 70°C for 16 hours or until analytical hplc-ms indicated that reaction was complete. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give the corresponding 6-(cyclicamino)-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine.

General Synthetic Method 4

General procedure for the reaction of a 6-chloro-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine with the acid salt of a cyclic amine

A solution of the acid salt of a cyclic amine (0.55 mmol) in ethanol (1 mL) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.050 g, 0.22

mmol). The reaction mixture was treated with diisopropylethylamine (1 equivalent/acid salt) and the mixture was heated at 70°C for 16 hours or until analytical hplc-ms indicated that reaction was complete. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give the corresponding 6-(cyclicamino)-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine.

General Synthetic Method 5

General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.049 g, 0.2 mmol) was added to the aldehyde (0.2 mmol) followed by a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 40 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted-methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

The 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazine-1-carboxylate

A mixture of tert-butyl piperazine-1-carboxylate (8.29 g, 44.5 mmol) and ethanol (90 mL) was added to a mixture of diisopropylethylamine (9.16 mL, 52.6 mmol) and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (9.0 g, 40.4 mmol) in ethanol (90 mL) The mixture was heated at 70°C for 11 hours and then allowed to cool to ambient temperature to give a precipitate. The precipitate was collected by filtration, washed with chilled ethanol and then with water, and dried under vacuum to afford tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazine-1-carboxylate (13.64 g, 90.6%) as a white solid that was used without further purification.

1H NMR (300.132 MHz, DMSO) d 1.43 (s, 9H), 3.48 (m, 4H), 3.62 (m, 4H), 7.58 (d, 1H), 8.28 (d, 1H); m/z 373 $(M+H)^+$.

Preparation of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Trifluoroacetic acid (25 mL, 324.49 mmol) was added to a mixture of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazine-1-carboxylate (6.7 g,

17.99 mmol) and dichloromethane (100 mL) at ambient temperature and the resulting solution was stirred at ambient temperature for 1 hour. The reaction mixture was evaporated to give an involatile residue that was treated with saturated aqueous sodium bicarbonate solution (100 mL) and then extracted with dichloromethane (4 x 200mL). The organic phases were combined and dried over Na_2SO_4, filtered, and evaporated to give 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.78 g, 98 %) as a white solid that was used without further purification.

1H NMR (300.132 MHz, DMSO) δ 2.43 (s, 1H), 2.74 - 2.87 (m, 4H), 3.45 - 3.59 (m, 4H), 7.57 (d, 1H), 8.22 (d, 1H); m/z 273 $(M+H)^+$.

General Synthetic Method 6

General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde

A solution of the aldehyde (0.2 mmol) in dichloromethane (0.5 mL) was added to a mixture of (polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.049 g, 0.2 mmol), 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.184 mmol) and a mixture of acetic acid and dichloromethane (1:9; 2 mL). The reaction mixture was shaken for 16 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted-methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

General Synthetic Method 7

General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.061 g, 0.25 mmol) was added to the aldehyde (0.25 mmol) followed by a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 4 days and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted-methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

General Synthetic Method 8

General procedure for the reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.049 g, 0.2 mmol) was added to the aldehyde (0.2 mmol) followed by a solution of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.053 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 16 hours and then filtered. The filtrate was evaporated and the residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted-methyl)-1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

The 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine used as starting material was prepared as follows:-

Preparation of tert-butyl 4-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,4-diazepane-1-carboxylate

tert-Butyl 1,4-diazepane -1-carboxylate (4.00 g, 20.0 mmol) was added to a mixture of diisopropylethylamine (4.11 mL, 23.7 mmol) and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (4.0 g, 18.2 mmol) in ethanol (80 mL). The mixture was heated under reflux for 6 hours and then allowed to cool to ambient temperature to give a precipitate. The precipitate was collected by filtration, washed with ethanol, and dried under vacuum to afford tert-butyl 4-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,4-diazepane-1-carboxylate (5.94 g, 85.4 %) as a white solid. 1H NMR (300.132 MHz, DMSO) δ 1.15 (9H, d), 1.72 - 1.93 (2H, m), 3.27 - 3.39 (2H, m), 3.50 - 3.63 (2H, m), 3.66 - 3.75 (2H, m), 3.83 (2H, t), 7.46 - 7.56 (1H, m), 8.19 - 8.31 (1H, m); apparently as a mixture of rotamers; m/z 387 $(M+H)^+$.

Preparation of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine

Trifluoroacetic acid (8 mL, 103.68 mmol) was added to a mixtrure of tert-butyl 4-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,4-diazepane-1-carboxylate (5.9 g, 15.3 mmol) and dichloromethane (80 mL) at ambient temperature and the resulting solution was stirred at ambient temperature for 6 hours. The reaction mixture was evaporated to give an involatile residue that was treated with saturated aqueous sodium bicarbonate solution (100 mL) and then extracted with dichloromethane (4 x 200 mL). The

organic phases were combined and dried over Na_2SO_4, filtered, and evaporated to give 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (3.8 g, 86.9 %) as a white solid. 1H NMR (300.132 MHz, DMSO) δ 1.68 - 1.84 (m, 2H), 2.69 (t, 2H), 2.88 (t, 2H), 3.60 - 3.79 (m, 4H), 7.46 (d, 1H), 8.19 (d, 1H); m/z. 287 $(M+H)^+$.

General Synthetic Method 9

General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with an aldehyde

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.061 g, 0.25 mmol) was added to the aldehyde (0.25 mmol) followed by a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.050 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 40 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography yield the corresponding 6-(4-(substituted-methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

The 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine used as starting material was prepared as follows:-

Preparation of 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

A mixture of polyphosphoric acid (20 mL, 175 mmol) and N'-(5-bromopyridin-2-yl)-2,2,2-trifluoroacetohydrazide (1.9 g, 6.69 mmol) was was stirred at 120 °C for 20 hours and then poured in to water. The mixture was then basified with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (3 x 250 mL). The organic phases were combined and washed with brine (1 x 100 mL), dried with $MgSO_4$ and evaporated to give an involatile residue. The residue was purified by flash chromatography on silica-gel using an increasing gradient of ethyl acetate in isohexane as eluant to give 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (1.39 g, 78 %) as a beige solid.

1H NMR (300.132 MHz, DMSO) δ 7.74 - 7.81 (m, 1H), 8.00 - 8.07 (m, 1H), 8.92 (s, 1H); m/z 266 and 268 $(M+H^+)$.

Preparation of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)piperazine-1-carboxylate

A solution of tert-butyl piperazine-1-carboxylate (1.30 g, 6.99 mmol)], 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.93 g, 3.50 mmol),

bis(dibenzylideneacetone)palladium (0.101 g, 0.17 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.163 g, 0.26 mmol) and sodium tert-butoxide (0.84g, 8.74 mmol) in xylenes (30 mL) was sealed into a microwave tube and degassed for 10 minutes. The reaction mixture was heated at 100 °C for 30 minutes and then cooled to ambient temperature. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (2 x 40 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and evaporated to give an involatile residue. The residue was purified by flash chromatography on silica-gel using an increasing gradient of ethyl acetate in isohexane as eluant to give tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)piperazine-1-carboxylate (0.86 g, 66.2 %) as a yellow solid.

1H NMR (300.132 MHz, DMSO) δ 1.43 (s, 9H), 3.12 - 3.20 (m, 4H), 3.46 - 3.54 (m, 4H), 7.59 (s, 1H), 7.69 - 7.78 (m, 1H), 7.95 (d, 1H); m/z 372 ($M+H^+$).

Preparation of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

Trifluoroacetic acid (5 mL, 64.90 mmol) was added to a mixture of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)piperazine-1-carboxylate (0.86 g, 2.32 mmol) and dichloromethane (20 mL). The resulting solution was stirred at 20 °C for 90 minutes and then evaporated to leave an involatile residue. The residue was purified by ion-exchange chromatography on an SCX column using aqueous ammonia (7M) in methanol as eluant to give 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.540 g, 86 %) as a yellow solid that was used without further purification.

1H NMR (300.132 MHz, DMSO) δ 2.79 - 2.92 (m, 4H), 3.03 - 3.13 (m, 4H), 7.49 (s, 1H), 7.67 - 7.76 (m, 1H), 7.91 (d, 1H); m/z 272 ($M+H^+$).

General Synthetic Method 10

General procedure for the reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.061 g, 0.25 mmol) was added to the aldehyde (0.25 mmol) followed by a solution of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.055 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 16 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to

yield the corresponding 6-(2-(substitutedmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

The 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Trifluoroacetic acid (15 mL, 194.70 mmol) was added to a mixture of tert-butyl 5-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (3 g, 7.53 mmol) and dichloromethane (60 mL). The resulting solution was stirred at ambient temperature for 1 hour and then evaporated to leave an involatile residue. The residue was purified purified by ion-exchange chromatography on an SCX column using aqueous ammonia (7M) in methanol as eluant to give 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.200 g, 98 %) as a white solid that was used without further purification. 1H NMR (300.132 MHz, DMSO) δ 2.61 - 2.74 (m, 2H), 2.82 - 2.96 (m, 4H), 3.27 - 3.38 (m under H_2O, 2H), 3.67 - 3.80 (m, 2H), 7.27 (d, 1H), 8.20 (d, 1H); m/z 299 ($M+H^+$).

Example 1

Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzhydrylpiperazine and 6-chloro-3-(2,2,3,3-tetrafluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzhydrylpiperazin-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine. 1H NMR (700.03 MHz, DMSO-d6) δ 2.46 (4H, t), 3.63 (4H, t), 4.39 (1H, s), 7.07 - 7.23 (3H, m), 7.33 (4H, t), 7.48 (4H, d), 7.51 - 7.52 (1H, m), 8.23 (1H, d); m/z = 471 [M+H]+.

Example 2

Preparation of 6-(4-benzyl-1,4-diazepan-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzyl-1,4-diazepane and 6-chloro-3-(2,2,3,3-tetrafluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzyl-1,4-diazepan-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.85 - 1.90 (2H, m), 2.61 (2H, t), 2.72 - 2.76 (2H, m), 3.63 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.05 - 7.21 (1H, m), 7.21 - 7.24 (1H, m), 7.24 - 7.27 (4H, m), 7.46 (1H, d), 8.19 (1H, d); m/z = 409 [M+H]+.

Example 3

Preparation of 6-piperidin-1-yl-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of piperidine and 6-chloro-3-(3,3,3-trifluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-piperidin-1-yl-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.59 - 1.62 (4H, m), 1.65 (2H, d), 3.60 (4H, t), 4.20 (2H, q), 7.43 (1H, d), 8.06 (1H, d); m/z = 286 [M+H]+.

Example 4

Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzhydrylpiperazine and 6-chloro-3-(3,3,3-trifluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzhydrylpiperazin-1-yl)-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.46 (4H, t), 3.62 (4H, t), 4.19 (2H, q), 4.39 (1H, s), 7.22 (2H, t), 7.33 (4H, t), 7.37 (1H, d), 7.48 (4H, d), 8.11 (1H, d); m/z = 453 [M+H]+.

Example 5

Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzhydrylpiperazine and 6-chloro-3-difluoromethyl-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzhydrylpiperazin-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.46 (4H, t), 3.63 (4H, t), 4.40 (1H, s), 7.21 - 7.23 (2H, m), 7.33 (4H, t), 7.28 - 7.57 (1H, m), 7.45 - 7.49 (5H, m), 8.18 - 8.19 (1H, m); m/z = 421 [M+H]+.

Example 6

Preparation of 6-(4-benzyl-1,4-diazepan-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzyl-1,4-diazepane and 6-chloro-3-difluoromethyl-1,2,4-triazolo[4,3-

b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzyl-1,4-diazepan-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.86 - 1.90 (2H, m), 2.61 (2H, t), 2.74 (2H, t), 3.63 (2H, s), 3.73 (2H, t), 3.75 (2H, t), 7.21 - 7.24 (1H, m), 7.26 (4H, t), 7.41 (1H, d), 7.40 - 7.55 (1H, m), 8.14 (1H, d); m/z = 359 [M+H]+.

Example 7

Preparation of 6-piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-amine

A mixture of piperidine and 3-amino-6-chloro-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-amine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.58 - 1.63 (6H, m), 3.53 (4H, t), 6.00 (2H, s), 7.07 (1H, d), 7.72 (1H, d); m/z = 219 [M+H]+.

Example 8

Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-chloro-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzhydrylpiperazine and 3,6-dichloro-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-(4-benzhydrylpiperazin-1-yl)-3-chloro-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.46 (4H, t), 3.63 (4H, t), 4.40 (1H, s), 7.21 - 7.23 (2H, m), 7.33 (4H, t), 7.41 (1H, d), 7.47 (4H, d), 8.11 (1H, d); m/z = 405 [M+H]+.

Example 9

Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzhydrylpiperazine and 6-chloro-3-methylsulfanyl-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-(4-benzhydrylpiperazin-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.46 (4H, t), 2.68 (3H, s), 3.58 (4H, t), 4.39 (1H, s), 7.21 - 7.23 (2H, m), 7.31 (1H, d), 7.33 (4H, t), 7.47 (4H, d), 8.05 (1H, d); m/z = 417 [M+H]+.

Example 10

Preparation of 6-(4-benzyl-1,4-diazepan-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzyl-1,4-diazepane and 6-chloro-3-methylsulfanyl-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-(4-benzyl-1,4-diazepan-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.86 - 1.90 (2H, m), 2.60 (2H, t), 2.67 (3H, s), 2.74 (2H, t), 3.63 (2H, s), 3.72 (2H, t), 3.74 (2H, t), 7.22 - 7.24 (1H, m), 7.25 (1H, d), 7.26 - 7.28 (4H, m), 8.01 (1H, d); m/z = 355 [M+H]+.

Example 11

Preparation of 6-[4-(5-bromopyridin-2-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(5-bromopyridin-2-yl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine in ethanol (7 mL) was stirred at 80 °C for 20 hours. The reaction mixture was concentrated and partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate solution (25 mL). The aqueous phase was extracted twice with dichloromethane (2 x 50 mL). The organic phases were combined, washed with water (100 mL), and concentrated to give a residue that was purified by flash chromatography on silica-gel using ethyl acetate as eluant to give 6-[4-(5-bromopyridin-2-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine 0.353 g, 73.4 %)

1H NMR (300.132 MHz, DMSO) δ 3.64 - 3.77 (8H, m), 6.90 (1H, d), 7.65 (1H, d), 7.71 - 7.76 (1H, m), 8.20 - 8.22 (1H, m), 8.29 (1H, d); m/z = 430 not assigned (Br).

Example 12

Preparation of 4-((4-(8-Methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile

A mixture of 1-(4-cyanobenzyl)-piperazine (0.158 g, 0.79 mmol) and 6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine 0.062 g, 0.26 mmol) in ethanol (5 mL) was heated to 70 °C for 20 hours. The reaction mixture was allowed to cool and then concentrated to give an involatile residue that was purified by flash chromatography on silica-gel using an increasing gradient of ethyl acetate in dichloromethane to give 4-((4-(8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile (0.0676 g, 64.3 %) as a white solid; 1H NMR spectrum ($CDCl_3$) δ 2.47 - 2.55 (4H, m), 2.61 (3H, d), 3.50 - 3.60 (6H, m), 6.72 - 6.76 (1H, m), 7.42 (2H, d), 7.57 (2H, d); m/z 402.69 (M+1)+.

The 6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows

Preparation of a mixture of 6-chloro-4-methylpyridazin-3-yl hydrazine and 6-chloro-5-methylpyridazin-3-yl hydrazine

Hydrazine hydrate (1.79 mL, 36.81 mmol) was added to a stirred suspension of 3,6-dichloro-4-methylpyridazine (0.50 g, 3.07 mmol) in water (10 mL) and the reaction mixture was heated at 80 °C for 4 hours. The reaction mixture was allowed to cool and evaporated under resuced pressure to give a mixture of 3-chloro-6-hydrazinyl-4-methylpyridazine compound and 6-chloro-3-hydrazinyl-4-methylpyridazine (0.452 g) as an off-white solid that was used without further purification. m/z 159.41 (M+1)+.

Preparation of 6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A suspension of a mixture of 3-chloro-6-hydrazinyl-4-methylpyridazine compound and 6-chloro-3-hydrazinyl-4-methylpyridazine (0.200 g) in trifluoroacetic acid (10 mL) was heated under reflux for 20 hours. The reaction mixture was allowed to cool and then concentrated to give an involatile residue that was purified by flash chromatography on silica-gel using dichloromethane as eluant to give pure fractions of:
6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.0620 g) as a white solid. 1H NMR ($CDCl_3$) δ 2.74 (3H, d), 7.05 (1H, q); m/z 237.37 (M+1)+; and
6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.078 g) as a white solid. 1H NMR ($CDCl_3$) δ 2.49 (3H, d), 7.97 (1H, q); m/z 237.37 (M+1)+.

Example 13

Preparation of 4-((4-(7-Methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile

The method of Example 12 was repeated using a mixture of 6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.078 g, 0.33mmol) and 1-(4-cyanobenzyl)-piperazine (0.199 g, 0.99 mmol) to give 4-((4-(7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile (0.099 g, 75%). 1H NMR ($CDCl_3$) δ 2.37 (3H, d), 2.53 - 2.63 (4H, m), 3.23 - 3.32 (4H, m), 3.57 (2H, s), 7.42 (2H, d), 7.57 (2H, d), 7.73 - 7.76 (1H, m); m/z 402.71 (M+1)+.

The 6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as described in Example 12.

Example 14

Preparation of 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-[(4-chlorophenyl)methyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. 1H NMR (499.802 MHz, DMSO-d6) δ 2.48-2.51 (4H, m), 3.52 (2H, s), 3.56-3.62 (4H, m), 7.37 (4H, q), 7.57 (1H, d), 8.23 (1H, d) (Signal at 2.5 obscured by DMSO); m/z = 397 [M+H]+.

Example 15

Preparation of 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-[(4-methoxyphenyl)methyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d6) δ 2.44-2.51 (4H, m), 3.47 (2H, s), 3.57-3.64 (4H, m), 3.75 (3H, s), 6.91 (2H, d), 7.25 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 393 [M+H]+.

Example 16

Preparation of 6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(2,6-dimethylphenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing

0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.
1H NMR (700.03 MHz, DMSO-d6) δ 2.31 (6H, s), 3.17 (4H, t), 3.73 (4H, t), 6.95 - 6.97 (1H, m), 7.00 (2H, d), 7.66 (1H, d), 8.27 (1H, d); m/z = 377 [M+H]+.

Example 17

Preparation of 1-[4-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenyl]ethanone

A mixture of 1-(4-piperazin-1-ylphenyl)ethanone and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-[4-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenyl]ethanone.
1H NMR (700.03 MHz, DMSO-d6) δ 2.47 (3H, s), 3.56 (4H, t), 3.79 (4H, t), 7.03 - 7.04 (2H, m), 7.66 (1H, d), 7.84 - 7.86 (2H, m), 8.30 (1H, d); m/z = 391 [M+H]+.

Example 18

Preparation of 6-[4-[4,4-bis(4-fluorophenyl)butyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-[4,4-bis(4-fluorophenyl)butyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[4,4-bis(4-fluorophenyl)butyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.
1H NMR (700.03 MHz, DMSO-d6) δ 1.34 - 1.38 (2H, m), 2.02 (2H, q), 2.34 (2H, t), 2.42 (4H, t), 3.57 (4H, t), 4.01 (1H, t), 7.09 - 7.13 (4H, m), 7.32 - 7.35 (4H, m), 7.58 (1H, d), 8.23 (1H, d); m/z = 517 [M+H]+.

Example 19

Preparation of 6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(3,5-dichloropyridin-4-yl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The

crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 3.45 - 3.46 (4H, m), 3.78 (4H, t), 7.67 (1H, d), 8.30 (1H, d), 8.50 (2H, s); m/z = 418 [M+H]+.

Example 20

Preparation of 1-phenyl-8-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,8-triazaspiro[4.5]decan-4-one

A mixture of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-phenyl-8-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,8-triazaspiro[4.5]decan-4-one.

1H NMR (700.03 MHz, DMSO-d6) δ 1.79 - 1.81 (2H, m), 2.55 (2H, d), 3.79 (2H, d), 4.19 - 4.22 (2H, m), 4.63 (2H, s), 6.67 (2H, d), 6.71 (1H, t), 7.07 - 7.09 (2H, m), 7.66 (1H, d), 8.29 (1H, d), 8.81 (1H, s); m/z = 418 [M+H]+.

Example 21

Preparation of 6-[4-(4-nitrophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(4-nitrophenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(4-nitrophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 3.66-3.74 (4H, m), 3.76-3.85 (4H, m), 7.06 (2H, d), 7.64 (1H, d), 8.10 (2H, d), 8.30 (1H, d); m/z = 394 [M+H]+.

Example 22

Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-benzhydrylpiperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Phenomenex Luna C18 100A column (10μ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-(4-benzhydrylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.46 (4H, t), 3.63 (4H, t), 4.40 (1H, s), 7.21 - 7.23 (2H, m), 7.32 - 7.34 (4H, m), 7.46 - 7.48 (4H, m), 7.54 (1H, d), 8.25 (1H, d); m/z = 439 [M+H]+.

Example 23

Preparation of 6-(4-phenethylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-phenethylpiperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-(4-phenethylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.58 - 2.60 (6H, m), 2.79 (2H, t), 3.62 (4H, t), 7.18 - 7.21 (1H, m), 7.25 - 7.26 (2H, m), 7.28 - 7.30 (2H, m), 7.61 (1H, d), 8.25 (1H, d); m/z = 377 [M+H]+.

Example 24

Preparation of 1-piperidin-1-yl-2-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethanone

A mixture of 2-piperazin-1-yl-1-piperidin-1-ylethanone and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-piperidin-1-yl-2-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethanone.

1H NMR (700.03 MHz, DMSO-d6) δ 1.44 (2H, s), 1.53 (2H, d), 1.58 - 1.61 (2H, m), 2.58 (4H, t), 3.21 (2H, s), 3.42 (2H, t), 3.48 (2H, t), 3.61 (4H, t), 7.60 (1H, d), 8.26 (1H, d); m/z = 398 [M+H]+.

Example 25

Preparation of 6-[4-[(4-methoxyphenyl)-phenylmethyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-[(4-methoxyphenyl)-phenylmethyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)-phenylmethyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.45 (4H, t), 3.62 (4H, t), 3.72 (3H, s), 4.34 (1H, s), 6.88 - 6.90 (2H, m), 7.20 - 7.24 (1H, m), 7.31 - 7.33 (2H, m), 7.35 - 7.37 (2H, m), 7.44 - 7.45 (2H, m), 7.54 (1H, d), 8.25 (1H, d); m/z = 469 [M+H]+.

Example 26

Preparation of 6-[4-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.45 - 2.49 (4H, m), 3.64 (4H, t), 4.57 (1H, s), 7.24 - 7.26 (1H, m), 7.35 (2H, t), 7.47 - 7.48 (2H, m), 7.54 (1H, d), 7.69 - 7.73 (4H, m), 8.26 (1H, d); m/z = 507 [M+H]+.

Example 27

Preparation of 6-[4-(6-bromonaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(6-bromonaphthalen-2-yl)sulfonylpiperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(6-bromonaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 3.16 (4H, t), 3.72 (4H, t), 7.49 (1H, d), 7.81 - 7.83 (1H, m), 7.84 - 7.86 (1H, m), 8.16 (1H, d), 8.19 (1H, d), 8.21 (1H, d), 8.39 (1H, d), 8.52 (1H, d); m/z = 543 not assigned (Br).

Example 28

Preparation of N-[[(9aR)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,4,6,7,8,9,9a-octahydropyrido[1,6-a]pyrazin-7-yl]methyl]-2-methylquinolin-4-amine

A mixture of N-[[(9aR)-2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,6-a]pyrazin-7-yl]methyl]-2-methylquinolin-4-amine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[[(9aR)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,4,6,7,8,9,9a-octahydropyrido[1,6-a]pyrazin-7-yl]methyl]-2-methylquinolin-4-amine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.06 - 1.10 (1H, m), 1.24 - 1.26 (1H, m), 1.69 - 1.71 (1H, m), 1.79 (1H, d), 1.91 - 1.94 (1H, m), 1.96 (1H, d), 2.09 - 2.12 (1H, m), 2.17 - 2.21 (1H, m), 2.47 (3H, s), 2.70 (1H, d), 2.85 - 2.87 (1H, m), 2.98 (1H, d), 3.02 - 3.06 (1H, m), 3.15 (2H, t), 4.13 (1H, d), 4.19 (1H, d), 6.37 (1H, s), 7.05 (1H, s), 7.33 - 7.36 (1H, m), 7.56 (1H, d), 7.62 (1H, d), 7.68 - 7.69 (1H, m), 8.19 (1H, d), 8.25 (1H, d); m/z = 497 [M+H]+.

Example 29

Preparation of 6-[4-(2,4-difluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(2,4-difluorophenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The

crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,4-difluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 3.13 (4H, t), 3.78 (4H, t), 7.01 - 7.04 (1H, m), 7.12 - 7.16 (1H, m), 7.22 - 7.25 (1H, m), 7.66 (1H, d), 8.29 (1H, d); m/z = 385 [M+H]+.

Example 30

Preparation of 6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepane and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.04 (2H, d), 3.76 (2H, t), 3.80 (2H, t), 3.96 (2H, d), 4.02 (2H, s), 7.52 (1H, d), 7.96 (1H, s), 8.20 (1H, d), 8.29 (1H, d); m/z = 466 [M+H]+.

Example 31

Preparation of 6-[4-[4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazol-1-yl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 4-[5-(4-fluorophenyl)-3-piperidin-4-ylimidazol-4-yl]-2-methoxypyrimidine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazol-1-yl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.07 - 2.13 (2H, m), 2.19 - 2.21 (2H, m), 3.13 (2H, d), 3.98 (3H, s), 4.43 - 4.45 (2H, m), 4.76 - 4.79 (1H, m), 6.96 (1H, d), 7.16 (2H, d), 7.42 - 7.44 (2H, m), 7.67 (1H, d), 8.17 (1H, s), 8.29 (1H, d), 8.56 (1H, d); m/z = 540 [M+H]+.

Example 32

Preparation of 6-[4-(2-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(2-methylphenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.32 (3H, s), 3.00 (4H, t), 3.77 (4H, t), 6.99 - 7.01 (1H, m), 7.06 (1H, d), 7.16 - 7.18 (1H, m), 7.20 (1H, d), 7.66 (1H, d), 8.28 (1H, d); m/z = 363 [M+H]+.

Example 33

Preparation of 6-[4-[(2-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-[(2-chlorophenyl)methyl]-1,4-diazepane and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d6) δ 1.81-1.92 (2H, m), 2.65-2.70 (2H, m), 2.77-2.83 (2H, m), 3.70 (2H, s), 3.71-3.76 (2H, m), 3.76-3.80 (2H, m), 7.18-7.27 (2H, m), 7.34 (1H, d), 7.41 (1H, d), 7.49 (1H, d), 8.21 (1H, d); m/z = 411 [M+H]+.

Example 34

Preparation of 1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one

A mixture of 1-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)butan-1-one and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.2% aqueous ammonia) and acetonitrile

as eluents to give 1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one.

1H NMR (300.132 MHz, DMSO-d6) δ 0.88 (3H, t), 1.51 (2H, sextet), 2.16-2.25 (2H, m), 2.94-3.19 (2H, m), 3.25-3.34 (1H, m), 3.35-3.50 (3H, m), 3.54-3.64 (1H, m), 3.66-3.83 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Signal at 3.3 partially obscured by water); m/z = 369 [M+H]+.

Example 35

Preparation of tert-butyl (1S,5R)-3-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

A mixture of tert-butyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give tert-butyl (1S,5R)-3-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate.

1H NMR (300.132 MHz, DMSO-d6) δ 1.37 (9H, s), 1.59-1.69 (2H, m), 1.76-1.89 (2H, m), 3.00-3.10 (2H, m), 3.84-3.95 (2H, m), 4.18-4.25 (2H, m), 7.47 (1H, d), 8.20 (1H, d); m/z = 399 [M+H]+.

Example 36

Preparation of 6-[4-(3-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(3-methylphenyl)piperazine dihydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(3-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 2.28 (3H, s), 3.76 (4H, t), 6.65 (1H, d), 6.80 - 6.81 (1H, m), 6.83 (1H, s), 7.13 (1H, t), 7.67 (1H, d), 8.29 (1H, d) (Some peaks obscured by solvent); m/z = 363 [M+H]+.

Example 37

Preparation of 6-[4-(2-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(2-chlorophenyl)piperazine hydrate hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 3.15 (4H, t), 3.79 (4H, t), 7.08 - 7.11 (1H, m), 7.21 - 7.22 (1H, m), 7.32 - 7.35 (1H, m), 7.45 - 7.47 (1H, m), 7.67 (1H, d), 8.30 (1H, d); m/z = 383 [M+H]+.

Example 38

Preparation of 6-[4-(6-chloronaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 1-(6-chloronaphthalen-2-yl)sulfonylpiperazine hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(6-chloronaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 3.16 (4H, t), 3.72 (4H, t), 7.49 (1H, d), 7.71 - 7.72 (1H, m), 7.85 - 7.86 (1H, m), 8.16 (1H, d), 8.21 (1H, d), 8.23 (1H, d), 8.27 (1H, d), 8.53 (1H, d); m/z = 497 [M+H]+.

Example 39

Preparation of 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-4H-3,1-benzoxazin-2-one

A mixture of 1-piperidin-4-yl-4H-3,1-benzoxazin-2-one hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar

mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-4H-3,1-benzoxazin-2-one.

1H NMR (700.03 MHz, DMSO-d6) δ 1.95 - 1.97 (2H, m), 2.53 - 2.57 (2H, m), 3.22 (1H, d), 4.25 - 4.28 (1H, m), 4.41 - 4.43 (2H, m), 5.16 (2H, s), 7.12 - 7.15 (1H, m), 7.30 - 7.31 (1H, m), 7.37 (1H, d), 7.39 - 7.41 (1H, m), 7.67 (1H, d), 8.26 (1H, d) (Some peaks obscured by solvent); m/z = 419 [M+H]+.

Example 40

Preparation of 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-3,4-dihydroquinolin-2-one

A mixture of 1-piperidin-4-yl-3,4-dihydroquinolin-2-one hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Phenomenex Luna C18 100A column (10μ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-3,4-dihydroquinolin-2-one.

1H NMR (700.03 MHz, DMSO-d6) δ 1.83 - 1.85 (2H, m), 2.43 - 2.45 (2H, m), 2.61 - 2.67 (2H, m), 2.80 (2H, t), 3.15 - 3.18 (2H, m), 4.32 - 4.36 (1H, m), 4.39 - 4.41 (2H, m), 7.01 - 7.03 (1H, m), 7.23 - 7.26 (2H, m), 7.31 (1H, d), 7.66 (1H, d), 8.26 (1H, d); m/z = 417 [M+H]+.

Example 41

Preparation of 6-(5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

A mixture of (1R,4R)-6-benzyl-3,6-diazabicyclo[2.2.1]heptane dihydrobromide and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.2% aqueous ammonia) and acetonitrile as eluents to give 6-(5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.83 - 1.84 (1H, m), 2.00 (1H, d), 2.88 (1H, d), 3.63 (2H, s), 3.73 (2H, s), 7.23 (1H, d), 7.29 - 7.31 (2H, m), 7.32 (3H, t), 8.21 (1H, d) (Some peaks obscured by solvent); m/z = 375 [M+H]+.

Example 42

Preparation of 6-[4-(pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d6) δ 2.55-2.62 (4H, m), 3.61-3.66 (4H, m), 3.68 (2H, s), 7.26-7.32 (1H, m), 7.49 (1H, d), 7.59 (1H, d), 7.76-7.82 (1H, m), 8.25 (1H, d), 8.52 (1H, d); m/z = 364 [M+H]+.

Example 43

Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formylbenzonitrile was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile.

1H NMR (499.802 MHz, DMSO-d6) δ 2.51-2.57 (4H, m), 3.60-3.66 (6H, m), 7.54-7.62 (2H, m), 7.71 (1H, d), 7.76 (1H, d), 7.79 (1H, s), 8.26 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 388 [M+H]+.

Example 44

Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-formylbenzonitrile was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile.

1H NMR (499.802 MHz, DMSO-d6) δ 2.51-2.56 (4H, m), 3.59-3.68 (6H, m), 7.53-7.62 (3H, m), 7.82 (2H, d), 8.26 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 388 [M+H]+.

Example 45

Preparation of 6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d6) δ 2.48-2.52 (4H, m), 3.53 (2H, s), 3.58-3.66 (4H, m), 7.17 (2H, t), 7.34-7.41 (2H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 381 [M+H]+.

Example 46

Preparation of 6-[4-[(2-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-

[4-[(2-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d6) δ 2.33 (3H, s), 2.49-2.53 (4H, m), 3.48 (2H, s), 3.56-3.61 (4H, m), 7.12-7.18 (3H, m), 7.25 (1H, d), 7.57 (1H, d), 8.23 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 377 [M+H]+.

Example 47

Preparation of 6-[4-[(4-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d6) δ 2.30 (3H, s), 2.45-2.51 (4H, m), 3.50 (2H, s), 3.56-3.65 (4H, m), 7.15 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 377 [M+H]+.

Example 48

Preparation of 6-[4-(1,3-benzothiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzothiazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-benzothiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.73 (4H, t), 3.66 (4H, t), 4.04 (2H, s), 7.40 - 7.43 (1H, m), 7.46 - 7.51 (1H, m), 7.60 (1H, d), 7.94 (1H, d), 8.06 (1H, d), 8.25 (1H, d); m/z = 420 [M+H]+.

Example 49

Preparation of 6-[4-(1,3-benzoxazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzoxazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-benzoxazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.72 (4H, t), 3.65 (4H, t), 3.97 (2H, s), 7.36 - 7.44 (2H, m), 7.59 (1H, d), 7.72 - 7.77 (2H, m), 8.25 (1H, d); m/z = 404 [M+H]+.

Example 50

Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoline-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline.

1H NMR (499.802 MHz, DMSO) δ 2.65 (4H, t), 3.64 (4H, t), 4.04 (2H, s), 7.56 1H, d), 7.60 (1H, d), 7.63 - 7.67 (1H, m), 7.75 - 7.80 (1H, m), 8.05 (1H, d), 8.26 (1H, d), 8.33 (1H, d), 8.88 (1H, d); m/z = 414 [M+H]+.

Example 51

Preparation of 6-[4-(1,3-thiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-thiazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly

polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-thiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.64 (4H, t), 3.63 (4H, t), 3.91 (2H, s), 7.58 (1H, d), 7.67 (1H, d), 7.73 (1H, d), 8.24 (1H, d); m/z = 370 [M+H]+.

Example 52

Preparation of 6-[4-(1-benzothiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-benzothiophene-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1-benzothiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.62 (4H, t), 3.65 (4H, t), 3.88 (2H, s), 7.30 - 7.38 (3H, m), 7.60 (1H, d), 7.78 (1H, d), 7.91 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]+.

Example 53

Preparation of 6-[4-(thiadiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with thiadiazole-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(thiadiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.62 (4H, t), 3.63 (4H, t), 4.13 (2H, s), 7.59 (1H, d), 8.25 (1H, d), 9.10 (1H, s); m/z = 371 [M+H]+.

Example 54

Preparation of 6-[4-[(1-methylbenzimidazol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylbenzimidazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylbenzimidazol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.62 (4H, t), 3.62 (4H, t), 3.85 - 3.89 (5H, m), 7.16 - 7.22 (1H, m), 7.22 - 7.28 (1H, m), 7.54 (1H, d), 7.57 - 7.62 (2H, m), 8.25 (1H, d); m/z = 417 [M+H]+.

Example 55

Preparation of 6-[4-(pyrazin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyrazine-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(pyrazin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.61 (4H, t), 3.64 (4H, t), 3.75 (2H, s), 7.60 (1H, d), 8.26 (1H, d), 8.57 (1H, d), 8.60 - 8.62 (1H, m), 8.74 (1H, d); m/z = 365 [M+H]+.

Example 56

Preparation of 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoline-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline.

1H NMR (499.802 MHz, DMSO) δ 2.61 (4H, t), 3.63 (4H, t), 3.83 (2H, s), 7.55 - 7.60 (2H, m), 7.67 (1H, d), 7.71 - 7.76 (1H, m), 7.96 (2H, t), 8.23 (1H, d), 8.34 (1H, d); m/z = 414 [M+H]+.

Example 57

Preparation of 6-[4-[(2-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.60 (4H, t), 3.44 (3H, s), 3.62 (4H, t), 3.96 (2H, s), 7.58 - 7.67 (3H, m), 7.70 - 7.75 (1H, m), 7.99 - 8.02 (1H, m), 8.27 (1H, d); m/z = 441 [M+H]+.

Example 58

Preparation of 6-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoxaline-6-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.63 (4H, t), 3.81 (2H, s), 7.57 (1H, d), 7.86 - 7.89 (1H, m), 8.02 (1H, s), 8.07 (1H, d), 8.23 (1H, d), 8.91 (1H, d), 8.93 (1H, d); m/z = 415 [M+H]+.

Example 59

Preparation of 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-formylbenzonitrile was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.63 (4H, t), 3.74 (2H, s), 7.50 (1H, t), 7.60 (1H, d), 7.64 (1H, d), 7.69 - 7.74 (1H, m), 7.84 (1H, d), 8.26 (1H, d); m/z = 388 [M+H]+.

Example 60

Preparation of 6-[4-(1-benzothiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-benzothiophene-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1-benzothiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.62 (4H, t), 3.81 (2H, s), 7.36 - 7.44 (2H, m), 7.58 (1H, d), 7.63 (1H, s), 7.99 (1H, d), 8.03 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]+.

Example 61

Preparation of 6-[4-(1,3-thiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-thiazole-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-thiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.62 (4H, t), 3.75 (2H, s), 7.56 - 7.61 (2H, m), 8.25 (1H, d), 9.06 (1H, d); m/z = 370 [M+H]+.

Example 62

Preparation of 6-[4-[(2-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-chlorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.61 - 3.67 (6H, m), 7.30 - 7.34 (1H, m), 7.34 - 7.39 (1H, m), 7.44 - 7.47 (1H, m), 7.53 - 7.57 (1H, m), 7.60 (1H, d), 8.26 (1H, d); m/z = 397 [M+H]+.

Example 63

Preparation of 6-[4-(1H-indol-7-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-7-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-7-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.64 (4H, t), 3.82 (2H, s), 6.44 - 6.46 (1H, m), 6.94 - 7.03 (2H, m), 7.33 (1H, t), 7.48 (1H, d), 7.58 (1H, d), 8.25 (1H, d), 10.84 (1H, s); m/z = 402 [M+H]+.

Example 64

Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoline-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.63 (4H, t), 3.76 (2H, s), 7.55 - 7.62 (2H, m), 7.71 - 7.76 (1H, m), 7.97 (1H, d), 8.01 (1H, d), 8.21 - 8.26 (2H, m), 8.88 (1H, d); m/z = 414 [M+H]+.

Example 65

Preparation of 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]isoquinoline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with isoquinoline-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]isoquinoline.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.58 (4H, t), 3.95 (2H, s), 7.56 (1H, d), 7.61 - 7.66 (1H, m), 7.74 (1H, d), 8.06 (1H, d), 8.13 (1H, d), 8.23 (1H, d), 8.53 (1H, d), 9.31 (1H, s); m/z = 414 [M+H]+.

Example 66

Preparation of 6-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with naphthalene-1-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to

give 6-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.58 (4H, t), 3.94 (2H, s), 7.43 - 7.58 (5H, m), 7.83 - 7.88 (1H, m), 7.90 - 7.94 (1H, m), 8.23 (1H, d), 8.29 (1H, d); m/z = 413 [M+H]+.

Example 67

Preparation of 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.50 (1H, t), 7.60 (1H, d), 7.67 - 7.75 (2H, m), 7.84 (1H, d), 8.26 (1H, d); m/z = 431 [M+H]+.

Example 68

Preparation of 6-[4-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,2-difluoro-1,3-benzodioxole-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.56 (4H, t), 3.62 (4H, t), 3.67 (2H, s), 7.19 - 7.25 (2H, m), 7.32 - 7.35 (1H, m), 7.59 (1H, d), 8.25 (1H, d); m/z = 443 [M+H]+.

Example 69

Preparation of 6-[4-[(1-methylindol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylindole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylindol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.56 (4H, t), 3.59 (4H, t), 3.70 (2H, s), 3.78 (3H, s), 6.36 (1H, s), 6.99 (1H, t), 7.09 - 7.13 (1H, m), 7.40 (1H, d), 7.48 (1H, d), 7.57 (1H, d), 8.23 (1H, d); m/z = 416 [M+H]+.

Example 70

Preparation of 6-[4-(thiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with thiophene-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(thiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.55 (4H, t), 3.62 (4H, t), 3.77 (2H, s), 6.98 - 7.02 (2H, m), 7.45 - 7.47 (1H, m), 7.59 (1H, d), 8.25 (1H, d); m/z = 369 [M+H]+.

Example 71

Preparation of 6-[4-[(1-methylindol-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylindole-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylindol-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.55 (4H, t), 3.60 (4H, t), 3.70 (2H, s), 3.77 (3H, s), 7.04 (1H, t), 7.15 (1H, t), 7.26 (1H, s), 7.40 (1H, d), 7.56 (1H, d), 7.67 (1H, d), 8.23 (1H, d) (Signal at 2.55 partially under DMSO); m/z = 416 [M+H]+.

Example 72

Preparation of 6-[4-[(2-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-fluorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.55 (4H, t), 3.59 - 3.65 (6H, m), 7.16 - 7.23 (2H, m), 7.32 - 7.38 (1H, m), 7.43 - 7.48 (1H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.55 partially under DMSO); m/z = 381 [M+H]+.

Example 73

Preparation of 6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.54 4H, t), 3.60 (2H, s), 3.64 (4H, t), 7.37 (2H, m), 7.59 (1H, d), 8.26 (1H, d), 8.52 - 8.55 (2H, m) (Signal at 2.54 partially obscured by DMSO); m/z = 364 [M+H]+.

Example 74

Preparation of 6-[4-[(3-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.53 (4H, t), 3.21 (3H, s), 3.62 (4H, t), 3.66 (2H, s), 7.57 (1H, d), 7.63 (1H, t), 7.69 (1H, d), 7.83 (1H, d), 7.88 (1H, s), 8.24 (1H, d); m/z = 441 [M+H]+.

Example 75

Preparation of 6-[4-[(2-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methoxybenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.52 (4H, t), 3.53 (2H, s), 3.60 (4H, t), 3.77 (3H, s), 6.90 - 6.95 (1H, m), 6.98 (1H, d), 7.21 - 7.26 (1H, m), 7.31 - 7.35 (1H, m), 7.56 (1H, d), 8.22 (1H, d); m/z = 393 [M+H]+.

Example 76

Preparation of 6-[4-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,3-dihydro-1,4-benzodioxine-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as

eluents to give 6-[4-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.52 (4H, t), 3.50 (2H, s), 3.59 (4H, t), 4.19 - 4.25 (4H, m), 6.73 - 6.80 (2H, m), 6.87 - 6.89 (1H, m), 7.56 (1H, d), 8.22 (1H, d); m/z = 421 [M+H]+.

Example 77

Preparation of 6-[4-(1H-indol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.52 - 2.54 (4H, m), 3.58 - 3.63 (6H, m), 6.38 - 6.41 (1H, m), 7.06 - 7.10 (1H, m), 7.32 (1H, t), 7.35 (1H, d), 7.47 (1H, s), 7.58 (1H, d), 8.24 (1H, d), 11.02 (1H, s) (Signal at 2.52 under DMSO); m/z = 402 [M+H]+.

Example 78

Preparation of 6-[4-(1H-indol-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-6-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.51 - 2.55 (4H, m), 3.60 - 3.64 (6H, m), 6.38 - 6.41 (1H, m), 6.96 - 7.00 (1H, m), 7.31 (1H, t), 7.35 (1H, s), 7.49 (1H, d), 7.58 (1H, d), 8.24 (1H, d), 10.99 (1H, s) (Signal at 2.51 under DMSO); m/z = 402 [M+H]+.

Example 79

Preparation of 6-[4-(furan-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with furan-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(furan-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. 1H NMR (499.802 MHz, DMSO) δ 2.51 - 2.55 (4H, m), 3.58 (2H, s), 3.61 (4H, t), 6.33 (1H, d), 6.40 - 6.44 (1H, m), 7.58 (1H, d), 7.60 - 7.62 (1H, m), 8.25 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 353 [M+H]+.

Example 80

Preparation of 6-[4-(1H-pyrazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-pyrazole-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-pyrazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.51 - 2.54 (4H, m), 3.51 - 3.65 (6H, m), 6.18 (1H, s), 7.41 (0H, s), 7.55 - 7.70 (2H, m), 8.24 (1H, d) (Signal at 2.51 obscured by DMSO); m/z = 353 [M+H]+.

Example 81

Preparation of 6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar

mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.50 - 2.53 (4H, m), 3.57 (2H, s), 3.60 (4H, t), 7.34 - 7.39 (1H, m), 7.57 (1H, d), 7.71 - 7.76 (1H, m), 8.23 (1H, d), 8.46 - 8.49 (1H, m), 8.52 (1H, d) (Signal at 2.5 obscured by DMSO peak); m/z = 364 [M+H]+.

Example 82

Preparation of 6-[4-[(3-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methoxybenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.49 - 2.51 (4H, m), 3.50 (2H, s), 3.60 (4H, t), 3.74 (3H, s), 6.81 - 6.84 (1H, m), 6.87 - 6.91 (2H, m), 7.24 (1H, t), 7.56 (1H, d), 8.23 (1H, d) (Signal at 2.49 obscured by DMSO); m/z = 393 [M+H]+.

Example 83

Preparation of 6-[4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-pyrrole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.48 (4H, t), 3.48 (2H, s), 3.60 (4H, t), 5.89 - 5.92 (1H, m), 5.94 (1H, q), 6.64 - 6.67 (1H, m), 7.58 (1H, d), 8.24 (1H, d), 10.68 (1H, s) (Signal at 2.48 partially obscured by DMSO); m/z = 352 [M+H]+.

Example 84

Preparation of 6-[4-(2,3-dihydro-1-benzofuran-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,3-dihydro-1-benzofuran-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,3-dihydro-1-benzofuran-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.47 - 2.51 (4H, m), 3.17 (2H, t), 3.45 (2H, s), 3.60 (4H, t), 4.51 (2H, t), 6.71 (1H, d), 7.02 (1H, d), 7.19 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.47 partially obscured by DMSO); m/z = 405 [M+H]+.

Example 85

Preparation of 6-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzodioxole-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.47 - 2.50 (4H, m), 3.46 (2H, s), 3.61 (4H, t), 6.00 (2H, s), 6.77 - 6.80 (1H, m), 6.86 (1H, d), 6.90 (1H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.47 partially obscured by DMSO); m/z = 407 [M+H]+.

Example 86

Preparation of 6-[4-(thiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with thiophene-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep

C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(thiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.47 - 2.49 (4H, m), 3.54 (2H, s), 3.59 (4H, t), 7.05 - 7.08 (1H, m), 7.32 - 7.35 (1H, m), 7.47 - 7.50 (1H, m), 7.56 (1H, d), 8.23 (1H, d) (Signal at 2.47 partially under DMSO); m/z = 369 [M+H]+.

Example 87

Preparation of 6-[4-[(1-methylpyrrol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylpyrrole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylpyrrol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.46 (4H, t), 3.44 (2H, s), 3.57 (4H, t), 3.60 (3H, s), 5.86 - 5.90 (2H, m), 6.67 (1H, t), 7.56 (1H, d), 8.23 (1H, d) (Signal at 2.46 partially obscured by DMSO); m/z = 366 [M+H]+.

Example 88

Preparation of 6-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,3-dihydro-1,4-benzodioxine-6-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.46 (4H, t), 3.40 (2H, s), 3.58 (4H, t), 4.21 (4H, s), 6.74 - 6.77 (1H, m), 6.78 (1H, s), 6.79 (1H, d), 7.56 (1H, d), 8.22 (1H, d) (Signal at 2.46 partially under DMSO); m/z = 421 [M+H]+.

Example 89

Preparation of 6-[4-[(3-methylimidazol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylimidazole-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylimidazol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.46 - 2.50 (4H, m), 3.49 (2H, s), 3.58 (4H, t), 3.62 (3H, s), 6.77 (1H, s), 7.55 (1H, s), 7.57 (1H, d), 8.23 (1H, d) (Signal at 2.46 under DMSO); m/z = 367 [M+H]+.

Example 90

Preparation of 6-[4-(furan-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with furan-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(furan-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.46 - 2.49 (4H, m), 3.39 (2H, s), 3.59 (4H, t), 6.43 - 6.45 (1H, m), 7.56 (1H, s), 7.57 - 7.59 (1H, m), 7.61 (1H, t), 8.23 (1H, d) (Signal at 2.46 obscured by DMSO); m/z = 353 [M+H]+.

Example 91

Preparation of 6-[4-[(3-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO) δ 2.29 (3H, s), 2.47 (4H, t), 3.48 (2H, s), 3.59 (4H, t), 7.06 (1H, d), 7.10 (1H, d), 7.13 (1H, s), 7.21 (1H, t), 7.56 (1H, d), 8.22 (1H, d) (Signal at 2.29 obscured by DMSO); m/z = 377 [M+H]+.

Example 92

Preparation of 6-[4-(1H-benzimidazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-benzimidazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-benzimidazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 2.60-2.67 (4H, m), 3.61-3.69 (4H, m), 3.81 (2H, s), 7.09-7.21 (2H, m), 7.43-7.48 (1H, m), 7.53-7.62 (2H, m), 8.25 (1H, d), 12.33 (1H, s); m/z = 403 [M+H]+.

Example 93

Preparation of 6-[4-(1-benzofuran-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-benzofuran-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to

give 6-[4-(1-benzofuran-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 2.58-2.67 (4H, m), 3.59-3.68 (4H, m), 3.76 (2H, s), 6.82 (1H, s), 7.18-7.32 (2H, m), 7.52-7.63 (3H, m), 8.24 (1H, d); m/z = 403 [M+H]+.

Example 94

Preparation of 6-[4-(1H-indol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 2.51-2.59 (4H, m), 3.54-3.65 (4H, m), 3.71 (2H, s), 6.95-7.03 (1H, m), 7.04-7.12 (1H, m), 7.26 (1H, d), 7.36 (1H, d), 7.56 (1H, d), 7.66 (1H, d), 8.22 (1H, d), 10.94 (1H, s) (Signal at 2.5 partially obscured by DMSO); m/z = 402 [M+H]+.

Example 95

Preparation of 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 2.50-2.57 (4H, m), 3.57-3.69 (6H, m), 7.54-7.71 (5H, m), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 431 [M+H]+.

Example 96

Preparation of 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 21 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 2.50-2.56 (4H, m), 3.57 (2H, s), 3.59-3.66 (4H, m), 7.05-7.21 (3H, m), 7.34-7.44 (1H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 381 [M+H]+.

Example 97

Preparation of 6-[4-[(3-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-chlorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 2.50-2.54 (4H, m), 3.56 (2H, s), 3.59-3.66 (4H, m), 7.27-7.43 (4H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 397 [M+H]+.

Example 98

Preparation of 6-[4-[(4,5-dimethylfuran-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4,5-dimethylfuran-2-carbaldehyde was carried out according to General Synthetic Method 6. The crude product was purified by hplc using a Waters XBridge Prep

C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4,5-dimethylfuran-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 1.88 (3H, s), 2.15 (3H, s), 3.45 (2H, s), 3.60 (4H, t), 6.07 (1H, s), 7.58 (1H, d), 8.24 (1H, d) (Some peaks obscured by solvent); m/z = 381 [M+H]+.

Example 99

Preparation of 6-[4-(cyclohexylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with cyclohexanecarbaldehyde was carried out according to General Synthetic Method 6. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(cyclohexylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (700.03 MHz, DMSO-d6) δ 0.84 - 0.89 (2H, m), 1.15 - 1.18 (1H, m), 1.20 - 1.26 (2H, m), 1.51 - 1.54 (1H, m), 1.63 - 1.69 (3H, m), 1.76 (2H, d), 2.14 (2H, d), 2.46 (4H, t), 3.60 (4H, t), 7.59 (1H, d), 8.24 (1H, d); m/z = 369 [M+H]+.

Example 100

Preparation of 6-[4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,2-difluoro-1,3-benzodioxole-5-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Phenomenex Luna C18 100A, 10m silica, 21mm diameter, 150mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.132 MHz, DMSO-d6) δ 2.50-2.55 (4H, m), 3.56 (2H, s), 3.58-3.65 (4H, m), 7.14-7.20 (1H, m), 7.33-7.40 (2H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 obscured by DMSO); m/z = 443 [M+H]+.

Example 101

Preparation of 6-[4-(1H-indol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-2-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (500.133 MHz, DMSO-d6) δ 2.52-2.58 (4H, m), 3.58-3.65 (4H, m), 3.68 (2H, s), 6.29 (1H, s), 6.93 (1H, t), 7.02 (1H, t), 7.31 (1H, d), 7.44 (1H, d), 7.57 (1H, d), 8.22 (1H, d), 11.00 (1H, s); m/z = 402 [M+H]+.

Example 102

Preparation of 6-[4-(1,3-benzodioxol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzodioxole-4-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-benzodioxol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (500.133 MHz, DMSO-d6) δ 2.49-2.54 (4H, m), 3.51 (2H, s), 3.57-3.61 (4H, m), 5.98 (2H, s), 6.79-6.86 (3H, m), 7.56 (1H, d), 8.22 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 407 [M+H]+.

Example 103

Preparation of 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoxaline-5-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline.

1H NMR (500.133 MHz, DMSO-d6) δ 2.60-2.66 (4H, m), 3.60-3.66 (4H, m), 4.24 (2H, s), 7.57 (1H, d), 7.85-7.90 (1H, m), 7.95 (1H, d), 8.03 (1H, s), 8.23 (1H, d), 8.96 (2H, s); m/z = 415 [M+H]+.

Example 104

Preparation of 6-[4-(1H-pyrrol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-pyrrole-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-pyrrol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (500.133 MHz, DMSO-d6) δ 2.43-2.48 (4H, m), 3.36 (2H, s), 3.54-3.60 (4H, m), 5.96 (1H, s), 6.63 (1H, s), 6.65-6.68 (1H, m), 7.56 (1H, d), 8.21 (1H, d), 10.57 (1H, s); m/z = 352 [M+H]+.

Example 105

Preparation of 6-[4-[[3-(4-methylphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-methylphenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to

give 6-[4-[[3-(4-methylphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.30 (3H, s), 2.49 – 2.52 (4H, m), 3.53 (2H, s), 3.60 (4H, t), 6.86 - 6.88 (1H, m), 6.92 - 6.94 (2H, m), 6.96 (1H, s), 7.08 (1H, d), 7.21 (2H, d), 7.34 (1H, t), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 469 [M+H]+.

Example 106

Preparation of N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-dimethylaminobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline.

1H NMR (499.8 MHz, DMSO-d6) δ 2.45 - 2.49 (4H, t), 2.88 (6H, s), 3.31 (2H, s), 3.60 (4H, t), 6.70 (2H, d), 7.13 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Benzyl signal obscured by water); m/z = 406 [M+H]+.

Example 107

Preparation of N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with N-(4-formylphenyl)acetamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide.

1H NMR (499.8 MHz, DMSO-d6) δ 2.04 (3H, s), 2.50 (4H, t), 3.48 (2H, s), 3.61 (4H, t), 7.24 (2H, d), 7.54 (2H, d), 7.58 (1H, d), 8.25 (1H, d), 9.90 (1H, s) (Signal at 2.5 partially obscured by DMSO); m/z = 420 [M+H]+.

Example 108

Preparation of 6-[4-[(4-ethoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.33 (3H, t), 2.48 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 4.02 (2H, q), 6.89 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 407 [M+H]+.

Example 109

Preparation of 6-[4-[(4-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-butoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 0.94 (3H, t), 1.41 - 1.48 (2H, m), 1.67 - 1.73 (2H, m), 2.48 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 3.96 (2H, t), 6.89 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 435 [M+H]+.

Example 110

Preparation of 6-[4-[(3-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-nitrobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar

mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.57 (4H, t), 3.62 (4H, t), 3.71 (2H, s), 7.57 (1H, d), 7.64 (1H, t), 7.80 (1H, d), 8.12 - 8.15 (1H, m), 8.21 (1H, s), 8.24 (1H, d); m/z = 408 [M+H]+.

Example 111

Preparation of 6-[4-[(4-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-nitrobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.60 (1H, d), 7.65 (2H, d), 8.23 (2H, d), 8.26 (1H, d); m/z = 408 [M+H]+.

Example 112

Preparation of N,N-dimethyl-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]propan-1-amine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(3-dimethylaminopropoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]propan-1-amine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.81 - 1.87 (2H, m), 2.15 (6H, s), 2.36 (2H, t), 2.49 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 3.98 (2H, t), 6.89 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 464 [M+H]+.

Example 113

Preparation of 6-[4-[(4-pyrrolidin-1-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-pyrrolidin-1-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Phenomenex Luna C18 100A, 10m silica, 21mm diameter, 150mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-pyrrolidin-1-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.13 MHz, DMSO-d6) δ 1.92 - 1.97 (4H, m), 2.46 (4H, t), 3.21 (4H, t), 3.40 (2H, s), 3.59 (4H, t), 6.50 (2H, d), 7.10 (2H, d), 7.57 (1H, d), 8.23 (1H, d); m/z = 432 [M+H]+.

Example 114

Preparation of 6-[4-[[4-[(2-methylpropan-2-yl)oxy]phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-[(2-methylpropan-2-yl)oxy]benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-[(2-methylpropan-2-yl)oxy]phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.30 (9H, s), 2.48 - 2.52 (4H, m), 3.50 (2H, s), 3.61 (4H, t), 6.94 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 435 [M+H]+.

Example 115

Preparation of 6-[4-[(4-propan-2-yloxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-propan-2-yloxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep

C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-propan-2-yloxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.27 (6H, d), 2.49 (4H, t), 3.46 (2H, s), 3.61 (4H, t), 4.56 - 4.61 (1H, m), 6.88 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 421 [M+H]+.

Example 116

Preparation of 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethylsulfanyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethylsulfanyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethylsulfanyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.52 - 2.55 (4H, m), 3.63 (6H, d), 7.54 (1H, t), 7.59 (2H, d), 7.64 (1H, d), 7.70 (1H, s), 8.26 (1H, d) (Signal at 2.54 partially obscured by DMSO); m/z = 463 [M+H]+.

Example 117

Preparation of 6-[4-[(4-pyridin-3-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-pyridin-3-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-pyridin-3-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.56 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.48 - 7.51 (3H, m), 7.59 (1H, d), 7.72 (2H, d), 8.07 - 8.10 (1H, m), 8.26 (1H, d), 8.57 - 8.58 (1H, m), 8.91 (1H, d); m/z = 440 [M+H]+.

Example 118

Preparation of 6-[4-[(3-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-bromobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.50 - 2.54 (4H, m), 3.56 (2H, s), 3.63 (4H, t), 7.32 (1H, t), 7.35 - 7.37 (1H, m), 7.47 - 7.49 (1H, m), 7.55 (1H, s), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 441 not assigned (Br).

Example 119

Preparation of 6-[4-[[3-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-chlorophenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[3-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.53 (4H, m), 3.56 (2H, s), 3.61 (4H, t), 6.94 - 6.96 (1H, m), 7.03 - 7.06 (3H, m), 7.15 (1H, d), 7.38 (1H, d), 7.43 - 7.46 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 489 [M+H]+.

Example 120

Preparation of 6-[4-[[3-(4-methoxyphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-methoxyphenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[3-(4-methoxyphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.49 - 2.51 (4H, m), 3.52 (2H, s), 3.60 (4H, t), 3.76 (3H, s), 6.81 - 6.83 (1H, m), 6.93 (1H, s), 6.96 - 6.98 (2H, m), 7.01 - 7.02 (2H, m), 7.05 (1H, d), 7.31 (1H, t), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 485 [M+H]+.

Example 121

Preparation of methyl 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzoate

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with methyl 4-formylbenzoate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give methyl 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzoate.

1H NMR (499.8 MHz, DMSO-d6) δ 2.53 (4H, t), 3.62 - 3.64 (6H, m), 3.86 (3H, s), 7.51 (2H, d), 7.59 (1H, d), 7.95 (2H, d), 8.25 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 421 [M+H]+.

Example 122

Preparation of 6-[4-[(4-tert-butylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-tert-butylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give

6-[4-[(4-tert-butylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.29 (9H, s), 2.49 - 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.26 (2H, d), 7.37 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 419 [M+H]+.

Example 123

Preparation of 6-[4-[[4-(2-methylpropyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(2-methylpropyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(2-methylpropyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 0.87 (6H, d), 1.81 - 1.86 (1H, m), 2.44 (2H, d), 2.48 - 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.13 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 419 [M+H]+.

Example 124

Preparation of 6-[4-[[6-(4-methylphenyl)sulfanylpyridin-3-yl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-(4-methylphenyl)sulfanylpyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[6-(4-methylphenyl)sulfanylpyridin-3-yl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.38 (3H, s), 2.48 - 2.51 (4H, m), 3.51 (2H, s), 3.60 (4H, t), 6.89 (1H, d), 7.32 (2H, d), 7.48 (2H, d), 7.59 (2H, d), 8.25 (1H, d), 8.34 - 8.34 (1H, m) (Signal at 2.50 partially obscured by DMSO); m/z = 486 [M+H]+.

Example 125

Preparation of 6-[4-[[3-(4-fluorophenyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-fluorophenyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[3-(4-fluorophenyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.56 (4H, t), 3.63 - 3.64 (6H, m), 7.28 - 7.32 (2H, m), 7.35 (1H, d), 7.45 (1H, t), 7.57 (3H, d), 7.70 - 7.73 (2H, m), 8.25 (1H, d); m/z = 457 [M+H]+.

Example 126

Preparation of 6-[4-[[4-(4-fluorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(4-fluorophenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(4-fluorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 6.97 (2H, d), 7.05 - 7.09 (2H, m), 7.21 - 7.26 (2H, m), 7.34 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 473 [M+H]+.

Example 127

Preparation of 6-[4-[(4-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-bromobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18

OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.49 - 2.52 (4H, m), 3.53 (2H, s), 3.62 (4H, t), 7.31 (2H, d), 7.54 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 443 not assigned (Br).

Example 128

Preparation of N,N-diethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-diethylaminobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-diethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline.

1H NMR (499.8 MHz, DMSO-d6) δ 1.09 (6H, t), 2.47 (4H, t), 3.39 (2H, s), 3.60 (4H, t), 6.62 (2H, d), 7.09 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Aminomethylene signals obscured by water); m/z = 434 [M+H]+.

Example 129

Preparation of 6-[4-[(4-methylsulfanylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylsulfanylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylsulfanylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.48 (3H, s), 2.49 - 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.25 (2H, d), 7.29 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially

obscured by DMSO); m/z = 409 [M+H]+.

Example 130

Preparation of 6-[4-[(4-propan-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-propan-2-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-propan-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.21 (6H, d), 2.48 - 2.51 (4H, m), 2.86 - 2.91 (1H, m), 3.50 (2H, s), 3.61 (4H, t), 7.21 (2H, d), 7.25 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 405 [M+H]+.

Example 131

Preparation of 6-[4-[[4-(trifluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(trifluoromethoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(trifluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.54 (4H, m), 3.58 (2H, s), 3.62 (4H, t), 7.34 (2H, d), 7.48 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 447 [M+H]+.

Example 132

Preparation of 6-[4-[[4-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(4-chlorophenoxy)benzaldehyde was carried out according to General

Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.54 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.01 - 7.04 (4H, m), 7.36 - 7.38 (2H, m), 7.42 - 7.45 (2H, m), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 489 [M+H]+.

Example 133

Preparation of 6-[4-[(4-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethynylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.50 - 2.53 (4H, m), 3.57 (2H, s), 3.62 (4H, t), 7.36 (2H, d), 7.46 (2H, d), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.52 obscured by DMSO); m/z = 387 [M+H]+.

Example 134

Preparation of 6-[4-[(4-pyridin-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-pyridin-2-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-pyridin-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.56 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.34 - 7.37 (1H, m), 7.47 (2H, d), 7.60 (1H, d), 7.87 - 7.91 (1H, m), 7.96 (1H, d), 8.07 (2H, d), 8.25 (1H, d), 8.67 - 8.68 (1H, m); m/z = 440 [M+H]+.

Example 135

Preparation of 6-[4-[(4-ethylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethylsulfonylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.12 (3H, t), 2.55 (4H, t), 3.24 - 3.29 (2H, m), 3.64 (4H, t), 3.68 (2H, s), 7.59 (1H, d), 7.64 (2H, d), 7.87 (2H, d), 8.26 (1H, d) (Signal at 3.27 partially obscured water); m/z = 455 [M+H]+.

Example 136

Preparation of 6-[4-[(3-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-prop-2-enoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.50 - 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 4.56 - 4.58 (2H, m), 5.25 - 5.28 (1H, m), 5.38 - 5.43 (1H, m), 6.02 - 6.09 (1H, m), 6.85 - 6.87 (1H, m), 6.92 (2H, d), 7.25 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.51 obscured by DMSO); m/z = 419 [M+H]+.

Example 137

Preparation of 6-[4-[(6-chloropyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-

1H NMR (499.8 MHz, DMSO-d6) δ 2.56 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.34 - 7.37 (1H, m), 7.47 (2H, d), 7.60 (1H, d), 7.87 - 7.91 (1H, m), 7.96 (1H, d), 8.07 (2H, d), 8.25 (1H, d), 8.67 - 8.68 (1H, m); m/z = 440 [M+H]+.

Example 135

Preparation of 6-[4-[(4-ethylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethylsulfonylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.12 (3H, t), 2.55 (4H, t), 3.24 - 3.29 (2H, m), 3.64 (4H, t), 3.68 (2H, s), 7.59 (1H, d), 7.64 (2H, d), 7.87 (2H, d), 8.26 (1H, d) (Signal at 3.27 partially obscured water); m/z = 455 [M+H]+.

Example 136

Preparation of 6-[4-[(3-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-prop-2-enoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.50 - 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 4.56 - 4.58 (2H, m), 5.25 - 5.28 (1H, m), 5.38 - 5.43 (1H, m), 6.02 - 6.09 (1H, m), 6.85 - 6.87 (1H, m), 6.92 (2H, d), 7.25 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.51 obscured by DMSO); m/z = 419 [M+H]+.

Example 137

Preparation of 6-[4-[(6-chloropyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-

[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-chloropyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-chloropyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.52 - 2.55 (4H, m), 3.60 (2H, s), 3.62 (4H, t), 7.51 (1H, d), 7.59 (1H, d), 7.82 - 7.84 (1H, m), 8.25 (1H, d), 8.37 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 398 [M+H]+.

Example 138

Preparation of N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with N-(3-formylphenyl)acetamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide.

1H NMR (499.8 MHz, DMSO-d6) δ 2.04 (3H, s), 2.50 - 2.53 (4H, m), 3.51 (2H, s), 3.62 (4H, t), 7.00 (1H, d), 7.25 (1H, t), 7.51 (1H, d), 7.56 - 7.61 (2H, m), 8.25 (1H, d), 9.90 (1H, s) (Signal at 2.51 obscured by DMSO); m/z = 420 [M+H]+.

Example 139

Preparation of 6-[4-[(4-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-prop-2-enoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to

give 6-[4-[(4-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.49 (4H, t), 3.47 (2H, s), 3.61 (4H, t), 4.55 - 4.57 (2H, m), 5.25 - 5.28 (1H, m), 5.38 - 5.42 (1H, m), 6.02 - 6.09 (1H, m), 6.92 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]+.

Example 140

Preparation of N,N-dimethyl-2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]ethanamine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(2-dimethylaminoethoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]ethanamine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.22 (6H, s), 2.47 - 2.51 (4H, m), 2.62 (2H, t), 3.47 (2H, s), 3.61 (4H, t), 4.04 (2H, t), 6.91 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.25 (1H, d); m/z = 450 [M+H]+.

Example 141

Preparation of N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-formyl-N,N-dimethylbenzamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide.

1H NMR (499.8 MHz, DMSO-d6) δ 2.52 - 2.55 (4H, m), 2.90 - 3.02 (6H, m), 3.59 (2H, s), 3.63 (4H, t), 7.37 - 7.41 (4H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 434 [M+H]+.

Example 142

Preparation of 6-[4-[(6-methoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-methoxypyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-methoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.49 - 2.52 (4H, m), 3.50 (2H, s), 3.61 (4H, t), 3.85 (3H, s), 6.81 (1H, d), 7.59 (1H, d), 7.66 - 7.68 (1H, m), 8.09 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 394 [M+H]+.

Example 143

Preparation of 6-[4-[(6-morpholin-4-ylpyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-morpholin-4-ylpyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-morpholin-4-ylpyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.47 - 2.51 (4H, m), 3.41 - 3.45 (6H, m), 3.60 (4H, t), 3.70 (4H, t), 6.83 (1H, d), 7.51 - 7.54 (1H, m), 7.58 (1H, d), 8.05 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO. Some signals distorted by water); m/z = 449 [M+H]+.

Example 144

Preparation of 6-[4-[(6-phenoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-phenoxypyridine-3-carbaldehyde was carried out according to General

Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-phenoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.54 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.02 (1H, d), 7.12 - 7.14 (2H, m), 7.20 - 7.23 (1H, m), 7.41 - 7.44 (2H, m), 7.59 (1H, d), 7.81 - 7.83 (1H, m), 8.09 (1H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 456 [M+H]+.

Example 145

Preparation of 6-[4-[(3-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-ethynylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.50 - 2.53 (4H, m), 3.55 (2H, s), 3.62 (4H, t), 4.17 (1H, s), 7.37 - 7.41 (3H, m), 7.45 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO.); m/z = 387 [M+H]+.

Example 146

Preparation of tert-butyl N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]carbamate

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with tert-butyl N-(4-formylphenyl)carbamate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give tert-butyl N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]carbamate.

1H NMR (499.8 MHz, DMSO-d6) δ 1.48 (9H, s), 2.48 (4H, t), 3.46 (2H, s), 3.61 (4H, t), 7.20 (2H, d), 7.42 (2H, d), 7.58 (1H, d), 8.24 (1H, d), 9.29 (1H, s); m/z = 478 [M+H]+.

Example 147

Preparation of 6-[4-[(6-ethoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-ethoxypyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-ethoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.32 (3H, t), 2.48 - 2.51 (4H, m), 3.49 (2H, s), 3.61 (4H, t), 4.30 (2H, q), 6.78 (1H, d), 7.59 (1H, d), 7.64 - 7.67 (1H, m), 8.06 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 408 [M+H]+.

Example 148

Preparation of 6-[4-[(6-propan-2-yloxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-propan-2-yloxypyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-propan-2-yloxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.29 (6H, d), 2.49 - 2.52 (4H, m), 3.48 (2H, s), 3.61 (4H, t), 5.21 - 5.26 (1H, m), 6.72 (1H, d), 7.59 (1H, d), 7.62 - 7.65 (1H, m), 8.06 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 422 [M+H]+.

Example 149

Preparation of [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]methanol

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(hydroxymethyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]methanol.

1H NMR (499.8 MHz, DMSO-d6) δ 2.50 - 2.53 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 4.51 (2H, d), 5.15 (1H, t), 7.21 (2H, t), 7.28 - 7.32 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 393 [M+H]+.

Example 150

Preparation of N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]methanesulfonamide

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with N-(3-formylphenyl)methanesulfonamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]methanesulfonamide.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.54 (4H, m), 2.99 (3H, s), 3.53 (2H, s), 3.62 (4H, t), 7.08 (1H, d), 7.13 (1H, d), 7.22 (1H, s), 7.31 (1H, t), 7.59 (1H, d), 8.25 (1H, d), 9.69 (1H, s) (Signal at 2.52 partially obscured by DMSO); m/z = 456 [M+H]+.

Example 151

Preparation of [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with (3-formylphenyl) methanesulfonate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to

give [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate.

1H NMR (499.8 MHz, DMSO-d6) δ 2.52 - 2.56 (4H, m), 3.36 (3H, s), 3.61 - 3.64 (6H, m), 7.26 - 7.28 (1H, m), 7.34 (1H, s), 7.37 (1H, d), 7.47 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.54 partially obscured by DMSO. Methyl signal distorted by water); m/z = 457 [M+H]+.

Example 152

Preparation of [4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with (4-formylphenyl) methanesulfonate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give [4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.55 (4H, m), 3.38 (3H, s), 3.58 (2H, s), 3.63 (4H, t), 7.32 - 7.34 (2H, m), 7.46 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 457 [M+H]+.

Example 153

Preparation of 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetamide

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(4-formylphenoxy)acetamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetamide.

1H NMR (499.8 MHz, DMSO-d6) δ 2.48 - 2.51 (4H, m), 3.48 (2H, s), 3.61 (4H, t), 4.42 (2H, s), 6.93 (2H, d), 7.26 (2H, d), 7.36 (1H, s), 7.49 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 436 [M+H]+.

Example 154

Preparation of 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetonitrile

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(4-formylphenoxy)acetonitrile was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 2.49 - 2.52 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 5.16 (2H, s), 7.05 (2H, d), 7.33 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 418 [M+H]+.

Example 155

Preparation of 6-[4-[[4-(4-methylpiperazin-1-yl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(4-methylpiperazin-1-yl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Phenomenex Luna C18 100A, 10m silica, 21mm diameter, 150mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(4-methylpiperazin-1-yl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (300.13 MHz, DMSO-d6) δ 2.23 (3H, s), 2.43 - 2.51 (8H, m), 3.12 (4H, t), 3.43 (2H, s), 3.56 - 3.62 (4H, m), 6.89 (2H, d), 7.15 (2H, d), 7.57 (1H, d), 8.24 (1H, d) (Signal at 2.46 partially obscured by DMSO); m/z = 461 [M+H]+.

Example 156

Preparation of N,N-dimethyl-3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formyl-N,N-dimethylbenzamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep

C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.55 (4H, m), 2.90 - 3.01 (6H, m), 3.59 (2H, s), 3.63 (4H, t), 7.29 - 7.32 (1H, m), 7.36 (1H, s), 7.39 - 7.43 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 434 [M+H]+.

Example 157

Preparation of 6-[4-[(3-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-butoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 0.94 (3H, t), 1.41 - 1.49 (2H, m), 1.67 - 1.73 (2H, m), 2.50 - 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 3.97 (2H, t), 6.82 - 6.84 (1H, m), 6.90 (2H, t), 7.25 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.52 obscured by DMSO); m/z = 435 [M+H]+.

Example 158

Preparation of 6-[4-[(4-propylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-propylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-propylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 0.90 (3H, t), 1.56 - 1.63 (2H, m), 2.48 - 2.51 (4H, m), 2.55 (2H, t), 3.51 (2H, s), 3.61 (4H, t), 7.16 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 405 [M+H]+.

Example 159

Preparation of 6-[4-[(4-ethylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.19 (3H, t), 2.48 - 2.51 (4H, m), 2.60 (2H, q), 3.50 (2H, s), 3.61 (4H, t), 7.18 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 391 [M+H]+.

Example 160

Preparation of 6-[4-[(4-morpholin-4-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-morpholin-4-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-morpholin-4-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.48 (4H, t), 3.09 (4H, t), 3.45 (2H, s), 3.60 (4H, t), 3.74 (4H, t), 6.91 (2H, d), 7.18 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 448 [M+H]+.

Example 161

Preparation of 6-[4-[[4-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(difluoromethoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.49 - 2.52 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.16 (2H, d), 7.22 (1H, t), 7.39 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 429 [M+H]+.

Example 162

Preparation of 6-[4-[[3-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(difluoromethoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[3-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.51 - 2.55 (4H, m), 3.58 (2H, s), 3.63 (4H, t), 7.07 - 7.11 (1H, m), 7.16 (1H, s), 7.23 (1H, d), 7.24 (1H, t), 7.41 (1H, t), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 429 [M+H]+.

Example 163

Preparation of ethyl (*E*)-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]prop-2-enoate

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with ethyl (*E*)-3-(4-formylphenyl)prop-2-enoate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile

as eluents to give ethyl (*E*)-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]prop-2-enoate.

1H NMR (499.8 MHz, DMSO-d6) δ 1.27 (3H, t), 2.51 - 2.54 (4H, m), 3.59 (2H, s), 3.63 (4H, t), 4.21 (2H, q), 6.62 (1H, d), 7.40 (2H, d), 7.59 (1H, d), 7.64 - 7.67 (1H, m), 7.70 (2H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 461 [M+H]+.

Example 164

Preparation of 6-[4-[(2-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.86 - 1.92 (2H, m), 2.67 (2H, t), 2.79 - 2.83 (2H, m), 3.27 (3H, s), 3.74 (2H, t), 3.78 (2H, t), 4.03 (2H, s), 7.51 (1H, d), 7.55 - 7.60 (3H, m), 7.95 (1H, d), 8.23 (1H, d); m/z = 455 [M+H]+.

Example 165

Preparation of 6-[4-[(3-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.86 - 1.92 (2H, m), 2.64 (2H, t), 2.77 -2.81 (2H, m), 3.18 (3H, s), 3.73 - 3.78 (6H, m), 7.50 (1H, d), 7.53 (1H, d), 7.61 (1H, d), 7.80 (1H, d), 7.84 (1H, s), 8.22 (1H, d); m/z = 455 [M+H]+.

Example 166

Preparation of 6-[4-[(4-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.86 - 1.92 (2H, m), 2.64 (2H, t), 2.77 (2H, t), 3.19 (4H, s), 3.73 - 3.78 (6H, m), 7.50 (1H, d), 7.53 (2H, d), 7.81 (2H, d), 8.23 (1H, d); m/z = 455 [M+H]+.

Example 167

Preparation of 6-[4-[(2-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methoxybenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.85 - 1.92 (2H, m), 2.63 (2H, t), 2.76 (2H, t), 3.61 (2H, s), 3.70 - 3.74 (5H, m), 3.76 (2H, t), 6.83 (1H, t), 6.94 (1H, d), 7.19 (1H, t), 7.26 (1H, d), 7.49 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]+.

Example 168

Preparation of 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep

C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.85 - 1.91 (2H, sm, 2.65 (2H, t), 2.75 (2H, t), 3.73 - 3.77 (6H, m), 7.46 (2H, d), 7.50 (1H, d), 7.58 (2H, d), 8.23 (1H, d); m/z = 445 [M+H]+.

Example 169

Preparation of 6-[4-[(2-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-fluorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.85 - 1.91 (2H, m), 2.64 (2H, t), 2.76 (2H, t), 3.68 (2H, s), 3.71 (2H, t), 3.76 (2H, t), 7.06 - 7.11 (2H, m), 7.25 - 7.28 (1H, m), 7.36 (1H, t), 7.48 (1H, d), 8.21 (1H, d); m/z = 395 [M+H]+.

Example 170

Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-formylbenzonitrile was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 1.84 - 1.91 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.72 (2H, s), 3.73 - 3.79 (4H, m), 7.45 (2H, d), 7.49 (1H, d), 7.69 (2H, d), 8.23 (1H, d); m/z = 402 [M+H]+.

Example 171

Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formylbenzonitrile was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 1.84 - 1.91 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.69 (2H, s), 3.72 - 3.77 (4H, m), 7.45 (1H, t), 7.50 (1H, d), 7.59 (1H, d), 7.69 (2H, d), 8.22 (1H, d); m/z = 402 [M+H]+.

Example 172

Preparation of 6-[4-[(3-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.84 - 1.90 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.65 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.01 - 7.04 (2H, m), 7.08 (1H, d), 7.26 - 7.30 (1H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 395 [M+H]+.

Example 173

Preparation of 6-[4-[(3-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methoxybenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18

OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.84 - 1.90 (2H, m), 2.61 (2H, t), 2.74 (2H, t), 3.60 (2H, s), 3.67 (3H, s), 3.73 - 3.77 (4H, m), 6.77 - 6.82 (3H, m), 7.16 (1H, t), 7.49 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]+.

Example 174

Preparation of 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.83 - 1.90 (2H, m), 2.65 (2H, t), 2.77 (2H, t), 3.76 (6H, d), 7.42 (1H, t), 7.45 - 7.52 (2H, m), 7.65 (2H, t), 8.22 (1H, d); m/z = 445 [M+H]+.

Example 175

Preparation of 6-[4-[(3-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-chlorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.83 - 1.90 (2H, m), 2.64 (2H, t), 2.75 (2H, t), 3.64 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.19 - 7.21 (1H, m), 7.24 - 7.28 (3H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 411 [M+H]+.

Example 176

Preparation of 6-[4-[(4-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-chlorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.83 - 1.90 (2H, m), 2.61 (2H, t), 2.73 (2H, t), 3.62 (2H, s), 3.71 - 3.76 (4H, m), 7.25 - 7.30 (4H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 411 [M+H]+.

Example 177

Preparation of 6-[4-[(4-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.83 - 1.90 (2H, m), 2.61 (2H, t), 2.72 (2H, t), 3.61 (2H, s), 3.71 - 3.75 (4H, m), 7.05 (2H, t), 7.26 - 7.29 (2H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 395 [M+H]+.

Example 178

Preparation of 6-[4-[(3-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18

OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.83 - 1.90 (2H, m), 2.22 (3H, s), 2.61 (2H, t), 2.73 (2H, t), 3.58 (2H, s), 3.70 - 3.77 (4H, m), 7.03 (3H, d), 7.13 (1H, t), 7.49 (1H, d), 8.22 (1H, d); m/z = 391 [M+H]+.

Example 179

Preparation of 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.83 - 1.89 (2H, m), 2.65 (2H, t), 2.77 (2H, t), 3.71 – 3.79 (6H, m), 7.45 - 7.51 (2H, m), 7.53 - 7.59 (3H, m), 8.22 (1H, d); m/z = 445 [M+H]+.

Example 180

Preparation of 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-formylbenzonitrile was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 1.82 - 1.89 (2H, m), 2.69 (2H, t), 2.80 (2H, t), 3.71 – 3.78 (6H, m), 7.42 (1H, t), 7.46 – 7.51 (2H, m), 7.57 (1H, t), 7.70 (1H, d), 8.20 (1H, d); m/z = 402 [M+H]+.

Example 181

Preparation of 6-[4-[(4-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methoxybenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.82 - 1.89 (2H, m), 2.59 (2H, t), 2.71 (2H, t), 3.54 (2H, s), 3.70 - 3.74 (7H, m), 6.79 (2H, d), 7.14 (2H, d), 7.48 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]+.

Example 182

Preparation of 6-[4-[(4-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.82 - 1.89 (2H, m), 2.26 (3H, s), 2.60 (2H, t), 2.71 (2H, t), 3.57 (2H, s), 3.70 - 3.74 (4H, m), 7.03 (2H, d), 7.11 (2H, d), 7.48 (1H, d), 8.21 (1H, d); m/z = 391 [M+H]+.

Example 183

Preparation of 6-[4-[(2-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18

OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 1.78 - 1.85 (2H, m), 2.15 (3H, s), 2.61 (2H, t), 2.71 - 2.77 (2H, m), 3.55 (2H, s), 3.71 (2H, t), 3.75 (2H, t), 7.04 - 7.09 (2H, m), 7.08 - 7.15 (1H, m), 7.16 - 7.18 (1H, m), 7.48 (1H, d), 8.20 (1H, d); m/z = 391 [M+H]+.

Example 184

Preparation of 3-(trifluoromethyl)-6-[4-[[6-(trifluoromethyl)pyridin-3-yl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 6-(trifluoromethyl)pyridine-3-carbaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[6-(trifluoromethyl)pyridin-3-yl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.60 (4H, t), 3.22 (4H, t), 3.73 (2H, s), 7.54 (1H, s), 7.72 - 7.75 (1H, m), 7.90 - 7.94 (2H, m), 8.05 - 8.07 (1H, m), 8.75 (1H, s); m/z = 431 [M+H]+.

Example 185

Preparation of 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 3-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.58 (4H, t), 3.22 (4H, t), 3.68 (2H, s), 7.54 (1H, s), 7.60 (1H, t), 7.66 (2H, d), 7.70 (1H, s), 7.72 - 7.74 (1H, m), 7.93 (1H, d); m/z = 430 [M+H]+.

Example 186

Preparation of 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.58 (4H, t), 3.22 (4H, t), 3.67 (3H, s), 7.54 (1H, s), 7.58 - 7.60 (2H, m), 7.71 - 7.74 (3H, m), 7.92 - 7.94 (1H, m); m/z = 430 [M+H]+.

Example 187

Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-formylbenzonitrile was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 2.58 (4H, t), 3.22 (4H, t), 3.67 (2H, s), 7.54 (1H, s), 7.57 (2H, d), 7.72 - 7.74 (1H, m), 7.83 (2H, d), 7.93 (1H, d); m/z = 387 [M+H]+.

Example 188

Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 3-formylbenzonitrile was carried out according to General Synthetic

Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 2.57 (4H, t), 3.22 (4H, t), 3.64 (2H, s), 7.54 (1H, s), 7.58 (1H, t), 7.72 - 7.74 (2H, m), 7.75 - 7.77 (1H, m), 7.80 (1H, s), 7.93 (1H, d); m/z = 387 [M+H]+.

Example 189

Preparation of 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.57 (4H, t), 3.21 (4H, t), 3.60 (2H, s), 7.08 - 7.12 (1H, m), 7.16 - 7.21 (2H, m), 7.38 - 7.42 (1H, m), 7.54 (1H, s), 7.72 - 7.74 (1H, m), 7.93 (1H, d); m/z = 380 [M+H]+.

Example 190

Preparation of 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-chlorobenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.55 (4H, t), 3.20 (4H, t), 3.56 (2H, s), 7.39 (4H, d), 7.53 (1H, s), 7.71 - 7.74 (1H, m), 7.93 (1H, d); m/z = 396 [M+H]+.

Example 191

Preparation of 6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.55 (4H, t), 3.20 (4H, t), 3.55 (2H, s), 7.18 (2H, t), 7.37 - 7.40 (2H, m), 7.53 (1H, s), 7.71 - 7.74 (1H, m), 7.93 (1H, d); m/z = 380 [M+H]+.

Example 192

Preparation of 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-methoxybenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.53 (4H, t), 3.19 (4H, t), 3.49 (2H, s), 3.76 (3H, s), 6.88 - 6.92 (2H, m), 7.25 (2H, d), 7.53 (1H, s), 7.71 - 7.73 (1H, m), 7.92 (1H, d); m/z = 392 [M+H]+.

Example 193

Preparation of 6-[2-(pyridin-4-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-4-carbaldehyde was carried out according to

General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-(pyridin-4-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.98 (2H, s), 3.42 (1H, d), 3.62 (2H, s), 3.75 - 3.78 (2H, m), 7.30 - 7.33 (3H, m), 8.23 (1H, d), 8.48 (2H, q) (Some peaks obscured by solvent); m/z = 390 [M+H]+.

Example 194

Preparation of 6-[2-[(3-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methoxybenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(3-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.96 (2H, s), 3.55 (2H, s), 3.70 (3H, s), 3.72 - 3.76 (2H, m), 6.79 - 6.81 (1H, m), 6.85 - 6.86 (2H, m), 7.21 (1H, t), 7.31 (1H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 419 [M+H]+.

Example 195

Preparation of 6-[2-[(4-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methoxybenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(4-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.94 - 2.95 (2H, m), 3.40 (2H, s), 3.50 (2H, s), 3.73 (5H, s), 6.85 (2H, d), 7.19 (2H, d), 7.30 (1H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 419 [M+H]+.

Example 196

Preparation of 3-(trifluoromethyl)-6-[2-[[3-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[2-[[3-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.61 - 2.64 (2H, m), 2.97 - 2.98 (2H, m), 3.34 (1H, s), 3.68 (2H, s), 3.72 - 3.75 (2H, m), 7.31 (1H, d), 7.54 (1H, t), 7.59 - 7.67 (3H, m), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 457 [M+H]+.

Example 197

Preparation of 3-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formylbenzonitrile was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 2.60 - 2.63 (2H, m), 2.97 - 2.98 (2H, m), 3.64 (2H, s), 3.73 - 3.77 (2H, m), 7.31 (1H, d), 7.53 (1H, t), 7.65 (1H, d), 7.71 (2H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 414 [M+H]+.

Example 198

Preparation of 6-[2-[(3-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-

c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-chlorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(3-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.59 - 2.62 (2H, m), 2.97 (2H, d), 3.32 - 3.35 (245H, m), 3.59 (2H, s), 3.72 - 3.76 (2H, m), 7.25 - 7.35 (5H, m), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 423 [M+H]+.

Example 199

Preparation of 3-(trifluoromethyl)-6-[2-[[4-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[2-[[4-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.59 - 2.62 (1H, m), 2.97 - 3.01 (2H, m), 3.67 (2H, s), 3.74 - 3.77 (2H, m), 7.31 (1H, d), 7.52 (2H, d), 7.66 (2H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 457 [M+H]+.

Example 200

Preparation of 6-[2-[(3-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with

decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(3-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.58 - 2.65 (1H, m), 2.97 (2H, d), 3.60 (2H, s), 3.73 - 3.77 (2H, m), 7.03 - 7.07 (1H, m), 7.11 (1H, d), 7.13 (1H, d), 7.30 (1H, t), 7.33 - 7.36 (1H, m), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 407 [M+H]+.

Example 201

Preparation of 3-(trifluoromethyl)-6-[2-[[6-(trifluoromethyl)pyridin-3-yl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-(trifluoromethyl)pyridine-3-carbaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[2-[[6-(trifluoromethyl)pyridin-3-yl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.58 - 2.64 (4H, m), 2.98 - 3.02 (2H, m), 3.34 (1H, s), 3.73 - 3.75 (4H, m), 3.77 (1H, s), 7.31 (1H, d), 7.84 (1H, d), 7.99 (1H, d), 8.22 (1H, d), 8.69 (1H, s) (Some peaks obscured by solvent); m/z = 458 [M+H]+.

Example 202

Preparation of 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]-1H-pyridin-2-one

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-hydroxypyridine-4-carbaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]-1H-pyridin-2-one.

1H NMR (499.8 MHz, DMSO-d6) δ 2.58 - 2.59 (2H, m), 2.98 - 2.99 (2H, m), 3.78 (2H, t), 6.11 (1H, d), 6.21 (1H, s), 7.25 (1H, d), 7.32 (1H, d), 8.22 (1H, d) (Some peaks obscured

by solvent); m/z = 406 [M+H]+.

Example 203

Preparation of 6-[2-[(4-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(4-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.56 –2.59) (2H, m), 2.96 (2H, s), 3.56 (2H, s), 3.73 – 3.76 (2H, m), 7.11 (2H, t), 7.31 (1H, d), 7.32 (2H, t), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 407 [M+H]+.

Example 204

Preparation of 6-[2-[(4-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-chlorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(4-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.56 - 2.59 (2H, m), 2.96 (2H, s), 3.57 (2H, s), 3.74 (1H, d), 3.77 (1H, s), 7.29 - 7.36 (5H, m), 8.21 - 8.23 (1H, m) (Some peaks obscured by solvent); m/z = 423 [M+H]+.

Example 205

Preparation of 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-

[1,2,4]triazolo[4,3-b]pyridazine with 4-formylbenzonitrile was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile.

1H NMR (499.8 MHz, DMSO-d6) δ 2.54 – 2.62 (4H, m), 2.97 – 2.98 (2H, m), 3.67 (2H, s), 3.78 – 3.74 (2H, m), 7.31 (1H, d), 7.50 (2H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 414 [M+H]+.

Example 206

Preparation of 6-[2-(pyridin-3-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-3-carbaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-(pyridin-3-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d6) δ 2.53 - 2.56 (2H, m), 2.59 - 2.62 (2H, m), 2.93 - 3.01 (2H, m), 3.61 (2H, s), 3.72 - 3.76 (2H, m), 7.28 - 7.31 (1H, m), 7.33 (1H, d), 7.68 - 7.70 (1H, m), 8.22 (1H, d), 8.45 - 8.46 (1H, m), 8.49 (1H, d) (Some peaks obscured by solvent); m/z = 390 [M+H]+.

Example 207

Preparation of (3-methoxyphenyl)-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]methanone

The amine 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was acylated with 3-methoxybenzoyl chloride by General Synthetic Method 11. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as

eluents to give (3-methoxyphenyl)-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]methanone.

1H NMR (300.132 MHz, DMSO-d6) δ 2.96-3.17 (2H, m), 3.34-3.60 (4H, m), 3.62-3.90 (7H, m), 6.98-7.11 (3H, m), 7.23 (1H, d), 7.34 (1H, t), 8.23 (1H, d); m/z = 433 [M+H]+.

Example 208

Preparation of 2-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]propan-1-one

The amine 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was acylated with 2-methylpropanoyl chloride by General Synthetic Method 11. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 2-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]propan-1-one.

1H NMR (300.132 MHz, DMSO-d6) δ 0.94-1.05 (6H, m), 2.59-2.70 (1H, m), 2.95-3.19 (2H, m), 3.24-3.29 (1H, m), 3.35-3.54 (3H, m), 3.55-3.64 (1H, m), 3.71-3.83 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Signal at 3.3 partially obscured by water); m/z = 369 [M+H]+.

Example 209

Preparation of 3-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one

The amine 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was acylated with 3-methylbutanoyl chloride by General Synthetic Method 11. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one.

1H NMR (300.132 MHz, DMSO-d6) δ 0.84-0.94 (6H, m), 1.92-2.06 (1H, m), 2.09-2.15 (2H, m), 2.92-3.18 (2H, m), 3.24-3.35 (1H, m), 3.35-3.48 (3H, m), 3.54-3.64 (1H, m), 3.67-3.82 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Signal at 3.3 partially obscured by water); m/z = 383 [M+H]+.

Example 210

Preparation of 6-(5-benzyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine

2-Benzyl-3,3a,4,5,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole hydrochloride (0.129 g, 0.54 mmol) and then diisopropylethylamine (0.070 g, 0.54 mmol) were added sequentially to a solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.080 g, 0.36 mmol) in ethanol (2mL). The reaction mixture was heated at 70°C for 4 hours and then evaporated to leave an involatile residue. The residue was purified by preparative hplc using a Phenomenex Luna C18 100A column (10μ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give a partially purified product that was further purified by ion exchange chromatography an SCX column eluted with 7M aqueous ammonia in methanol as eluents to give 6-(5-benzyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.116 g, 83%) as a white solid.
1H NMR (300.132 MHz, CDCl3) 2.57-2.71 (4H, m), 2.96-3.09 (2H, m), 3.39-3.49 (2H, m), 3.61 (2H, s), 3.74-3.86 (2H, m), 6.87 (1H, d), 7.20-7.34 (5H, m), 7.89 (1H, d); m/z =389 [M+H]+.

Example 211

Preparation of tert-butyl 5-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate

tert-Butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (3.15 g, 14.83 mmol) was added to a mixture of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3 g, 13.48 mmol) and diisopropyethylamine (4.66 mL, 26.96 mmol) and ethanol (50 mL). The mixture was warmed to 70°C over a period of 10 minutes, stirred at 70 °C for 1 hour, and then allowed to cool to ambient temperature to give a precipitate. The precipitate was collected by filtration, washed with ethanol (50 mL), and and dried under vacuum to afford tert-butyl 5-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (3.00 g, 55.9 %) as a white solid.
1H NMR (300.132 MHz, DMSO) d 1.39 (s, 9H), 2.96 - 3.09 (m, 2H), 3.16 - 3.26 (m, 2H), 3.35 - 3.47 (m, 2H), 3.48 - 3.60 (m, 2H), 3.67 - 3.80 (m, 2H), 7.23 (d, 1H), 8.22 (d, 1H); m/z 399 ($M+H^+$).

Example 212

Preparation of 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)aniline

A mixture of trifluoroacetic acid (0.5 mL, 0.15 mmol) and tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate (0.072 g, 0.15 mmol) in dichloromethane (2 mL) was stirred at ambient temperature for 2 hours and then evaporated to give an involatile residue. The residue was purified by hplc using a Phenomenex Luna C18 100A column (10μ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents to give a partially purified product that was further purified by ion exchange chromatography using an SCX column eluted 7M aquous ammonia in methanol to give 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)aniline (0.032 g, 56.2 %) as a white solid.
1H NMR (300.132 MHz, DMSO-d6) δ 2.24-2.32 (4H, m), 3.18 (2H, s), 3.35-3.49 (4H, m), 4.79 (2H, s), 6.36 (2H, d), 6.79 (2H, d), 7.41 (1H, d), 8.07 (1H, d); m/z = 378 [M+H]+.

The tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate used as starting material was prepared as follows:-

Preparation of tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate

A solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.079 g, 0.29 mmol) in a mixture of acetic acid and dichloromethane (1:9; 3 mL) was added to a mixture of (polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.097 g, 0.4 mmol) and N-(4-formylphenyl)carbamic acid tert-butyl ester (0.088.4 g, 0.4 mmol). The reaction mixture was shaken for 4 days and then filtered. The filtrate was evaporated and the and the involatile residue was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 21mm diameter, 100mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate (0.0722 g, 52 %) as a white solid, which was used without further purification.

Example 213

N-(4-fluorophenyl)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxamide

1-Fluoro-4-isocyanatobenzene (0.026 g, 0.19 mmol) was added to a suspension of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.17 mmol) in toluene (1.5 mL). The reaction mixture was heated at 70°C for 1 hour and evaporated to give an involatile residue. The residue was purified by hplc using a Phenomenex Luna C18 100A column (10µ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give N-(4-fluorophenyl)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxamide (0.0309 g, 42 %) as a white solid.

Example 214

N,N-dimethyl-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-sulfonamide

N,N-Dimethylsulfamoyl chloride (0.027 g, 0.19 mmol) and then dichloromethane were added sequentially to a mixture of diisopropylethylamineamine (0.044 g, 0.34 mmol) and 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.17 mmol) in toluene (1.5 mL). The reaction mixture was stirred for 1 hour and evaporated to give an involatile residue. The residue was purified by preparative hplc using a Phenomenex Luna C18 100A column (10µ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give N,N-dimethyl-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-sulfonamide (0.0206 g, 30 %) as a white solid.

1H NMR (300.132 MHz, DMSO-d6) δ 2.75 (6H, s), 3.05-3.15 (2H, m), 3.17-3.24 (2H, m), 3.40-3.55 (4H, m), 3.72-3.81 (2H, m), 7.27 (1H, d), 8.23 (1H, d); m/z = 406 [M+H]+.

Example 215

6-(5-ethylsulfonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine

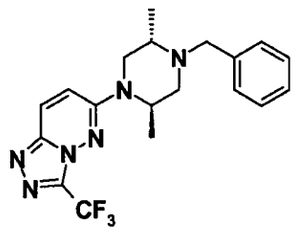
Ethanesulfonyl chloride (0.024 g, 0.19 mmol) and then dichloromethane (0.5 mL) were added sequentially to a mixture of diisopropylethylamine (0.044 g, 0.34 mmol) and 6-

(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.050 g, 0.17 mmol) in toluene (1.5 mL). The reaction mixture was stirred for 1 hour at ambient temperature and then for 1.5 hours at 50°C and then evaporated to give an involatile residue. The residue was purified by preparative hplc using a Phenomenex Luna C18 100A column (10µ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give 6-(5-ethylsulfonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.0143 g, 22 %) as a white solid.

1H NMR (300.132 MHz, DMSO-d6) δ 2.75 (6H, s), 3.05-3.15 (2H, m), 3.17-3.24 (2H, m), 3.40-3.55 (4H, m), 3.72-3.81 (2H, m), 7.27 (1H, d), 8.23 (1H, d); m/z = 406 [M+H]+.

Example 216

Preparation of 6-[(2R,5S)-4-benzyl-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

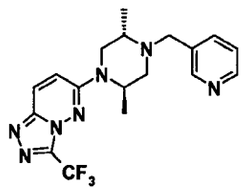


A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.45 g, 20 mmol), (2S,5R)-1-benzyl-2,5-dimethylpiperazine (4.90 g, 24.00 mmol) and DIPEA (5.14 mL, 30.00 mmol) in DMF (40 mL) was heated at 125°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and washed sequentially with 1M aqueous K_2CO_3, water and saturated brine. The organic layer was dried over MgSO4, filtered and evaporated. The crude product was purified by MPLC silica chromatography, eluting with 75% EtOAc / isohexane. Pure fractions were evaporated to dryness to afford 6-[(2R,5S)-4-benzyl-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (6.16 g, 79%) as a tan gum.

1H NMR (399.9 MHz, DMSO-d6) δ 1.01 - 1.03 (3H, m), 1.26 (3H, d), 2.34 - 2.37 (1H, m), 2.80 - 2.84 (1H, m), 3.11 (1H, t), 3.44 - 3.48 (1H, m), 3.53 (1H, d), 3.66 (1H, d), 3.93 (1H, d), 4.42 (1H, s), 7.24 - 7.30 (1H, m), 7.31 - 7.41 (4H, m), 7.56 - 7.59 (1H, m), 8.22 - 8.26 (1H, m); m/z = 391 [M+H]+.

Example 217

Preparation of 6-[(2R,5S)-2,5-dimethyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of pyridine-3-carboxaldehyde and 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2R,5S)-2,5-dimethyl-4-(3-pyridylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine in 84% yield.

1H NMR (399.9 MHz, CDCl3) δ 1.09 - 1.11 (3H, m), 1.33 (3H, d), 2.36 - 2.40 (1H, m), 2.88 - 2.95 (1H, m), 3.15 - 3.18 (1H, m), 3.53 - 3.59 (2H, m), 3.69 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.03 (1H, d), 7.28 - 7.30 (1H, m), 7.71 - 7.74 (1H, m), 7.91 (1H, d), 8.52 - 8.54 (1H, m), 8.60 (1H, d); m/z = 392 [M+H]+.

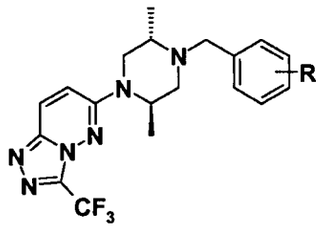
The 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

A solution of 6-[(2R,5S)-4-benzyl-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (6.1 g, 15.62 mmol) in ethanol (150 mL) and 5M hydrochloric acid (9.37 mL, 46.87 mmol) was hydrogenated over 10% palladium on charcoal (1 g, 9.40 mmol) under hydrogen at 1 atmosphere for 3 days. The catalyst was filtered off and the filtrate was evaporated. The residue was taken into DCM and washed with 2M aqueous K_2CO_3. The organic phase was dried over MgSO4 and evaporated. The crude product was purified by MPLC silica chromatography, elution gradient 2 to 5% methanolic ammonia in DCM. Product fractions were evaporated to near dryness and crystallised from ether to afford 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1.430 g, 30.5%) as a white crystalline solid.

1H NMR (400.1 MHz, CDCl3) δ 1.23 - 1.25 (3H, m), 1.33 (3H, d), 2.71 - 2.75 (1H, m), 3.32 - 3.39 (2H, m), 3.47 (1H, d), 3.59 - 3.64 (1H, m), 4.15 - 4.19 (1H, m), 7.04 (1H, d), 7.92 (1H, d) ; m/z = 301 [M+H]+

Examples 218-222

The following compounds were prepared in 73-82% yield by General Synthetic Method 5, starting from 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

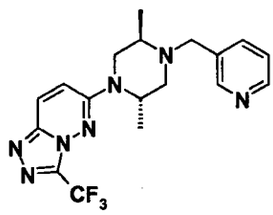


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
218	4-CN	δ 1.09 - 1.10 (3H, m), 1.35 (3H, d), 2.33 - 2.36 (1H, m), 2.90 - 2.94 (1H, m), 3.16 (1H, d), 3.58 (2H, d), 3.72 - 3.75 (1H, m), 3.85 (1H, d), 4.32 (1H, s), 7.03 (1H, d), 7.51 (2H, d), 7.63 (2H, d), 7.92 (1H, d)	416
219	3,4-di-F	δ 1.07 (3H, d), 1.33 - 1.35 (3H, m), 2.35 - 2.38 (1H, m), 2.87 - 2.91 (1H, m), 3.13 - 3.16 (1H, m), 3.50 (1H, d), 3.53 - 3.57 (1H, m), 3.62 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.02 - 7.15 (3H, m), 7.21 - 7.30 (1H, m), 7.91 (1H, d)	427
220	3,5-di-F	δ 1.07 - 1.09 (3H, m), 1.36 (3H, d), 2.36 - 2.40 (1H, m), 2.89 - 2.93 (1H, m), 3.14 - 3.17 (1H, m), 3.51 - 3.59 (2H, m), 3.66 (1H, d), 3.85 (1H, d), 4.32 (1H, d), 6.68 - 6.74 (1H, m), 6.91 - 6.95 (2H, m), 7.04 (1H, d), 7.92 (1H, d)	427
221	4-F	δ 1.07 (3H, d), 1.32 (3H, d), 2.35 - 2.39 (1H, m), 2.86 - 2.90 (1H, m), 3.13 - 3.16 (1H, m), 3.50 - 3.56 (2H, m), 3.63 (1H, d), 3.83 (1H, d), 4.30 (1H, t), 7.00 - 7.05 (3H, m), 7.32 - 7.35 (2H, m), 7.89 - 7.91 (1H, m)	409
222	3-CN, 4-F	δ 1.09 (3H, d), 1.34 (3H, d), 2.31 - 2.35 (1H, m), 2.89 - 2.93 (1H, m), 3.12 - 3.16 (1H, m), 3.52 - 3.58 (2H,	434

		m), 3.65 - 3.69 (1H, m), 3.84 - 3.87 (1H, m), 4.33 (1H, s), 7.04 (1H, d), 7.20 (1H, t), 7.60 - 7.67 (2H, m), 7.92 (1H, d)	

Example 223

Preparation of 6-[(2S,5R)-2,5-dimethyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of pyridine-3-carboxaldehyde and 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2S,5R)-2,5-dimethyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 84% yield.

1H NMR (399.9 MHz, CDCl3) δ 1.09 - 1.11 (3H, m), 1.33 (3H, d), 2.36 - 2.40 (1H, m), 2.88 - 2.95 (1H, m), 3.15 - 3.18 (1H, m), 3.53 - 3.59 (2H, m), 3.69 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.03 (1H, d), 7.28 - 7.30 (1H, m), 7.71 - 7.74 (1H, m), 7.91 (1H, d), 8.52 - 8.54 (1H, m), 8.60 (1H, d); m/z = 392 [M+H]+.

The 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of (2R,5S)-tert-butyl 2,5-dimethyl-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.45 g, 20 mmol), (2R,5S)-tert-butyl 2,5-dimethylpiperazine-1-carboxylate (5.14, 24 mmol) and DIPEA (5.14 mL, 30.00 mmol) in DMF (40.0 mL) was heated at 125°C for 2.5 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and washed sequentially with 1M aqueous K_2CO_3, water and saturated brine. The organic layer was dried over MgSO4, filtered and evaporated. The crude product was purified by MPLC silica chromatography, eluting with EtOAc. Product fractions were evaporated and triturated with ether. The solid was collected by filtration, washed with ether and dried under vacuum to afford (2R,5S)-tert-butyl 2,5-dimethyl-4-[3-(trifluoromethyl)-

[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (6.09 g, 76%) as a white crystalline solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.14 - 1.21 (6H, m), 1.44 (9H, s), 3.36 - 3.42 (2H, m), 3.71 (1H, d), 3.88 (1H, d), 4.25 - 4.35 (1H, m), 4.47 (1H, s), 7.59 (1H, d), 8.28 (1H, d); m/z = 401 [M+H]+.

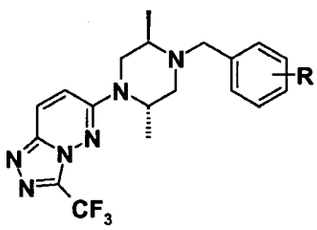
Preparation of 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

(2R,5S)-tert-Butyl 2,5-dimethyl-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (6.01 g, 15 mmol) was added in portions to stirred TFA (25 mL) over 5 minutes. There was a moderate exotherm and the reaction mixture was allowed to stir for a further 15 minutes. The bulk of the TFA was evaporated and the residue was basified with 1M aqueous K_2CO_3. It was extracted thoroughly with DCM (4 x 200 mL) and the combined organic phase was dried over MgSO4 and evaporated to give an oil which rapidly crystallised. The solid was collected by filtration and dried under vacuum to give 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3.52 g, 78%) as a white crystalline solid.

1H NMR (400.1 MHz, CDCl3) δ 1.23 - 1.25 (3H, m), 1.33 (3H, d), 2.71 - 2.75 (1H, m), 3.32 - 3.39 (2H, m), 3.47 (1H, d), 3.59 - 3.64 (1H, m), 4.15 - 4.19 (1H, m), 7.04 (1H, d), 7.92 (1H, d); m/z = 301 [M+H]+.

Examples 224-228

The following compounds were prepared in 63-84% yield by by General Synthetic Method 5, starting from 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

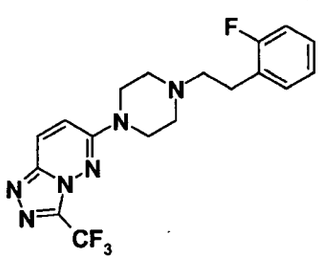


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
224	3,4-di-F	δ 1.07 (3H, d), 1.33 - 1.35 (3H, m), 2.35 - 2.38 (1H, m), 2.87 - 2.91 (1H, m), 3.13 - 3.16 (1H, m), 3.50	427

		(1H, d), 3.53 - 3.57 (1H, m), 3.62 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.02 - 7.15 (3H, m), 7.21 - 7.30 (1H, m), 7.91 (1H, d)	
225	3,5-di-F	δ 1.07 - 1.09 (3H, m), 1.36 (3H, d), 2.36 - 2.40 (1H, m), 2.89 - 2.93 (1H, m), 3.14 - 3.17 (1H, m), 3.51 - 3.59 (2H, m), 3.66 (1H, d), 3.85 (1H, d), 4.32 (1H, d), 6.68 - 6.74 (1H, m), 6.91 - 6.95 (2H, m), 7.04 (1H, d), 7.92 (1H, d)	426
226	4-F	δ 1.07 (3H, d), 1.32 (3H, d), 2.35 - 2.39 (1H, m), 2.86 - 2.90 (1H, m), 3.13 - 3.16 (1H, m), 3.50 - 3.56 (2H, m), 3.63 (1H, d), 3.83 (1H, d), 4.30 (1H, t), 7.00 - 7.05 (3H, m), 7.32 - 7.35 (2H, m), 7.89 - 7.91 (1H, m)	408
227	3-CN, 4-F	δ 1.09 (3H, d), 1.34 (3H, d), 2.31 - 2.35 (1H, m), 2.89 - 2.93 (1H, m), 3.12 - 3.16 (1H, m), 3.52 - 3.58 (2H, m), 3.65 - 3.69 (1H, m), 3.84 - 3.87 (1H, m), 4.33 (1H, s), 7.04 (1H, d), 7.20 (1H, t), 7.60 - 7.67 (2H, m), 7.92 (1H, d)	434
228	4-CN	δ 1.10 (3H, d), 1.35 (3H, d), 2.33 - 2.36 (1H, m), 2.90 - 2.94 (1H, m), 3.14 - 3.17 (1H, m), 3.54 - 3.62 (2H, m), 3.72 - 3.75 (1H, m), 3.85 (1H, s), 4.33 (1H, d), 7.04 (1H, d), 7.50 - 7.52 (2H, m), 7.63 - 7.65 (2H, m), 7.92 (1H, d).	416

Example 229

Preparation of 6-[4-[2-(2-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

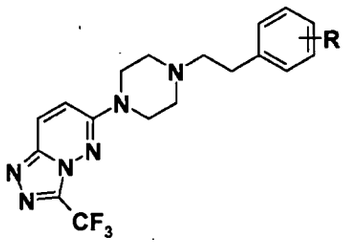


A stirred solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine dihydrochloride (0.173 g, 0.5 mmol), DIPEA (0.300 mL, 1.75 mmol) and 2-fluorophenethyl bromide (0.084 mL, 0.60 mmol) in DMF (2 mL) was heated at 100°C for 2.5 hours. The reaction was incomplete and further DIPEA (0.300 mL, 1.75 mmol) and 2-fluorophenethyl bromide (0.084 mL, 0.60 mmol) were added. The solution was stirred at 100°C for a further 90 minutes. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[2-(2-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (0.131 g, 66.4%) as a crisp foam.

1H NMR (399.9 MHz, DMSO-d6) δ 2.53 - 2.61 (6H, m), 2.81 - 2.85 (2H, m), 3.61 (4H, t), 7.12 - 7.17 (2H, m), 7.23 - 7.27 (1H, m), 7.34 - 7.39 (1H, m), 7.61 (1H, d), 8.25 (1H, d); m/z = 395 [M+H]+.

Examples 230-235

The following compounds were prepared in 24-64% yield by an analogous method to Example 229, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate phenethyl bromide:-

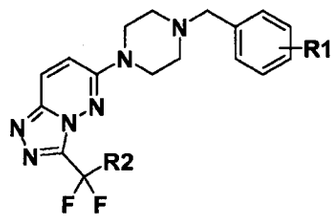


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
230	4-F	δ 2.63 - 2.67 (6H, m), 2.79 - 2.83 (2H, m), 3.65 (4H, t), 6.96 - 7.01 (2H, m), 7.07 (1H, d), 7.15 - 7.19 (2H, m), 7.93 (1H, d)	395
231	4-Cl	δ 2.63 - 2.67 (6H, m), 2.79 - 2.82 (2H, m), 3.64 (4H, t), 7.06 (1H, d), 7.13 - 7.16 (2H, m), 7.25 - 7.28 (2H, m), 7.93 (1H, d)	411

232	2-Cl	δ 2.66 - 2.71 (6H, m), 2.95 - 2.99 (2H, m), 3.66 (4H, t), 7.07 (1H, d), 7.14 - 7.22 (2H, m), 7.25 (1H, d), 7.34 - 7.36 (1H, m), 7.93 (1H, d)	411
233	3-Cl	δ 2.64 - 2.68 (6H, m), 2.79 - 2.83 (2H, m), 3.65 (4H, t), 7.05 - 7.11 (2H, m), 7.18 - 7.25 (3H, m), 7.93 (1H, s)	411
234	3-F	δ 2.64 - 2.70 (6H, m), 2.82 - 2.86 (2H, m), 3.65 (4H, t), 6.88 - 6.95 (2H, m), 6.99 (1H, s), 7.07 (1H, d), 7.23 - 7.28 (1H, m), 7.93 (1H, d)	395
235	4-CN	δ 2.64 - 2.70 (6H, m), 2.87 - 2.91 (2H, m), 3.64 (4H, t), 7.06 (1H, d), 7.32 - 7.34 (2H, m), 7.58 - 7.61 (2H, m), 7.93 (1H, d)	402

Examples 236-247

The following compounds were prepared in 33-89% yield by an analogous method to Example 216, starting from the appropriate 3-substituted 6-chloro-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in the corresponding footnote) and the appropriate benzyl piperazine:-



Ex.	Note	R1	R2	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
236	[1]	4-F	H	δ 2.57 (4H, t), 3.54 (2H, s), 3.61 (4H, t), 6.99 - 7.05 (3H, m), 7.12 (1H, t), 7.25 - 7.33 (2H, m), 7.88 - 7.91 (1H, m)	363
237	[1]	4-CN	H	δ 2.59 (4H, t), 3.62 - 3.64 (6H, m), 7.02 (1H, d), 7.12 (1H, t), 7.49 (2H, d), 7.62 - 7.65 (2H, m), 7.91 (1H, d)	370
238	[1]	3-CN	H	δ 2.59 (4H, t), 3.60 (2H, s), 3.63 (4H, t), 7.03 (1H, d), 7.12 (1H, t), 7.45 (1H, t), 7.57 - 7.60 (2H, m), 7.69 (1H, t), 7.91 (1H, d)	370

239	[1]	3-F	H	δ 2.59 (4H, t), 3.57 (2H, s), 3.63 (4H, t), 6.95 - 6.99 (1H, m), 7.02 (1H, d), 7.08 - 7.12 (2H, m), 7.12 (1H, t), 7.25 - 7.32 (1H, m), 7.90 (1H, d)	363
240	[2]	4-F	Me	δ 2.30 (3H, t), 2.57 (4H, t), 3.53 (2H, s), 3.60 (4H, t), 6.98 - 7.01 (1H, m), 7.00 - 7.05 (2H, m), 7.29 - 7.32 (2H, m), 7.88 (1H, d)	377
241	[2]	4-CN	Me	δ 2.30 (3H, t), 2.59 (4H, t), 3.61 - 3.63 (6H, m), 7.00 (1H, d), 7.48 (2H, d), 7.62 - 7.65 (2H, m), 7.90 (1H, d)	384
242	[2]	3-CN	Me	δ 2.30 (3H, t), 2.59 (4H, t), 3.60 (2H, s), 3.63 (4H, t), 7.00 (1H, d), 7.45 (1H, t), 7.56 - 7.60 (2H, m), 7.69 - 7.69 (1H, m), 7.90 (1H, d)	384
243	[2]	3-F	Me	δ 2.30 (3H, t), 2.59 (4H, t), 3.56 (2H, s), 3.62 (4H, t), 6.94 - 6.99 (1H, m), 7.00 (1H, d), 7.08 - 7.11 (2H, m), 7.26 - 7.32 (1H, m), 7.89 (1H, d)	377
244	[3]	4-F	Et	δ 1.18 (3H, t), 2.56 - 2.70 (6H, m), 3.53 (2H, s), 3.60 (4H, t), 6.98 - 7.01 (1H, m), 6.99 - 7.05 (2H, m), 7.28 - 7.32 (2H, m), 7.87 - 7.89 (1H, m)	391
245	[3]	4-CN	Et	δ 1.18 (3H, t), 2.60 (4H, q), 2.56 - 2.70 (2H, m), 3.57 - 3.62 (4H, m), 3.60 - 3.63 (2H, m), 7.00 (1H, d), 7.48 (2H, d), 7.62 - 7.65 (2H, m), 7.90 (1H, d)	398
246	[3]	3-CN	Et	δ 1.18 (3H, t), 2.59 - 2.61 (2H, m), 2.56 - 2.70 (4H, m), 3.60 (2H, s), 3.62 (4H, t), 7.00 (1H, d), 7.45 (1H, t), 7.57 - 7.60 (2H, m), 7.68 - 7.69 (1H, m), 7.90 (1H, d)	398
247	[3]	3-F	Et	δ 1.18 (3H, t), 2.56 - 2.70 (6H, m), 3.56 (2H, s), 3.61 (4H, t), 6.94 - 7.00 (1H, m), 7.00 (1H,	391

				d), 7.08 - 7.11 (2H, m), 7.27 - 7.32 (1H, m), 7.89 (1H, d)	

[1] Starting from 6-chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine, obtained as described in General Synthetic Method 1, preparation of starting materials.

[2] Starting from 6-chloro-3-(1,1-difluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine, obtained in 66% yield by an analogous method to General Synthetic Method 1, preparation of starting materials, starting from 3-chloropyridazin-6-yl hydrazine and 2,2-difluoropropanoic acid.

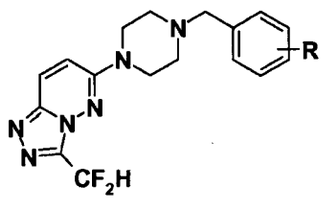
1H NMR (399.9 MHz, CDCl3) δ 2.37 (3H, t), 7.25 (1H, d), 8.15 (1H, d); m/z = 219 [M+H]+.

[3] Starting from 6-chloro-3-(1,1-difluoropropyl)-[1,2,4]-triazolo[4,3-b]pyridazine, obtained in 52% yield by an analogous method to General Synthetic Method 1, preparation of starting materials, starting from 3-chloropyridazin-6-yl hydrazine and 2,2-difluorobutanoic acid.

1H NMR (399.9 MHz, CDCl3) δ 1.23 (3H, t), 2.60 - 2.74 (2H, m), 7.24 (1H, d), 8.15 (1H, d); m/z = 274 [M+H]+.

Examples 248-263

The following compounds were prepared in 35-83% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
248	3-Cl	δ 2.60 (4H, d), 3.55 (2H, s), 3.63 (4H, t), 7.02 (1H, d), 6.99 - 7.25 (1H, m), 7.22 - 7.31 (3H, m), 7.37 (1H, s), 7.90 (1H, d)	379
249	2,4-di-F	δ 2.63 (4H, s), 3.62 (3H, s), 3.63 (3H, s), 6.79 - 6.84 (1H, m), 6.85 - 6.90 (1H, m), 7.02 (1H,	381

		d), 7.12 (1H, t), 7.38 (1H, q), 7.90 (1H, d)	
250	3,4-di-F	δ 2.59 (4H, s), 3.53 (2H, s), 3.63 (4H, t), 7.02 (1H, d), 7.06 - 7.13 (2H, m), 6.99 - 7.25 (1H, m), 7.15 - 7.24 (1H, m), 7.90 (1H, d)	381
251	3,5-di-F	δ 2.60 (4H, s), 3.55 (2H, s), 3.64 (4H, s), 6.70 - 6.75 (1H, m), 6.90 - 6.92 (2H, m), 7.03 (1H, d), 7.12 (1H, t), 7.91 (1H, d)	381
252	2,6-di-F	δ 2.66 (4H, s), 3.62 (4H, t), 3.79 (2H, s), 6.89 - 6.94 (2H, m), 6.99 (1H, t), 6.98 - 7.24 (1H, m), 7.23 - 7.31 (1H, m), 7.88 (1H, s)	381
253	2-F, 4-OMe	δ 2.61 - 2.62 (4H, m), 3.60 - 3.63 (6H, m), 3.80 (3H, s), 6.60 - 6.64 (1H, m), 6.68 - 6.70 (1H, m), 7.01 (1H, d), 6.99 - 7.25 (1H, m), 7.24 - 7.28 (1H, m), 7.89 (1H, d)	393
254	3-Br	δ 2.59 (4H, s), 3.55 (2H, s), 3.63 (4H, s), 7.02 (1H, d), 7.12 (1H, t), 7.19 - 7.23 (1H, m), 7.28 - 7.31 (1H, m), 7.42 (1H, d), 7.52 - 7.53 (1H, m), 7.90 (1H, d)	423
255	3-CF3	δ 2.61 (4H, s), 3.63 (6H, s), 7.02 (1H, d), 7.12 (1H, t), 7.46 (1H, t), 7.55 (2H, d), 7.63 (1H, s), 7.89 - 7.92 (1H, m)	413
256	2,3-di-F	δ 2.64 (4H, t), 3.63 (4H, t), 3.68 (2H, s), 7.02 (1H, d), 7.06 - 7.16 (3H, m), 7.12 (1H, t), 7.90 (1H, d)	381
257	3-OMe, 4-F	δ 2.58 (4H, t), 3.51 (2H, d), 3.62 (4H, t), 3.91 (3H, s), 6.82 - 6.86 (1H, m), 6.99 - 7.05 (3H, m), 7.12 (1H, t), 7.89 - 7.91 (1H, m)	393
258	2-F, 5-OMe	δ 2.64 (4H, t), 3.63 (4H, s), 3.64 (2H, s), 3.80 (3H, s), 6.75 - 6.79 (1H, m), 6.93 - 6.96 (1H, m), 6.97 - 6.99 (1H, m), 7.02 (1H, d), 6.99 - 7.25 (1H, m), 7.89 (1H, d)	393

259	2,5-di-F	δ 2.65 (4H, s), 3.63 (6H, s), 6.92 - 6.99 (1H, m), 7.01 - 7.04 (2H, m), 7.25 (1H, t), 7.12 - 7.18 (1H, m), 7.90 (1H, s)	381
260	3-CN, 4-F	δ 2.59 (4H, t), 3.56 (2H, s), 3.63 (4H, t), 7.03 (1H, d), 7.12 (1H, t), 7.20 (1H, t), 7.58 - 7.62 (1H, m), 7.64 - 7.66 (1H, m), 7.91 (1H, d)	388
261	3-F, 4-OMe	δ 2.57 (4H, t), 3.50 (2H, s), 3.62 (4H, t), 3.89 (3H, s), 6.92 (1H, t), 7.02 (2H, d), 7.10 - 7.13 (1H, m), 7.12 (1H, t), 7.89 (1H, d)	393
262	2-F, 4-CN	δ 2.64 (4H, t), 3.63 (4H, t), 3.69 (2H, s), 7.02 (1H, d), 7.12 (1H, t), 7.35 - 7.38 (1H, m), 7.46 - 7.48 (1H, m), 7.61 (1H, t), 7.91 (1H, d)	388
263	2,6-di-F, 4-CN	δ 2.65 (4H, t), 3.60 - 3.62 (4H, m), 3.78 (2H, t), 7.00 (1H, t), 7.12 (1H, t), 7.24 - 7.25 (2H, m), 7.89 (1H, d)	406

The 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of tert-butyl 4-[3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate

A stirred solution of 6-chloro-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3.07 g, 15 mmol), tert-butyl piperazine-1-carboxylate (3.35 g, 18.00 mmol) and DIPEA (3.85 mL, 22.50 mmol) in DMF (25 mL) was heated at 100°C for 1 hour. The reaction mixture was evaporated to dryness, redissolved in DCM and washed sequentially with 1M aqueous K_2CO_3, water and saturated brine. The organic layer was dried over MgSO4, filtered and evaporated. The crude product was triturated with ether and the solid was collected by filtration, washed with ether and dried under vacuum to afford tert-butyl 4-[3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (5.05 g, 95%) as a white crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 3.60 (8H, s), 7.04 (1H, d), 7.13 (1H, t), 7.94 (1H, d) ; m/z = 355 [M+H]+.

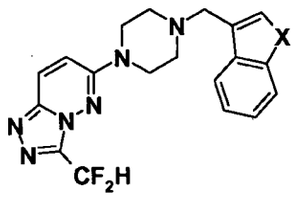
Preparation of 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine

4M Hydrogen chloride in dioxan (10.58 mL, 42.33 mmol) was added to a stirred partial solution of tert-butyl 4-[3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (5.0 g, 14.11 mmol) in 1,4-dioxan (14.11 mL) at ambient temperature and the mixture was stirred for 1 hour. During this time it gave a clear solution that precipitated a gum, which crystallised on further stirring. The precipitate was collected by filtration, washed with ether and dried giving the dihydrochloride salt. This was disolved in MeOH and adsorbed onto a SCX cartridge, then eluted with 2M ammonia in methanol. The product crystallised on evaporation and was triturated with ether. The solid was collected by filtration, washed with ether and dried under vacuum to afford 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (3.28 g, 91%) as a white crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 3.01 - 3.03 (4H, m), 3.59 (4H, t), 7.02 - 7.05 (1H, m), 7.13 (1H, t), 7.90 (1H, d) ; m/z = 255 [M+H]+.

Examples 264-265

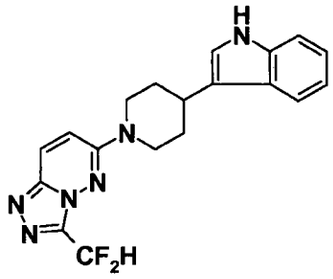
The following compounds were both prepared in 78% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and the appropriate aldehyde:-



Ex.	X	11H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
264	S	δ 2.65 (4H, t), 3.62 (4H, t), 3.83 (2H, s), 7.00 - 7.03 (1H, m), 7.25 (1H, t), 7.32 (1H, d), 7.35 - 7.41 (2H, m), 7.85 - 7.91 (2H, m), 7.98 - 8.02 (1H, m)	401
265	NH	δ 2.64 (4H, t), 3.61 (4H, t), 3.79 (2H, d), 7.00 (1H, d), 6.98 - 7.25 (1H, m), 7.12 - 7.16 (2H, m), 7.20 - 7.24 (1H, m), 7.37 - 7.40 (1H, m), 7.75 - 7.78 (1H, m), 7.87 (1H, d), 8.13 (1H, s)	384

Example 266

Preparation of 3-(difluoromethyl)-6-[4-(1H-indol-3-yl)piperidin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

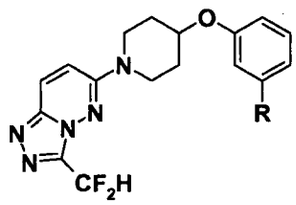


A mixture of 3-(piperidin-4-yl)-1H-indole and 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 216 to give 3-(difluoromethyl)-6-[4-(1H-indol-3-yl)piperidin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 85% yield.

1H NMR (399.9 MHz, CDCl3) δ 1.81 - 1.92 (2H, m), 2.23 - 2.26 (2H, m), 3.17 (1H, t), 3.18 - 3.25 (2H, m), 4.36 (2H, s), 6.99 - 6.99 (1H, m), 7.09 - 7.15 (2H, m), 7.15 (1H, t), 7.19 - 7.23 (1H, m), 7.38 - 7.40 (1H, m), 7.65 (1H, s), 7.90 (1H, s), 8.04 (1H, s); m/z = 369 [M+H]+.

Examples 267-268

The following compounds were prepared in 83-89% yield by an analogous method to Example 216, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryloxy piperidine:-

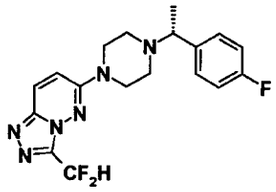


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
267	OMe	δ 1.94 - 2.10 (4H, m), 3.62 - 3.68 (2H, m), 3.80 (3H, s), 3.82 - 3.86 (2H, m), 4.58 - 4.62 (1H, m), 6.49 - 6.56 (3H, m), 7.07 (1H, d), 7.00 - 7.26 (1H, m), 7.20 (1H, t), 7.91 (1H, d)	376
268	F	δ 1.94 - 2.11 (4H, m), 3.63 - 3.69 (2H, m), 3.79 - 3.85 (2H,	364

		m), 4.58 - 4.62 (1H, m), 6.63 - 6.73 (3H, m), 7.08 (1H, d), 7.13 (1H, t), 7.24 (1H, q), 7.91 (1H, d)	

Example 269

Preparation of 3-(difluoromethyl)-6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

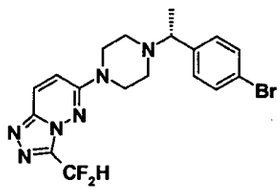


A stirred solution of 6-chloro-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (103 mg, 0.5 mmol), (R)-1-[1-(4-fluorophenyl)ethyl]piperazine (125 mg, 0. 6mmol) (prepared as described in J. Med. Chem. 2007, 50, 3528) and DIPEA (97 mg, 0.75 mmol, 129 µl) in DMF (2 mL) was heated at 100°C for 2 hours. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 3-(difluoromethyl)-6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine (158 mg, 84%) as a crisp foam.

1H NMR (399.9 MHz, CDCl3) δ 1.38 (3H, d), 2.48 - 2.54 (2H, m), 2.59 - 2.64 (2H, m), 3.43 (1H, q), 3.54 - 3.62 (4H, m), 6.99 - 7.05 (3H, m), 7.12 (1H, t), 7.28 - 7.31 (2H, m), 7.88 (1H, d) ; m/z = 377 [M+H]+.

Example 270

Preparation of 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine



A mixture of (R)-1-[1-(4-bromophenyl)ethyl]piperazine and 6-chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example

269 to give 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine in 75% yield.

1H NMR (399.9 MHz, CDCl3) δ 1.37 (3H, d), 2.49 - 2.54 (2H, m), 2.60 - 2.65 (2H, m), 3.41 (1H, q), 3.53 - 3.62 (4H, m), 6.99 (1H, d), 7.12 (1H, t), 7.20 - 7.24 (2H, m), 7.44 - 7.48 (2H, m), 7.88 (1H, d) ; m/z = 437 [M+H]+.

The (R)-1-[1-(4-bromphenyl)ethyl]piperazine used as starting material was prepared as follows:-

Preparation of (R)-1-[1-(4-bromophenyl)ethyl]-4-tosylpiperazine

N,N-Bis(2-chloroethyl)-4-methylbenzenesulfonamide (4.0 g, 13.50 mmol) and (R)-1-(4-bromophenyl)ethanamine (2.57 g, 12.83 mmol) in DIPEA (5 mL) were stirred and heated at 125°C for 32 hours. The resulting dark mixture was cooled to 80°C then a mixture of EtOH / water (70/30, 20 mL) added slowly to give a brown precipitate. The precipitate was collected by filtration, washed with EtOH / water (70/30) and iso-hexane and air dried to afford (R)-1-[1-(4-bromophenyl)ethyl]-4-tosylpiperazine (4.45 g, 78%) as a brown solid, which was used without further purification.

1H NMR (399.9 MHz, CDCl3) δ 1.27 (3H, d), 2.40 - 2.45 (5H, m), 2.52 - 2.57 (2H, m), 2.97 (4H, m), 3.32 (1H, q), 7.10 (2H, d), 7.32 (2H, d), 7.40 (2H, d), 7.62 (2H, d); m/z = 423/425 [M+H]+.

Preparation of (R)-1-[1-(4-bromophenyl)ethyl]piperazine

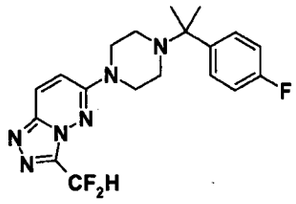
(R)-1-(1-(4-Bromophenyl)ethyl)-4-tosylpiperazine (4.44 g, 10.49 mmol) and 4-hydroxybenzoic acid (4.35 g, 31.46 mmol) in hydrobromic acid (33% in AcOH, 40 mL,) were stirred at room temperature for 48 hours. Water (40 mL) was then added to the dark mixture and stirring continued for a further 2 hours to give a beige solid, which was filtered off and washed with water (10 mL). The combined filtrate and washings were washed with toluene (3 x 50 mL) then cooled to 5°C and basified to pH >10 with 40% NaOH. The resulting mixture was extracted with tert butyl methyl ether (2 x 50 mL) and the combined extracts washed with saturated brine, dried over $MgSO_4$ and evaporated to give (R)-1-[1-(4-bromophenyl)ethyl]piperazine (2.69 g, 95%) as an orange, viscous oil.

1H NMR (399.9 MHz, CDCl3) δ 1.31 (3H, d), 2.29 - 2.35 (2H, m), 2.37 - 2.48 (2H, m), 2.85 (4H, t), 3.30 (1H, q), 7.19 (2H, d), 7.42 (2H, d); m/z = 269/271 [M+H]+.

Example 271

Preparation of 3-(difluoromethyl)-6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-

1-yl][1,2,4]triazolo[4,3-b]pyridazine

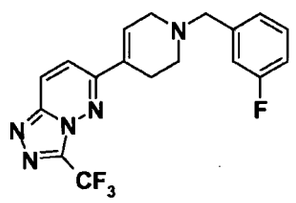


A mixture of 1-[1-(4-fluorophenyl)-1-methyl-ethyl]piperazine (obtained as described in J. Med. Chem. 2007, 50, 3528) and 6-chloro-3-(difluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 269 to give 3-(difluoromethyl)-6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 62% yield.

1H NMR (399.9 MHz, CDCl3) δ 1.37 (6H, s), 2.61 (4H, t), 3.56 (4H, t), 6.98 - 7.02 (3H, m), 6.98 - 7.24 (1H, m), 7.49 - 7.53 (2H, m), 7.86 - 7.89 (1H, m); m/z = 391 [M+H]+.

Example 272

Preparation of 6-[1-(3-fluorobenzyl)-1,2,3,6-tetrahydropyridin-4-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of 3-fluorobenzaldehyde and 6-(3,6-dihydro-2H-pyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[1-(3-fluorobenzyl)-1,2,3,6-tetrahydropyridin-4-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 46% yield.

1H NMR (399.9 MHz, CDCl3) δ 2.76 (4H, s), 3.29 (2H, d), 3.67 (2H, s), 6.72 (1H, t), 6.95 - 7.00 (1H, m), 7.10 - 7.15 (2H, m), 7.27 - 7.33 (1H, m), 7.54 (1H, d), 8.11 (1H, d); m/z = 376 [M-H]-.

The 6-(3,6-dihydro-2H-pyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of tert-butyl 4-(6-chloropyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate

Saturated aqueous $NaHCO_3$ solution (10 mL) was added to a stirred solution of 3,6-dichloropyridazine (0.968 g, 6.5 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.010 g, 6.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.376 g, 0.33 mmol) in DME (20 mL). The vessel was flushed with nitrogen and the initial suspension was heated at 80°C for 9 hours. The reaction mixture was diluted with DCM and washed with water. The organic phase was dried over MgSO4 and evaporated. The crude product was purified by MPLC silica chromatography, elution gradient 35 to 45% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford tert-butyl 4-(6-chloropyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.929 g, 48.3%) as a colourless crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 1.50 (9H, s), 2.77 - 2.78 (2H, m), 3.67 (2H, t), 4.18 (2H, q), 6.62 (1H, s), 7.45 (1H, d), 7.55 (1H, d); m/z = 240 [M+H-butylene]+.

Preparation of tert-butyl 4-(6-hydrazinylpyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate

A stirred mixture of tert-butyl 4-(6-chloropyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (870 mg, 2.94 mmol) and hydrazine hydrate (4.29 mL, 88.25 mmol) in acetonitrile (15 mL) was heated at 80°C for 4 hours. The mixture was partially evaporated (removing MeCN) and diluted with water (10 mL). The reaction mixture was extracted with DCM (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford crude product as a gum, which crystallised on trituration with ether. The precipitate was collected by filtration, washed with ether and dried under vacuum to afford tert-butyl 4-(6-hydrazinylpyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (503 mg, 58.7%) as a cream crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 2.76 - 2.79 (2H, m), 3.65 (2H, t), 4.00 (2H, s), 4.13 (2H, q), 6.07 (1H, s), 6.33 - 6.35 (1H, m), 6.95 (1H, d), 7.43 (1H, d); m/z = 292 [M+H]+.

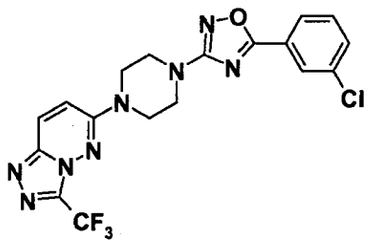
Preparation of 6-(1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

TFA (2 mL) was added in one portion to tert-butyl 4-(6-hydrazinylpyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (480 mg, 1.65 mmol) which dissolved with a vigorous effervescence. The solution was stirred for 24 hours at 70°C. The solution was evaporated and the residue was dissolved in methanol. It was run on an SCX cartridge,

eluting with 2M ammonia in methanol. Product containing fractions were evaporated to dryness and triturated with ether to afford 6-(1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (90 mg, 20.29%) as a cream solid. 1H NMR (399.9 MHz, DMSO-d6) δ 2.79 (2H, s), 3.37 (2H, t), 3.91 (2H, s), 6.99 (1H, s), 7.96 (1H, d), 8.49 (1H, d), NH not observed; m/z = 270 [M+H]+.

Example 273

Preparation of 6-[4-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



3-Chlorobenzoyl chloride (92 mg, 0.53 mmol) was added to a stirred partial solution of N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide (165 mg, 0.5 mmol) and DIPEA (97 mg, 0.75 mmol) in THF (3 mL). The reaction mixture became a clear solution over 30 minutes and LCMS after 1 hour showed complete initial acylation. The reaction mixture was heated at 150°C for 15 minutes by microwave after which LCMS showed complete cyclisation to the desired product. The reaction mixture was evaporated and the residue was boiled briefly with ethanol, cooled and filtered off to give 6-[4-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (104 mg, 46%) as a crystalline powder.

1H NMR (399.9 MHz, DMSO-d6) δ 3.60 - 3.63 (4H, m), 3.78 - 3.81 (4H, m), 7.65 - 7.69 (2H, m), 7.77 - 7.80 (1H, m), 8.01 - 8.06 (2H, m), 8.32 (1H, d); m/z = 451 [M+H]+.

The N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide used as starting material was prepared in as follows:-

Preparation of 4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carbonitrile

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3.48 g, 15.65 mmol), piperazine-1-carbonitrile (2 g, 17.99 mmol) and DIPEA (3.54 mL, 20.34 mmol) in DMF (20 mL) was heated at 70°C for 1 hour. The solution was evaporated

and partitioned between DCM and 1M aqueous K_2CO_3. The organic phase was washed with brine, dried over MgSO4, evaporated and triturated with ether. The precipitate was collected by filtration, washed with ether and dried under vacuum to afford 4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carbonitrile (4.29 g, 92%) as a cream crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 3.41 - 3.43 (4H, m), 3.75 (4H, t), 7.05 (1H, d), 8.02 (1H, d); m/z = 298 [M+H]+.

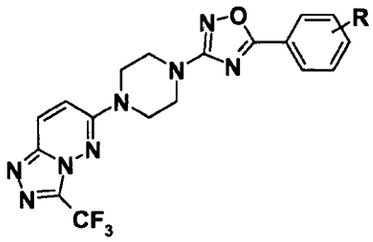
Preparation of N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide

Hydroxylamine (50% w/v aqueous solution) (0.667 mL, 10.09 mmol) was added to a stirred suspension of 4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carbonitrile (2.5 g, 8.41 mmol) in ethanol (16.82 mL) and the suspension was stirred at ambient temperature. Over 20 minutes the starting material largely dissolved and the product began to crystallise. The mixture was stirred for 2 hours and the precipitate was collected by filtration, washed with EtOH followed by ether and dried under vacuum to afford N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide (2.410 g, 87%) as a colourless crystalline solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.15 (3H, t), 3.44 - 3.47 (1H, m), 3.58 - 3.63 (4H, m), 5.24 - 5.26 (1H, m), 6.09 & 8.37 (1H, 2S), 7.63 (1H, d), 8.26 - 8.29 (1H, m), 8.38 (1H, s), one exchangeable not observed); m/z = 331 [M+H]+.

Examples 274-277

The following compounds were prepared in 43-55% yield by an analogous method to Example 273, starting from N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide and the appropriate benzoyl chloride:-

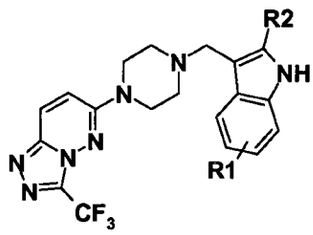


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
274	4-F	δ 3.59 - 3.62 (4H, m), 3.78 - 3.81 (4H, m), 7.45 - 7.50	433

		(2H, m), 7.66 (1H, d), 8.11 - 8.15 (2H, m), 8.32 (1H, d)	[M-H]-
275	H	3.60 - 3.63 (4H, m), 3.78 - 3.81 (4H, m), 7.61 - 7.73 (4H, m), 8.05 - 8.08 (2H, m), 8.31 - 8.34 (1H, m)	417
276	3-F	δ 3.60 - 3.63 (4H, m), 3.79 - 3.81 (4H, m), 7.58 (1H, d), 7.65 - 7.70 (2H, m), 7.82 - 7.85 (1H, m), 7.91 - 7.93 (1H, m), 8.33 (1H, s)	435
277	4-CN	δ 3.61 - 3.64 (4H, m), 3.79 - 3.81 (4H, m), 7.67 (1H, d), 8.09 - 8.12 (2H, m), 8.21 - 8.24 (2H, m), 8.33 (1H, d)	442

Examples 278-284

The following compounds were prepared in 9-71% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate indole-3-carboxaldehyde:-



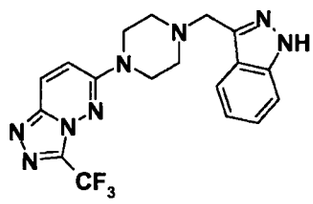
Ex.	R1	R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
278	5-CN	H	δ 2.55 (4H, t), 3.61 (4H, t), 3.75 (2H, s), 7.42 - 7.45 (1H, m), 7.50 (1H, s), 7.53 - 7.55 (1H, m), 7.57 (1H, d), 8.20 - 8.20 (1H, m), 8.23 (1H, d), 11.55 (1H, s)	427
279	H	Me	[1] δ 2.44 (3H, s), 2.62 (4H, t), 3.60 (4H, t), 3.71 (2H, s), 7.04 (1H, d), 7.08 - 7.16 (2H, m), 7.28 - 7.31 (1H, m), 7.65 (1H, d), 7.89 (2H, m)	416
280	5-Cl	H	δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.07 - 7.10 (1H, m), 7.35 - 7.40 (2H, m), 7.57 (1H, d), 7.69 (1H, d), 8.23 (1H, d), 11.16 (1H, s)	436
281	5-Br	H	δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.68 (2H, s), 7.18 - 7.21 (1H, m), 7.34 - 7.36 (2H, m), 7.58 (1H, d), 7.83 (1H, d), 8.23 (1H, d), 11.17 (1H, s)	480
282	4-Cl	H	δ 2.56 - 2.61 (4H, m), 3.60 (4H, s), 3.86 (2H, s),	436

			7.00 - 7.07 (2H, m), 7.34 - 7.37 (2H, m), 7.59 (1H, d), 8.24 (1H, d), 11.33 (1H, s)	
283	5-F	H	δ 2.54 - 2.57 (4H, m), 3.60 (4H, t), 3.68 (2H, s), 6.90 - 6.95 (1H, m), 7.34 - 7.41 (3H, m), 7.57 (1H, d), 8.23 (1H, d), 11.05 (1H, s)	420
284	6-F	H	δ 2.54 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 6.83 - 6.89 (1H, m), 7.12 - 7.15 (1H, m), 7.27 (1H, d), 7.57 (1H, d), 7.64 - 7.68 (1H, m), 8.23 (1H, d), 11.01 (1H, s)	420

[1] Spectrum recorded in CDCl3

Example 285

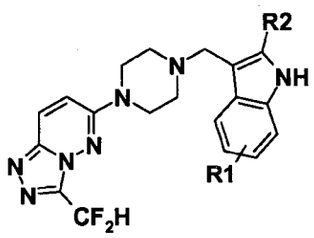
Preparation of 6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



1H-Indazole-3-carboxaldehyde (75 mg, 0.51 mmol) and (polystyrylmethyl)trimethylammonium cyanoborohydride (125 mg, 0.51 mmol) were added to a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (100 mg, 0.37 mmol) in DCM (2 mL) / acetic acid (0.2 mL). The mixture was stirred at ambient temperature for 18 hours. The resin was filtered off and the filtrate was evaporated. The crude product was purified by preparative HPLC (Waters XTerra C18 column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (89 mg, 60%) as a white solid.
1H NMR (399.9 MHz, DMSO-d6) δ 2.60 (4H, t), 3.61 (4H, t), 3.92 (2H, s), 7.09 - 7.13 (1H, m), 7.33 - 7.36 (1H, m), 7.50 (1H, d), 7.57 (1H, d), 7.90 (1H, d), 8.23 (1H, d), 12.85 (1H, s); m/z = 403 [M+H]+.

Examples 286-292

The following compounds were prepared in 57-74% yield by by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate indole-3-carboxaldehyde:-

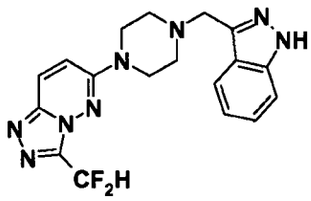


Ex.	R1	R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
286	5-CN	H	δ 2.53 - 2.56 (4H, m), 3.61 (4H, t), 3.75 (2H, s), 7.43 - 7.45 (1H, m), 7.49 - 7.65 (4H, m), 8.15 - 8.21 (2H, m), 11.55 (1H, s)	409
287	5-Cl	H	δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.07 - 7.10 (1H, m), 7.37 (2H, t), 7.49 - 7.51 (1H, m), 7.52 (1H, t), 7.70 (1H, d), 8.15 - 8.18 (1H, m), 11.17 (1H, s).	418
288	5-Br	H	δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.18 - 7.21 (1H, m), 7.34 (2H, s), 7.52 (1H, t), 7.52 (1H, d), 7.84 (1H, d), 8.15 - 8.18 (1H, m), 11.17 (1H, s).	462
289	4-Cl	H	δ 2.61 (4H, t), 3.60 (4H, t), 3.86 (2H, s), 7.00 - 7.08 (2H, m), 7.34 - 7.37 (2H, m), 7.50 - 7.53 (1H, m), 7.53 (1H, t), 8.17 (1H, d), 11.17 (1H, s).	418
290	5-F	H	δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 6.92 (1H, d), 7.34 - 7.42 (3H, m), 7.50 (1H, d), 7.52 (1H, t), 8.15 - 8.18 (1H, m), 11.05 (1H, s)	402
291	H	Cl	δ 2.56 (4H, t), 3.60 (4H, t), 3.69 (2H, s), 7.07 (1H, s), 7.13 - 7.14 (1H, m), 7.29 - 7.31 (1H, m), 7.48 - 7.51 (1H, m), 7.52 (1H, t), 7.66 (1H, s), 8.15 -	418

			8.17 (1H, m), 11.79 (1H, s)	
292	6-F	H	δ 2.52 (4H, t), 3.59 (4H, s), 3.69 (2H, s), 6.83 - 6.89 (1H, m), 7.12 - 7.15 (1H, m), 7.27 (1H, s), 7.50 (1H, d), 7.39 - 7.64 (1H, m), 7.66 - 7.68 (1H, m), 8.17 (1H, d), 11.01 (1H, s)	402

Example 293

Preparation of 3-(difluoromethyl)-6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

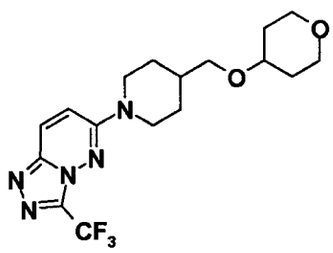


A mixture of indazole-3-carboxaldehyde and 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 3-(difluoromethyl)-6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 65% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 2.57 - 2.61 (4H, m), 3.61 (4H, t), 3.92 (2H, s), 7.11 (1H, t), 7.33 - 7.37 (1H, m), 7.48 - 7.52 (2H, m), 7.52 (1H, t), 7.91 (1H, s), 8.17 (1H, d), 12.85 (1H, s); m/z = 385 [M+H]+.

Example 294

Preparation of 6-[4-[(tetrahydro-2H-pyran-4-yloxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Sodium hydride (60% dispersion in oil, 42 mg, 1.05 mmol) was added to stirred tetrahydro-4H-pyran-4-ol (1 g). 6-[4-(Methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (133 mg, 0.35 mmol) was added and the mixture was stirred at 80°C for 3 hours. The reaction mixture was diluted with MeOH and

run down a 20 g SCX cartridge, eluting with 2M ammonia in methanol. The solution was evaporated and the crude product was purified by preparative HPLC (Waters XTerra C18 column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 66-[4-[(tetrahydro-2H-pyran-4-yloxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (43 mg, 32%) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 1.25 - 1.33 (2H, m), 1.46 - 1.55 (2H, m), 1.78 - 1.87 (5H, m), 2.93 - 3.00 (2H, m), 3.27 - 3.28 (2H, m), 3.34 - 3.42 (3H, m), 3.83 - 3.88 (2H, m), 4.16 - 4.20 (2H, m), 7.01 (1H, d), 7.83 (1H, d); m/z = 386 [M+H]+.

The 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (5.56 g, 25 mmol), piperidin-4-ylmethanol (3.17 g, 27.50 mmol) and DIPEA (5.66 mL, 32.50 mmol) in DMF (50 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between DCM and 1M aqueous K_2CO_3. The organic phase was washed with brine, dried over MgSO4, evaporated and triturated with ether. The precipitate was collected by filtration, washed with ether and dried under vacuum to afford [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (6.68 g, 89%) as a cream crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 1.31 - 1.41 (2H, m), 1.80 - 1.93 (3H, m), 3.00 - 3.07 (2H, m), 3.57 (2H, t), 4.25 - 4.29 (2H, m), 7.09 (1H, d), 7.90 (1H, d), OH not observed; m/z = 302 [M+H]+.

Preparation of 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

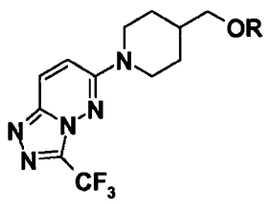
Methanesulfonyl chloride (2.83 mL, 36.51 mmol) in DCM (30 mL) was added dropwise to a stirred partial solution of [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (10 g, 33.19 mmol) and triethylamine (5.09 mL, 36.51 mmol) in DCM (140 mL). The reaction was stirred for 20 minutes, quenched with water (100 mL) and extracted with DCM (2 x 75 mL). The organic layer was dried over

MgSO4, filtered and evaporated to afford a yellow solid. The crude solid was triturated with ether to give a solid which was collected by filtration and dried under vacuum to give 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (7.60 g, 60.4%) as a white solid.

1H NMR (400.1 MHz, DMSO) δ 1.32 (2H, ddd), 1.82 (2H, d), 2.09 - 2.02 (1H, m), 3.05 (2H, t), 3.18 (3H, s), 4.11 (2H, d), 4.30 (2H, d), 7.61 (1H, d), 8.22 (1H, d); m/z = 380 [M+H]+.

Examples 295-298

The following compounds were prepared in 17-71% yield by an analogous method to Example 294, starting from 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate alcohol:-

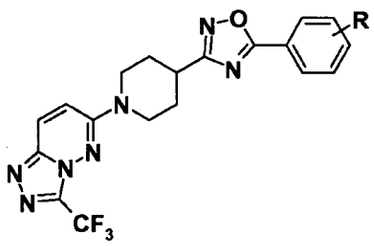


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
295	cyclopropylmethyl	δ 0.12 - 0.15 (2H, m), 0.45 - 0.49 (2H, m), 0.95 - 1.01 (1H, m), 1.22 - 1.32 (2H, m), 1.84 - 1.90 (3H, m), 2.92 - 2.99 (2H, m), 3.20 - 3.21 (2H, m), 3.26 (2H, d), 4.15 - 4.20 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	356
296	2-methoxyethyl	δ 1.21 - 1.31 (2H, m), 1.83 - 1.93 (3H, m), 2.91 - 2.98 (2H, m), 3.28 - 3.30 (2H, m), 3.32 (3H, s), 3.46 - 3.49 (2H, m), 3.49 - 3.54 (2H, m), 4.14 - 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	360
297	2-morpholinoethyl	δ 1.21 - 1.31 (2H, m), 1.80 - 1.89 (3H, m), 2.49 - 2.56 (6H, m), 2.91 - 2.98 (2H, m), 3.25 - 3.27 (2H, m), 3.54 (2H, s), 3.69 (4H, s), 4.15 - 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	415

298	2-propyl	δ 1.08 (6H, d), 1.20 - 1.30 (2H, m), 1.78 - 1.86 (3H, m), 2.92 - 2.99 (2H, m), 3.22 (2H, d), 3.44 - 3.50 (1H, m), 4.15 - 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	344

Examples 299-303

The following compounds were prepared in 1-84% yield by an analogous method to Example 273, starting from N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide and the appropriate benzoyl chloride.



Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
299	3-Cl	δ 2.01 - 2.10 (2H, m), 2.23 - 2.27 (2H, m), 3.20 - 3.27 (1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.29 (2H, m), 7.13 (1H, d), 7.47 (1H, t), 7.56 - 7.59 (1H, m), 7.95 (1H, d), 7.99 - 8.02 (1H, m), 8.12 (1H, t)	450
300	4-F	δ 2.00 - 2.10 (2H, m), 2.22 - 2.27 (2H, m), 3.18 - 3.26 (1H, m), 3.28 - 3.35 (2H, m), 4.23 - 4.29 (2H, m), 7.13 (1H, d), 7.19 - 7.25 (2H, m), 7.95 (1H, d), 8.11 - 8.16 (2H, m)	434
301	H	δ 2.00 - 2.12 (2H, m), 2.23 - 2.28 (2H, m), 3.20 - 3.27 (1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.29 (2H, m), 7.13 (1H, d), 7.51 - 7.55 (2H, m), 7.58 - 7.62 (1H, m), 7.95 (1H, d), 8.11 - 8.14 (2H, m)	416
302	3-F	δ 2.01 - 2.11 (2H, m), 2.23 - 2.28 (2H, m), 3.20 - 3.27 (1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.29 (2H, m), 7.13 (1H, d), 7.28 - 7.33 (1H, m), 7.49 - 7.54 (1H, m), 7.80 - 7.84 (1H, m), 7.91 - 7.96 (2H, m)	434
303	3-CN	δ 2.00 - 2.10 (2H, m), 2.24 - 2.29 (2H, m), 3.21 - 3.28	441

		(1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.30 (2H, m), 7.13 (1H, d), 7.67 - 7.71 (1H, m), 7.87 - 7.89 (1H, m), 7.96 (1H, d), 8.34 - 8.36 (1H, m), 8.42 - 8.43 (1H, m)	

The N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide used as starting material was prepared as follows:-

Preparation of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carbonitrile

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (5.56 g, 25 mmol), piperidine-4-carbonitrile (3.03 g, 27.50 mmol) and DIPEA (5.66 mL, 32.50 mmol) in DMF (50 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between DCM and 1M aqueous K_2CO_3. The organic phase was washed with brine, dried over MgSO4, evaporated and the residue was triturated with ether. The solid was collected by filtration, washed with ether and dried under vacuum to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carbonitrile (6.86 g, 93%) as a cream crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 1.97 - 2.12 (4H, m), 2.95 - 3.01 (1H, m), 3.62 - 3.68 (2H, m), 3.80 - 3.86 (2H, m), 7.08 (1H, d), 7.97 (1H, d); m/z = 297 [M+H]+.

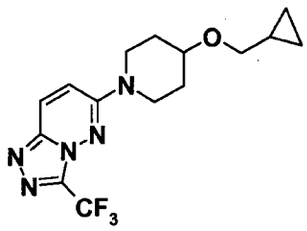
Preparation of N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide

Hydroxylamine (50% w/v aqueous solution) (0.669 mL, 10.13 mmol) was added to a stirred suspension of 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidine-4-carbonitrile (2.5 g, 8.44 mmol) in ethanol (16.88 mL) and the suspension was stirred at ambient temperature. Additional hydroxylamine (50% w/v aqueous solution) (3 mL) was added and stirring was continued for 18 hours. The mixture was then heated for 1 hour. The precipitate was collected by filtration, washed with EtOH and ether and dried under vacuum to afford N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide (2.380 g, 86%) as a colourless crystalline solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.61 - 1.71 (2H, m), 1.81 - 1.86 (2H, m), 2.32 - 2.38 (1H, m), 3.01 - 3.08 (2H, m), 4.29 (2H, d), 5.32 - 5.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d), 8.81 (1H, s); m/z = 330 [M+H]+.

Example 304

Preparation of 6-[4-(cyclopropylmethoxy)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

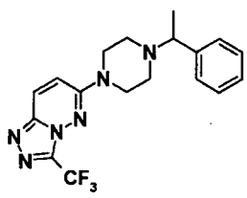


A mixture of 4-(cyclopropylmethoxy)piperidine and 6-(piperazin-1-yl)-3-(trifluoromethyl)- [1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 216 to give 6-[4-(cyclopropylmethoxy)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 69% yield.

1H NMR (399.9 MHz, CDCl3) δ 0.20 - 0.24 (2H, m), 0.54 - 0.59 (2H, m), 1.02 - 1.12 (1H, m), 1.70 - 1.79 (2H, m), 1.94 - 2.00 (2H, m), 3.34 (2H, d), 3.40 - 3.44 (2H, m), 3.61 - 3.66 (1H, m), 3.87 - 3.93 (2H, m), 7.10 (1H, d), 7.91 (1H, d); m/z = 342 [M+H]+.

Example 305

Preparation of 6-[4-(1-phenylethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

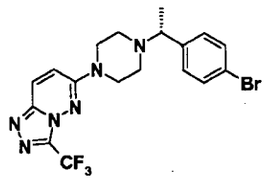


6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (400 mg, 1.80 mmol), 1-(1-phenylethyl)piperazine (342 mg, 1.80 mmol) and DIPEA (0.34 mL, 1.98 mmol) in DMF (4 mL) were stirred and heated at 80°C for 30 minutes. The mixture was cooled to ambient temperature then applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol. Fractions containing pure product were evaporated to give a solid which was recrystallised from MTBE / isohexane to give 6-[4-(1-phenylethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (516 mg, 76%).

1H NMR (399.9 MHz, CDCl3) δ 1.41 (3H, d), 2.50 - 2.56 (2H, m), 2.60 - 2.66 (2H, m), 3.44 (1H, q), 3.55 - 3.64 (4H, m), 7.03 (1H, d), 7.24 - 7.35 (5H, m), 7.89 (1H, d); m/z = 377 [M+H]+.

Example 306

Preparation of 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

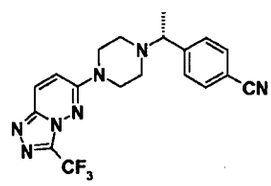


6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (251 mg, 1.13 mmol), (R)-1-[1-(4-bromophenyl)ethyl]piperazine (obtained as described in Example 270, preparation of starting materials, 304 mg, 1.13 mmol) and DIPEA (0.20 mL, 1.13 mmol) in DMF (3 mL) were stirred and heated at 80°C for 1 hour. The resulting solution was cooled to ambient temperature then quenched with water (10 mL) to give a pale brown precipitate. The precipitate was collected by filtration, washed sequentially with water, acetonitrile and ether and dried under vacuum to afford 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (437 mg, 85%) as a pale brown solid.

1H NMR (399.9 MHz, CDCl3) δ 1.37 (3H, d), 2.48 - 2.54 (2H, m), 2.59 - 2.65 (2H, m), 3.40 (1H, q), 3.54 - 3.64 (4H, m), 7.03 (1H, d), 7.21 (2H, d), 7.46 (2H, d), 7.90 (1H, d); m/z = 455/457 [M+H]+.

Example 307

Preparation of 4-[(1R)-1-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethyl]benzonitrile



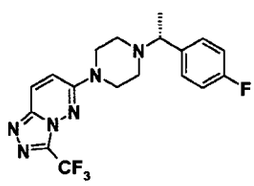
6-[4-[(1R)-1-(4-Bromophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 306) (250 mg, 0.55 mmol), zinc cyanide (38.7 mg, 0.33 mmol), tris(dibenzylideneacetone)dipalladium(0) (5.0 mg, 5.49 μmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (6.3 mg, 10.98 μmol) and N,N,N',N'-tetramethylethylenediamine (0.017 mL, 0.11 mmol) were suspended in DMF (2.5 mL) and sealed into a microwave tube. The reaction was heated to 160°C for 5 minutes in a

microwave reactor and cooled to ambient temperature. The resulting mixture was applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol. Fractions containing product were combined and evaporated then purified by preparative HPLC (Waters XTerra C18 column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-[(1R)-1-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethyl]benzonitrile (168 mg, 76%) as a colourless solid.

1H NMR (399.9 MHz, CDCl3) δ 1.39 (3H, d), 2.48 - 2.53 (2H, m), 2.63 - 2.68 (2H, m), 3.49 (1H, q), 3.55 - 3.65 (4H, m), 7.04 (1H, d), 7.48 (2H, d), 7.64 (2H, d), 7.92 (1H, d); m/z = 402 [M+H]+.

Example 308

Preparation of 6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

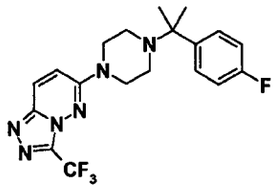


A mixture of (R)-1-[1-(4-fluorophenyl)ethyl]piperazine (obtained as described in J. Med. Chem. 2007, 50, 3528) and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method described in Example 306 to give 6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 87% yield.

1H NMR (399.9 MHz, CDCl3) δ 1.38 (3H, d), 2.49 - 2.54 (2H, m), 2.59 - 2.65 (2H, m), 3.43 (1H, q), 3.54 - 3.64 (4H, m), 6.99 - 7.04 (3H, m), 7.29 (2H, dd), 7.90 (1H, d); m/z = 395 [M+H]+.

Example 309

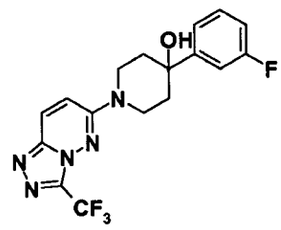
Preparation of 6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (120 mg, 0.54 mmol), DIPEA (0.094 mL, 0.54 mmol) and 1-[2-(4-fluorophenyl)propan-2-yl]piperazine (obtained as described in J. Med. Chem. 2007, 50, 3528) (120 mg, 0.54 mmol) in DMF (1.5 mL) were stirred and heated at 80°C for 1 hour. The resulting solution was cooled to room temperature then applied to an SCX column and eluted with MeOH followed by 2M ammonia in methanol. Fractions containing product were combined and evaporated, then purified by preparative HPLC (Waters XTerra C18 column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (155 mg, 70%) as a colourless solid. 1H NMR (399.9 MHz, CDCl3) δ 1.37 (6H, s), 2.62 (4H, t), 3.57 (4H, t), 6.99 (2H, d), 7.04 (1H, d), 7.51 (2H, dd), 7.90 (1H, d); m/z = 409 [M+H]+.

Example 310

Preparation of 4-(3-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



3-Fluorophenylmagnesium bromide (1.0M in THF, 1.68 mL, 1.68 mmol) was added dropwise to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one (400 mg, 1.40 mmol) in THF (10 mL) cooled to 0°C over a period of 10 minutes. The resulting mixture was stirred at 0°C for 20 minutes, then quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate. The extract was washed with saturated brine, dried over $MgSO_4$ and evaporated to a pale orange oil which was triturated with DCM to give a beige solid. The solid was filtered, washed with DCM

and dried, then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-(3-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (96 mg, 18%) as a colourless solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.71 - 1.74 (2H, m), 2.00 - 2.08 (2H, m), 3.40 - 3.46 (2H, m), 4.20 - 4.24 (2H, m), 5.37 (1H, s), 7.02 - 7.08 (1H, m), 7.31 - 7.40 (3H, m), 7.66 (1H, d), 8.24 (1H, d).; m/z = 382 [M+H]+.

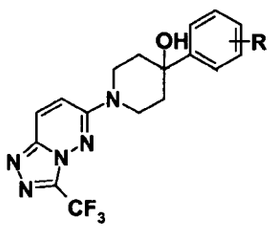
The 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one used as starting material was prepared as follows:-

6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (10.0 g, 44.93 mmol), 4-piperidone monohydrate hydrochloride (8.48 g, 49.43 mmol) and DIPEA (16.3 mL, 98.85 mmol) in DMF (100 mL) were stirred and heated at 90°C for 1 hour. The DMF was then evaporated *in vacuo* and the residue purified by flash silica chromatography, eluting with 2% MeOH in DCM. Pure fractions were concentrated to give a pale yellow precipitate. The precipitate was collected by filtration, washed with ether and air dried to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one (10.61 g, 83%) as a pale yellow solid.

1H NMR (399.9 MHz, CDCl3) δ 2.65 (4H, t), 3.98 (4H, t), 7.15 (1H, d), 8.02 (1H, d); m/z = 286 [M+H]+.

Examples 311-314

The following compounds were prepared in 27-37% yield by an analogous method to Example 310, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one and the appropriate aryl magnesium bromide:-

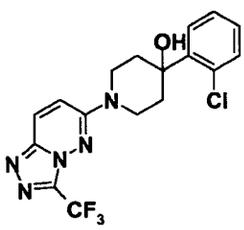


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
311	4-OMe	δ 1.71 - 1.74 (2H, m), 1.95 - 2.03 (2H, m), 3.40 - 3.46	394

		(2H, m), 3.74 (3H, s), 4.17 - 4.20 (2H, m), 5.12 (1H, s), 6.88 (2H, d), 7.41 (2H, d), 7.65 (1H, d), 8.23 (1H, d).	
312	3-OMe	δ 1.71 - 1.74 (2H, m), 1.99 - 2.06 (2H, m), 3.40 - 3.46 (2H, m), 3.76 (3H, s), 4.19 - 4.22 (2H, m), 5.22 (1H, s), 6.80 (1H, dd), 7.05 - 7.09 (2H, m), 7.24 (1H, t), 7.66 (1H, d), 8.24 (1H, d).	394
313	3-Cl	δ 1.70 - 1.73 (2H, m), 2.00 - 2.08 (2H, m), 3.40 - 3.46 (2H, m), 4.21 - 4.24 (2H, m), 5.39 (1H, s), 7.29 (1H, d), 7.36 (1H, t), 7.46 (1H, d), 7.57 (1H, m), 7.66 (1H, d), 8.24 (1H, d).	398
314	2-OMe	δ 1.55 - 1.58 (2H, m), 2.52 - 2.58 (2H, m), 3.40 - 3.48 (2H, m), 3.63 (3H, s), 4.14 - 4.17 (2H, m), 5.10 (1H, s), 6.94 - 6.98 (2H, m), 7.21 - 7.25 (1H, m), 7.61 (1H, m), 7.67 (1H, d), 8.25 (1H, d).	394

Example 315

Preparation of 4-(2-chlorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



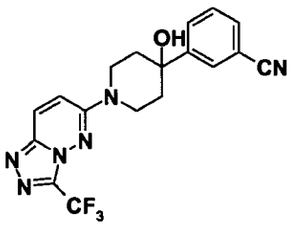
Isopropylmagnesium chloride-lithium chloride complex (1.0M in THF, 10 mL, 10.00 mmol) was added dropwise to 1-bromo-2-chlorobenzene (1.91 g, 9.98 mmol) in THF (2.0 mL) cooled to 0°C over a period of 10 minutes. The resulting solution was stirred at 0°C for 1 hour then a 2.0 mL aliquot was added dropwise to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one (400 mg, 1.40 mmol) in THF (10 mL) cooled to 0°C over a period of 10 minutes. The resulting solution was stirred at 0°C for 10 minutes then allowed to warm slowly to room temperature and stirred for a further hour. The reaction mixture was then quenched with saturated ammonium chloride (30 mL) and

extracted with EtOAc. The extract was washed with saturated brine, dried over $MgSO_4$ and concentrated by evaporation, then purified by flash silica chromatography, eluting with EtOAc. Pure fractions were evaporated to dryness to afford 4-(2-chlorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (230 mg, 41%) as a colourless solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.68 - 1.71 (2H, m), 2.61 - 2.69 (2H, m), 3.44 - 3.51 (2H, m), 4.20 - 4.24 (2H, m), 5.47 (1H, s), 7.26 - 7.30 (1H, m), 7.36 - 7.40 (2H, m), 7.69 (1H, d), 7.84 - 7.86 (1H, m), 8.26 (1H, d); m/z = 398 [M+H]+.

Example 316

Preparation of 3-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile

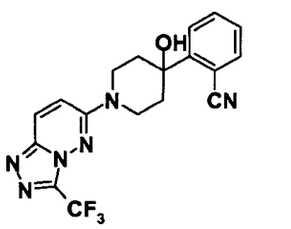


A mixture of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one and 3-bromobenzonitrile was allowed to react by the method of Example 315 to give 3-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile in 26% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.70 - 1.73 (2H, m), 2.04 - 2.11 (2H, m), 3.41 - 3.47 (2H, m), 4.22 - 4.25 (2H, m), 5.49 (1H, s), 7.55 (1H, t), 7.67 (1H, d), 7.71 (1H, m), 7.87 (1H, m), 7.95 (1H, m), 8.25 (1H, d); m/z = 389 [M+H]+.

Example 317

Preparation of 2-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile

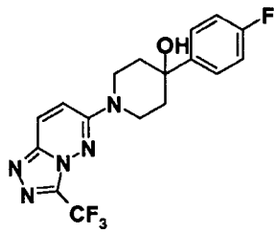


A mixture of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one and 2-bromobenzonitrile was allowed to react by the method of Example 315 to give 2-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile in 24% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.72 - 1.75 (2H, m), 2.23 - 2.30 (2H, m), 3.39 - 3.45 (2H, m), 4.39 - 4.43 (2H, m), 7.51 - 7.63 (4H, m), 7.72 (1H, d), 8.30 (1H, d), 8.04 (s) & 8.71 (s)(1H); m/z = 389 [M+H]+.

Example 318

Preparation of 4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol

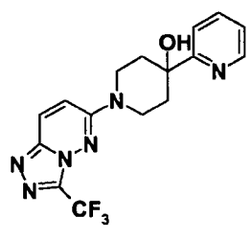


A mixture of 4-(4-fluorophenyl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 74% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.71 - 1.75 (2H, m), 1.98 - 2.06 (2H, m), 3.40 - 3.46 (2H, m), 4.19 - 4.22 (2H, m), 5.28 (1H, s), 7.14 (2H, t), 7.54 (2H, dd), 7.66 (1H, d), 8.24 (1H, d); m/z = 382 [M+H]+.

Example 319

Preparation of 4-pyridin-2-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



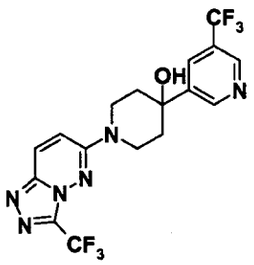
A mixture of 4-(pyridin-2-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to

give 4-pyridin-2-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 77% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.66 - 1.69 (2H, m), 2.18 - 2.25 (2H, m), 3.44 - 3.50 (2H, m), 4.20 - 4.23 (2H, m), 5.47 (1H, s), 7.24 - 7.27 (1H, m), 7.67 (1H, d), 7.72 (1H, d), 7.82 (1H, td), 8.25 (1H, d), 8.49 (1H, d); m/z = 365 [M+H]+.

Example 320

Preparation of 4-[5-(trifluoromethyl)pyridin-3-yl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



A mixture of 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-[5-(trifluoromethyl)pyridin-3-yl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 75% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.77 - 1.80 (2H, m), 2.12 - 2.20 (2H, m), 3.43 - 3.49 (2H, m), 4.25 - 4.28 (2H, m), 5.69 (1H, s), 7.68 (1H, d), 8.26 (2H, m), 8.87 (1H, d), 9.05 (1H, d); m/z = 433 [M+H]+.

The 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol used as starting material was prepared as follows:-

Preparation of benzyl 4-hydroxy-4-[5-(trifluoromethyl)pyridin-3-yl]piperidine-1-carboxylate

Isopropylmagnesium chloride-lithium chloride complex (1.0M in THF) (5.31 mL, 5.31 mmol) was added dropwise to 3-bromo-5-(trifluoromethyl)pyridine (1.20 g, 5.31 mmol) in THF (10 mL) cooled to 0 °C over a period of 10 minutes. The resulting solution was stirred at 0°C for 1 hour then benzyl 4-oxo-1-piperidinecarboxylate (1.24 g, 5.31 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm slowly to room temperature and stirred for a further 1 hour before quenching with aqueous ammonium chloride (25 mL). The mixture was then extracted with tert butyl methyl ether.

The extract was washed with water followed by saturated brine, dried over $MgSO_4$, concentrated by evaporation then purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl 4-hydroxy-4-[5-(trifluoromethyl)pyridin-3-yl]piperidine-1-carboxylate (1.32 g, 65%) as a pale yellow oil.

1H NMR (399.9 MHz, CDCl3) δ 1.76 - 1.79 (2H, m), 1.94 - 2.08 (2H, m), 3.26 - 3.37 (2H, m), 4.12 - 4.27 (2H, m), 5.16 (2H, s), 5.17 (1H, s), 7.32 - 7.38 (5H, m), 8.05 (1H, m), 8.79 (1H, d), 8.90 (1H, d); m/z = 381 [M+H]+.

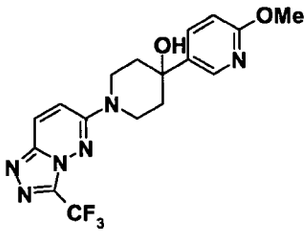
Preparation of 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol

Benzyl 4-hydroxy-4-[5-(trifluoromethyl)pyridin-3-yl]piperidine-1-carboxylate (1.30 g, 3.42 mmol), 5% palladium on activated carbon (50 mg) and ammonium formate (2.0 g) in ethanol (20 mL) were stirred and heated under reflux for 1 hour then cooled to ambient temperature and filtered through diatomaceous earth . The filtrate was applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol. Fractions containing product were combined and evaporated then purified by flash silica chromatography, elution gradient 10 to 20% 2M ammonia in methanol in DCM. Pure fractions were evaporated to dryness to afford 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol (0.417 g, 50%) as a pale yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.56 - 1.59 (2H, m), 1.86 - 1.93 (2H, m), 2.77 - 2.80 (2H, m), 2.92 - 2.98 (2H, m), 5.27 (1H, s), 8.17 (1H, s), 8.85 (1H, s), 8.98 (1H, s); m/z = 247 [M+H]+.

Example 321

Preparation of 4-(6-methoxypyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



A mixture of 4-(6-methoxypyridin-3-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to

give 4-(6-methoxypyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 58% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.75 - 1.78 (2H, m), 1.99 - 2.04 (2H, m), 3.41 - 3.47 (2H, m), 3.84 (3H, s), 4.18 - 4.21 (2H, m), 5.30 (1H, s), 6.77 (1H, d), 7.66 (1H, d), 7.81 (1H, d), 8.24 (1H, d), 8.28 (1H, s); m/z = 395 [M+H]+.

The 4-(6-methoxypyridin-3-yl)piperidin-4-ol used as starting material was prepared as follows:-

Preparation of benzyl 4-hydroxy-4-(6-methoxypyridin-3-yl)piperidine-1-carboxylate

n-Butyllithium (1.6M in hexanes, 6.65 mL, 10.64 mmol) was added dropwise to 5-bromo-2-methoxypyridine (2.0 g, 10.64 mmol) in ether (30 mL) cooled to -78 °C over a period of 15 minutes. The resulting solution was stirred at -78°C for 40 minutes then a solution of benzyl 4-oxo-1-piperidinecarboxylate (2.48 g, 10.64 mmol) in ether (10 mL) was added dropwise. The reaction was allowed to warm slowly to room temperature then quenched with ammonium chloride solution (50 mL) and extracted with EtOAc. The extract was washed sequentially with water and saturated brine, dried over $MgSO_4$ and concentrated by evaporation then purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl 4-hydroxy-4-(6-methoxypyridin-3-yl)piperidine-1-carboxylate (1.90 g, 52%) as a pale orange oil.

1H NMR (399.9 MHz, CDCl3) δ 1.75 - 1.79 (2H, m), 1.88 - 2.02 (2H, m), 3.29 - 3.35 (2H, m), 3.92 (3H, s), 4.03 - 4.16 (2H, m), 5.14 (2H, s), 6.72 (1H, d), 7.36 (5H, m), 7.66 (1H, dd), 8.24 (1H, d); m/z = 343 [M+H]+.

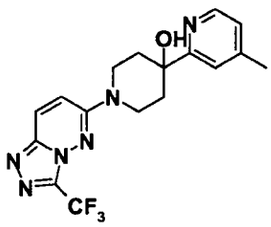
Preparation of 4-(6-methoxypyridin-3-yl)piperidin-4-ol

Obtained in 39% yield by an analogous method to Example 320, preparation of starting materials, starting from benzyl 4-hydroxy-4-(6-methoxypyridin-3-yl)piperidine-1-carboxylate.

1H NMR (399.9 MHz, DMSO-d6) δ 1.65 - 1.68 (2H, m), 1.92 - 1.99 (2H, m), 2.92 - 2.95 (2H, m), 3.01 - 3.07 (2H, m), 3.84 (3H, s), 5.13 (1H,br s), 6.79 (1H, d), 7.76 (1H, dd), 8.23 (1H, d); m/z = 209 [M+H]+.

Example 322

Preparation of 4-(4-methylpyridin-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



A mixture of 4-(4-methylpyridin-2-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(4-methylpyridin-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 81% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.64 - 1.67 (2H, m), 2.20 (2H, td), 2.35 (3H, s), 3.42 - 3.49 (2H, m), 4.19 - 4.22 (2H, m), 5.43 (1H, s), 7.09 (1H, d), 7.55 (1H, s), 7.66 (1H, d), 8.24 (1H, d), 8.34 (1H, d); m/z = 379 [M+H]+.

The 4-(4-methylpyridin-2-yl)piperidin-4-ol used as starting material was prepared as follows:-

Preparation of benzyl 4-hydroxy-4-(4-methylpyridin-2-yl)piperidine-1-carboxylate

Obtained in 56% yield by an analogous method to Example 321, preparation of starting materials, starting from benzyl 4-oxo-1-piperidinecarboxylate and 2-bromo-4-methylpyridine.

1H NMR (399.9 MHz, CDCl3) δ 1.58 - 1.61 (2H, m), 1.87 - 2.00 (2H, m), 3.21 (3H, s), 3.29 - 3.45 (2H, m), 4.09 - 4.29 (2H, m), 5.17 (2H, s), 5.32 (1H, s), 7.03 (1H, d), 7.10 (1H, s), 7.30 - 7.41 (5H, m), 8.37 (1H, d); m/z = 327 [M+H]+.

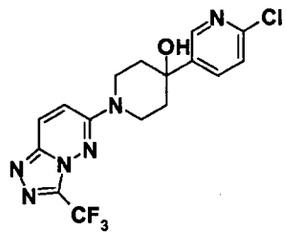
Preparation of 4-(4-methylpyridin-2-yl)piperidin-4-ol

Obtained in 56% yield by an analogous method to Example 321, preparation of starting materials, starting from benzyl 4-hydroxy-4-(4-methylpyridin-2-yl)piperidine-1-carboxylate.

1H NMR (399.9 MHz, DMSO-d6) δ 1.39 - 1.42 (2H, m), 2.01 (2H, td), 2.33 (3H, s), 2.73 - 2.76 (2H, m), 2.88 - 2.94 (2H, m), 4.96 (1H, s), 7.06 (1H, d), 7.47 (1H, s), 8.36 (1H, d); m/z = 193 [M+H]+.

Example 323

Preparation of 4-(6-chloropyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



A mixture of 4-(6-chloropyridin-3-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(6-chloropyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 80% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.74 - 1.78 (2H, m), 2.06 (2H, td), 3.44 (2H, t), 4.21 - 4.25 (2H, m), 5.54 (1H, s), 7.47 (1H, d), 7.67 (1H, d), 7.96 (1H, dd), 8.25 (1H, d), 8.55 (1H, d); m/z = 399 [M+H]+.

The 4-(6-chloropyridin-3-yl)piperidin-4-ol used as starting material was prepared as follows:-

Preparation of tert-butyl 4-hydroxy-4-(6-chloropyridin-3-yl)piperidine-1-carboxylate

n-Butyl lithium (1.6M in hexanes, 6.50 mL, 10.39 mmol) was added dropwise to 5-bromo-2-chloropyridine (2.0 g, 10.39 mmol) in ether (30 mL) cooled to -78 °C over a period of 15 minutes. The resulting solution was stirred at -78°C for 45 minutes then a solution of tert-butyl 4-oxo-1-piperidinecarboxylate (1.66 g, 8.31 mmol) in ether (10 mL) was added dropwise. The reaction was allowed to warm slowly to room temperature then quenched with ammonium chloride solution (50 mL) and extracted with EtOAc. The extract was washed sequentially with water and saturated brine, dried over $MgSO_4$ and concentrated by evaporation, then purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford tert-butyl 4-(6-chloropyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (1.33 g, 41%) as a cream solid.

1H NMR (399.9 MHz, CDCl3) δ 1.48 (9H, s), 1.72 - 1.76 (2H, m), 1.90 - 2.01 (2H, m), 3.16 - 3.27 (2H, m), 3.99 - 4.13 (2H, m), 7.31 (1H, d), 7.76 (1H, dd), 8.50 (1H, d); m/z = 313 [M+H]+.

Preparation of 4-(6-chloropyridin-3-yl)piperidin-4-ol

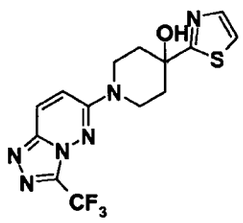
HCl (4M in dioxan, 4.22 mL, 16.88 mmol) was added in one portion to a stirred suspension of tert-butyl 4-(6-chloropyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (1.32

g, 4.22 mmol) in ethyl acetate (20 mL) at ambient temperature. The resulting mixture was stirred at 50°C for 90 minutes then cooled to room temperature, diluted with ether (20 mL) and filtered. The filtered solid was washed with ether and dried then taken up in methanol, applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol. Product-containing fractions were combined and evaporated then purified by flash silica chromatography, elution gradient 10 to 20% 2M ammonia in methanol in DCM. Pure fractions were evaporated to dryness to afford 4-(6-chloropyridin-3-yl)piperidin-4-ol (0.43 g, 48%) as a pale orange solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.53 - 1.56 (2H, m), 1.80 (2H, td), 2.72 - 2.75 (2H, m), 2.89 - 2.96 (2H, m), 5.09 (1H, s), 7.46 (1H, d), 7.90 (1H, dd), 8.49 (1H, d); m/z = 213 [M+H]+.

Example 324

Preparation of 4-(1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



A mixture of 4-(1,3-thiazol-2-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 65% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.86 - 1.89 (2H, m), 2.15 (2H, td), 3.44 - 3.51 (2H, m), 4.16 - 4.19 (2H, m), 6.28 (1H, s), 7.62 (1H, d), 7.66 (1H, d), 7.72 (1H, d), 8.26 (1H, d); m/z = 371 [M+H]+.

The 4-(1,3-thiazol-2-yl)piperidin-4-ol used as starting material was prepared as follows:-

Preparation of tert-butyl 4-hydroxy-4-(1,3-thiazol-2-yl)piperidine-1-carboxylate

Obtained in 80% yield by an analogous method to Example 323, preparation of starting materials, starting from tert-butyl 4-oxo-1-piperidinecarboxylate and 2-bromothiazole.

1H NMR (399.9 MHz, CDCl3) δ 1.47 (9H, s), 1.85 - 1.88 (2H, m), 2.11 (2H, td), 3.24 - 3.35 (2H, m), 3.92 - 4.08 (2H, m), 7.30 (1H, d), 7.71 (1H, d); m/z = 285 [M+H]+.

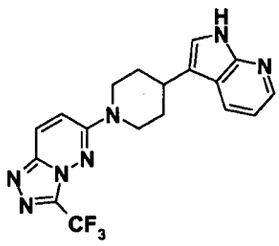
Preparation of 4-(1,3-thiazol-2-yl)piperidin-4-ol

Obtained in 82% yield by an analogous method to Example 323, preparation of starting materials, starting from tert-butyl 4-hydroxy-4-(2-thiazolyl)piperidine-1-carboxylate.

1H NMR (399.9 MHz, DMSO-d6) δ 1.77 - 1.80 (2H, m), 2.14 (2H, td), 3.02 - 3.04 (4H, m), 6.17 (1H, br s), 7.61 (1H, d), 7.74 (1H, d); m/z = 185 [M+H]+.

Example 325

Preparation of 6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (160 mg, 0.72 mmol), 3-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine (145 mg, 0.72 mmol) and DIPEA (0.14 mL, 0.79 mmol) in DMF (2.0 mL) were stirred and heated at 80°C for 1 hour. The resulting mixture was then cooled to ambient temperature and quenched in water (10 mL) to give a beige solid. The solid was collected by filtration, washed sequentially with water, acetonitrile and ether, and air dried to give 6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (217 mg, 78%) as a colourless solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.70 - 1.81 (2H, m), 2.09 - 2.12 (2H, m), 3.12 - 3.26 (3H, m), 4.40 - 4.43 (2H, m), 7.03 (1H, dd), 7.25 (1H, d), 7.67 (1H, d), 8.04 (1H, d), 8.19 (1H, dd), 8.24 (1H, d), 11.34 (1H, s); m/z = 388 [M+H]+.

The 4-(1H-pyrrolo[5,4-b]pyridin-3-yl)piperidine used as starting material was prepared as follows:-

Preparation of tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate

Potassium hydroxide (1.90 g, 33.86 mmol) was added to 1H-pyrrolo[2,3-b]pyridine (1.0 g, 8.46 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (3.37 g, 16.93 mmol) in methanol (25 mL) at ambient temperature, then the resulting solution was stirred at 65°C for 18 hours. The mixture was cooled to ambient temperature, quenched in dilute aqueous ammonium chloride (80 mL) and extracted with ethyl acetate. The extract was washed sequentially with water and saturated brine, dried over $MgSO_4$, concentrated by evaporation and purified by flash silica chromatography, using 5% MeOH in DCM eluent. Pure fractions were combined and concentrated by evaporation, then triturated with ether to give a colourless precipitate. The precipitate was collected by filtration, washed with ether and air dried to afford tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.37 g, 54%) as a colourless solid.

1H NMR (399.9 MHz, CDCl3) δ 1.51 (9H, s), 2.57 (2H, m), 3.68 (2H, m), 4.14 (2H, m), 6.15 (1H, m), 7.13 (1H, dd), 7.33 (1H, s), 8.20 (1H, d), 8.34 (1H, d), 10.29 (1H, s); m/z = 300 [M+H]+.

Preparation of tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate

tert-Butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.35 g, 4.51 mmol), ammonium formate (1.42 g, 22.55 mmol) and 5% palladium on activated carbon (50 mg) in ethanol (25 mL) were stirred and refluxed for 1 hour. The resulting mixture was cooled to room temperature and filtered through diatomaceous earth . The filtrate was concentrated by evaporation then treated with dilute aqueous ammonium chloride (50 mL) and extracted with DCM. The extract was washed with water, dried over MgSO4 and evaporated to a colourless solid. The solid was triturated with ether then collected by filtration and dried under vacuum to give tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate (1.088 g, 80%) as a colourless solid.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 1.64 - 1.74 (2H, m), 2.00 - 2.03 (2H, m), 2.86 - 3.00 (3H, m), 4.16 - 4.34 (2H, m), 7.06 - 7.10 (2H, m), 7.96 (1H, d), 8.31 (1H, s), 9.73 (1H, s); m/z = 302 [M+H]+.

Preparation of 4-(1H-pyrrolo[5,4-b]pyridin-3-yl)piperidine

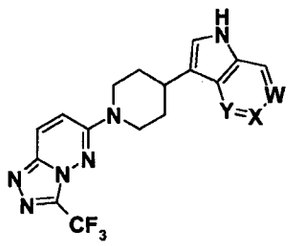
TFA (5.0 mL, 3.58 mmol) was added in one portion at ambient temperature to a stirred suspension of tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate (1.08 g, 3.58 mmol) in DCM (8 mL). The resulting solution was stirred for 30 minutes then

applied to an SCX column and eluted with MeOH followed by 2M ammonia in methanol. Pure fractions were combined and concentrated by evaporation, then triturated with ether to give a solid which was collected by filtration and air-dried to give 3-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine (0.64 g, 88%) as a colourless solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.54 - 1.63 (2H, m), 1.86 - 1.89 (2H, m), 2.62 - 2.68 (2H, m), 2.81 - 2.87 (1H, m), 3.02 - 3.05 (2H, m), 7.01 (1H, dd), 7.18 (1H, s), 7.98 (1H, d), 8.17 (1H, d), 11.28 (1H, s); m/z = 202 [M+H]+.

Examples 326-328

The following compounds were prepared in 40-60% yield by an analogous method to Example 325, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-(1H-pyrrolopyridin-3-yl)piperidine:-

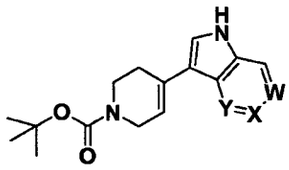


Ex.	W	X	Y	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
326	CH	N	CH	δ 1.72 - 1.82 (2H, m), 2.13 - 2.16 (2H, m), 3.18 - 3.27 (3H, m), 4.40 - 4.43 (2H, m), 7.22 (1H, dd), 7.32 (1H, d), 7.68 (1H, d), 8.14 (1H, d), 8.24 (1H, d), 8.93 (1H, s), 11.23 (1H, s).	388
327	N	CH	CH	δ 1.71 - 1.81 (2H, m), 2.09 - 2.12 (2H, m), 3.12 - 3.27 (3H, m), 4.40 - 4.43 (2H, m), 7.40 (1H, d), 7.60 (1H, d), 7.68 (1H, d), 8.07 (1H, d), 8.25 (1H, d), 8.70 (1H, d), 11.33 (1H, s).	388
328	CH	CH	N	δ 1.81 - 1.92 (2H, m), 2.17 - 2.20 (2H, m), 3.18 - 3.30 (3H, m), 4.40 (2H, d), 7.08 (1H, dd), 7.42 (1H, d), 7.67 (1H, d), 7.71 (1H, dd), 8.24 (1H, d), 8.29 (1H, dd), 11.02 (1H, s).	388

The isomeric 4-(1H-pyrrolopyridin-3-yl)piperidines used as starting materials in Examples 326-328 were prepared in 3 steps as follows:-

Preparation of tert-butyl 4-(1H-pyrrolopyridin-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylates

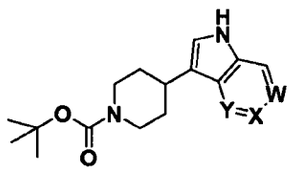
Obtained in 49-54% yield by an analogous procedure to Example 325, preparation of starting materials, starting from tert-butyl 4-oxopiperidine-1-carboxylate and the appropriate 1H-pyrrolopyridine.



Precursor to Ex.	W	X	Y	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
326	CH	N	CH	δ 1.51 (9H, s), 2.55 - 2.61 (2H, m), 3.69 (2H, t), 4.16 (2H, m), 6.23 (1H, m), 7.22 (1H, s), 7.31 (1H, d), 8.33 (1H, d), 9.20 (2H, m).	300
327	N	CH	CH	δ 1.51 (9H, s), 2.54 - 2.62 (2H, m), 3.68 - 3.71 (2H, m), 4.12 - 4.19 (2H, m), 6.16 (1H, m), 7.38 (1H, s), 7.77 (1H, d), 8.29 (1H, d), 8.83 (1H, s), 9.63 (1H, br s).	300
328	CH	CH	N	δ 1.49 (9H, s), 2.57 - 2.60 (2H, m), 3.68 - 3.71 (2H, m), 4.17 - 4.19 (2H, m), 7.13 (1H, dd), 7.20 (1H, m), 7.36 (1H, d), 7.65 (1H, dd), 8.36 (1H, s), 8.53 (1H, dd).	300

Preparation of tert-butyl 4-(1H-pyrrolopyridin-3-yl)piperidine-1-carboxylates

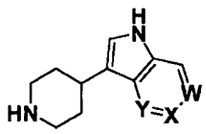
Obtained in 75-81% yield by an analogous procedure to Example 325, preparation of starting materials, starting from the appropriate tert-butyl 4-(1H-pyrrolopyridin-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylate.



Precursor to Ex.	W	X	Y	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
326	CH	N	CH	δ 1.49 (9H, s), 1.63 - 1.74 (2H, m), 2.04 - 2.07 (2H, m), 2.88 - 2.95 (2H, m), 3.00 - 3.08 (1H, m), 4.16 - 4.34 (2H, m), 7.03 (1H, s), 7.31 (1H, dd), 8.29 (1H, d), 8.96 (1H, d), 9.04 (1H, br s).	302
327	N	CH	CH	δ 1.49 (9H, s), 1.64 - 1.74 (2H, m), 1.98 - 2.02 (2H, m), 2.86 - 2.92 (2H, m), 2.97 - 3.05 (1H, m), 4.16 - 4.37 (2H, m), 6.25 (1H, br s), 7.58 (1H, s), 7.76 (1H, d), 8.11 (1H, d), 9.26 (1H, s).	302
328	CH	CH	N	δ 1.48 (9H, s), 1.60 - 1.70 (2H, m), 2.14 - 2.17 (2H, m), 2.90 - 2.96 (2H, m), 3.22 - 3.30 (1H, m), 4.21 (2H, m), 7.11 (1H, dd), 7.18 (1H, d), 7.64 (1H, dd), 8.31 (1H, s), 8.47 (1H, dd).	302

Preparation of 4-(1H-pyrrolopyridin-3-yl)piperidines

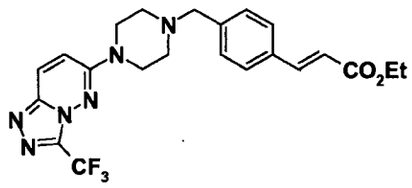
Obtained in 72-100% yield by an analogous procedure to Example 325, preparation of starting materials, starting from the appropriate tert-butyl 4-(1H-pyrrolopyridin-3-yl)piperidine-1-carboxylates.



Precursor to Ex.	W	X	Y	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
326	CH	N	CH	δ 1.60 - 1.70 (2H, m), 1.92 - 1.95 (2H, m), 2.69 - 2.75 (2H, m), 2.91 - 2.99 (1H, m), 3.07 - 3.10 (2H, m), 7.17 (1H, s), 7.32 (1H, d), 8.13 (1H, d), 8.89 (1H, s), 11.20 (1H, s).	202
327	N	CH	CH	δ 1.53 - 1.64 (2H, m), 1.85 - 1.88 (2H, m), 2.63 - 2.68 (2H, m), 2.82 - 2.88 (1H, m), 3.02 - 3.05 (2H, m), 7.33 (1H, s), 7.55 (1H, d), 8.05 (1H, d), 8.69 (1H, s), 11.27 (1H, s).	202
328	CH	CH	N	δ 1.59 - 1.69 (2H, m), 1.96 - 2.00 (2H, m), 2.63 - 2.70 (2H, m), 2.96 - 3.06 (3H, m), 7.06 (1H, dd), 7.35 (1H, d), 7.69 (1H, dd), 8.28 (1H, dd), 10.96 (1H, s).	202

Example 329

Preparation of ethyl (2E)-3-[4-([4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl)phenyl]prop-2-enoate

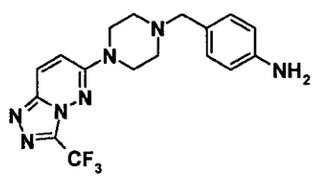


A mixture of ethyl (E)-3-(4-formylphenyl)prop-2-enoate and 6-(piperazin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 7 to give ethyl (2E)-3-[4-([4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl)phenyl]prop-2-enoate in 59% yield.

1H NMR (300.1 MHz, DMSO-d6) δ 1.27 (3H, t), 2.49 - 2.51 (4H, m), 3.58 (2H, s), 3.62 (4H, t), 4.20 (2H, q), 6.61 (1H, d), 7.39 (2H, d), 7.54 - 7.73 (4H, m), 8.24 (1H, d); m/z = 461 [M+H]+.

Example 330

Preparation of 4-[[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline

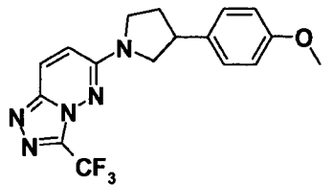


TFA (0.5 mL, 0.15 mmol) was added to tert-butyl N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]carbamate (obtained as described in Example 146, 72 mg, 0.15 mmol) in DCM (2 mL). The resulting solution was stirred at ambient temperature for 2 hours and then evaporated to dryness. The crude product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 0.1% TFA) and MeCN as eluents. Fractions containing the desired compound were evaporated and further purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford 4-[[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline (32 mg, 56%).

1H NMR (300.1 MHz, DMSO-d6) δ 2.29 (4H, t), 3.18 (2H, s), 3.42 (4H, t), 4.79 (2H, s), 6.36 (2H, d), 6.79 (2H, d), 7.41 (1H, d), 8.07 (1H, d); m/z = 378 [M+H]+.

Example 331

Preparation of 6-[3-(4-methoxyphenyl)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

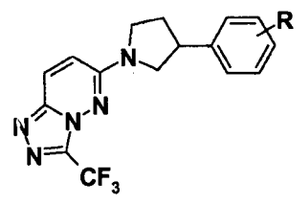


A solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (50 mg, 0.22 mmol) in ethanol (1 mL) was added to 3-(4-methoxyphenyl)pyrrolidine hydrochloride (71 mg, 0.33 mmol). The reaction mixture was treated with DIPEA (86 mg, 0.66 mmol) and the mixture was heated at 70°C for 16 hours. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give 6-[3-(4-methoxyphenyl)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (45 mg, 55%).

1H NMR (300.1 MHz, DMSO-d6) δ 2.00 - 2.18 (1H, m), 2.30 - 2.42 (1H, m), 3.33 - 3.66 (3H, m), 3.68 - 3.83 (4H, m), 3.89 - 4.06 (1H, m), 6.88 - 6.96 (2H, m), 7.24 - 7.34 (3H, m), 8.23 (1H, d); m/z = 364 [M+H]+.

Examples 332-334

The following compounds were prepared in 64-77% yield by an analogous method to Example 331, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aryl pyrrolidine hydrochloride:-

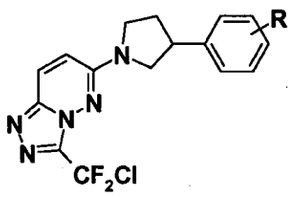


Ex.	R	1H NMR (300.1 MHz, DMSO-d6)	m/z [M+H]+
332	3-CN	6-cδ 2.08 - 2.25 (1H, m), 2.37 - 2.48 (1H, m), 3.41 - 3.71 (3H, m), 3.72 - 3.86 (1H, m), 3.98 - 4.11 (1H, m), 7.31 (1H, d), 7.58 (1H, t), 7.72 - 7.77 (2H, m),	359

		7.88 (1H, t), 8.26 (1H, d)	
333	2-CO2Me	6-cδ 2.14 - 2.30 (1H, m), 2.31 - 2.44 (1H, m), 3.41 - 3.68 (2H, m), 3.71 - 3.83 (1H, m), 3.86 (3H, s), 3.97 (1H, t), 4.10 - 4.23 (1H, m), 7.31 (1H, d), 7.36 - 7.43 (1H, m), 7.55 - 7.61 (2H, m), 7.77 (1H, d), 8.24 (1H, d)	392
334	3-CO2Me	6-cδ 2.15 - 2.33 (1H, m), 2.47 - 2.58 (1H, m), 3.47 - 3.81 (3H, m), 3.82 - 3.92 (1H, m), 3.94 (3H, s), 4.06 - 4.21 (1H, m), 7.41 (1H, d), 7.60 (1H, t), 7.73 - 7.79 (1H, m), 7.92 - 7.98 (1H, m), 8.03 (1H, t), 8.32 (1H, d)	392

Examples 335-338

The following compounds were prepared in 52-74% yield by an analogous method to Example 331, starting from 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aryl pyrrolidine hydrochloride:-



Ex.	R	1H NMR (300.1 MHz, CDCl3)	m/z [M+H]+
335	4-CF3	δ 2.17 - 2.32 (1H, m), 2.49 - 2.61 (1H, m), 3.54 - 3.75 (3H, m), 3.81 - 3.91 (1H, m), 4.03 - 4.11 (1H, m), 6.89 (1H, d), 7.42 (2H, d), 7.64 (2H, d), 7.95 (1H, d)	418
336	3-CF3	δ 2.18 - 2.34 (1H, m), 2.49 - 2.61 (1H, m), 3.52 - 3.75 (3H, m), 3.83 - 3.93 (1H, m), 4.04 - 4.13 (1H, m), 6.89 (1H, d), 7.47 - 7.53 (2H, m), 7.53 - 7.60 (2H, m), 7.95 (1H, d)	418
337	H (S-enantiomer)	δ 2.16 - 2.32 (1H, m), 2.45 - 2.56 (1H, m), 3.52 - 3.72 (3H, m), 3.80 - 3.91 (1H, m), 3.98 - 4.11 (1H, m), 6.89 (1H, d), 7.27 - 7.33 (3H,	350

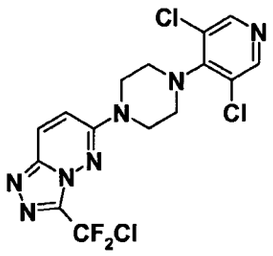
		m), 7.34 - 7.42 (2H, m), 7.93 (1H, d)	
338	H (R-enantiomer)	δ 2.16 - 2.31 (1H, m), 2.45 - 2.56 (1H, m), 3.51 - 3.72 (3H, m), 3.79 - 3.90 (1H, m), 3.98 - 4.10 (1H, m), 6.89 (1H, d), 7.27 - 7.33 (3H, m), 7.34 - 7.42 (2H, m), 7.92 (1H, d)	350

The 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was obtained in 70% yield by an analogous method to General Synthetic Method 1, preparation of starting materials, starting from 3-chloropyridazin-6-yl hydrazine and chlorodifluoroacetic acid.

1H NMR (300.1 MHz, DMSO) d 7.77 (d, 1H), 8.68 (d, 1H); m/z = 239 [M+H]+.

Example 339

Preparation of 3-[chloro(difluoro)methyl]-6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine



A solution of 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 335-338, preparation of starting materials) (53 mg, 0.22 mmol) in ethanol (1 mL) was added to 1-(3,5-dichloropyridin-4-yl)piperazine (77 mg, 0.33 mmol). The reaction mixture was treated with DIPEA (43 mg, 0.33 mmol) and the mixture was heated at 70°C for 4 hours. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give 3-[chloro(difluoro)methyl]-6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine (28 mg, 29%).

1H NMR (300.1 MHz, CDCl3) δ 3.48 - 3.54 (4H, m), 3.78 - 3.84 (4H, m), 7.13 (1H, d), 7.99 (1H, d), 8.41 (2H, s); m/z = 434 [M+H]+.

Examples 340-343

The following compounds were prepared in 50-73% yield by an analogous method to Example 339, starting from 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate benzyl piperazine:-

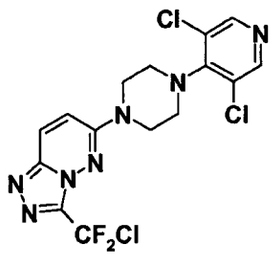
		m), 7.34 - 7.42 (2H, m), 7.93 (1H, d)	
338	H (R-enantiomer)	δ 2.16 - 2.31 (1H, m), 2.45 - 2.56 (1H, m), 3.51 - 3.72 (3H, m), 3.79 - 3.90 (1H, m), 3.98 - 4.10 (1H, m), 6.89 (1H, d), 7.27 - 7.33 (3H, m), 7.34 - 7.42 (2H, m), 7.92 (1H, d)	350

The 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was obtained in 70% yield by an analogous method to General Synthetic Method 1, preparation of starting materials, starting from 3-chloropyridazin-6-yl hydrazine and chlorodifluoroacetic acid.

1H NMR (300.1 MHz, DMSO) d 7.77 (d, 1H), 8.68 (d, 1H); m/z = 239 [M+H]+.

Example 339

Preparation of 3-[chloro(difluoro)methyl]-6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

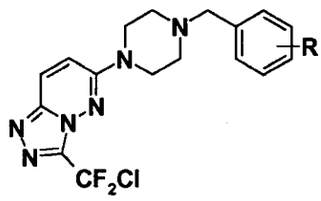


A solution of 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 335-338, preparation of starting materials) (53 mg, 0.22 mmol) in ethanol (1 mL) was added to 1-(3,5-dichloropyridin-4-yl)piperazine (77 mg, 0.33 mmol). The reaction mixture was treated with DIPEA (43 mg, 0.33 mmol) and the mixture was heated at 70°C for 4 hours. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give 3-[chloro(difluoro)methyl]-6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine (28 mg, 29%).

1H NMR (300.1 MHz, CDCl3) δ 3.48 - 3.54 (4H, m), 3.78 - 3.84 (4H, m), 7.13 (1H, d), 7.99 (1H, d), 8.41 (2H, s); m/z = 434 [M+H]+.

Examples 340-343

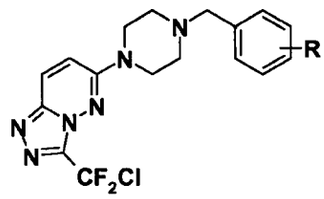
The following compounds were prepared in 50-73% yield by an analogous method to Example 339, starting from 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate benzyl piperazine:-



Ex.	R	1H NMR (300.1 MHz, CDCl3)	m/z [M+H]+
340	H	δ 2.60 (4H, t), 3.58 (2H, s), 3.64 (4H, t), 7.06 (1H, d), 7.27 - 7.37 (5H, m), 7.92 (1H, d)	379
341	4-F	δ 2.58 (4H, t), 3.54 (2H, s), 3.63 (4H, t), 6.98 - 7.09 (3H, m), 7.27 - 7.35 (2H, m), 7.92 (1H, d)	397
342	4-CN	δ 2.60 (4H, t), 3.60 - 3.69 (6H, m), 7.07 (1H, d), 7.49 (2H, d), 7.64 (2H, d), 7.94 (1H, d)	404
343	3-CN	δ 2.60 (4H, t), 3.60 (2H, s), 3.66 (4H, t), 7.07 (1H, d), 7.46 (1H, t), 7.56 - 7.62 (2H, m), 7.70 (1H, s), 7.94 (1H, d)	404

Examples 344-348

The following compounds were prepared in 24-76% yield by an analogous method to Example 339, starting from 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate benzyl piperazine:-

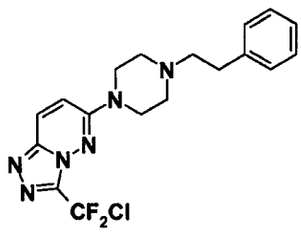


Ex.	R	1H NMR (300.1 MHz, DMSO-d6)	m/z [M+H]+
344	3-Br	δ 2.49 - 2.52 (4H, m), 3.56 (2H, s), 3.63 (4H, t), 7.28 - 7.38 (2H, m), 7.45 - 7.50 (1H, m), 7.53 - 7.55 (1H, m), 7.58 (1H, d), 8.24 (1H, d)	459
345	3-F	δ 2.50 - 2.55 (4H, m), 3.57 (2H, s), 3.64 (4H, t), 7.05 - 7.21 (3H, m), 7.34 - 7.44 (1H, m), 7.58 (1H, d), 8.24 (1H, d)	397
346	4-CF3	δ 2.50 - 2.57 (4H, m), 3.60 - 3.69 (6H, m), 7.55 - 7.62 (3H, m), 7.68 - 7.75 (2H, m), 8.25 (1H, d)	447

347	3-CF3	δ 2.50 - 2.53 (4H, m), 3.60 - 3.68 (6H, m), 7.55 - 7.70 (5H, m), 8.24 (1H, d)	447
348	4-Br	δ 2.49 - 2.52 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 7.31 (2H, d), 7.50 - 7.61 (3H, m), 8.24 (1H, d)	459

Example 349

Preparation of 3-[chloro(difluoro)methyl]-6-[4-(2-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

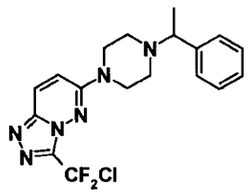


A mixture of 1-phenethylpiperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(2-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 71% yield.

1H NMR (300.1 MHz, CDCl3) δ 2.64 - 2.73 (6H, m), 2.81 - 2.89 (2H, m), 3.67 (4H, t), 7.08 (1H, d), 7.19 - 7.34 (5H, m), 7.93 (1H, d); m/z = 393 [M+H]+.

Example 350

Preparation of 3-[chloro(difluoro)methyl]-6-[4-(1-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

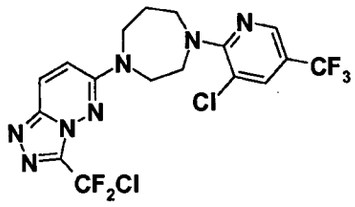


A mixture of 1-(1-phenylethyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(1-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 64% yield.

1H NMR (499.8 MHz, DMSO-d6) δ 1.32 (3H, d), 2.39 - 2.57 (4H, m), 3.47 (1H, q), 3.58 (4H, t), 7.22 - 7.27 (1H, m), 7.30 - 7.35 (4H, m), 7.53 (1H, d), 8.20 (1H, d); m/z = 393 [M+H]+.

Example 351

Preparation of 3-[chloro(difluoro)methyl]-6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl][1,2,4]triazolo[4,3-b]pyridazine

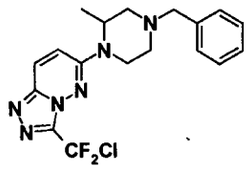


A mixture of 1-(3-chloro-5-trifluoromethyl-2-pyridyl)-1,4-diazepane and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 62% yield.

1H NMR (300.1 MHz, CDCl3) δ 2.09 - 2.19 (2H, m), 3.75 (2H, t), 3.81 (2H, t), 4.01 (4H, s), 7.04 (1H, d), 7.70 - 7.72 (1H, m), 7.94 (1H, d), 8.29 - 8.31 (1H, m); m/z = 482 [M+H]+.

Example 352

Preparation of 6-(4-benzyl-2-methylpiperazin-1-yl)-3-[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine

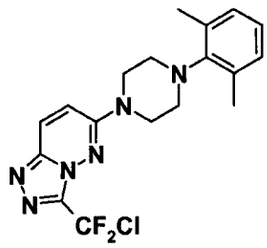


A mixture of 1-benzyl-3-methyl-piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 6-(4-benzyl-2-methylpiperazin-1-yl)-3-[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine in 41% yield.

1H NMR (300.1 MHz, DMSO-d6) δ 1.26 (3H, d), 2.06 - 2.19 (1H, m), 2.22 - 2.30 (1H, m), 2.75 (1H, d), 2.94 (1H, d), 3.14 - 3.27 (1H, m), 3.53 (2H, q), 4.04 (1H, d), 4.41 - 4.53 (1H, m), 7.23 - 7.39 (5H, m), 7.56 (1H, d), 8.24 (1H, d); m/z = 393 [M+H]+.

Example 353

Preparation of 3-[chloro(difluoro)methyl]-6-[4-(2,6-dimethylphenyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

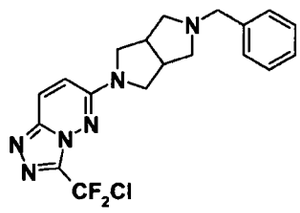


A mixture of 1-(2,6-dimethylphenyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(2,6-dimethylphenyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 64% yield.

1H NMR (300.1 MHz, CDCl3) δ 2.35 (6H, s), 3.26 (4H, t), 3.74 (4H, t), 7.00 - 7.05 (3H, m), 7.14 (1H, d), 7.95 (1H, d); m/z = 393 [M+H]+.

Example 354

Preparation of 6-(5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine

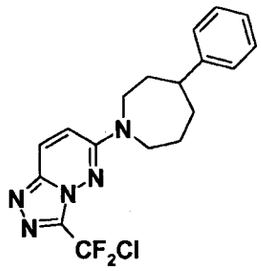


A mixture of 2-benzylhexahydropyrrolo[3,4-c]pyrrole hydrochloride and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 331 to give 6-(5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine in 66% yield.

1H NMR (300.1 MHz, CDCl3) δ 2.58 - 2.75 (4H, m), 3.04 (2H, s), 3.41 - 3.50 (2H, m), 3.63 (2H, s), 3.76 - 3.85 (2H, m), 6.88 (1H, d), 7.22 - 7.33 (5H, m), 7.90 (1H, d); m/z = 405 [M+H]+.

Example 355

Preparation of 3-[chloro(difluoro)methyl]-6-(4-phenylazepan-1-yl)[1,2,4]triazolo[4,3-b]pyridazine

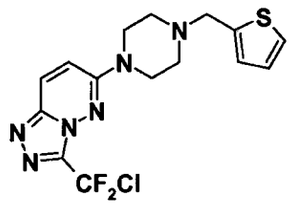


A mixture of 4-phenylazepane hydrochloride and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 331 to give 3-[chloro(difluoro)methyl]-6-(4-phenylazepan-1-yl)[1,2,4]triazolo[4,3-b]pyridazine in 69% yield.

1H NMR (499.8 MHz, DMSO-d6) δ 1.64 - 1.90 (4H, m), 1.98 - 2.09 (2H, m), 2.68 (1H, t), 3.59 - 3.75 (2H, m), 3.76 - 3.86 (1H, m), 3.87 - 3.96 (1H, m), 7.10 - 7.20 (3H, m), 7.24 (2H, t), 7.49 (1H, d), 8.20 (1H, d); m/z = 378 [M+H]+.

Example 356

Preparation of 3-[chloro(difluoro)methyl]-6-[4-(thiophen-2-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

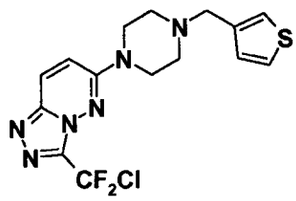


A mixture of 1-(thiophen-2-ylmethyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(thiophen-2-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 74% yield.

1H NMR (300.1 MHz, DMSO-d6) δ 2.52 - 2.59 (4H, m), 3.63 (4H, t), 3.77 (2H, s), 6.97 - 7.01 (2H, m), 7.44 - 7.48 (1H, m), 7.58 (1H, d), 8.24 (1H, d); m/z = 385 [M+H]+.

Example 357

Preparation of 3-[chloro(difluoro)methyl]-6-[4-(thiophen-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

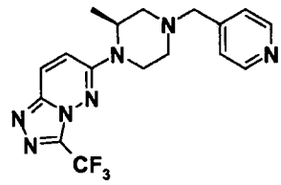


A mixture of 1-(thiophen-3-ylmethyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(thiophen-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 70% yield.

1H NMR (300.1 MHz, DMSO-d6) δ 2.49 - 2.52 (4H, m), 3.56 (2H, s), 3.62 (4H, t), 7.06 - 7.10 (1H, m), 7.33 - 7.37 (1H, m), 7.49 - 7.52 (1H, m), 7.58 (1H, d), 8.24 (1H, d); m/z = 385 [M+H]+.

Example 358

Preparation of 6-[(2S)-2-methyl-4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of pyridine-4-carboxaldehyde and 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2S)-2-methyl-4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 53% yield.

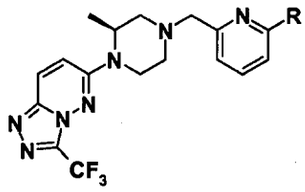
1H NMR (399.9 MHz, DMSO-d6) δ 1.29 (3H, d), 2.15 - 2.21 (1H, m), 2.30 - 2.34 (1H, m), 2.74 (1H, d), 2.94 (1H, d), 3.22 - 3.28 (1H, m), 3.52 (1H, d), 3.63 (1H, d), 4.04 (1H, d), 4.48 (1H, s), 7.39 (2H, d), 7.39 (1H, s), 7.58 (1H, d), 8.26 (1H, d), 8.54 - 8.55 (2H, m); m/z = 378 [M+H]+.

The 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 64% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (3S)-tert-butyl 3-methylpiperazine-1-carboxylate.

1H NMR (399.9 MHz, DMSO-d6) δ 1.23 (3H, d), 2.42 (1H, m), 2.65 (1H, m), 2.85 (2H, m), 3.04 (2H, m), 3.91 (1H, m), 4.35 (1H, m), 7.56 (1H, d), 8.23 (1H, d); m/z = 387 [M+H]+.

Examples 359-360

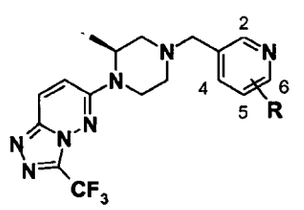
The following compounds were prepared in 31 - 84% yield by General Synthetic Method 5, starting from 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 358, preparation of starting materials) and the appropriate aldehyde:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
359	H	δ 1.27 - 1.29 (3H, m), 2.18 - 2.25 (1H, m), 2.35 - 2.39 (1H, m), 2.79 (1H, d), 2.96 - 2.99 (1H, m), 3.21 - 3.27 (1H, m), 3.62 (1H, d), 3.70 (1H, d), 4.03 (1H, d), 4.48 (1H, s), 7.27 - 7.31 (1H, m), 7.52 (1H, s), 7.54 (1H, s), 7.58 (1H, d), 7.79 - 7.83 (1H, m), 8.26 (1H, d), 8.51 - 8.53 (1H, m)	378
360	Br	δ 1.28 - 1.30 (3H, m), 2.20 - 2.27 (1H, m), 2.37 - 2.41 (1H, m), 2.79 (1H, d), 2.97 (1H, d), 3.22 - 3.27 (1H, m), 3.61 (1H, d), 3.69 (1H, d), 4.04 (1H, d), 4.49 (1H, s), 7.56 (2H, t), 7.58 (1H, d), 7.79 (1H, t), 8.26 (1H, d)	456

Examples 361-366

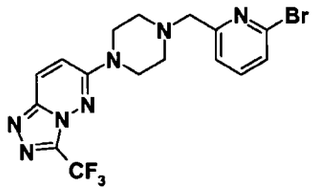
The following compounds were prepared in 32 - 84% yield by General Synthetic Method 5, starting from 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
361	6-CF3	δ 1.27 - 1.28 (3H, m), 2.16 - 2.23 (1H, m), 2.33 - 2.37 (1H, m), 2.77 (1H, d), 2.95 (1H, d), 3.20 - 3.27 (1H, m), 3.66 (1H, d), 3.74 (1H, d), 4.03 (1H, d), 4.49 (1H, d), 7.58 (1H, d), 7.91 (1H, d), 8.06 - 8.08 (1H, m), 8.26 (1H, d), 8.76 (1H, d)	446
362	2-Cl	δ 1.28 - 1.29 (3H, m), 2.22 - 2.29 (1H, m), 2.42 - 2.46 (1H, m), 2.80 (1H, d), 2.95 (1H, d), 3.20 - 3.27 (1H, m), 3.62 (2H, s), 4.04 (1H, d), 4.50 (1H, t), 7.46 - 7.49 (1H, m), 7.59 (1H, d), 7.99 - 8.01 (1H, m), 8.26 (1H, d), 8.34 - 8.36 (1H, m)	421
363	2-Cl, 5-F	δ 1.29 - 1.31 (3H, m), 2.24 - 2.31 (1H, m), 2.46 - 2.49 (1H, m), 2.82 (1H, d), 2.97 (1H, d), 3.24 - 3.28 (1H, m), 3.63 (2H, s), 4.03 (1H, d), 4.50 (1H, t), 7.60 (1H, d), 7.91 - 7.94 (1H, m), 8.27 (1H, d), 8.41 (1H, d)	430
364	6-OMe	δ 1.23 (3H, d), 2.24 - 2.27 (1H, m), 2.74 (1H, d), 3.43 (1H, d), 3.53 (1H, d), 3.86 (2H, s), 4.02 (1H, d), 4.47 (1H, d), 6.81 - 6.83 (1H, m), 7.57 (1H, d), 7.67 - 7.70 (1H, m), 8.10 (1H, d), 8.25 (1H, d)	409
365	5-Br, 2-F	δ 1.25 - 1.27 (3H, m), 2.18 - 2.24 (1H, m), 2.36 - 2.40 (1H, m), 2.79 (1H, d), 2.96 (1H, d), 3.22 - 3.27 (1H, m), 3.56 - 3.64 (2H, m), 4.01 - 4.05 (1H, m), 4.49 (1H, d), 7.58 (1H, d), 8.20 (1H, d), 8.26 (1H, d), 8.32 - 8.33 (1H, m)	476
366	5-F	δ 1.26 - 1.27 (3H, m), 2.14 - 2.21 (1H, m), 2.31 - 2.35 (1H, m), 2.76 (1H, d), 2.95 (1H, d), 3.20 - 3.27 (1H, m), 3.59 (1H, d), 3.67 (1H, d), 4.03 (1H, d), 4.48 (1H, s), 7.58 (1H, d), 7.67 - 7.71 (1H, m), 8.26 (1H, d), 8.45 (1H, t), 8.50 (1H, d)	396

Example 367

Preparation of 6-[4-[(6-bromopyridin-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

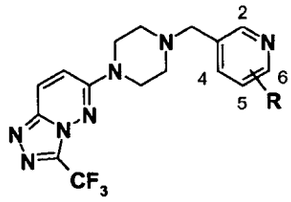


A mixture of 6-bromopyridine-2-carboxaldehyde and 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[4-[(6-bromopyridin-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 66% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 2.56 - 2.61 (4H, m), 3.64 (4H, t), 3.66 (2H, s), 7.53 - 7.54 (1H, m), 7.55 - 7.56 (1H, m), 7.60 (1H, d), 7.77 (1H, t), 8.26 (1H, d); m/z = 444 [M+H]+.

Examples 368-377

The following compounds were prepared in 20 - 79% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



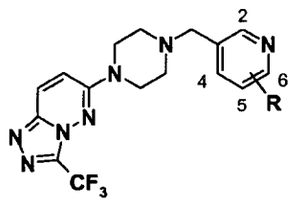
Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
368	6-CF3	δ 2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.60 (1H, d), 7.90 (1H, d), 8.04 - 8.07 (1H, m), 8.26 (1H, d), 8.74 (1H, d)	474 [1]
369	2-Cl	δ 2.61 (4H, t), 3.66 (6H, s), 7.45 - 7.48 (1H, m), 7.61 (1H, d), 7.97 - 7.99 (1H, m), 8.27 (1H, d), 8.34 - 8.35 (1H, m)	398
370	2-Cl, 5-F	δ 2.64 (4H, t), 3.66 - 3.67 (6H, m), 7.62 (1H, d), 7.90 - 7.93 (1H, m), 8.27 (1H, d), 8.40 (1H, d)	416

371	5-F	δ 2.55 (4H, t), 3.63 (6H, t), 7.60 (1H, d), 7.67 - 7.71 (1H, m), 8.26 (1H, d), 8.44 (1H, t), 8.50 (1H, d)	424 [1]
372	5-Br, 2-F	δ 2.58 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.59 (1H, d), 8.20 (1H, d), 8.26 (1H, d), 8.32 - 8.33 (1H, m)	462
373	4-OMe	δ 2.56 (4H, t), 3.53 (2H, s), 3.63 (4H, t), 3.88 (3H, s), 6.99 - 7.02 (1H, m), 7.59 (1H, d), 7.72 - 7.75 (1H, m), 8.08 - 8.10 (1H, m), 8.25 (1H, d)	394
374	6-Br	δ 2.54 (4H, s), 3.57 - 3.61 (2H, m), 3.62 - 3.63 (4H, m), 7.59 (1H, d), 7.64 (1H, d), 7.72 - 7.74 (1H, m), 8.26 (1H, d), 8.36 (1H, d)	444
375	5-OMe	δ 2.53 - 2.56 (4H, m), 3.59 - 3.62 (2H, m), 3.63 (4H, d), 3.84 (3H, s), 7.33 (1H, q), 7.58 (1H, d), 8.14 (1H, d), 8.21 - 8.22 (1H, m), 8.23 - 8.25 (1H, m)	394
376	2-Br	δ 2.53 - 2.57 (4H, m), 3.60 - 3.64 (6H, m), 7.59 (1H, d), 8.02 (1H, t), 8.26 (1H, d), 8.54 (1H, d), 8.63 (1H, d)	444
377	4-Br	δ 2.59 - 2.63 (4H, m), 3.62 - 3.66 (4H, m), 3.68 (2H, s), 7.61 (1H, d), 7.72 (1H, d), 8.27 (1H, d), 8.36 (1H, d), 8.62 (1H, s)	444

[1] Detected as adduct with acetonitrile used as solvent for mass spectral determination

Examples 378-379

The following compounds were prepared in 33 - 54% yield by an analogous method to Example 307, starting from the appropriate bromopyridine (obtained as described in the corresponding footnote):-



Ex.	R	Note	H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
378	2-CN	[1]	δ 2.61 (4H, t), 3.63 (4H, t), 3.78 (2H, s), 7.61	389

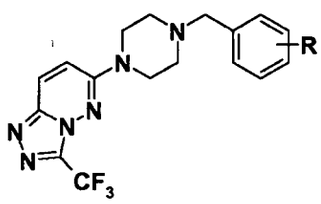
			(1H, d), 7.74 - 7.77 (1H, m), 8.08 - 8.10 (1H, m), 8.27 (1H, d), 8.68 - 8.70 (1H, m)	
379	4-CN	[2]	δ 2.61 (4H, s), 3.63 (4H, s), 3.76 (2H, s), 7.60 (1H, d), 7.88 (1H, s), 8.26 (1H, d), 8.75 (1H, s), 8.85 (1H, s)	389

[1] Starting from 6-[4-[(2-bromopyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, obtained as described in Example 376.

[2] Starting from 6-[4-[(4-bromopyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, obtained as described in Example 377.

Examples 380-393

The following compounds were prepared in 23 - 93% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

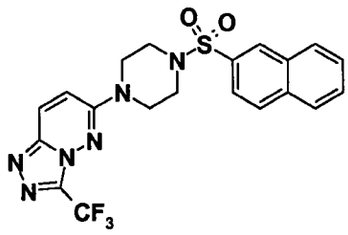


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
380	2,6-di-F, 4-CN	δ 2.65 (4H, m), 3.62 (4H, m), 3.78 (2H, s), 7.03 (1H, d), 7.25 (2H, m), 7.92 (1H, d)	424
381	2,3-di-F	δ 2.64 (4H, m), 3.63 (4H, m), 3.69 (2H, s), 7.13 (4H, m), 7.92 (1H, d)	399
382	2,4-di-F	1H NMR (399.9 MHz, DMSO-d6) δ 2.52 (4H, m), 3.30 (2H, s), 3.61 (4H, m), 7.09 (1H, m), 7.22 (1H, m), 7.50 (1H, m), 7.58 (1H, d), 8.25 (1H, d)	399
383	3,4-di-F	1H NMR (399.9 MHz, DMSO-d6) δ 3.29 (4H, m), 3.55 (2H, s), 3.62 (4H, m), 7.19 (1H, m), 7.40 (2H, m), 7.59 (1H, d), 8.26 (1H, d)	399
384	2,6-di-F	δ 2.76 (4H, m), 3.67 (4H, m), 3.85 (2H, s),	399

		7.08 (2H, m), 7.44 (2H, m), 8.15 (1H, d)	
385	2-F, 4-OMe	δ 2.91 (4H, s), 3.74 (4H, s), 3.81 (3H, s), 3.91 (2H, s), 6.82 (2H, m), 7.40 (1H, m), 7.49 (1H, d), 8.18 (1H, d)	411
386	2,5-di-F	δ 2.78 (4H, m), 3.70 (4H, m), 3.80 (2H, s), 7.16 (1H, m), 7.22 (1H, m), 7.31 (1H, m), 7.49 (1H, d), 8.16 (1H, d)	399
387	3-CN, 4-F	1H NMR (399.9 MHz, DMSO-d6) δ 3.29 (4H, m), 3.60 (2H, s), 3.63 (4H, m), 7.52 (1H, m), 7.60 (1H, d), 7.77 (1H, m), 7.87 (1H, m), 8.26 (1H, d)	406
388	3-F, 4-OMe	1H NMR (399.9 MHz, DMSO-d6) δ 3.30 (4H, m), 3.49 (2H, s), 3.62 (4H, m), 3.84 (3H, s), 7.14 (3H, m), 7.59 (1H, d), 8.25 (1H, d)	411
389	2-F, 4-CN	1H NMR (399.9 MHz, DMSO-d6) δ 2.57 (4H, m), 3.30 (2H, s), 3.63 (4H, m), 7.60 (1H, d), 7.70 (2H, m), 7.85 (1H, m), 8.26 (1H, d)	406
390	2-F, 5-OMe	1H NMR (399.9 MHz, DMSO-d6) δ 2.55 (4H, m), 3.30 (3H, s), 3.62 (4H, m), 3.76 (2H, s), 6.88 (1H, m), 6.98 (1H, m), 7.12 (1H, m), 7.59 (1H, d), 8.25 (1H, d)	411
391	3,5-di-F	1H NMR (399.9 MHz, DMSO-d6) δ 3.30 (4H, m), 3.59 (2H, s), 3.64 (4H, m), 7.11 (3H, m), 7.60 (1H, d), 8.26 (1H, d)	399
392	3-OMe, 4-F	1H NMR (399.9 MHz, DMSO-d6) δ 2.52 (4H, m), 3.52 (2H, s), 3.63 (4H, m), 3.85 (3H, s), 6.90 (1H, m), 7.15 (2H, m), 7.59 (1H, d), 8.26 (1H, d)	411
393	3-F, 4-CN	δ 2.55 (4H, m), 3.65 (4H, m), 3.67 (2H, s), 7.42 (1H, m), 7.51 (1H, m), 7.60 (1H, d), 7.91 (1H, m), 8.26 (1H, d)	406

Example 394

Preparation of 6-[4-(naphthalen-2-ylsulfonyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

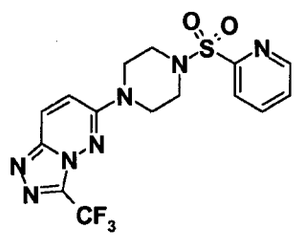


Naphthalene-2-sulfonyl chloride (175 mg, 0.77 mmol) was added to 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (150 mg, 0.55 mmol) in pyridine (2 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was evaporated to remove the pyridine. The crude product was purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-(naphthalen-2-ylsulfonyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (168 mg, 66%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.15 (4H, m), 3.72 (4H, m), 7.49 (1H, d), 7.74 (3H, m), 8.07 (1H, d), 8.19 (3H, m), 8.49 (1H, s); m/z = 463 [M+H]+.

Example 395

Preparation of 6-[4-(pyridin-2-ylsulfonyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

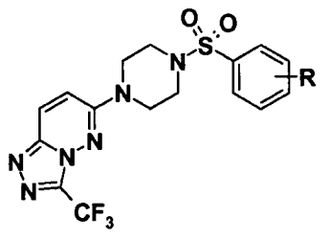


Obtained in 32% yield by an analogous method to Example 394, starting from pyridine-2-sulfonyl chloride and 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (399.9 MHz, DMSO-d6) δ 3.28 (4H, m), 3.63 (4H, m), 7.47 (1H, d), 7.64 (1H, m), 7.90 (1H, m), 8.06 (1H, m), 8.20 (1H, d), 8.68 (1H, m); m/z = 414 [M+H]+.

Examples 396-405

The following compounds were prepared in 7 - 90% yield by an analogous method to Example 394, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate sulfonyl chloride:-

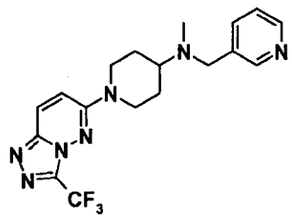


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
396	3-OMe	δ 3.09 (4H, m), 3.71 (4H, m), 3.85 (3H, s), 7.23 (1H, m), 7.32 (2H, m), 7.56 (2H, m), 8.25 (1H, d)	443
397	2-OMe	δ 3.27 (4H, m), 3.67 (4H, m), 3.89 (3H, s), 7.12 (1H, m), 7.26 (1H, m), 7.56 (1H, d), 7.65 (1H, m), 7.78 (1H, m), 8.28 (1H, d)	443
398	4-OMe	δ 2.96 (4H, m), 3.63 (4H, m), 3.76 (3H, s), 7.09 (2H, m), 7.44 (1H, d), 7.63 (2H, m), 8.17 (1H, d)	443
399	2,5-di-OMe	δ 3.20 (4H, m), 3.59 (4H, m), 3.70 (3H, s), 3.76 (3H, s), 7.16 (3H, m), 7.48 (1H, d), 8.20 (1H, d)	473
400	2-F	δ 3.16 (4H, m), 3.64 (4H, m), 7.42 (3H, m), 7.72 (2H, m), 8.19 (1H, d)	431
401	3-F	δ 3.14 (4H, m), 3.72 (4H, m), 7.63 (5H, m), 8.26 (1H, d)	431
402	3,4-di-OMe	δ 3.06 (4H, m), 3.71 (4H, m), 3.85 (6H, m), 7.18 (2H, m), 7.36 (1H, m), 7.53 (1H, d), 8.26 (1H, d)	473
403	2-CN	δ 3.29 (4H, m), 3.74 (4H, m), 7.57 (1H, d), 7.94 (2H, m), 8.07 (1H, m), 8.18 (1H, m), 8.28 (1H, d)	438
404	2,4-di-OMe	δ 3.21 (4H, m), 3.67 (4H, m), 3.85 (3H, s), 3.87 (3H, s), 6.68 (1H, m), 6.73 (1H, m), 7.56 (1H, d), 7.69 (1H, d), 8.27 (1H, d)	473
405	4-F	δ 3.09 (4H, m), 3.72 (4H, m), 7.51 (3H, m), 7.86	431

		(2H, m), 8.26 (1H, d)	

Example 406

Preparation of N-methyl-N-(pyridin-3-ylmethyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine



DIPEA (0.174 mL, 1.00 mmol) was added to N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine (100 mg, 0.34 mmol) and 3-(bromomethyl)pyridine hydrobromide (127 mg, 0.50 mmol) in DMA (2 mL) and the mixture was sealed into a microwave tube. The reaction was heated to 150°C for 15 minutes in the microwave reactor and cooled to ambient temperature. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-methyl-N-(pyridin-3-ylmethyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine (113 mg, 78%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.59 (2H, m), 1.91 (2H, m), 2.12 (2H, s), 2.75 (1H, m), 3.03 (2H, m), 3.61 (3H, s), 4.34 (2H, m), 7.35 (1H, m), 7.63 (1H, d), 7.70 (1H, m), 8.23 (1H, d), 8.48 (2H, m); m/z = 392 [M+H]+.

The N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine used as starting material was prepared as follows:-

Preparation of tert-butyl methyl[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]carbamate

DIPEA (1.355 mL, 7.78 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.865 g, 3.89 mmol) and tert-butyl methyl(piperidin-4-yl)carbamate (1 g, 4.67 mmol) in DMA (15 mL). The resulting solution was stirred at 50°C for 2 hours. The reaction mixture was evaporated and diluted with DCM (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer

was dried over MgSO4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford tert-butyl methyl[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]carbamate (1.500 g, 96%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.40 (9H, s), 1.71 (4H, m), 2.67 (3H, s), 3.05 (2H, m), 4.06 (1H, s), 4.38 (2H, m), 7.63 (1H, d), 8.24 (1H, d); m/z = 401 [M+H]+.

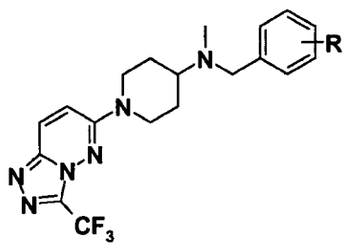
Preparation of N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine

tert-Butyl methyl[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]carbamate (1.5 g, 3.75 mmol) was dissolved in TFA (5 mL) and DCM (5 mL). The resulting solution was stirred at ambient temperature for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol and pure fractions were evaporated to dryness to afford N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine (1.090 g, 97%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.30 (2H, m), 1.91 (2H, m), 2.59 (1H, m), 3.16 (2H, m), 3.30 (3H, s), 4.11 (2H, m), 7.61 (1H, d), 8.22 (1H, d); m/z = 301 [M+H]+.

Examples 407-411

The following compounds were prepared in 39 - 78% yield by an analogous method to Example 406, starting from N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine and the appropriate benzyl bromide:-

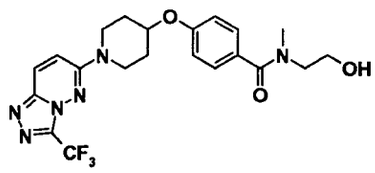


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
407	4-F	δ 1.58 (2H, m), 1.90 (2H, m), 2.11 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.56 (3H, s), 4.32 (2H, m), 7.13 (2H, m), 7.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d)	409

408	3,4-di-F	δ 1.57 (2H, m), 1.89 (2H, m), 2.13 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.56 (3H, s), 4.33 (2H, m), 7.16 (1H, m), 7.35 (2H, m), 7.63 (1H, d), 8.23 (1H, d)	427
409	4-CN	δ 1.59 (2H, m), 1.90 (2H, m), 2.13 (2H, s), 2.65 (1H, m), 3.05 (2H, m), 3.66 (3H, s), 4.34 (2H, m), 7.65 (4H, m), 7.98 (1H, m), 8.27 (1H, m)	416
410	3,5-di-F	δ 1.57 (2H, m), 1.89 (2H, m), 2.15 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.61 (3H, s), 4.33 (2H, m), 7.06 (3H, m), 7.63 (1H, d), 8.23 (1H, d)	427
411	3-CN, 4-F	δ 1.58 (2H, m), 1.89 (2H, m), 2.13 (2H, s), 2.74 (1H, m), 3.04 (2H, m), 3.60 (3H, s), 4.33 (2H, m), 7.48 (1H, m), 7.63 (1H, d), 7.73 (1H, m), 7.82 (1H, m), 8.23 (1H, d)	434

Example 412

Preparation of N-(2-hydroxyethyl)-N-methyl-4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzamide



DIPEA (0.087 mL, 0.5 mmol) was added to 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid (100 mg, 0.25 mmol), 2-(methylamino)ethanol (20.28 mg, 0.27 mmol) and HATU (114 mg, 0.3 mmol) in DMF (2 mL). The resulting solution was stirred at room temperature for 24 hours. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 21 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-(2-hydroxyethyl)-N-methyl-4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzamide (64 mg, 55%).

1H NMR (399.9 MHz, DMSO-d6) δ 1.75 (2H, m), 2.10 (2H, m), 2.98 (3H, s), 3.56 (6H, m), 3.99 (2H, m), 4.76 (1H, m), 7.04 (2H, d), 7.39 (2H, d), 7.65 (1H, d), 8.27 (1H, d);

m/z = 465 [M+H]+.

The 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid used as starting material was prepared as follows:-

Preparation of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol

4-Hydroxypiperidine (10.91 g, 107.84 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (20 g, 89.87 mmol) and DIPEA (23.48 mL, 134.80 mmol) in DMF (200 mL). The resulting solution was stirred at 125°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to give a beige solid which was stirred with ether then filtered to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (22.64 g, 88%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.46 (2H, m), 1.85 (2H, m), 3.32 (2H, m), 3.78 (1H, m), 3.96 (2H, m), 4.78 (1H, d), 7.61 (1H, d), 8.22 (1H, d); m/z = 288 [M+H]+.

Preparation of ethyl 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoate

DIAD (2.262 mL, 11.49 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (3 g, 10.44 mmol), ethyl 4-hydroxybenzoate (1.909 g, 11.49 mmol) and triphenylphosphine (3.01 g, 11.49 mmol) in THF (50 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 4 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol. The crude solid was triturated with MeOH to give a solid which was collected by filtration and dried under vacuum to give ethyl 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoate (2.220 g, 49%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.33 (3H, t), 1.76 (2H, m), 2.11 (2H, m), 3.55 (2H, m), 3.98 (2H, m), 4.29 (2H, q), 4.83 (1H, m), 7.13 (2H, m), 7.66 (1H, d), 7.92 (2H, m), 8.27 (1H, d); m/z = 436 [M+H]+.

Preparation of 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid

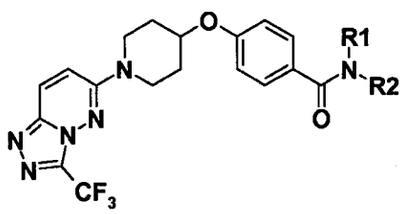
Lithium hydroxide monohydrate (0.488 g, 20.40 mmol) was added to ethyl 4-[[1-

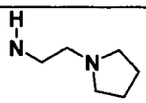
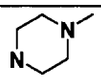
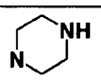
[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoate (2.22 g, 5.10 mmol) in MeOH (80 mL) and water (40.0 mL). The resulting suspension was stirred at 50°C for 2 days. The reaction was cooled to room temperature, the methanol was evaporated and the aqueous residues treated with citric acid until precipitation ceased. The precipitate was collected by filtration, washed with water and dried to afford 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid (2.020 g, 97%) as a solid.

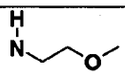
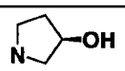
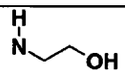
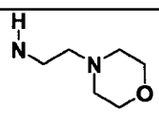
1H NMR (399.9 MHz, DMSO-d6) δ 1.76 (2H, m), 2.12 (2H, m), 3.54 (2H, m), 3.99 (2H, m), 4.82 (1H, m), 7.10 (2H, m), 7.66 (1H, d), 7.90 (2H, m), 8.26 (1H, d), 12.60 (1H, s); m/z = 408 [M+H]+.

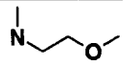
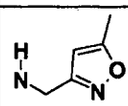
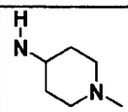
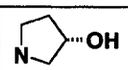
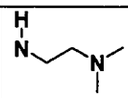
Examples 413-429

The following compounds were prepared in 9 - 62% yield by an analogous method to Example 412, starting from 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid and the appropriate amine:-



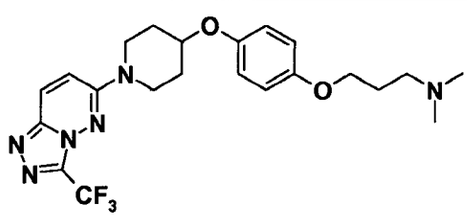
Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
413		δ 1.72 (6H, m), 2.10 (2H, m), 2.49 (4H, m), 2.57 (2H, m), 3.37 (2H, m), 3.55 (2H, m), 3.99 (2H, m), 4.79 (1H, m), 7.07 (2H, d), 7.65 (1H, d), 7.82 (2H, d), 8.26 (2H, m)	504
414		δ 1.75 (2H, m), 2.10 (2H, m), 2.20 (3H, s), 2.32 (4H, m), 3.50 (6H, m), 3.98 (2H, m), 4.76 (1H, m), 7.06 (2H, d), 7.35 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	490
415		δ 1.75 (2H, m), 2.10 (2H, m), 2.68 (4H, m), 3.41 (4H, m), 3.54 (2H, m), 3.98 (2H, m), 4.75 (1H, m), 7.05 (2H, m), 7.34 (2H, m), 7.65 (1H, d), 8.26 (1H, d)	476

416		1H NMR (499.803 MHz, DMSO-d6) δ 1.72 (2H, m), 2.08 (2H, m), 3.26 (3H, s), 3.41 (4H, m), 3.51 (2H, m), 3.96 (2H, m), 4.77 (1H, m), 7.05 (2H, d), 7.63 (1H, d), 7.82 (2H, d), 8.24 (1H, d), 8.33 (1H, m)	465
417	NMe2	δ 1.76 (2H, m), 2.11 (2H, m), 2.97 (6H, s), 3.53 (2H, m), 3.99 (2H, m), 4.76 (1H, m), 7.05 (2H, d), 7.38 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	435
418		δ 1.76 (3H, m), 1.94 (1H, m), 2.10 (2H, m), 3.53 (5H, m), 3.98 (2H, m), 4.28 (1H, m), 4.77 (1H, m), 4.94 (1H, m), 7.05 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.26 (1H, d)	477
419		δ 1.80 (6H, m), 2.10 (2H, m), 3.50 (6H, m), 3.98 (2H, m), 4.76 (1H, m), 7.04 (2H, d), 7.51 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	461
420		δ 1.75 (2H, m), 2.10 (2H, m), 3.56 (10H, m), 3.98 (2H, m), 4.77 (1H, m), 7.07 (2H, m), 7.39 (2H, m), 7.65 (1H, d), 8.26 (1H, d)	477
421	NHMe	δ 1.75 (2H, m), 2.10 (2H, m), 2.77 (3H, m), 3.53 (2H, m), 3.98 (2H, m), 4.79 (1H, m), 7.06 (2H, d), 7.65 (1H, m), 7.81 (2H, d), 8.27 (2H, m)	421
422	NHEt	δ 1.12 (3H, t), 1.75 (2H, m), 2.10 (2H, m), 3.30 (2H, m), 3.54 (2H, m), 3.98 (2H, m), 4.79 (1H, m), 7.06 (2H, d), 7.66 (1H, d), 7.82 (2H, d), 8.27 (2H, m)	435
423		δ 1.75 (2H, m), 2.11 (2H, m), 3.34 (2H, m), 3.53 (4H, m), 3.98 (2H, m), 4.69 (1H, t), 4.79 (1H, m), 7.07 (2H, d), 7.66 (1H, d), 7.84 (2H, d), 8.27 (2H, m)	451
424		δ 1.75 (2H, m), 2.10 (2H, m), 2.42 (4H, m), 2.57 (2H, m), 3.38 (2H, m), 3.55 (6H, m), 3.98 (2H,	520

		m), 4.79 (1H, m), 7.07 (2H, d), 7.65 (1H, d), 7.81 (2H, d), 8.25 (2H, m)	
425		δ 1.74 (2H, m), 2.11 (2H, m), 2.98 (3H, s), 3.25 (3H, m), 3.52 (6H, m), 3.99 (2H, m), 4.75 (1H, m), 7.05 (2H, d), 7.36 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	479
426		δ 1.75 (2H, m), 2.11 (2H, m), 2.37 (3H, s), 3.54 (2H, m), 3.99 (2H, m), 4.45 (2H, d), 4.80 (1H, m), 6.14 (1H, s), 7.09 (2H, d), 7.66 (1H, d), 7.87 (2H, d), 8.26 (1H, d), 8.90 (1H, m)	502
427		δ 1.63 (2H, m), 1.80 (4H, m), 1.99 (2H, m), 2.14 (2H, m), 2.22 (3H, s), 2.82 (2H, m), 3.60 (2H, m), 3.77 (1H, m), 4.02 (2H, m), 4.84 (1H, m), 7.11 (2H, d), 7.70 (1H, d), 7.88 (2H, d), 8.10 (1H, d), 8.31 (1H, d)	504
428		δ 1.76 (3H, m), 1.93 (1H, m), 2.10 (2H, m), 3.55 (5H, m), 3.98 (2H, m), 4.29 (1H, m), 4.77 (1H, m), 4.94 (1H, m), 7.05 (2H, d), 7.50 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	477
429		1H NMR (500.13 MHz, DMSO-d6) δ 1.72 (2H, m), 2.08 (2H, m), 2.16 (6H, s), 2.37 (2H, m), 3.32 (2H, m), 3.51 (2H, m), 3.95 (2H, m), 4.77 (1H, m), 7.04 (2H, d), 7.63 (1H, d), 7.80 (2H, d), 8.19 (1H, m), 8.24 (1H, m)	478

Example 430

Preparation of N,N-dimethyl-3-[4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenoxy]propan-1-amine



DIAD (0.05 mL, 0.29 mmol) was added to 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol, 3-dimethylamino-1-propanol (100 mg, 0.26 mmol (33 mg, 0.32 mmol) and triphenylphosphine (76 mg, 0.29 mmol) in THF (2 mL). The resulting solution was stirred at ambient temperature for 4 hours. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the product (19.1 mg, 16%) as a gum.
1H NMR (399.9 MHz, DMSO-d6) δ 1.74 (2H, m), 1.86 (2H, m), 2.08 (2H, m), 2.19 (6H, s), 2.39 (2H, m), 3.57 (2H, m), 3.99 (4H, m), 4.58 (1H, m), 6.94 (4H, m), 7.69 (1H, d), 8.30 (1H, d); m/z = 465 [M+H]+.

The 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol used as starting material was prepared as follows:-

Preparation of 6-[4-[4-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

DIAD (2.262 mL, 11.49 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (3 g, 10.44 mmol), 4-(benzyloxy)phenol (2.300 g, 11.49 mmol) and triphenylphosphine (3.01 g, 11.49 mmol) in THF (50 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 4 hours. The crude oil was triturated with MeOH to give a solid which was collected by filtration and dried under vacuum to give 6-[4-[4-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.53 g, 52%) as a solid.
1H NMR (399.9 MHz, DMSO-d6) δ 1.75 (2H, m), 2.08 (2H, m), 3.56 (2H, m), 3.99 (2H, m), 4.60 (1H, m), 5.10 (2H, s), 7.00 (4H, m), 7.44 (5H, m), 7.69 (1H, d), 8.30 (1H, d); m/z = 470 [M+H]+.

Preparation of 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4yl]oxy]phenol

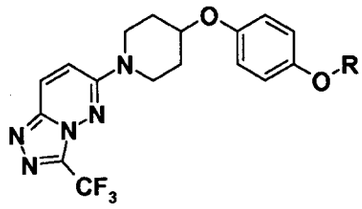
10% Palladium on carbon (0.574 g, 0.54 mmol) was added to 6-[4-[4-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.53 g, 5.39 mmol) in MeOH (30 mL) under an atmosphere of hydrogen. The resulting suspension was stirred at ambient temperature for 24 hours. The reaction mixture was evaporated. The crude product was purified by flash silica chromatography, elution

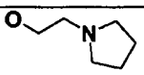
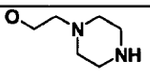
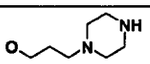
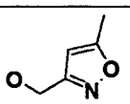
gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4yl]oxy]phenol (1.760 g, 86%) as a gum which crystallised on standing.

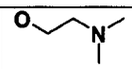
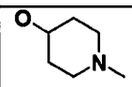
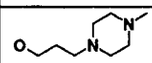
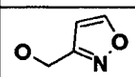
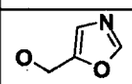
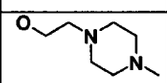
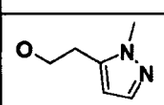
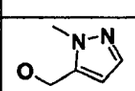
1H NMR (399.9 MHz, DMSO-d6) δ 1.69 (2H, m), 2.01 (2H, m), 3.51 (2H, m), 3.94 (2H, m), 4.46 (1H, m), 6.69 (2H, m), 6.83 (2H, m), 7.64 (1H, d), 8.25 (1H, d), 8.94 (1H, s); m/z = 380 [M+H]+.

Examples 431-442

The following compounds were prepared in 8 - 43% yield by an analogous method to Example 430, starting from 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol and the appropriate alcohol:-

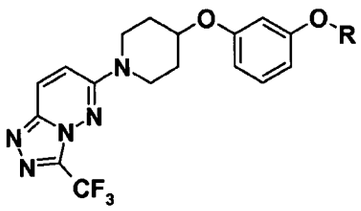


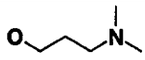
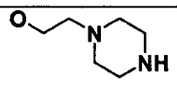
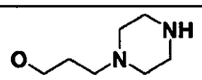
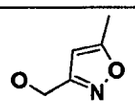
Ex.	OR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
431		δ 1.70 (6H, m), 2.03 (2H, m), 2.52 (4H, m), 2.76 (2H, m), 3.52 (2H, m), 3.97 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)	477
432		δ 1.74 (2H, m), 2.08 (2H, m), 2.44 (2H, m), 2.67 (4H, m), 2.74 (4H, m), 3.23 (2H, m), 3.55 (2H, m), 4.05 (2H, m), 4.59 (1H, m), 6.74 (1H, m), 6.94 (4H, m), 7.69 (1H, d), 8.30 (1H, d)	492
433		δ 1.68 (2H, m), 1.81 (2H, m), 2.01 (2H, m), 2.27 (4H, m), 2.35 (2H, m), 2.66 (4H, m), 3.49 (2H, m), 3.92 (4H, m), 4.52 (1H, m), 6.84 (2H, m), 6.91 (2H, m), 7.62 (1H, d), 8.23 (1H, d)	506
434		δ 1.75 (2H, m), 2.08 (2H, m), 2.47 (3H, s), 3.57 (2H, m), 4.00 (2H, m), 4.61 (1H, m), 5.13 (2H, m), 6.37 (1H, m), 7.01 (4H, m), 7.69 (1H, d), 8.30 (1H, d)	475

435		δ 1.70 (2H, m), 2.03 (2H, m), 2.22 (6H, s), 2.61 (2H, m), 3.52 (2H, m), 3.96 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)	451
436		δ 1.68 (4H, m), 1.94 (2H, m), 2.08 (2H, m), 2.19 (3H, m), 2.64 (4H, m), 3.56 (2H, m), 3.99 (2H, m), 4.26 (1H, m), 4.59 (1H, m), 6.95 (4H, m), 7.69 (1H, d), 8.30 (1H, d)	477
437		δ 1.70 (2H, m), 1.84 (2H, m), 2.03 (2H, m), 2.15 (3H, s), 2.34 (10H, m), 3.52 (2H, m), 3.94 (4H, m), 4.53 (1H, m), 6.86 (2H, m), 6.94 (2H, m), 7.64 (1H, d), 8.25 (1H, d)	520
438		δ 1.68 (2H, m), 2.01 (2H, m), 3.49 (2H, m), 3.93 (2H, m), 4.54 (1H, m), 5.15 (2H, s), 6.67 (1H, d), 6.95 (4H, m), 7.62 (1H, d), 8.23 (1H, d), 8.92 (1H, d)	461
439		δ 1.70 (2H, m), 2.04 (2H, m), 3.52 (2H, m), 3.95 (2H, m), 4.56 (1H, m), 5.12 (2H, s), 6.97 (4H, m), 7.31 (1H, s), 7.64 (1H, d), 8.25 (1H, d), 8.41 (1H, s)	461
440		δ 1.70 (2H, m), 2.03 (2H, m), 2.15 (3H, s), 2.39 (8H, m), 2.66 (2H, m), 3.51 (2H, m), 3.97 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)	506
441		δ 1.70 (2H, m), 2.03 (2H, m), 2.82 (2H, t), 3.52 (2H, m), 3.79 (3H, s), 3.95 (2H, m), 4.03 (2H, t), 4.54 (1H, m), 6.91 (4H, m), 7.56 (1H, s), 7.56 (1H, s), 7.64 (1H, d), 8.25 (1H, d)	488
442		δ 1.71 (2H, m), 2.04 (2H, m), 3.53 (2H, m), 3.84 (3H, s), 3.95 (2H, m), 4.58 (1H, m), 5.11 (2H, s), 6.35 (1H, m), 6.98 (4H, m), 7.38 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	474

Examples 443-446

The following compounds were prepared in 7 - 33% yield by an analogous method to Example 430, starting from 3-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol and the appropriate alcohol:-



Ex.	OR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
443		δ 1.72 (2H, m), 1.84 (2H, m), 2.06 (2H, m), 2.15 (6H, s), 2.35 (2H, m), 3.54 (2H, m), 3.97 (4H, m), 4.69 (1H, m), 6.55 (3H, m), 7.18 (1H, m), 7.64 (1H, d), 8.26 (1H, d)	465
444		δ 1.73 (2H, m), 2.06 (2H, m), 2.40 (4H, m), 2.66 (6H, m), 3.53 (2H, m), 3.96 (2H, m), 4.06 (2H, m), 4.69 (1H, m), 6.56 (3H, m), 7.18 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	492
445		δ 1.69 (2H, m), 1.83 (2H, m), 2.04 (2H, m), 2.29 (4H, m), 2.36 (2H, m), 2.70 (4H, m), 3.51 (2H, m), 3.94 (4H, m), 4.66 (1H, m), 6.53 (3H, m), 7.16 (1H, m), 7.63 (1H, d), 8.24 (1H, d)	506
446		δ 1.72 (2H, m), 2.07 (2H, m), 2.42 (3H, s), 3.52 (2H, m), 3.97 (2H, m), 4.69 (1H, m), 5.13 (2H, s), 6.33 (1H, s), 6.64 (3H, m), 7.21 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	475

The 3-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol used as starting material was prepared as follows:-

Preparation of 6-[4-[3-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

Obtained in 40% yield by an analogous procedure to Example 430, preparation of

starting materials, starting from 3-(benzyloxy)phenol and 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.71 (2H, m), 2.05 (2H, m), 3.51 (2H, m), 3.96 (2H, m), 4.67 (1H, m), 5.10 (2H, s), 6.63 (3H, m), 7.19 (1H, m), 7.40 (5H, m), 7.64 (1H, d), 8.26 (1H, d); m/z = 470 [M+H]+.

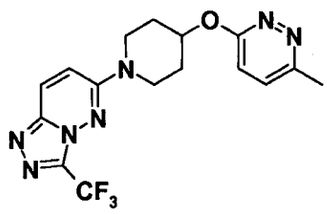
Preparation of 3-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol

Obtained in 80% yield by an analogous procedure to Example 430, preparation of starting materials, starting from 6-[4-[3-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (399.9 MHz, DMSO-d6) δ 1.71 (2H, m), 2.06 (2H, m), 3.53 (2H, m), 3.95 (2H, m), 4.60 (1H, m), 6.40 (3H, m), 7.07 (1H, m), 7.64 (1H, d), 8.25 (1H, d), 9.36 (1H, s); m/z = 380 [M+H]+.

Example 447

Preparation of 6-[4-[(6-methylpyridazin-3-yl)oxy]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



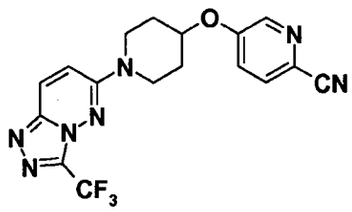
DIAD (0.102 mL, 0.52 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 310, preparation of starting materials) (135 mg, 0.47 mmol), 6-methylpyridazin-3(2H)-one (56.9 mg, 0.52 mmol) and triphenylphosphine (136 mg, 0.52 mmol) in THF (5 mL). The resulting solution was stirred at ambient temperature for 3 days. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol and evaporated to give crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[(6-methylpyridazin-3-

yl)oxy]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (22.00 mg, 12%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.91 (4H, m), 2.25 (3H, s), 3.22 (2H, m), 4.42 (2H, m), 5.10 (1H, m), 6.89 (1H, d), 7.32 (1H, d), 7.66 (1H, d), 8.27 (1H, d); m/z = 380 [M+H]+.

Example 448

Preparation of 5-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]pyridine-2-carbonitrile

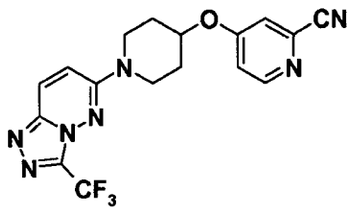


A solution of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (150 mg, 0.52 mmol) and sodium hydride (60% dispersion in oil, 22.98 mg, 0.57 mmol) in DMF (5 mL) was stirred for 30 minutes at ambient temperature under nitrogen. 5-Chloropicolinonitrile (80 mg, 0.57 mmol) was added to the reaction mixture. The resulting solution was stirred at 50°C for 18 hours. The reaction mixture was diluted with a few drops of MeOH. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 5-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]pyridine-2-carbonitrile (55.0 mg, 27%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.78 (2H, m), 2.13 (2H, m), 3.53 (2H, m), 3.99 (2H, m), 4.95 (1H, m), 7.69 (2H, m), 8.02 (1H, d), 8.27 (1H, d), 8.50 (1H, m); m/z = 390 [M+H]+.

Example 449

Preparation of 4-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]pyridine-2-carbonitrile

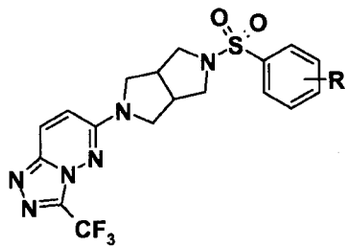


Obtained in 62% yield by an analogous procedure to Example 448, starting from 4-chloro-2-cyanopyridine and 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.76 (2H, m), 2.14 (2H, m), 3.51 (2H, m), 4.01 (2H, m), 4.95 (1H, m), 7.37 (1H, m), 7.66 (1H, d), 7.81 (1H, m), 8.27 (1H, d), 8.55 (1H, m); m/z = 390 [M+H]+.

Examples 450-455

The following compounds were prepared in 16 - 83% yield by an analogous method to Example 394, starting from 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in General Synthetic Method 10, preparation of starting materials) and the appropriate sulfonyl chloride:-

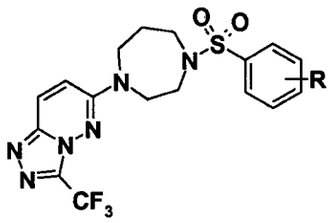


Ex.	R	1H NMR (399.9 MHz, $CDCl_3$)	m/z [M+H]+
450	3-F	δ 3.04 - 3.10 (2H, m), 3.28 - 3.32 (2H, m), 3.35 - 3.39 (2H, m), 3.46 - 3.50 (2H, m), 3.75 - 3.79 (2H, m), 6.79 (1H, d), 7.29 - 7.35 (1H, m), 7.51 - 7.57 (2H, m), 7.62 - 7.64 (1H, m), 7.93 (1H, d)	457
451	2-OMe	δ 3.06 - 3.11 (2H, m), 3.38 - 3.44 (4H, m), 3.67 - 3.72 (2H, m), 3.76 - 3.80 (2H, m), 3.90 (3H, s), 6.81 (1H, d), 6.99 - 7.07 (2H, m), 7.50 - 7.54 (1H, m), 7.90 - 7.94 (2H, m)	469
452	2-F	δ 3.09 - 3.13 (2H, m), 3.38 - 3.46 (4H, m), 3.66 (2H,	457

		q), 3.79 (2H, q), 6.81 (1H, d), 7.18 - 7.31 (2H, m), 7.55 - 7.61 (1H, m), 7.89 - 7.95 (2H, m)	
453	4-F	δ 3.03 - 3.10 (2H, m), 3.27 - 3.30 (2H, m), 3.36 - 3.46 (4H, m), 3.78 (2H, q), 6.78 (1H, d), 7.21 - 7.25 (2H, m), 7.83 - 7.87 (2H, m), 7.93 (1H, d)	457
454	3-OMe	δ 3.01 - 3.06 (2H, m), 3.27 - 3.30 (2H, m), 3.34 - 3.38 (2H, m), 3.45 - 3.49 (2H, m), 3.73 - 3.77 (2H, m), 3.84 (3H, s), 6.77 (1H, d), 7.11 - 7.14 (1H, m), 7.33 (1H, t), 7.38 - 7.47 (2H, m), 7.92 (1H, d)	469
455	4-OMe	δ 3.00 - 3.05 (2H, m), 3.23 - 3.27 (2H, m), 3.35 - 3.44 (4H, m), 3.73 - 3.77 (2H, m), 3.86 (3H, s), 6.77 (1H, d), 6.98 - 7.01 (2H, m), 7.75 - 7.79 (2H, m), 7.92 (1H, d)	469

Examples 456-461

The following compounds were prepared in 54 - 96% yield by an analogous method to Example 394, starting from 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in General Synthetic Method 8, preparation of starting materials) and the appropriate sulfonyl chloride:-

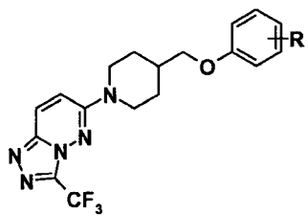


Ex.	R	1H NMR (399.9 MHz, $CDCl_3$)	m/z [M+H]+
456	3-F	δ 2.05 - 2.11 (2H, m), 3.36 (2H, t), 3.54 (2H, t), 3.82 (2H, t), 3.90 (2H, t), 6.94 (1H, d), 7.14 - 7.19 (1H, m), 7.36 - 7.41 (1H, m), 7.43 - 7.46 (1H, m), 7.52 - 7.55 (1H, m), 7.93 (1H, d)	445
457	4-F	δ 2.06 - 2.12 (2H, m), 3.29 (2H, t), 3.51 (2H, t), 3.83 (2H, t), 3.90 (2H, t), 6.95 (1H, d), 7.09 - 7.15 (2H, m), 7.75 - 7.80 (2H, m), 7.94 (1H, d)	445
458	3-OMe	δ 2.03 - 2.09 (2H, m), 3.37 (2H, t), 3.54 (2H, t), 3.78 -	457

		3.81 (5H, m), 3.88 (2H, t), 6.90 - 6.95 (2H, m), 7.22 - 7.23 (1H, m), 7.28 - 7.31 (2H, m), 7.90 (1H, d)	
459	2-OMe	δ 2.07 - 2.13 (2H, m), 3.31 (2H, t), 3.56 - 3.58 (2H, m), 3.87 - 3.91 (7H, m), 6.94 - 7.04 (3H, m), 7.46 - 7.50 (1H, m), 7.90 - 7.94 (2H, m)	457
460	2-F	δ 2.06 - 2.12 (2H, m), 3.41 (2H, t), 3.60 (2H, t), 3.85 (2H, t), 3.90(2H, t), 6.98 (1H, d), 7.03 - 7.08 (1H, m), 7.19 - 7.23 (1H, m), 7.44 - 7.50 (1H, m), 7.85 - 7.89 (1H, m), 7.94 (1H, d)	445
461	4-OMe	δ 2.02 - 2.08 (2H, m), 3.34 (2H, t), 3.50 (2H, t), 3.78 - 3.81 (5H, m), 3.87 (2H, t), 6.81 - 6.84 (2H, m), 6.91 (1H, d), 7.64 - 7.67 (2H, m), 7.90 (1H, d)	457

Examples 462-476

The following compounds were prepared in 15 - 70% yield by an analogous method to Example 447, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) and the appropriate phenol:-



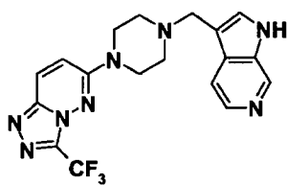
Ex.	R	1H NMR (399.9 MHz, DMSO-d_6)	m/z [M+H]+
462	2-OMe	δ 1.32 - 1.43 (2H, m), 1.90 - 1.94 (2H, m), 2.09 - 2.15 (1H, m), 3.05 - 3.12 (2H, m), 3.76 (3H, s), 3.85 (2H, d), 4.30 - 4.34 (2H, m), 6.85 - 6.92 (2H, m), 6.95 - 6.98 (2H, m), 7.63 (1H, d), 8.23 (1H, d)	408
463	4-F	δ 1.33 - 1.42 (2H, m), 1.89 - 1.92 (2H, m), 2.07 - 2.13 (1H, m), 3.03 - 3.11 (2H, m), 3.85 (2H, d), 4.30 - 4.34 (2H, m), 6.94 - 6.97 (2H, m), 7.09 - 7.13 (2H, m), 7.63 (1H, d), 8.23 (1H, d)	396
464	3-F	δ 1.33 - 1.43 (2H, m), 1.88 - 1.92 (2H, m), 2.07 - 2.14	396

		(1H, m), 3.04 - 3.11 (2H, m), 3.90 (2H, d), 4.30 - 4.34 (2H, m), 6.73 - 6.84 (3H, m), 7.28 - 7.34 (1H, m), 7.63 (1H, d), 8.23 (1H, d)	
465	4-OMe	δ 1.31 - 1.41 (2H, m), 1.88 - 1.92 (2H, m), 2.05 - 2.11 (1H, m), 3.03 - 3.10 (2H, m), 3.70 (3H, s), 3.81 (2H, d), 4.30 - 4.34 (2H, m), 6.84 - 6.89 (4H, m), 7.63 (1H, d), 8.23 (1H, d)	408
466	3-OMe	δ 1.32 - 1.42 (2H, m), 1.89 - 1.93 (2H, m), 2.05 - 2.14 (1H, m), 3.04 - 3.11 (2H, m), 3.73 (3H, s), 3.86 (2H, d), 4.30 - 4.34 (2H, m), 6.49 - 6.54 (3H, m), 7.17 (1H, t), 7.63 (1H, d), 8.23 (1H, d)	408
467	2-F	δ 1.34 - 1.44 (2H, m), 1.89 - 1.93 (2H, m), 2.11 - 2.18 (1H, m), 3.05 - 3.12 (2H, m), 3.96 (2H, d), 4.30 - 4.34 (2H, m), 6.91 - 6.97 (1H, m), 7.10 - 7.23 (3H, m), 7.63 (1H, d), 8.23 (1H, d)	396
468	4-CF3	δ 1.34 - 1.44 (2H, m), 1.89 - 1.94 (2H, m), 2.10 - 2.19 (1H, m), 3.05 - 3.12 (2H, m), 3.97 (2H, d), 4.31 - 4.34 (2H, m), 7.13 (2H, d), 7.62 - 7.66 (3H, m), 8.24 (1H, d)	446
469	2-CN	δ 1.39 - 1.49 (2H, m), 1.91 - 1.94 (2H, m), 2.15 - 2.22 (1H, m), 3.07 - 3.14 (2H, m), 4.06 (2H, d), 4.32 - 4.36 (2H, m), 7.08 - 7.12 (1H, m), 7.26 (1H, d), 7.63 - 7.68 (2H, m), 7.71 - 7.73 (1H, m), 8.24 (1H, d)	403
470	4-Cl	δ 1.32 - 1.42 (2H, m), 1.88 - 1.92 (2H, m), 2.05 - 2.14 (1H, m), 3.03 - 3.10 (2H, m), 3.87 (2H, d), 4.29 - 4.33 (2H, m), 6.95 - 6.99 (2H, m), 7.29 - 7.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d)	412
471	2-CF3	δ 1.39 - 1.49 (2H, m), 1.88 - 1.91 (2H, m), 2.12 - 2.19 (1H, m), 3.06 - 3.13 (2H, m), 4.02 (2H, d), 4.31 - 4.35 (2H, m), 7.09 (1H, t), 7.25 (1H, d), 7.60 - 7.65 (3H, m), 8.24 (1H, d)	446

472	3-CF3	δ 1.35 - 1.45 (2H, m), 1.91 - 1.94 (2H, m), 2.09 - 2.18 (1H, m), 3.05 - 3.12 (2H, m), 3.97 (2H, d), 4.31 - 4.34 (2H, m), 7.24 - 7.30 (3H, m), 7.53 (1H, t), 7.64 (1H, d), 8.24 (1H, d)	446
473	3-Cl	δ 1.32 - 1.42 (2H, m), 1.87 - 1.92 (2H, m), 2.07 - 2.15 (1H, m), 3.04 - 3.11 (2H, m), 3.91 (2H, d), 4.30 - 4.33 (2H, m), 6.92 - 6.94 (1H, m), 6.98 - 7.00 (1H, m), 7.03 (1H, t), 7.31 (1H, t), 7.63 (1H, d), 8.23 (1H, d)	412
474	4-CN	δ 1.33 - 1.44 (2H, m), 1.87 - 1.92 (2H, m), 2.08 - 2.17 (1H, m), 3.05 - 3.11 (2H, m), 3.99 (2H, d), 4.30 - 4.34 (2H, m), 7.11 - 7.14 (2H, m), 7.63 (1H, d), 7.75 - 7.78 (2H, m), 8.23 (1H, d)	403
475	2-Cl	δ 1.37 - 1.48 (2H, m), 1.92 - 1.96 (2H, m), 2.12 - 2.19 (1H, m), 3.06 - 3.13 (2H, m), 3.98 (2H, d), 4.31 - 4.35 (2H, m), 6.93 - 6.97 (1H, m), 7.14 - 7.16 (1H, d), 7.28 - 7.32 (1H, m), 7.41 - 7.43 (1H, m), 7.64 (1H, d), 8.24 (1H, d)	412
476	3-CN	δ 1.34 - 1.43 (2H, m), 1.88 - 1.92 (2H, m), 2.10 - 2.16 (1H, m), 3.05 - 3.12 (2H, m), 3.96 (2H, d), 4.30 - 4.34 (2H, d), 7.29 - 7.32 (1H, m), 7.39 - 7.41 (1H, m), 7.43 - 7.44 (1H, m), 7.47 - 7.51 (1H, m), 7.63 (1H, d), 8.24 (1H, d)	403

Example 477

Preparation of 6-[4-(1H-pyrrolo[2,3-c]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

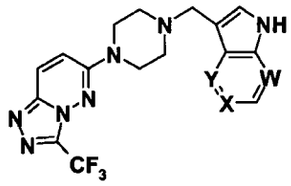


Obtained in 68% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 1H-pyrrolo[2,3-c]pyridine-3-carboxaldehyde (obtained as described in J. Chem. Soc. (C) 1970, 498).

1H NMR (399.9 MHz, DMSO-d6) δ 2.25 (4H, t), 3.60 (4H, t), 3.73 (2H, s), 7.53 (1H, s), 7.57 (1H, d), 7.63 - 7.65 (1H, m), 8.10 (1H, d), 8.23 (1H, d), 8.72 (1H, d), 11.47 (1H, s); m/z = 403 [M+H]+.

Examples 478-480

The following compounds were prepared in 61-82% yield by General Synthetic Method 5, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 1H-pyrrolopyridine-3-carboxaldehyde (obtained as described in the corresponding footnote):-



Ex.	W	X	Y	Note	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
478	N	CH	CH	[1]	δ 2.55 (4H, s), 3.60 (4H, s), 3.71 (2H, s), 7.04 - 7.07 (1H, m), 7.39 (1H, s), 7.57 (1H, d), 8.07 (1H, d), 8.20 - 8.24 (2H, m), 11.48 (1H, s)	403
479	CH	CH	N	[2]	δ 2.59 (4H, t), 3.60 (4H, t), 3.81 (2H, s), 7.08 - 7.11 (1H, m), 7.55 - 7.58 (2H, m), 7.73 - 7.75 (1H, m), 8.22 (1H, d), 8.32 - 8.34 (1H, m), 11.21 (1H, s)	403
480	CH	N	CH	[3]	δ 2.56 (4H, t), 3.62 (4H, t), 3.77 (2H, s), 7.34 - 7.35 (1H, m), 7.36 (1H, d), 7.58 (1H, d), 8.16 (1H, d), 8.23 (1H, d), 8.97 (1H, d), 11.34 (1H, s)	403

Obtained from 1H-pyrrolo[2,3-b]pyridine-3-carboxaldehyde, prepared as described in Bioorg. Med. Chem. 2004, 12 , 5505.

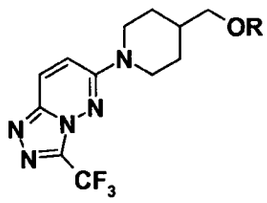
[2] Obtained from 1H-pyrrolo[3,2-b]pyridine-3-carboxaldehyde, prepared as described in US Pat Appl. 2007/0123535, page 35.

[3] Obtained from 1H-pyrrolo[3,2-c]pyridine-3-carboxaldehyde, prepared as follows:-

A solution of 1H-pyrrolo[3,2-c]pyridine (2.95 g, 25 mmol) and hexamethylenetetramine (5.26 g, 37.50 mmol) in acetic acid (25 mL) and water (50 mL) was heated under reflux for 4 hours. The reaction mixture was evaporated and the residue was purified by MPLC silica chromatography, elution gradient 5 to 10% ammonia-methanol in DCM. Product containing fractions were evaporated to dryness and tritutated with MeCN to afford 1H-pyrrolo[3,2-c]pyridine-3-carbaldehyde (0.170 g, 4.65%) as a white crystalline solid.
1H NMR (399.9 MHz, DMSO-d6) δ 7.52 - 7.54 (1H, m), 8.36 (1H, d), 8.42 (1H, s), 9.30 (1H, d), 10.01 (1H, s), 12.41 (1H, s); m/z = 188 [M+H]+ (detected as adduct with acetonitrile used in mass spectral determination).

Examples 481-482

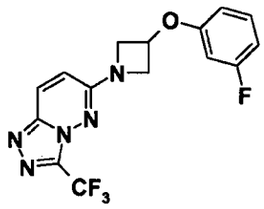
The following compounds were prepared in 10-48% yield by an analogous method to Example 294, starting from 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate alcohol:-



Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
481	oxetan-3-yl	δ 1.31 - 1.42 (2H, m), 1.86 - 1.97 (3H, m), 3.00 - 3.07 (2H, m), 3.24 (2H, d), 4.23 - 4.28 (2H, m), 4.50 - 4.55 (1H, m), 4.57 - 4.60 (2H, m), 4.75 - 4.78 (2H, m), 7.09 (1H, d), 7.90 (1H, d)	358
482	2,2,2-trifluoroethyl	δ 1.35 - 1.39 (2H, m), 1.90 - 1.99 (3H, m), 2.99 - 3.06 (2H, m), 3.50 - 3.52 (2H, m), 3.83 (2H, q), 4.24 - 4.28 (2H, m), 7.09 (1H, d), 7.91 (1H, d)	384

Example 483

Preparation of 6-[3-(3-fluorophenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A stirred partial solution of 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (169 mg, 0.5 mmol), 3-fluorophenol (112 mg, 1.5 mmol) and potassium carbonate (207 mg, 1.5 mmol) in DMF (3 mL) was heated at 100°C for 24 hours. The reaction mixture was filtered and the product was isolated by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 6-[3-(3-fluorophenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (58 mg, 33%) as a solid.

1H NMR (399.9 MHz, CDCl3) δ 4.17 - 4.21 (2H, m), 4.50 - 4.54 (2H, m), 5.05 - 5.10 (1H, m), 6.44 - 6.47 (1H, m), 6.50 - 6.52 (1H, m), 6.60 (1H, d), 6.66 - 6.71 (1H, m), 7.18 - 7.24 (1H, m), 7.88 (1H, d); m/z = 354 [M+H]+.

The starting 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was prepared as follows:-

Preparation of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-ol

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (5.56 g, 25 mmol), azetidin-3-ol hydrochloride (3.01 g, 27.50 mmol) and DIPEA (10.89 mL, 62.50 mmol) in DMF (50 mL) was heated at 70°C for 1 hour. The solution was slowly diluted with water and the product crystallised. The precipitate was collected by filtration, washed with water, drained well and washed with ether. It was dried under vacuum to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-ol (5.30 g, 82%) as a white crystalline solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.88 (2H, q), 4.32 - 4.36 (2H, m), 4.61 - 4.65 (1H, m), 5.82 - 5.83 (1H, m), 7.04 (1H, d), 8.22 (1H, d); m/z = 260 [M+H]+.

Preparation of 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

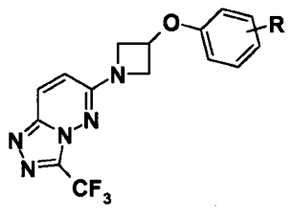
Methanesulfonyl chloride (0.929 mL, 12 mmol) was added dropwise to a stirred

partial solution of 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)azetidin-3-ol (2.59 g, 10 mmol) and triethylamine (1.951 mL, 14 mmol) in DCM (17 mL) at 0°C. The solution was allowed to warm to ambient temperature and stirred for 30 minutes. The precipitate was collected by filtration, washed with a little DCM, a little ethanol and ether. It was dried under vacuum to afford 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.400 g, 71.2%) as a white crystalline solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.32 (3H, s), 4.25 - 4.29 (2H, m), 4.54 - 4.59 (2H, m), 5.45 - 5.50 (1H, m), 7.11 (1H, d), 8.29 (1H, d); m/z = 338 [M+H]+.

Examples 484-486

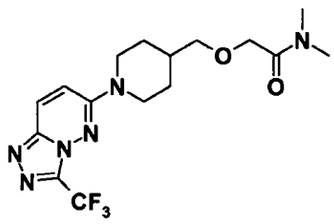
The following compounds were prepared in 49-56% yield by an analogous method to Example 483, starting from 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate phenol:-



Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
484	4-F	δ 4.16 - 4.20 (2H, m), 4.48 - 4.52 (2H, m), 5.02 - 5.07 (1H, m), 6.60 (1H, d), 6.66 - 6.70 (2H, m), 6.92 - 6.98 (2H, m), 7.88 (1H, d)	354
485	3-OMe	δ 3.74 (3H, s), 4.16 - 4.20 (2H, m), 4.48 - 4.53 (2H, m), 5.05 - 5.10 (1H, m), 6.29 - 6.32 (2H, m), 6.51 - 6.54 (1H, m), 6.60 (1H, d), 7.13 - 7.18 (1H, m), 7.88 (1H, d)	366
486	4-OMe	δ 3.72 (3H, s), 4.15 - 4.19 (2H, m), 4.46 - 4.50 (2H, m), 5.00 - 5.05 (1H, m), 6.60 (1H, d), 6.65 - 6.69 (2H, m), 6.77 - 6.82 (2H, m), 7.88 (1H, d)	366

Example 487

Preparation of N,N-dimethyl-2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetamide



A stirred solution of methyl 2-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetate (95 mg, 0.25 mmol) in 2M dimethylamine in methanol (2.0 mL, 4.00 mmol) was heated at 120°C in a microwave reactor for 1 hour. The reaction mixture was evaporated and the crude product was purified by preparative LCMS (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N,N-dimethyl-2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetamide (48.0 mg, 48.8%) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 1.32 - 1.43 (2H, m), 1.93 (2H, d), 1.98 - 2.02 (1H, m), 2.96 (3H, s), 3.00 (3H, s), 3.03 - 3.07 (2H, m), 3.41 - 3.43 (2H, m), 4.15 (2H, s), 4.25 (2H, d), 7.09 (1H, d), 7.90 (1H, d); m/z = 387 [M+H]+.

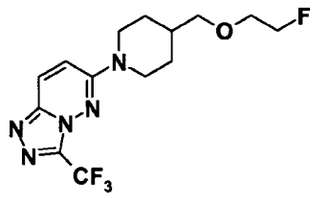
The methyl 2-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetate used as starting material was prepared as follows:-

Sodium hydride (60% dispersion in oil, 0.120 g, 3.0 mmol) was added to neat methyl glycolate (1.544 mL, 20.0 mmol). When the effervescence had subsided 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.759 g, 2.0 mmol) was added and the mixture was heated at 100°C for 40 minutes. The reaction mixture was partitioned between DCM and water. The organic phase was washed with water and brine, dried over $MgSO_4$ and evaporated. The product was isolated by MPLC silica chromatography, eluting with ethyl acetate. The product containing fractions were evaporated to an oil which crystallised from ether, giving methyl 2-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetate (0.130 g, 17%).

1H NMR (399.9 MHz, CDCl3) δ 1.33 - 1.43 (2H, m), 1.92 - 2.02 (3H, m), 3.00 - 3.07 (2H, m), 3.42 - 3.44 (2H, m), 3.76 (3H, s), 4.09 (2H, s), 4.23 - 4.26 (2H, m), 7.08 (1H, d), 7.90 (1H, d); m/z = 374 [M+H]+.

Example 488

Preparation of 6-[4-[(2-fluoroethoxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



(Diethylamino)sulfur trifluoride (0.059 mL, 0.45 mmol) was added dropwise to a stirred solution of 2-[[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl)methoxy]ethanol (104 mg, 0.3 mmol) in DCM (3 mL) at -70°C. The solution was allowed to warm to ambient temperature and stir for 18 hours. The solution was diluted with DCM and washed with 2M aqueous K_2CO_3. The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[(2-fluoroethoxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (22.0 mg, 21%) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 1.30 - 1.40 (2H, m), 1.90 - 2.01 (3H, m), 2.99 - 3.06 (2H, m), 3.40 (2H, d), 3.65 - 3.74 (2H, m), 4.23 - 4.27 (2H, m), 4.49 - 4.63 (2H, m), 7.09 (1H, d), 7.90 (1H, d); m/z = 348 [M+H]+.

The starting 2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]ethanol was prepared as follows:-

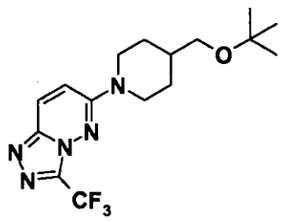
Sodium hydride (60% dispersion in oil, 0.180 g, 4.5 mmol) was added to neat tetrahydropyranylethyleneglycol (3 g, 20.5 mmol). When the effervescence had subsided 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 294, preparation of starting materials) (1.138 g, 3 mmol) was added and the mixture was heated at 100°C for 40 minutes. The reaction mixture was partitioned between DCM and water. The organic phase was washed

with water and brine, dried over $MgSO_4$ and evaporated. The crude intermediate was disolved in methanol (20 mL) and p-toluenesulfonic acid monohydrate (0.855 g, 4.5 mmol) was added. The solution was stirred for 1 hour and then evaporated. The reaction mixture was partitioned between DCM and water and the organic phase was washed with water and brine, dried over $MgSO_4$ and evaporated. The product was isolated by MPLC silica chromatography, eluting with 5% methanol / DCM. The product containing fractions were evaporated giving a crystalline solid which was triturated with ether, giving 2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]ethanol (0.563 g, 54%)

1H NMR (399.9 MHz, CDCl3) δ 1.31 - 1.41 (2H, m), 1.89 - 2.00 (3H, m), 2.99 - 3.06 (2H, m), 3.38 - 3.39 (2H, m), 3.55 - 3.57 (2H, m), 3.74 - 3.76 (2H, m), 4.23 - 4.27 (2H, m), 7.08 (1H, d), 7.90 (1H, d), OH not observed; m/z = 346 [M+H]+.

Example 489

Preparation of 6-[4-(tert-butoxymethyl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



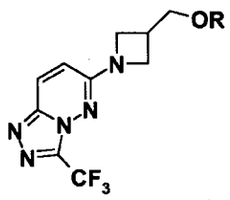
A stirred solution of [1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) (151 mg, 0.5 mmol) and p-toluenesulfonic acid monohydrate (190 mg, 1.0 mmol) in DCM (2 mL) was cooled to -70°C and 2-methylpropene (1 mL, 10.48 mmol) was condensed in from a cylinder. The mixture was stirred for 2 days at ambient temperature in a sealed tube. The tube was re-cooled to open then allowed to warm to ambient temperature with stirring. The solution was diluted with DCM and washed with 2M aqueous K_2CO_3. The organic phase was dried over $MgSO_4$ and evaporated. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness

to afford 6-(4-(tert-butoxymethyl)piperidin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (98 mg, 54%) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 1.18 (9H, s), 1.24 - 1.35 (2H, m), 1.79 - 1.84 (1H, m), 1.92 (2H, d), 2.98 - 3.05 (2H, m), 3.23 (2H, d), 4.25 (2H, d), 7.09 (1H, d), 7.89 (1H, d); m/z = 358 [M+H]+.

Examples 490-493

The following compounds were prepared in 43-63% yield by an analogous method to Example 447, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-yl]methanol and the appropriate phenol:-



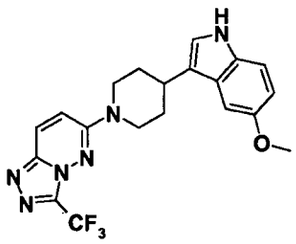
Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
490	3-fluorophenyl	δ 3.26 - 3.33 (1H, m), 4.08 - 4.11 (2H, m), 4.18 (2H, d), 4.34 (2H, t), 6.61 - 6.66 (2H, m), 6.68 - 6.73 (2H, m), 7.21 - 7.27 (1H, m), 7.92 (1H, s)	368
491	3-fluorophenyl	δ 3.25 - 3.32 (1H, m), 4.08 - 4.11 (2H, m), 4.15 (2H, d), 4.34 (2H, t), 6.64 (1H, d), 6.84 - 6.87 (2H, m), 6.96 - 7.02 (2H, m), 7.91 (1H, d)	368
492	pyridin-3-yl	δ 3.30 - 3.37 (1H, m), 4.10 - 4.13 (2H, m), 4.26 (2H, d), 4.37 (2H, t), 6.65 (1H, d), 7.20 - 7.26 (2H, m), 7.93 (1H, d), 8.27 - 8.28 (1H, m), 8.34 (1H, q)	351
493	pyrimidin-2-yl	δ 3.32 - 3.40 (1H, m), 4.10 - 4.13 (2H, m), 4.34 (2H, t), 4.61 - 4.63 (2H, m), 6.64 (1H, d), 7.00 (1H, t), 7.90 (1H, d), 8.54 (2H, d)	352

The starting [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-yl]methanol was prepared as follows:-

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.44 g, 20.0 mmol), azetidin-3-ylmethanol (2.25 g, 22.0 mmol) and DIPEA (5.21 mL, 30.0 mmol) in DMF (40 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between water and 2M aqueous K_2CO_3. The organic phase was washed with water and brine and dried over $MgSO_4$. The crude product was purified by MPLC silica chromatography, eluting with 5% MeOH in DCM. Pure fractions were evaporated to dryness and triturated with ether, giving [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-yl]methanol (1.65 g, 30%) as a cream crystalline solid.
1H NMR (399.9 MHz, DMSO-d6) δ 2.87 (1H, t), 3.59 (2H, t), 3.86 - 3.89 (2H, m), 4.14 (2H, t), 4.88 (1H, t), 7.03 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]+.

Example 494

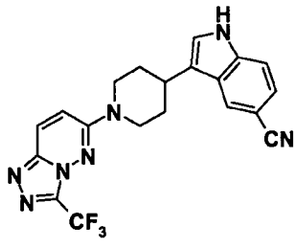
Preparation of 6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (160 mg, 0.72 mmol), 5-methoxy-3-(piperidin-4-yl)-1H-indole (obtained as described in PCT Int. Appl. WO 2004006922, Intermediate 37) (166 mg, 0.72 mmol) and DIPEA (0.138 mL, 0.79 mmol) in DMF (2 mL) were stirred and heated at 80°C for 1 hour. The resulting mixture was cooled to room temperature and quenched in water (10 mL) to give a precipitate. The solid was collected by filtration, washed sequentially with water, acetonitrile and ether, and air dried to give 6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (189 mg, 63%) as a colourless solid.
1H NMR (399.9 MHz, DMSO-d6) δ 1.67 - 1.75 (2H, m), 2.10 - 2.13 (2H, m), 3.08 - 3.14 (1H, m), 3.18 - 3.25 (2H, m), 3.76 (3H, s), 4.39 - 4.42 (2H, m), 6.73 (1H, d), 7.07 (2H, s), 7.23 (1H, d), 7.67 (1H, d), 8.24 (1H, d), 10.63 (1H, s); m/z 417 [M+H]+.

Example 495

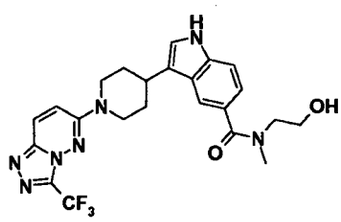
Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carbonitrile



Obtained in 88% yield by an analogous procedure to Example 494, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-(piperidin-4-yl)-1H-indole-5-carbonitrile (obtained as described in PCT Int. Appl. WO 2001043740, Example 3). 1H NMR (399.9 MHz, DMSO-d6) δ 1.68 - 1.78 (2H, m), 2.11 - 2.13 (2H, m), 3.18 - 3.24 (3H, m), 4.40 - 4.43 (2H, m), 7.36 (1H, s), 7.42 (1H, d), 7.51 (1H, d), 7.68 (1H, d), 8.24 (2H, m), 11.43 (1H, s); m/z 410 [M-H]-.

Example 496

Preparation of N-(2-hydroxyethyl)-N-methyl-3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxamide



HATU (139 mg, 0.37 mmol) was added portionwise at ambient temperature to a stirred mixture of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid (150 mg, 0.35 mmol), 2-(methylamino)ethanol (0.034 mL, 0.42 mmol) and DIPEA (0.073 mL, 0.42 mmol) in DMF (2.0 mL). The resulting solution was stirred for 2 hours then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-(2-hydroxyethyl)-N-methyl-

3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxamide (155 mg, 91%) as a colourless solid .

1H NMR (399.9 MHz, DMSO-d6) δ 1.68 - 1.78 (2H, m), 2.09 - 2.13 (2H, m), 3.01 (3H, s), 3.13 - 3.24 (3H, m), 3.29 - 3.70 (4H, m), 4.40 - 4.43 (2H, m), 4.78 (1H, t), 7.14 (1H, dd), 7.21 (1H, d), 7.36 (1H, d), 7.68 (1H, d), 7.71 (1H, s), 8.25 (1H, d), 11.03 (1H, s); m/z = 488 [M+H]+.

The 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid used as starting material was prepared as follows:-

Preparation of 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylic acid

Potassium hydroxide (5.17 g, 92.08 mmol) was added to 1H-indole-5-carboxylic acid (3.71 g, 23.02 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (9.17 g, 46.04 mmol) in methanol (80 mL) at ambient temperature and the resulting solution was stirred at 65°C for 18 hours. The mixture was then cooled to ambient temperature, quenched in water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The extracts were discarded and the aqueous phase acidified to pH 2-3 wth 2M hydrochloric acid to give a pale yellow solid. The solid was collected by filtration, washed sequentially with water and ether and air dried to give 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylic acid (5.62 g, 71.3%) as a colourless solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.45 (9H, s), 2.50 - 2.55 (2H, m), 3.59 (2H, t), 4.06 - 4.11 (2H, m), 6.16 (1H, m), 7.46 (1H, d), 7.55 (1H, d), 7.76 (1H, dd), 8.48 (1H, s), 11.51 (1H, s), 12.45 (1H, br s); m/z = 341 [M-H]-.

Preparation of methyl 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylate

Iodomethane (1.22 mL, 19.63 mmol) was added in one portion to 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylic acid (6.72 g, 19.63 mmol) and potassium carbonate (3.26 g, 23.55 mmol) in DMF (60 mL) at ambient temperature. The resulting mixture was stirred at ambient temperature for 3 hours then quenched in water (200 mL) and extracted with MTBE (2 x 100 mL). The extract was washed sequentially with water (3 x 100 mL) and saturated brine, dried over $MgSO_4$ and concentrated by evaporation then purified by flash silica chromatography, elution gradient 20 to 35% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl

3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylate (5.09 g, 73%) as a colourless solid.

1H NMR (399.9 MHz, CDCl3) δ 1.51 (9H, s), 2.55 - 2.58 (2H, m), 3.67 - 3.70 (2H, m), 3.95 (3H, s), 4.14 - 4.18 (2H, m), 6.23 (1H, m), 7.22 (1H, d), 7.38 (1H, d), 7.93 (1H, dd), 8.42 (1H, s), 8.63 (1H, s); m/z = 355 [M-H]-.

Preparation of methyl 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-5-carboxylate

Methyl 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylate (5.0 g, 14.03 mmol), ammonium formate (4.42 g, 70.14 mmol) and palladium (5% on activated carbon, 200 mg) in ethanol (80 mL) were stirred and refluxed for 1 hour. The resulting mixture was cooled to ambient temperature and filtered through diatomaceous earth. The filtrate was concentrated by evaporation then treated with dilute aqueous ammonium chloride (100 mL) and extracted with ethyl acetate. The extract was washed sequentially with water and saturated brine, dried over $MgSO_4$ and evaporated to a colourless solid. The solid was triturated with ether, then collected by filtration and air dried to give methyl 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-5-carboxylate (4.59 g, 91%) as a colourless solid.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 1.60 - 1.70 (2H, m), 2.03 - 2.06 (2H, m), 2.88 - 2.95 (2H, m), 3.03 (1H, tt), 3.94 (3H, s), 4.17 - 4.32 (2H, m), 7.01 (1H, d), 7.37 (1H, d), 7.90 (1H, dd), 8.26 (1H, s), 8.39 (1H, s); m/z = 357 [M-H]-.

Preparation of methyl 3-(piperidin-4-yl)-1H-indole-5-carboxylate

TFA (10 mL) was added in one portion at ambient temperature to a stirred solution of methyl 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-5-carboxylate (4.58 g, 12.78 mmol) in DCM (30 mL). The resulting solution was stirred for 30 minutes then applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol. Pure fractions were combined and concentrated by evaporation then triturated with ether to give a solid which was collected by filtration and air dried to give methyl 3-(piperidin-4-yl)-1H-indole-5-carboxylate (2.69 g, 81%) as a pale yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.53 - 1.63 (2H, m), 1.86 - 1.89 (2H, m), 2.64 - 2.70 (2H, m), 2.86 - 2.92 (1H, m), 3.02 - 3.05 (2H, m), 3.85 (3H, s), 7.21 (1H, d), 7.42 (1H, d), 7.71 (1H, dd), 8.26 (1H, s), 11.20 (1H, s); m/z = 257 [M-H]-.

Preparation of methyl 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylate

6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1.8 g, 8.09 mmol), methyl 3-(piperidin-4-yl)-1H-indole-5-carboxylate (2.09 g, 8.09 mmol) and DIPEA (1.55 mL, 8.90 mmol) in DMF (25 mL) were stirred and heated at 80°C for 1 hour. The resulting mixture was then cooled to ambient temperature and quenched in water (60 mL) to give a precipitate which was collected by filtration, washed sequentially with water, acetonitrile and ether and dried under vacuum to give methyl 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylate (3.29 g, 92%) as a cream solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.70 - 1.80 (2H, m), 2.09 - 2.12 (2H, m), 3.21 - 3.28 (3H, m), 3.85 (3H, s), 4.40 - 4.43 (2H, m), 7.28 (1H, d), 7.44 (1H, d), 7.68 (1H, d), 7.73 (1H, dd), 8.25 (1H, d), 8.31 (1H, d), 11.26 (1H, s); m/z = 445 [M+H]+.

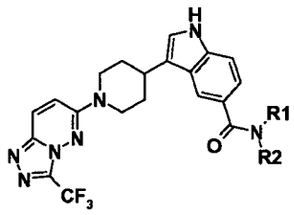
Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid

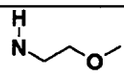
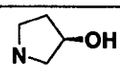
Methyl 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylate (3.28 g, 7.38 mmol) and 2M NaOH (10 mL, 7.38 mmol) in methanol (80 mL) were heated under reflux for 40 hours. The resulting solution was concentrated by evaporation, then acidified to pH 2-3 with 2M hydrochloric acid to give a colourless precipitate. The precipitate was collected by filtration, washed sequentially with water, acetonitrile and ether and dried under vacuum to afford 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid (2.83 g, 89%) as a colourless solid.

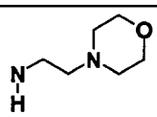
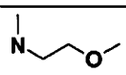
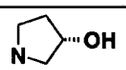
1H NMR (399.9 MHz, DMSO-d6) δ 1.69 - 1.79 (2H, m), 2.09 - 2.13 (2H, m), 3.18 - 3.26 (3H, m), 4.40 - 4.43 (2H, m), 7.23 (1H, d), 7.37 (1H, d), 7.68 (1H, d), 7.72 (1H, dd), 8.25 (1H, d), 8.29 (1H, s), 11.19 (1H, s); m/z = 431 [M+H]+.

Examples 497-505

The following compounds were prepared in 75-98% yield by an analogous method to Example 496, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid and the appropriate amine:-

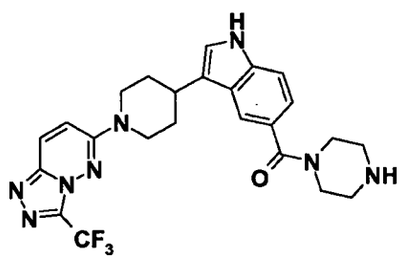


Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
497		δ 1.68 - 1.78 (2H, m), 2.08 - 2.12 (2H, m), 2.18 (3H, s), 2.25 - 2.35 (4H, m), 3.15 - 3.24 (3H, m), 3.42 - 3.61 (4H, m), 4.40 - 4.43 (2H, m), 7.11 (1H, dd), 7.23 (1H, d), 7.38 (1H, d), 7.68 (1H, s), 7.69 (1H, d), 8.26 (1H, d), 11.07 (1H, s)	513
498		δ 1.70 - 1.81 (2H, m), 2.14 - 2.17 (2H, m), 3.15 - 3.25 (3H, m), 3.29 (3H, s), 3.44 - 3.50 (4H, m), 4.43 - 4.46 (2H, m), 7.22 (1H, d), 7.36 (1H, d), 7.64 (1H, dd), 7.70 (1H, d), 8.20 (1H, s), 8.27 (1H, d), 8.41 (1H, t), 11.09 (1H, s)	488
499	NMe2	δ 1.68 - 1.78 (2H, m), 2.09 - 2.12 (2H, m), 2.99 (6H, s), 3.13 - 3.24 (3H, m), 4.40 - 4.43 (2H, m), 7.14 (1H, dd), 7.21 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.70 (1H, s), 8.25 (1H, d), 11.05 (1H, s).	458
500		δ 1.66 - 2.01 (4H, m), 2.09 - 2.12 (2H, m), 3.16 - 3.29 (3H, m), 3.46 - 3.70 (4H, m), 4.22 (m) & 4.34 (m, 1H), 4.40 - 4.43 (2H, m), 4.91 (d) & 5.02 (d, 1H), 7.22 (1H, d), 7.27 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.25 (1H, d), 11.06 (1H, s)	500
501		δ 1.68 - 1.93 (6H, m), 2.08 - 2.12 (2H, m), 3.15 - 3.24 (3H, m), 3.43 - 3.51 (4H, m), 4.40 - 4.43 (2H, m), 7.21 (1H, d), 7.27 (1H, dd), 7.36 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.26 (1H, d), 11.05 (1H, s)	484

502		δ 1.68 - 1.78 (2H, m), 2.09 - 2.12 (2H, m), 3.15 - 3.24 (3H, m), 3.47 - 3.65 (8H, m), 4.40 - 4.43 (2H, m), 7.14 (1H, dd), 7.23 (1H, d), 7.39 (1H, d), 7.69 (1H, d), 7.71 (1H, s), 8.26 (1H, d), 11.08 (1H, s)	500
503		δ 1.71 - 1.81 (2H, m), 2.14 - 2.16 (2H, m), 2.44 (4H, m), 2.47 - 2.50 (2H, m), 3.14 - 3.25 (3H, m), 3.42 (2H, q), 3.58 (4H, t), 4.43 - 4.46 (2H, m), 7.22 (1H, d), 7.37 (1H, d), 7.62 (1H, dd), 7.70 (1H, d), 8.16 (1H, s), 8.27 (1H, d), 8.28 (1H, t), 11.08 (1H, s)	543
504		δ 1.69 - 1.79 (2H, m), 2.09 - 2.12 (2H, m), 2.99 (3H, s), 3.14 - 3.29 (6H, m), 3.40 - 3.64 (4H, m), 4.40 - 4.44 (2H, m), 7.12 (1H, dd), 7.21 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.70 (1H, s), 8.25 (1H, d), 11.04 (1H, s)	502
505		δ 1.67 - 2.00 (4H, m), 2.09 - 2.12 (2H, m), 3.16 - 3.29 (3H, m), 3.45 - 3.70 (4H, m), 4.22 (m) & 4.34 (m, 1H), 4.40 - 4.43 (2H, m), 4.91 (d) & 5.02 (d, 1H), 7.22 (1H, d), 7.27 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.25 (1H, d), 11.06 (1H, s)	500

Example 506

Preparation of 6-[4-[5-(piperazin-1-ylcarbonyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



TFA (1 mL) was added in one portion at ambient temperature to a stirred solution of tert-butyl [4-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carbonyl]piperazine-1-carboxylate (190 mg, 0.32 mmol) in DCM (2 mL). The resulting solution was stirred for 1 hour then applied to an SCX column and eluted with MeOH followed by 2M ammonia in MeOH. Pure fractions were combined and concentrated by evaporation then triturated with ether to give a solid which was collected by filtration and air dried to give 6-[4-[5-(piperazin-1-ylcarbonyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (156 mg, 99%) as a colourless solid.

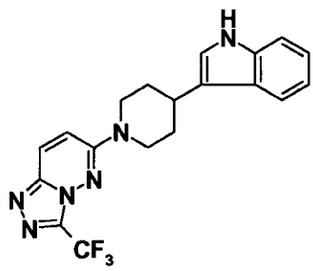
1H NMR (399.9 MHz, DMSO-d6) δ 1.68 - 1.78 (2H, m), 2.09 - 2.12 (2H, m), 2.83 - 2.93 (4H, m), 3.15 - 3.24 (3H, m), 3.50 - 3.64 (4H, m), 4.40 - 4.44 (2H, m), 7.14 (1H, dd), 7.23 (1H, d), 7.39 (1H, d), 7.69 (1H, d), 7.71 (1H, s), 8.26 (1H, d), 11.09 (1H, s); m/z = 499 [M+H]+.

The tert-butyl [4-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carbonyl]piperazine-1-carboxylate used as starting material was prepared in 91% yield by an analogous method to Example 496, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid and tert-butyl 1-piperazinecarboxylate.

m/z = 599 [M+H]+.

Example 507

Preparation of 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



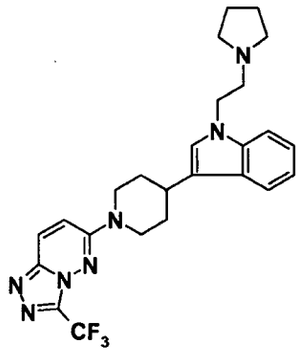
A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.223 g, 1.0 mmol), 3-(piperidin-4-yl)-1H-indole (0.240 g, 1.20 mmol) and DIPEA (0.257 mL, 1.50 mmol) in DMF (3 mL) was heated at 70°C for 1 hour. The reaction mixture was run onto an SCX cartridge, which was washed with MeOH and eluted with 2M ammonia in

methanol. The crude product was purified by MPLC silica chromatography, eluting with ethyl acetate. Pure fractions were evaporated to a gum which crystallised on trituration with ether to afford 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (0.119 g, 31%) as a colourless crystalline solid.

1H NMR (399.9 MHz, CDCl3) δ 1.81 - 1.92 (2H, m), 2.25 (2H, d), 3.15 - 3.27 (3H, m), 4.37 (2H, d), 6.99 - 6.99 (1H, m), 7.11 - 7.15 (2H, m), 7.19 - 7.24 (1H, m), 7.38 - 7.40 (1H, m), 7.64 (1H, d), 7.92 (1H, d), 8.02 (1H, s); m/z = 387 [M+H]+.

Example 508

Preparation of 6-[4-[1-(2-pyrrolidin-1-ylethyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



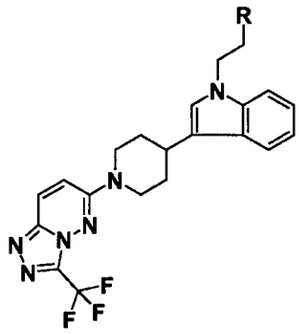
Sodium hydride (60% dispersion in oil, 31 mg, 0.75 mmol) was added to 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 507) (150 mg, 0.39 mmol) suspended in DMF (2 mL) at 0°C under nitrogen. The resulting mixture was stirred at 0°C for 30 minutes, then 1-(2-chloroethyl)pyrrolidine hydrochloride (72.6 mg, 0.43 mmol) in DMF (1 mL) was added . The resulting mixture was stirred at ambient temperature for 18 hours. The reaction mixture was evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 6-[4-[1-(2-pyrrolidin-1-ylethyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (52.0 mg, 27.7%) as a white solid.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.63 - 1.67 (4H, m), 1.71 - 1.76 (2H, m), 2.09 (1H, d), 2.11 (1H, s), 2.45 - 2.48 (4H, m), 2.76 (2H, t), 3.15 (1H, t), 3.19 - 3.25 (2H, m), 3.38 (1H,

s), 4.20 (2H, t), 4.40 (2H, d), 6.99 - 7.03 (1H, m), 7.10 - 7.14 (1H, m), 7.18 (1H, s), 7.42 (1H, d), 7.61 (1H, s), 7.67 (1H, d), 8.24 (1H, d); m/z 485 [M+H]+.

Examples 509-510

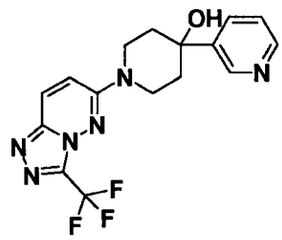
The following compounds were prepared in 26-32% yield by an analogous procedure to Example 508, starting from 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate alkyl chloride:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
509	Me2N	δ 1.70 - 1.74 (1H, m), 2.11 (2H, d), 2.18 (6H, s), 2.58 (2H, t), 3.15 (1H, t), 3.21 (1H, d), 3.25 - 3.26 (1H, m), 3.35 (1H, d), 4.18 (2H, t), 4.41 (2H, d), 7.00 (1H, t), 7.10 - 7.13 (1H, m), 7.18 (1H, s), 7.42 (1H, d), 7.63 (1H, s), 7.67 (1H, d), 8.24 (1H, d)	459
510	MeO	δ 1.70 - 1.74 (2H, m), 2.10 (1H, d), 2.12 (1H, s), 3.15 - 3.19 (1H, m), 3.22 (4H, s), 3.64 (2H, t), 4.26 (2H, t), 4.39 - 4.43 (2H, m), 6.99 - 7.03 (1H, m), 7.10 - 7.14 (1H, m), 7.15 (1H, s), 7.44 (1H, d), 7.61 (1H, s), 7.67 (1H, d), 8.25 (1H, d)	446

Example 511

Preparation of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.445 g, 2.0 mmol), 4-(pyridin-3-yl)piperidin-4-ol (obtained as described in Canadian Patent Application CA2076191, Example 87 (see also Example 87 in EP0533344B1)) (0.392 g, 2.20 mmol) and DIPEA (0.453 mL, 2.60 mmol) in DMF (4 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between DCM (20 mL) and 1M aqueous potassium carbonate (20 mL). The organic phase was washed with saturated aqueous sodium chloride, dried over $MgSO_4$ and evaporated to dryness, and the residue was triturated with ether. The precipitated solid was collected by filtration, washed with ether and dried under vacuum to afford 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (0.270 g, 37%) as a white crystalline solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.76 - 1.79 (2H, m), 2.03 - 2.11 (2H, m), 3.43 - 3.49 (2H, m), 4.23 (2H, d), 5.43 (1H, s), 7.33 - 7.37 (1H, m), 7.67 (1H, d), 7.87 - 7.90 (1H, m), 8.25 (1H, d), 8.45 - 8.46 (1H, m), 8.74 (1H, d); m/z = 363 [M-H]-.

Example 511.1

Large scale preparation of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (24.29 g, 109.15 mmol), 4-(pyridin-3-yl)piperidin-4-ol (21.40 g, 120.07 mmol) and DIPEA (24.72 ml, 141.90 mmol) in DMF (95 ml) was heated at 80°C for 1 hour. The solution was cooled to ambient temperature and slowly diluted with water, with seeding, to give a crystalline precipitate. The precipitate was collected by filtration, washed with water, acetonitrile and ether and dried under vacuum to afford 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (36.1 g, 91%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.76 (2H, d), 2.03 - 2.09 (2H, m), 3.41 - 3.47 (2H, m), 4.23 (2H, d), 5.47 (1H, s), 7.33 - 7.37 (1H, m), 7.68 (1H, d), 7.87 - 7.90 (1H, m), 8.26 (1H, d), 8.44 - 8.46 (1H, m), 8.74 (1H, d); m/z = 365 [M+H]+.

The 4-(pyridin-3-yl)piperidin-4-ol used as starting material was prepared as follows:-

Preparation of benzyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate

A solution of 3-bromopyridine (9.09 mL, 94.31 mmol) in diethyl ether (50 mL) was added

dropwise to a stirred solution of 1.6M n-butyl lithium in hexane (58.9 mL, 94.31 mmol) in diethyl ether (500 mL) cooled to -78°C, over a period of 15 minutes under nitrogen. The resulting suspension was stirred at -78°C for 1 hour. A solution of benzyl 4-oxopiperidine-1-carboxylate (20 g, 85.74 mmol) in diethyl ether (50 mL) and THF (50 mL) was added dropwise over 15 minutes. The reaction mixture was stirred at -78°C for 1 hour, warmed to 0°C over 2.5 hours and quenched with saturated ammonium chloride solution (500 ml). The mixture was extracted with ethyl acetate (2 x 500 mL) and the combined extracts were washed with brine (200 mL) then dried over $MgSO_4$ and filtered through a short pad of silica. The silica pad was washed through with ethyl acetate (4 x 250 mL) and the filtrate was concentrated under vacuum. The residue was purified by flash silica chromatography eluting with ethyl acetate. Pure fractions were evaporated to dryness to afford benzyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate (12.8 g, 48%) as an oil.

1H NMR (400.1 MHz, CDCl3) δ 1.71 - 1.82 (2H, m), 1.84 - 2.02 (2H, m), 3.25 - 3.43 (2H, m), 3.48 - 3.66 (1H, m), 4.03 - 4.19 (2H, m), 5.15 (2H, s), 7.27 - 7.39 (6H, m), 7.79 - 7.82 (1H, m), 8.37 - 8.40 (1H, m), 8.69 (1H, d); m/z = 313 [M+H]+.

Preparation of 4-(pyridin-3-yl)piperidin-4-ol

Benzyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate (32.7 g, 104.69 mmol) was dissolved in ethanol (350 mL) and hydrogenated over 10% palladium on carbon (3.2 g) at 2 bar pressure at 30°C. After hydrogen uptake was complete, the mixture was filtered through a pad of diatomaceous earth to remove the catalyst and the pad was washed with ethanol. The filtrate was concentrated to dryness under vacuum to give an oil which crystallised on standing overnight. The solid was triturated with MTBE (100 mL), collected by filtration, washed with MTBE (2 x 50 ml) and dried in a vacuum oven at 40°C to afford 4-(pyridin-3-yl)piperidin-4-ol (14.9 g, 80%) as a solid.

1H NMR (400.1 MHz, DMSO-d6) δ 1.53 - 1.61 (2H, m), 1.86 (2H, m), 2.74 - 2.83 (2H, m), 2.96 (2H, m), 7.34 (1H, m), 7.83 (1H, m), 8.43 (1H, m), 8.69 (1H, d).

Example 511.2

Preparation of crystalline 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (16.69 g, 75 mmol), 4-(pyridin-3-yl)piperidin-4-ol (14.70 g, 82.50 mmol) and N-ethyldiisopropylamine (16.98 mL, 97.50 mmol) in DMF (75 mL) was heated at 80 °C for

1hr. The solution was cooled to ambient temperature and slowly diluted with water, with seeding, giving a crystalline precipitate. The precipitate was collected by filtration, washed with water, acetonitrile and ether and dried under vacuum at 50°C to afford 4-(pyridin-3-yl)-1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-ol anhydrous Form A (25.2 g, 92 %) as a cream crystalline solid, which was used without further purification. Approximately 30mg of material was then slurried in approximately 1ml of ethyl acetate and stirred using a magnetic stirrer bar for 3 days at ambient temperature. The resultant material was air dried and analysed.

4-Pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 1. The intensity of the peaks at the corresponding 2θ values are shown in Table A below.

4-Pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A may thus also be characterised by providing at least one of the following 2θ values when measured using CuKa radiation: 9.18°, 15.51°, 16.01°, 18.94° and 24.59°.

Table A

Angle 2-Theta ° (2θ)	Intensity %
8.296	42
9.176	87.2
9.961	16.7
10.411	11.7
14.352	49
15.022	25.7
15.513	68.9
16.007	100
17.026	33.5
18.458	9.3
18.939	69.6
19.181	28

Angle 2-Theta ° (2θ)	Intensity %
20.609	17.9
21.804	51.4
22.653	17.5
23.377	38.5
24.151	10.5
24.585	71.2
25.43	55.6
26.12	18.3
26.349	40.1
26.592	14.4
27.431	15.6
29.375	25.7

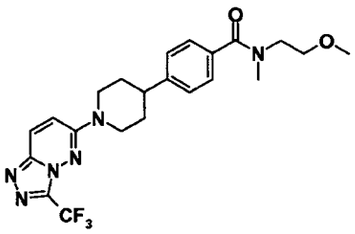
19.823	27.6
20.353	36.2

31.83	22.6
37.332	12.1

DSC analysis showed that 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A has an onset of melting at about 230°C and a peak of melting at about 232°C.

Example 512

Preparation of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide



A mixture of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (79 mg, 0.20 mmol), N-(2-methoxyethyl)methylamine (21 mg, 0.24 mmol), DIPEA (0.105 mL, 0.61 mmol) and HATU (92 mg, 0.24 mmol) in DMA (3 mL) was stirred at ambient temperature for 16 hours. The reaction mixture was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide (77 mg, 82%) as a solid.

1H NMR (399.9 MHz, CDCl3) δ 1.81 (2H, m), 2.02 (2H, m), 2.86 (1H, m), 3.04 - 3.17 (5H, m), 3.29 - 3.48 (5H, m), 3.69 (2H, m), 4.39 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.38 (2H, d), 7.94 (1H, d); m/z = 463 [M+H]+.

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid used as starting material was prepared as follows:-

Preparation of methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate

6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2 g, 8.99 mmol), methyl 4-(piperidin-4-yl)benzoate (CAS 281235-04-9, 2.168 g, 9.89 mmol) and DIPEA

(3.91 mL, 22.47 mmol) were dissolved in DMA (10 mL) and sealed into a microwave tube. The mixture was heated to 110°C for 5 minutes in the microwave reactor and cooled to room temperature. The reaction mixture was added dropwise to stirred water (30 mL), stirred for 10 minutes then the precipitate was collected by filtration, washed with ether (2 x 2 mL) and dried to give methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (3.32 g, 91%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.73 (2H, m), 1.92 (2H, m), 2.98 (1H, m), 3.13 (2H, m), 3.84 (3H, s), 4.44 (2H, m), 7.44 (2H, d), 7.68 (1H, d), 7.91 (2H, d), 8.27 (1H, d); m/z = 406 [M+H]+.

Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid

Lithium hydroxide monohydrate (0.154 g, 3.66 mmol) was added to methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (1.35 g, 3.33 mmol) in a mixture of methanol (30 mL) and water (15 mL). The resulting suspension was stirred at 50°C for 16 hours. The mixture was cooled to room temperature, the methanol evaporated and the aqueous residue treated with 1M citric acid until precipitation ceased. The precipitate was collected by filtration, washed with water and dried to give 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (1.26 g, 97%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.69 - 1.79 (2H, m), 1.93 (2H, m), 2.94 - 3.02 (1H, m), 3.11 - 3.17 (2H, m), 4.44 (2H, m), 7.41 (2H, d), 7.67 (1H, d), 7.89 (2H, d), 8.25 (1H, d), 12.79 (1H, s); m/z = 392 [M+H]+.

Example 512.1

Alternative method for the preparation of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide

4-Methylmorpholine (17.56 mL, 159.70 mmol) was added dropwise to 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (25 g, 63.88 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (13.46 g, 76.66 mmol) suspended in DMF (250 mL) at 0°C. The resulting suspension was stirred for 10 minutes, then 2-methoxy-N-methylethanamine (5.69 g, 63.88 mmol) was added and the mixture warmed to ambient temperature and stirred for 16 hours. The reaction mixture was concentrated and diluted with DCM (1000 mL) and washed with water (500 mL). The aqueous phase was

re-extracted with DCM (500 mL), then the combined organics were washed with saturated NaHCO3 (500 mL) and saturated brine (250 mL), and dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was titurated with ether, and the resulting solid was collected by filtration and dried under vacuum, then purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide (23.45 g, 79%) as a solid.

1H NMR (399.9 MHz, CDCl3) δ 1.81 (2H, m), 2.02 (2H, m), 2.86 (1H, m), 3.04 - 3.17 (5H, m), 3.30 - 3.49 (5H, m), 3.69 (2H, m), 4.39 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.39 (2H, d), 7.93 (1H, d); m/z = 463 [M+H]+.

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid used as starting material was prepared as follows:-

Preparation of sodium 4-(pyridin-4-yl)benzoate

A solution of sodium carbonate (830 g, 7834.20 mmol) in water (6800 mL) was added dropwise over 30 minutes to a stirred suspension of 4-boronobenzoic acid (520 g, 3133.68 mmol), 4-bromopyridine hydrochloride (622 g, 3196.35 mmol) and palladium(II) acetate (1.407 g, 6.27 mmol) in ethanol (2600 mL) and water (3600 mL) at 20°C. The reaction was stirred for 10 minutes then 3,3',3"-phosphinidynetris(benzenesulfonic acid) trisodium salt (30% w/w solution in water) (36.8 g, 18.80 mmol) was added and the mixture was heated to 85°C for 4 hours. The reaction mixture was cooled to 55°C and stirred for 2 hours, then the resulting suspension was stirred at 20°C for 16 hours. The solid was collected by filtration, washed with acetone (3 x 1250 mL), and dried in a vacuum oven at 60°C to afford sodium 4-(pyridin-4-yl)benzoate (690 g, 99%) as a solid.

1H NMR (400.1MHz, DMSO-d6) δ 7.72 (4H, m), 7.97 (2H, d), 8.62 (2H, d); m/z = 200 [M+H]+.

Preparation of methyl 4-(pyridin-4-yl)benzoate

Thionyl chloride (683 mL, 9358.59 mmol) was added dropwise over 20 minutes to a suspension of sodium 4-(pyridin-4-yl)benzoate (690 g, 3119.53 mmol) in methanol (15 L) at -10°C, keeping the temperature below 15°C. The mixture was stirred for 10 minutes then heated to 65°C for 15 hours. The reaction mixture was cooled to 20°C and the solvent was evaporated. The solid residue was partioned between ethyl acetate (14 L) and

aqueous saturated sodium bicarbonate solution (14 L). The organic layer was separated and the aqueous layer extracted with ethyl acetate (7 L). The combined organics were washed with water (14 L), saturated brine (7 L) dried over magnesium sulfate, filtered and evaporated to dryness to afford methyl 4-(pyridin-4-yl)benzoate (570 g, 86%) as a solid.

1H NMR (400.1MHz, DMSO-d6) δ 3.89 (3H, s), 7.78 (2H, d), 7.97 (2H, d), 8.09 (2H, d), 8.69 (2H, d); m/z = 214 [M+H]+.

Preparation of methyl 4-(piperidin-4-yl)benzoate

Methyl 4-(pyridin-4-yl)benzoate (285 g, 1336.57 mmol) and palladium (5% on carbon, 50% wet, JM Type 87L) (57 g, 13.39 mmol) in methanol (2850 mL) were stirred under an atmosphere of hydrogen at 5 bar and 70°C for 15 hours. The catalyst was removed by filtration and washed with methanol (2850 mL). The solvent was evaporated to dryness to afford methyl 4-(piperidin-4-yl)benzoate (291 g, 99%) as a solid.

1H NMR (400.1 MHz, DMSO-d6) δ 1.51 (2H, m), 1.68 (2H, m), 2.54 - 2.69 (3H, m), 3.02 (2H, m), 3.84 (3H, s), 7.37 (2H, d), 7.89 (2H, d); m/z = 220 [M+H]+.

Preparation of methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate

DIPEA (88 mL, 505.27 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (45.0 g, 202.11 mmol) and methyl 4-(piperidin-4-yl)benzoate (48.75 g, 222.32 mmol) in DMA (250 mL). The resulting suspension was stirred at 100°C for 1 hour then cooled to room temperature. The reaction mixture was added dropwise to water (1500 mL) with stirring. Stirring was continued for 10 minutes then the precipitate was collected by filtration, washed with water (300 mL) and ether (250 mL x 2) and dried to afford methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (76 g, 93%) as a solid.

1H NMR (400.1 MHz, DMSO-d6) d 1.63 - 1.83 (2H, m), 1.85 - 2.01 (2H, m), 2.94 - 3.03 (1H, m), 3.08 - 3.18 (2H, m), 3.84 (3H, s), 4.36 - 4.52 (2H, m), 7.44 (2H, d), 7.68 (1H, d), 7.91 (2H, d), 8.27 (1H, d); m/z = 406 [M+H]+.

Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid

Lithium hydroxide monohydrate (9.06 g, 215.94 mmol) was added to methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (79.58 g, 196.31 mmol) in a mixture of MeOH (800 mL) and water (400 mL). The resulting

suspension was stirred at 65°C for 16 hours. The mixture was cooled to room temperature, the methanol evaporated and the aqueous residues diluted with water (600 mL), filtered then treated with 1M citric acid until precipitation ceased. The precipitate was collected by filtration, washed with water and dried to afford 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (77 g, 101%) as a solid.

1H NMR (400.1 MHz, DMSO-d6) d 1.67 - 1.79 (2H, m), 1.88 - 1.96 (2H, m), 2.91 - 3.02 (1H, m), 3.07 - 3.18 (2H, m), 4.39 - 4.48 (2H, m), 7.41 (2H, d), 7.68 (1H, d), 7.88 (2H, d), 8.26 (1H, d); m/z = 392 [M+H]+.

Example 512.2

Preparation of crystalline N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A

4-methylmorpholine (17.56 mL, 159.70 mmol) was added dropwise to 4-(1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl)benzoic acid (25 g, 63.88 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (13.46 g, 76.66 mmol) suspended in DMF (250 mL) cooled to 0°C. The resulting suspension was stirred for 10 minutes then 2-methoxy-N-methylethanamine (5.69 g, 63.88 mmol) was added and the mixture warmed to ambient temperature and stirred for 16 hours. The reaction mixture was concentrated and diluted with DCM (1 L) and washed with water (500 mL). The aqueous was reextracted with DCM (500 mL) then the combined organics were washed with saturated $NaHCO_3$ (500 mL) followed by saturated brine (25 mL) then dried over $MgSO_4$, filtered and evaporated to afford crude product. This was then titurated in ether, filtered off the solid and dried under vacuum. LCMS shows there to be 2.5% impurity. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(2-methoxyethyl)-Nmethyl-4-(1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl)benzamide anhydrous Form A (23.45 g, 79%) as an off-white solid.

N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 2. The intensity of the peaks at the corresponding 2θ values are shown in Table B below.

N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A may thus also be characterised by providing at least one of the following 2θ values when measured using CuKa radiation: 12.34°, 15.78°, 20.42°, 23.75° and 24.73°.

Table B

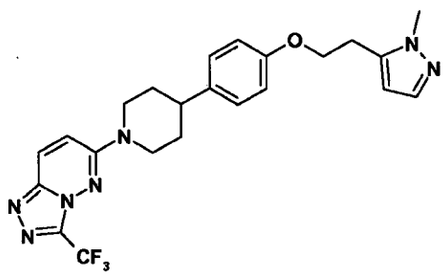
Angle 2-Theta ° (2θ)	Intensity %
6.283	8.3
7.922	1.3
9.65	1.5
12.341	12.3
12.689	7.1
14.92	4.6
15.78	100
16.893	1.5
18.783	4
19.283	7.9
20.424	17.7
20.986	3.3
21.574	2.7
22.494	3.9
23.311	2.6
23.746	18.8

Angle 2-Theta ° (2θ)	Intensity %
24.339	3.7
24.728	9.5
25.375	3.4
26.93	4.9
28.138	2.7
29.08	1.6
31.16	1.3
31.855	1.6
32.496	1.2
33.141	3.3
34.793	1.3
36.343	1.5
36.782	1.4
38.01	1.3
38.637	1.6

DSC analysis showed that N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A has an onset of melting at about 167°C and a peak of melting at about 169°C.

Example 513

Preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



DIAD (78 µl, 0.386 mmol) was added dropwise to 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (117 mg, 0.322 mmol), triphenylphosphine (101 mg, 0.386 mmol) and 2-(1-methyl-1H-pyrazol-5-yl)ethanol (obtained as described in PCT Int. Appl. WO 2007017222, Intermediate 1) (49 mg, 0.386 mmol) in THF (2 mL). The resulting mixture was stirred at ambient temperature for 16 hours and then added to a SCX column. The crude product was eluted using 2M ammonia in methanol and the product-containing fractions were evaporated. The product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (79 mg, 52%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.67 (2H, m), 1.88 (2H, m), 2.77 - 2.84 (3H, m), 3.10 (2H, m), 3.78 (3H, s), 4.05 (2H, t), 4.41 (2H, m), 6.88 (2H, d), 7.18 (2H, d), 7.33 (1H, s), 7.55 (1H, s), 7.66 (1H, d), 8.24 (1H, d); m/z = 472 [M+H]+.

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol used as starting material was prepared as follows:-

DIPEA (5.84 mL, 33.54 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.99 g, 13.41 mmol) and 4-(piperidin-4-yl)phenol hydrochloride (CAS 263139-27-1, 3.01 g, 14.08 mmol) in DMF (30 mL). The resulting solution was stirred at 80°C for 1 hour. The mixture was cooled to room temperature, evaporated to dryness and re-dissolved in DCM (200 mL). The solution was washed with

water (200 mL) and saturated brine (200 mL), dried over MgSO4 and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 70% ethyl acetate in isohexane. Pure fractions were evaporated to dryness to afford 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (4.47 g, 92%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.63 (2H, m), 1.86 (2H, m), 2.74 (1H, m), 3.08 (2H, m), 4.40 (2H, m), 6.69 (2H, d), 7.05 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.19 (1H, s); m/z = 364 [M+H]+.

Example 513.1

Large scale preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

DIAD (19.73 mL, 100.18 mmol) was added dropwise to 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (28 g, 77.06 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (14.53 g, 100.18 mmol) and triphenylphosphine (26.3 g, 100.18 mmol) in THF (250 mL). The resulting solution was stirred at ambient temperature for 3 days. The reaction mixture was evaporated to dryness and re-dissolved in DCM (1 L), and the solution was washed sequentially with 2M NaOH (300 mL x 2) and saturated brine (250 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with 75% EtOAc in isohexane followed by a gradient of 0 to 3% MeOH in DCM. Fractions containing the desired product were evaporated to dryness then re-dissolved in DCM (500 mL) and the solution washed with 2M NaOH (300 mL x 2) followed by brine (250 mL), then dried over $MgSO_4$, filtered and evaporated. The residue was further purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (18.21 g, 50.1%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.67 (2H, m), 1.88 (2H, m), 2.81 (1H, m), 3.07 - 3.14 (4H, m), 3.79 (3H, s), 4.18 (2H, t), 4.41 (2H, m), 6.14 (1H, d), 6.89 (2H, d), 7.19 (2H, d), 7.30 (1H, d), 7.66 (1H, d), 8.24 (1H, d); m/z = 472 [M+H]+.

The 2-(1-methyl-1H-pyrazol-5-yl)ethanol used as starting material was prepared as follows:-

n-Butyl lithium (1.6M in hexanes) (1226 mL, 1961.78 mmol) was added dropwise to 1-methyl-1H-pyrazole (153.4 g, 1868.37 mmol) in THF (3000 mL) cooled to –78 °C over a period of 1 hour under nitrogen. The resulting solution was stirred at –60°C for 30 minutes, then warmed to –10°C and stirred for a further 40 minutes. A solution of oxirane (210 mL, 4203.82 mmol) in THF (600 mL) was added slowly at -10°C followed by further THF (1000 mL) and the resulting slurry was stirred at -10°C for 30 minutes, then at 0°C for 30 minutes. The mixture was then allowed to gradually warm to room temp under nitrogen and stirred for 16 hours. The reaction mixture was quenched with saturated NH_4Cl solution (2000 ml), the layers separated and the aqueous phase extracted with n-butanol (3 x 1000 ml). The combined organics were washed with saturated brine (1500 ml), dried over $MgSO_4$, filtered and evaporated to give an oil, which was azeotroped with toluene (1000 ml) to leave an oil with some solid. The oil was dissolved in DCM and the insoluble solid was filtered off and washed with DCM. The filtrate was purified by chromatography using a silica Novasep prep HPLC column, eluting with a gradient of 5-10% methanol in DCM. Pure fractions were evaporated to dryness to afford 2-(1-methyl-1H-pyrazol-5-yl)ethanol (195 g, 83%) as an oil.

1H NMR (400.1 MHz, DMSO-d6) δ 2.77 (2H, t), 3.63 (2H, m), 3.74 (3H, s), 4.74 (1H, t), 6.04 (1H, m), 7.26 (1H, d).

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol used as starting material was prepared as follows:-

Preparation of benzyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate

A solution of benzyl 4-oxopiperidine-1-carboxylate (88.57 g, 379.70 mmol) in THF (300 mL) was added dropwise to lithium bis(trimethylsilyl)amide (1M in THF) (418 mL, 417.67 mmol) at -78 °C, over a period of 1 hour under nitrogen. The resulting mixture was stirred at -78°C for 90 minutes then a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (142 g, 398.68 mmol) in THF (600 mL) was added dropwise over a period of 1 hour. The resulting mixture was stirred at -78°C for 30 minutes, then allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was quenched with 2M NaOH (450 mL). The layers were separated and the organic layer was washed with 2M NaOH (360 mL). The solvent was evaporated, then the residue was re-dissolved in diethyl ether (1500 mL) and the solution washed with water

(500 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford benzyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (124 g, 81%) as an oil.

1H NMR (399.9 MHz, DMSO-d6) δ 2.43 (2H, m), 3.62 (2H, m), 4.06 (2H, m), 5.10 (2H, s), 6.02 (1H, m), 7.34 (5H, m).

Preparation of benzyl 4-(4-hydroxyphenyl)-5,6-dihydropyridine-1(2H)-carboxylate

Sodium carbonate (96 g, 909.79 mmol) was added to benzyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (123.1 g, 303.26 mmol) and 4-hydroxyphenylboronic acid (46.0 g, 333.59 mmol) in a mixture of dioxane (1000 mL) and water (250 mL). The resulting mixture was bubbled with nitrogen for 10 minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (5.49 g, 7.58 mmol) was added and the reaction mixture was heated at 80°C for 1 hour, then cooled to room temperature. The reaction mixture was diluted with DCM (2 L) and washed with water (2 L). The aqueous washing was re-extracted with DCM (1 L), then the combined organics were washed with saturated brine (500 mL), dried over MgSO4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% EtOAc in isohexane. Fractions containing the desired product were evaporated to dryness then triturated with isohexane, filtered and dried to afford benzyl 4-(4-hydroxyphenyl)-5,6-dihydropyridine-1(2H)-carboxylate (62.3 g, 66.4%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 2.44 (2H, m), 3.61 (2H, m), 4.05 (2H, m), 5.12 (2H, s), 5.99 (1H, m), 6.73 (2H, d), 7.26 (2H, d), 7.32 - 7.40 (5H, m), 9.45 (1H, s); m/z = 310 [M+H]+.

Preparation of 4-(piperidin-4-yl)phenol

Benzyl 4-(4-hydroxyphenyl)-5,6-dihydropyridine-1(2H)-carboxylate (37.7 g, 121.86 mmol) and 5% palladium on carbon (7.6 g, 3.57 mmol) in methanol (380 mL) were stirred under an atmosphere of hydrogen at 5 bar and 25°C for 2 hours. The catalyst was removed by filtration, washed with MeOH and the solvents evaporated. The crude material was triturated with diethyl ether, then the desired product collected by filtration and dried under vacuum to afford 4-(piperidin-4-yl)phenol (20.36 g, 94%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.46 (2H, m), 1.65 (2H, m), 2.45 (1H, m), 2.58 (2H, m), 3.02 (2H, m), 6.68 (2H, d), 7.00 (2H, d), 9.15 (1H, s); m/z = 178 [M+H]+.

Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol

DIPEA (48.2 mL, 276.86 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (24.65 g, 110.74 mmol) and 4-(piperidin-4-yl)phenol (20.61 g, 116.28 mmol) in DMF (200 mL). The resulting solution was stirred at 80°C for 1 hour. The reaction mixture was cooled to room temperature, then evaporated to dryness and re-dissolved in DCM (1 L) and washed with water (2 x 1 L). The organic layer was washed with saturated brine (500 mL), then dried over MgSO4, filtered and evaporated to afford crude product. The crude product was triturated with ether to afford 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (36.6 g, 91%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.64 (2H, m), 1.87 (2H, m), 2.75 (1H, m), 3.09 (2H, m), 4.40 (2H, m), 6.69 (2H, d), 7.05 (2H, d), 7.65 (1H, d), 8.24 (1H, d), 9.15 (1H, s); m/z = 364 [M+H]+.

Example 513.2

Preparation of crystalline 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A

DIAD (3.70 mL, 18.77 mmol) was added to 4-(1-(3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl)phenol (6.2 g, 17.06 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (2.368 g, 18.77 mmol) and triphenylphosphine (4.92 g, 18.77 mmol) in THF (150 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 1 day. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M NH_3/MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford crude product. Product was dissolved in DCM (100 mL) and washed with 2M NaOH (100 mL) twice. Organic layer was evaporated to afford 6-(4-(4-(2-(1-methyl-1H-pyrazol-5-yl)ethoxy)phenyl)piperidin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine anhydrous Form A (4.95 g, 61.5 %) as a white solid.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-

(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 3. The intensity of the peaks at the corresponding 2θ values are shown in Table C below.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A may thus also be characterised by providing at least one of the following 2θ values when measured using CuKa radiation: 4.90°, 13.47°, 15.93°, 16.64° and 22.83°.

Table C

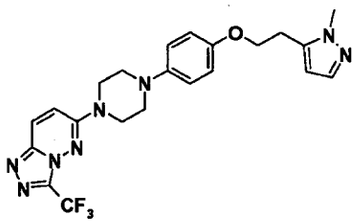
Angle 2-Theta ° (2θ)	Intensity %
4.898	100
9.784	8
11.503	17.1
11.942	2.7
12.966	4
13.473	24
14.719	13.8
15.934	26.6
16.642	33.4
17.359	6.5
18.322	1.8
18.669	6.5
19.195	22.1
19.666	4.9
20.257	2.8
20.581	11
20.866	2.2
21.334	3.4
21.641	2.4
22.834	24
23.7	3.1

Angle 2-Theta ° (2θ)	Intensity %
24	13.5
24.396	14.8
25.985	6.4
26.752	6.5
27.146	6.5
28.104	1.8
28.545	2.7
29.016	2
29.461	8.7
29.737	5.8
30.121	4.7
30.654	3
31.371	1.3
31.853	1.8
33.656	3.4
34.28	1.4
35.851	2.2
36.424	2.3
37.617	1.8
38.531	1.3

DSC analysis showed that 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A has an onset of melting at about 159°C and a peak of melting at about 162°C.

Example 514

Preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



DIAD (0.162 mL, 0.82 mmol) was added to 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (250 mg, 0.69 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (obtained as described in PCT Int. Appl. WO 2007017222, Intermediate 1) (130 mg, 1.03 mmol) and triphenylphosphine (270 mg, 1.03 mmol) in THF (5 mL). The resulting solution was stirred at ambient temperature for 18 hours then added to a SCX column. The crude product was eluted using 2M ammonia in methanol and the product-containing fractions were evaporated. The product was purified by flash silica chromatography, elution gradient 0 to 3% methanol in DCM. Pure fractions were evaporated to dryness to afford 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (111 mg, 34%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 2.81 (2H, t), 3.17 (4H, m), 3.75 (4H, m), 3.78 (3H, s), 4.02 (2H, t), 6.87 (2H, d), 6.96 (2H, d), 7.33 (1H, s), 7.56 (1H, s), 7.69 (1H, d), 8.30 (1H, d); m/z = 473 [M+H]+.

The 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol used as starting material was prepared as follows:-

DIPEA (12.15 mL, 69.78 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (10.35 g, 46.52 mmol) and 1-(4-hydroxyphenyl)piperazine (CAS 56621-48-8, 9.12 g, 51.17 mmol) in DMF (80 mL). The resulting solution was stirred at 80°C for 1 hour. The reaction mixture was cooled to room temperature,

evaporated to dryness and the residue re-dissolved in DCM (250 mL). The solution was washed with water (200 mL), dried over MgSO4 and evaporated to afford crude product, which was triturated with diethyl ether. The resulting solid was collected by filtration and dried under vacuum to give 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (14.27 g, 84%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.12 (4H, m), 3.75 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.67 (1H, d), 8.28 (1H, d), 8.87 (1H, s); m/z = 365 [M+H]+.

Example 514.1

Large scale preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

DIAD (20.73 mL, 105.27 mmol) was added dropwise to 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (32.0 g, 87.72 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (prepared as described in Example 513, preparation of starting materials) (16.6 g, 131.58 mmol) and triphenylphosphine (34.5 g, 131.58 mmol) in THF (320 mL) at 0°C under nitrogen. The resulting solution was stirred at ambient temperature for 3 days. The reaction mixture was evaporated to dryness and re-dissolved in DCM (700 mL), and the solution was washed sequentially with 2M NaOH (200 mL x 2) and saturated brine (200 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with a gradient of 80 to 100% EtOAc in isohexane followed by EtOAc, then a gradient of 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (28.7 g, 69.3%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.07 (2H, t), 3.18 (4H, m), 3.76 (4H, m), 3.79 (3H, s), 4.15 (2H, t), 6.14 (1H, d), 6.88 (2H, d), 6.97 (2H, d), 7.30 (1H, d), 7.67 (1H, d), 8.28 (1H, d); m/z = 473 [M+H]+.

The 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol used as starting material was prepared as follows:-

DIPEA (52.4 mL, 300.84 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (44.6 g, 200.56 mmol) and 1-(4-hydroxyphenyl)piperazine (39.32 g, 220.61 mmol) in DMF (450 mL). The resulting solution was stirred at 80°C for 2 hours. The reaction mixture was cooled to room temperature, then evaporated to dryness

and partitioned between DCM (2 L) and water (1 L) containing methanol (250 mL) to aid solubility. The insoluble material was collected by filtration, washed with methanol and dried to give the desired product. The organic filtrate was separated from the aqueous, then washed with saturated brine (500 mL), dried over $MgSO_4$ and evaporated to a brown gum. This was triturated with ether, the resulting solid was collected by filtration, washed with DCM followed by methanol, combined with the previous precipitate and dried to afford 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (63.8 g, 87%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.12 (4H, m), 3.75 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.67 (1H, d), 8.28 (1H, d), 8.87 (1H, s); m/z = 365 [M+H]+.

Example 514.2

Preparation of crystalline 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A

DIAD (7.78 mL, 39.53 mmol) was added dropwise to 4-(4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)phenol (12 g, 32.94 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (6.23 g, 49.41 mmol) and triphenylphosphine (12.96 g, 49.41 mmol) in THF (250 mL). The resulting solution was stirred at ambient temperature for 18 hours then split and added to a series of SCX columns (6). The crude product was eluted from the columns using 2M NH_3/MeOH and the solvents evaporated. The crude product was diluted with DCM (200 mL) and washed with 2M NaOH (200 mL x 2). The organic layer was dried over $MgSO_4$, filtered and evaporated then purified by flash silica chromatography, elution gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness giving a yellow solid, which was triturated with ether then dried to afford 6-(4-(4-(2-(1-methyl-1H-pyrazol-5-yl)ethoxy)phenyl)piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine anhydrous Form A (9.18g, 59.0 %) as a cream solid.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 4. The intensity of the peaks at the corresponding 2θ values are shown in Table D below.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A may thus also be

characterised by providing at least one of the following 2θ values when measured using CuKa radiation: 6.90°, 15.38°, 21.55°, 24.48° and 27.56°.

Table D

Angle 2-Theta ° (2θ)	Intensity %
6.903	23.4
9.6	8.6
10.776	11.2
12.818	13.3
13.162	3.3
13.845	10
14.436	3.1
15.376	19.2
16.436	11
17.457	4.1
18.247	3.6
18.916	14.9
19.266	3.4
20.182	3
21.03	4.3
21.545	100
22.36	12.4
22.625	3.3
23.552	5.6
23.76	4.7

Angle 2-Theta ° (2θ)	Intensity %
24.479	40.9
25.2	2.2
25.755	7.2
26.465	2.7
27.561	17.1
27.833	11.8
28.206	6.2
29.098	2.1
29.928	2.1
30.587	1.6
31.201	4.8
32.489	1.8
33.326	1.8
34.042	2.3
34.618	3
36.18	1.7
36.538	1.7
37.448	1.3
38.17	1.5
39.324	2.4

DSC analysis showed that 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A has an onset of melting at about 178°C and a peak of melting at about 179°C.

Example 514.3

Preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate

3ml of acetone was added to 50mg of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and heated to form a solution. 12.3mg of fumaric acid was dissolved in 3ml of acetone. The compound solution was added to the counter-ion solution and the resultant mixture shaken with heat. The solution was dried under air and once the volume had dramatically reduced, solid 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate precipitated out.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 5. The intensity of the peaks at the corresponding 2θ values are shown in Table E below.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate may thus also be characterised by providing at least one of the following 2θ values when measured using CuKa radiation: 11.72°, 16.46°, 17.58° and 21.89°.

Table E

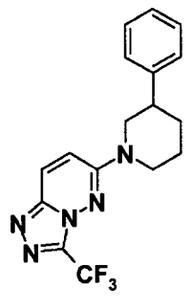
Angle 2-Theta ° (2θ)	Intensity %
4.514	20.3
5.897	14.2
11.724	56.6
12.215	12.3
13.225	6.9
16.464	73.5
17.582	61.3
19.738	17.4
20.261	15

Angle 2-Theta ° (2θ)	Intensity %
21.18	21.1
21.894	100
23.863	13
24.174	12.7
25.826	8.6
26.752	8.8
28.776	7.8
30.541	18.9
31.509	8.1

DSC analysis showed that 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate has a melting endotherm with onset at about 153°C and a peak at about 155°C (this is followed by a recrystallisation event and subsequent melt).

Example 515

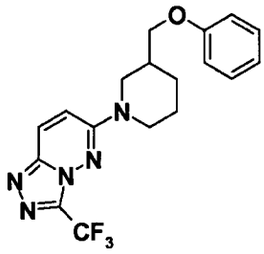
Preparation of 6-(3-phenylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (49 mg, 0.22 mmol) in EtOH (1.0 mL) was added to a mixture of 3-phenylpiperidine (53 mg, 0.33 mmol) and DIPEA (57 μL, 0.33 mmol) in EtOH (1.0 mL). The reaction mixture was heated to 70°C overnight and the crude product was purified by preparative LCMS (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 5% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 6-(3-phenylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (46 mg, 61%). 1H NMR (700.03 MHz, DMSO-d_6) δ 1.62 - 1.68 (1H, m), 1.82 - 1.88 (2H, m), 1.96 - 1.98 (1H, m), 2.83 - 2.87 (1H, m), 3.10 - 3.15 (1H, m), 4.30 - 4.36 (3H, m), 7.25 - 7.28 (1H, m), 7.33 - 7.38 (4H, m), 7.68 (1H, d), 8.23 (1H, d); m/z = 348 [M+H]+.

Example 516

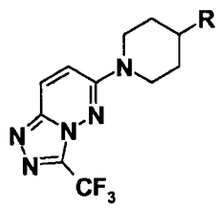
Preparation of 6-[3-(phenoxymethyl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 60% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-(phenoxymethyl)piperidine.
1H NMR (700.03 MHz, DMSO-d_6) δ 1.45 - 1.50 (1H, m), 1.56 - 1.61 (1H, m), 1.79 - 1.82 (1H, m), 1.90 - 1.92 (1H, m), 2.08 - 2.11 (1H, m), 3.07 (1H, dd), 3.16 - 3.20 (1H, m), 3.91 (1H, dd), 3.96 (1H, dd), 4.10 - 4.13 (1H, m), 4.31 (1H, dd), 6.93 - 6.97 (3H, m), 7.28 - 7.31 (2H, m), 7.60 (1H, d), 8.21 (1H, d); m/z = 378 [M+H]+.

Examples 517-518

The following compounds were prepared in 45-46% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-

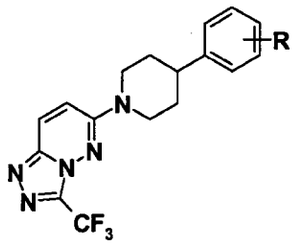


Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
517	ethoxymethyl	δ 1.11 (3H, t), 1.21 - 1.27 (2H, m), 1.79 (2H, d), 1.85 - 1.88 (1H, m), 3.00 - 3.04 (2H, m), 3.42 (2H, q), 4.27 (2H, d), 7.60 (1H, d), 8.21 (1H, d), (2H obscured by water)	330
518	propoxy	δ 0.89 (3H, t), 1.50 - 1.56 (4H, m), 1.91 - 1.95 (2H, m), 3.36 - 3.40 (1H, m), 3.41 (2H, t), 3.55 - 3.59 (1H, m), 3.89 - 3.92 (2H, m), 7.62 (1H, d), 8.22	330

		(1H, d), (1H obscured by water)	

Examples 519-526

The following compounds were prepared in 23-63% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryl piperidine:-

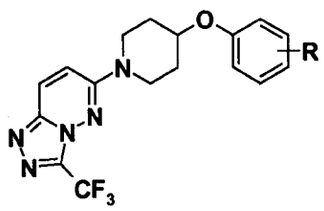


Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
519	H	δ 1.69 - 1.75 (2H, m), 1.92 (2H, d), 2.85 - 2.90 (1H, m), 3.10 - 3.14 (2H, m), 4.42 - 4.44 (2H, m), 7.20 - 7.22 (1H, m), 7.27 - 7.28 (2H, m), 7.30 - 7.32 (2H, m), 7.66 (1H, d), 8.24 (1H, d)	348
520	2-OMe	δ 1.67 - 1.73 (2H, m), 1.85 (2H, d), 3.10 - 3.14 (2H, m), 3.81 (3H, s), 4.42 (2H, d), 6.89 - 6.91 (1H, m), 6.99 (1H, d), 7.17 - 7.21 (2H, m), 7.65 (1H, d), 8.24 (1H, d), (2H obscured by water)	378
521	4-SO2Me	δ 1.73 - 1.79 (2H, m), 1.94 (2H, d), 3.01 - 3.06 (1H, m), 4.45 (2H, d), 7.57 (2H, d), 7.67 (1H, d), 7.86 - 7.87 (2H, m), 8.26 (1H, d), (5H obscured by water)	426
522	4-CONHMe	δ 1.70 - 1.76 (2H, m), 1.92 (2H, d), 2.78 (3H, d), 2.92 - 2.96 (1H, m), 3.11 - 3.15 (2H, m), 4.43 (2H, d), 7.36 (2H, d), 7.66 (1H, d), 7.76 - 7.78 (2H, m), 8.25 (1H, d), 8.32 (1H, q)	405
523	4-OMe	δ 1.64 - 1.70 (2H, m), 1.87 - 1.89 (2H, m), 2.79 - 2.84 (1H, m), 3.08 - 3.12 (2H, m), 3.73 (3H, s), 4.41 (2H, d), 6.86 - 6.88 (2H, m), 7.18 - 7.20 (2H, m), 7.66 (1H, d), 8.24 (1H, d)	378
524	4-CF3	δ 1.72 - 1.78 (2H, m), 1.94 (2H, d), 2.99 - 3.03 (1H,	416

		m), 3.12 - 3.16 (2H, m), 4.44 (2H, d), 7.53 (2H, d), 7.66 - 7.68 (3H, m), 8.25 (1H, s)	
525	3-F	δ 1.69 - 1.75 (2H, m), 1.92 (2H, d), 2.90 - 2.94 (1H, m), 3.09 - 3.14 (2H, m), 4.42 (2H, d), 7.01 - 7.04 (1H, m), 7.13 (2H, t), 7.34 - 7.37 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	366
526	3-OMe	δ 1.69 - 1.75 (2H, m), 1.90 - 1.92 (2H, m), 2.83 - 2.87 (1H, m), 3.09 - 3.13 (2H, m), 3.74 (3H, s), 4.42 (2H, d), 6.77 - 6.79 (1H, m), 6.83 (1H, d), 6.84 (1H, t), 7.22 (1H, t), 7.66 (1H, d), 8.24 (1H, d)	378

Examples 527-532

The following compounds were prepared in 56-65% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryloxy piperidine:-

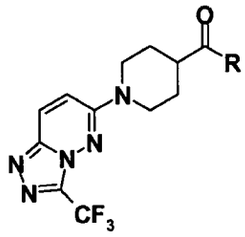


Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
527	3-OMe	δ 1.70 - 1.75 (2H, m), 2.05 - 2.08 (2H, m), 3.52 - 3.55 (2H, m), 3.74 (3H, s), 3.94 - 3.97 (2H, m), 4.67 - 4.70 (1H, m), 6.53 (1H, dd), 6.56 (1H, t), 6.60 (1H, dd), 7.20 (1H, t), 7.64 (1H, d), 8.25 (1H, d)	394
528	4-OMe	δ 1.68 - 1.73 (2H, m), 2.01 - 2.05 (2H, m), 3.50 - 3.54 (2H, m), 3.72 (3H, s), 3.92 - 3.96 (2H, m), 4.52 - 4.56 (1H, m), 6.86 - 6.88 (2H, m), 6.94 - 6.97 (2H, m), 7.64 (1H, d), 8.25 (1H, d)	394
529	2-F	δ 1.74 - 1.79 (2H, m), 2.07 - 2.10 (2H, m), 3.52 - 3.56 (2H, m), 3.94 - 3.98 (2H, m), 4.68 - 4.71 (1H, m), 6.98 - 7.01 (1H, m), 7.15 (1H, t), 7.22 - 7.25 (1H, m), 7.28 - 7.31 (1H, m), 7.64 (1H, d), 8.26 (1H, d)	382

530	2-Cl	δ 1.78 - 1.83 (2H, m), 2.05 - 2.09 (2H, m), 3.62 - 3.66 (2H, m), 3.87 - 3.91 (2H, m), 4.79 - 4.82 (1H, m), 6.98 - 7.01 (1H, m), 7.29 - 7.30 (1H, m), 7.31 - 7.33 (1H, m), 7.44 - 7.46 (1H, m), 7.64 (1H, d), 8.26 (1H, d)	398
531	2-OMe	δ 1.71 - 1.76 (2H, m), 2.01 - 2.04 (2H, m), 3.51 - 3.55 (2H, m), 3.77 (3H, s), 3.94 - 3.98 (2H, m), 4.55 - 4.58 (1H, m), 6.88 - 6.91 (1H, m), 6.95 - 6.97 (1H, m), 7.01 (1H, m), 7.08 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	394
532	3-F	δ 1.71 - 1.75 (2H, m), 2.06 - 2.10 (2H, m), 3.51 - 3.54 (2H, m), 3.95 - 3.99 (2H, m), 4.71 - 4.74 (1H, m), 6.76 - 6.79 (1H, m), 6.86 (1H, dd), 6.90 - 6.93 (1H, m), 7.31 - 7.34 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	382

Examples 533-534

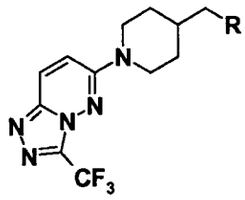
The following compounds were prepared in 43-62% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
533	phenyl	δ 1.62 - 1.68 (2H, m), 1.93 - 1.96 (2H, m), 3.79 - 3.84 (1H, m), 4.30 - 4.31 (2H, m), 7.56 - 7.58 (2H, m), 7.63 (1H, d), 7.66 - 7.69 (1H, m), 8.03 - 8.04 (2H, m), 8.24 (1H, d), (2H obscured by water)	376
534	4-fluorophenyl	δ 1.61 - 1.67 (2H, m), 1.92 - 1.95 (2H, m), 3.78 - 3.82 (1H, m), 4.30 (2H, d), 7.37 - 7.40 (2H, m), 7.63 (1H, d), 8.11 - 8.14 (2H, m), 8.24 (1H, d), (2H obscured by water)	394

Examples 535-539

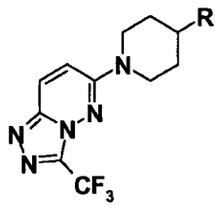
The following compounds were prepared in 53-63% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
535	phenyl	δ 1.21 - 1.27 (2H, m), 1.68 - 1.71 (2H, m), 1.83 - 1.89 (1H, m), 2.55 (2H, d), 2.95 - 2.99 (2H, m), 4.25 (2H, d), 7.19 - 7.21 (3H, m), 7.29 - 7.31 (2H, m), 7.58 (1H, d), 8.21 (1H, d)	362
536	4-fluorophenyl	δ 1.20 - 1.26 (2H, m), 1.67 - 1.69 (2H, m), 1.81 - 1.86 (1H, m), 2.55 (2H, d), 2.95 - 2.99 (2H, m), 4.25 (2H, d), 7.09 - 7.13 (2H, m), 7.21 - 7.24 (2H, m), 7.58 (1H, d), 8.21 (1H, d)	380
537	pyridin-2-yl	δ 1.26 - 1.32 (2H, m), 1.68 - 1.70 (2H, m), 2.08 - 2.13 (1H, m), 2.70 (2H, d), 2.98 - 3.02 (2H, m), 4.24 (2H, d), 7.20 - 7.22 (1H, m), 7.25 (1H, d), 7.59 (1H, d), 7.69 - 7.72 (1H, m), 8.21 (1H, d), 8.50 - 8.51 (1H, m)	363
538	pyridin-4-yl	δ 1.23 - 1.29 (2H, m), 1.67 - 1.69 (2H, m), 1.90 - 1.95 (1H, m), 2.58 (2H, d), 2.97 - 3.01 (2H, m), 4.25 (2H, d), 7.23 - 7.24 (2H, m), 7.59 (1H, d), 8.21 (1H, d), 8.47 - 8.48 (2H, m)	363
539	pyridin-3-yl	δ 1.23 - 1.29 (2H, m), 1.68 - 1.70 (2H, m), 1.86 - 1.91 (1H, m), 2.58 (2H, d), 2.96 - 3.00 (2H, m), 4.26 (2H, d), 7.33 (1H, dd), 7.59 (1H, d), 7.62 - 7.64 (1H, m), 8.21 (1H, d), 8.42 - 8.43 (2H, m)	363

Examples 540-543

The following compounds were prepared in 40-63% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-

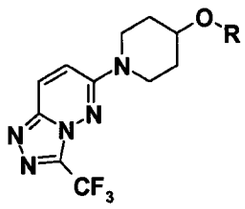


Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
540	pyridin-4-yl	δ 1.69 - 1.75 (2H, m), 1.94 (2H, d), 2.90 - 2.94 (1H, m), 3.11 - 3.15 (2H, m), 4.43 (2H, d), 7.31 - 7.32 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 8.48 - 8.49 (2H, m)	349
541	benzotriazol-1-yl	δ 2.27 - 2.32 (4H, m), 4.48 (2H, s), 5.27 - 5.32 (1H, m), 7.42 - 7.44 (1H, m), 7.57 - 7.59 (1H, m), 7.72 (1H, d), 7.98 (1H, d), 8.06 (1H, d), 8.30 (1H, d), (2H obscured by water)	389
542	indol-1-yl	δ 2.03 - 2.10 (4H, m), 4.49 (2H, d), 4.75 - 4.80 (1H, m), 6.45 (1H, d), 7.02 - 7.05 (1H, m), 7.14 - 7.17 (1H, m), 7.49 (1H, d), 7.55 (1H, d), 7.61 (1H, d), 7.70 (1H, d), 8.28 (1H, d), (2H obscured by water)	387
543	(3,5-dimethoxy)pyrimidin-2-yl	δ 1.81 - 1.87 (2H, m), 2.09 - 2.11 (2H, m), 3.00 - 3.04 (1H, m), 3.88 (6H, s), 4.31 - 4.33 (2H, m), 6.08	410

		(1H, s), 7.65 (1H, d), 8.24 (1H, d), (2H obscured by water)	

Examples 544-546

The following compounds were prepared in 33-57% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
544	pyrazinyl	δ 1.79 - 1.84 (2H, m), 2.12 - 2.16 (2H, m), 3.54 - 3.57 (2H, m), 3.98 - 4.02 (2H, m), 5.30 - 5.34 (1H, m), 7.66 (1H, d), 8.22 - 8.23 (2H, m), 8.26 (1H, d), 8.31 (1H, d)	366
545	pyridin-4-yl	δ 1.73 - 1.78 (2H, m), 2.10 - 2.14 (2H, m), 3.51 - 3.55 (2H, m), 3.97 - 4.00 (2H, m), 4.84 - 4.87 (1H, m), 7.03 - 7.04 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.39 - 8.40 (2H, m)	365
546	pyridin-2-yl	δ 1.74 - 1.79 (2H, m), 2.10 - 2.14 (2H, m), 3.51 - 3.54 (2H, m), 3.99 - 4.02 (2H, m), 5.30 - 5.33 (1H, m), 6.81 (1H, d), 6.97 - 6.99 (1H, m), 7.65 (1H, d), 7.70 - 7.73 (1H, m), 8.17 - 8.19 (1H, m), 8.25 (1H, d)	365

Examples 547-550

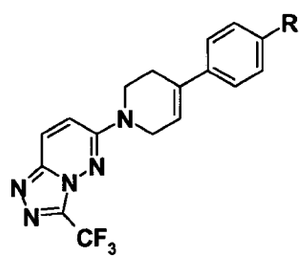
The following compounds were prepared in 25-65% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidin-4-ol:-



Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
547	phenyl	δ 1.74 (2H, d), 2.01 - 2.05 (2H, m), 3.43 - 3.47 (2H, m), 4.20 - 4.22 (2H, m), 5.20 (1H, s), 7.22 - 7.24 (1H, m), 7.32 - 7.34 (2H, m), 7.50 - 7.52 (2H, m), 7.66 (1H, d), 8.24 (1H, d)	364
548	benzyl	δ 1.50 (2H, d), 1.56 - 1.60 (2H, m), 2.73 (2H, s), 4.01 (2H, d), 4.51 (1H, s), 7.19 - 7.21 (1H, m), 7.23 - 7.24 (2H, m), 7.27 (2H, t), 7.58 (1H, d), 8.19 (1H, d), (2H obscured by water)	378
549	2-fluorophenyl	δ 1.76 (2H, d), 2.23 - 2.27 (2H, m), 3.45 (2H, t), 4.19 - 4.21 (2H, m), 5.47 (1H, s), 7.09 - 7.12 (1H, m), 7.21 - 7.23 (1H, m), 7.30 - 7.33 (1H, m), 7.66 - 7.70 (2H, m), 8.25 (1H, d)	382
550	pyridin-4-yl	δ 1.71 (2H, d), 2.01 - 2.06 (2H, m), 3.42 - 3.46 (2H, m), 4.22 - 4.24 (2H, m), 7.49 - 7.50 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 8.51 - 8.52 (2H, m)	365

Examples 551-552

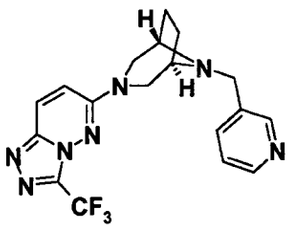
The following compounds were prepared in 50-56% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryl tetrahydropyridine:-



Ex.	R	1H NMR (700.03 MHz, DMSO-d_6)	m/z [M+H]+
551	H	δ 2.67 - 2.69 (2H, m), 3.90 (2H, t), 4.27 (2H, q), 6.31 - 6.32 (1H, m), 7.29 (1H, t), 7.37 - 7.39 (2H, m), 7.49 - 7.51 (2H, m), 7.68 (1H, d), 8.29 (1H, d)	346
552	F	δ 2.66 - 2.67 (2H, m), 3.89 (2H, t), 4.26 (2H, q), 6.29 - 6.30 (1H, m), 7.19 - 7.22 (2H, m), 7.52 - 7.55 (2H, m), 7.68 (1H, d), 8.29 (1H, d)	364

Example 553

Preparation of 6-[(1R,5S)-8-(pyridin-3-ylmethyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of pyridine-3-carboxaldehyde and 6-[(1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(1R,5S)-8-(pyridin-3-ylmethyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 68% yield.

1H NMR (399.9 MHz, DMSO-d6) δ 1.64 - 1.68 (2H, m), 2.03 - 2.06 (2H, m), 3.19 (2H, d), 3.31 - 3.34 (2H, m, partially obscured by solvent peak), 3.64 (2H, s), 3.82 - 3.85 (2H, m), 7.36 - 7.40 (1H, m), 7.51 (1H, d), 7.81 - 7.84 (1H, m), 8.24 (1H, d), 8.48 - 8.49 (1H, m), 8.59 (1H, d); m/z = 390 [M+H]+.

The 6-[(1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of (1R,5S)-tert-butyl 3-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (312 mg, 1.40 mmol), (1R,5S)-tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (312 mg, 1.47 mmol) and DIPEA (0.36 ml, 2.10 mmol) in ethanol (7.00 ml) was heated at 70°C

for 18 hours. On cooling a white precipitate formed which was collected by filtration, washed with ethanol (10 mL) and dried under vacuum to afford (1R,5S)-tert-butyl 3-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (384 mg, 69%) as a white crystalline solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.44 (9H, s), 1.71 - 1.72 (2H, m), 1.88 - 1.90 (2H, m), 3.13 (2H, d), 3.97 (2H, d), 4.29 (2H, s), 7.54 (1H, d), 8.28 (1H, d); m/z = 399 [M+H]+.

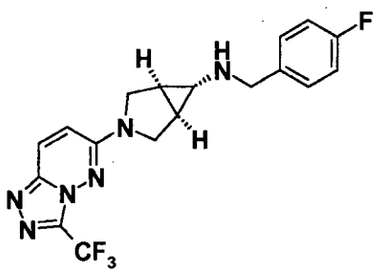
Preparation of 6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

TFA (2.42 ml, 31.4 mmol) was added to a stirred solution of (1R,5S)-tert-butyl 3-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (443 mg, 1.11 mmol) in DCM (4.50 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 hours. The reaction mixture was diluted with methanol and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted using 7M ammonia in methanol and evaporated to dryness to afford 6-[(1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (336 mg, 100%) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.61 - 1.71 (4H, m), 3.05 - 3.08 (2H, m), 3.55 (2H, s), 3.81 - 3.84 (2H, m), 7.50 (1H, d), 8.22 (1H, d), NH not observed; m/z = 299 [M+H]+.

Example 554

Preparation of (1α,5α,6α) N-(4-fluorobenzyl)-3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine



(1α,5α,6α) 3-[3-(Trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine (150 mg, 0.53 mmol), magnesium sulphate monohydrate (361 mg, 2.64 mmol) and 4-fluorobenzaldehyde (98 mg, 0.79 mmol) were added to DCM (10 mL) and the mixture was stirred overnight at 25°C. The crude mixture was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. The appropriate

fractions were evaporated to dryness, and the intermediate imine and acetic acid (0.2 mL, 3.49 mmol) were added to MeOH (15 mL). Sodium cyanoborohydride (0.040 mL, 0.70 mmol) was added and the mixture was stirred for 20 minutes. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 3.5M ammonia in methanol. The appropriate fractions were evaporated to dryness to afford a clear gum, which was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Product-containing fractions were evaporated to dryness and the residue was crystallised from a mixture of ether and isohexane to give (1α,5α,6α) N-(4-fluorobenzyl)-3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine (125 mg, 60%).

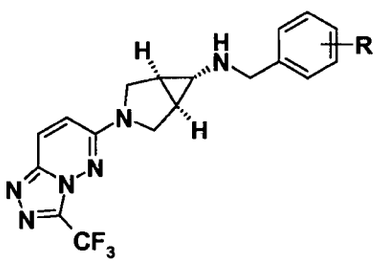
1H NMR (400.1 MHz, CDCl3) δ 1.81 (2H, s), 1.84 (1H, s), 2.02 (1H, t), 3.59 (2H, d), 3.68 (2H, d), 3.81 (2H, s), 6.76 (1H, d), 7.01 (2H, t), 7.27 (2H, t), 7.87 (1H, d); m/z = 393 [M+H]+.

The (1α,5α,6α) 3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine used as starting material was prepared in 2 steps in 78% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (1α,5α,6α) tert-butyl 3-azabicyclo[3.1.0]hex-6-ylcarbamate (obtained as described in Synlett. 1996, 1097).

1H NMR (400.1 MHz, CDCl3) δ 1.60 (2H, s), 1.77 (2H, s), 2.21 (1H, s), 3.61 (2H, d), 3.72 (2H, d), 6.78 (1H, d), 7.87 (1H, d); m/z = 285 [M+H]+.

Examples 555-557

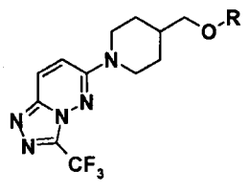
The following compounds were prepared in 50-85% yield by an analogous method to Example 554, starting from (1α,5α,6α) 3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine and the appropriate aldehyde:-



Ex.	R	1H NMR (400.1 MHz, CDCl3)	m/z [M+H]+
555	3-Cl	δ 1.82 (2H, s), 1.89 (1H, s), 2.02 (1H, t), 3.60 (2H, d), 3.68 (2H, d), 3.82 (2H, s), 6.76 (1H, d), 7.17 (1H, d), 7.28 - 7.24 (2H, m), 7.31 (1H, s), 7.87 (1H, d)	409
556	3-F	δ 1.83 (2H, s), 1.89 (1H, s), 2.04 (1H, t), 3.59 (2H, d), 3.68 (2H, d), 3.84 (2H, s), 6.76 (1H, d), 6.95 (1H, t), 7.02 (1H, d), 7.07 (1H, d), 7.31 - 7.26 (1H, m), 7.87 (1H, d)	393
557	4-CN	δ 1.82 (2H, s), 1.89 (1H, s), 2.05 (1H, t), 3.60 (2H, d), 3.68 (2H, d), 3.91 (2H, s), 6.76 (1H, d), 7.43 (2H, d), 7.62 (2H, d), 7.87 (1H, d)	399

Examples 558-559

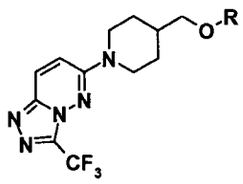
The following compounds were prepared in 5-36% yield by an analogous method to Example 448, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) and the appropriate chloro heterocycle:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
558	pyrimidin-2-yl	δ 1.39 (2H, ddd), 1.91 - 1.87 (2H, m), 2.21 - 2.08 (1H, m), 3.07 (2H, t), 4.21 (2H, d), 4.34 - 4.31 (2H, m), 7.14 (1H, t), 7.63 (1H, d), 8.23 (1H, d), 8.60 (2H, d)	380
559	3-bromopyridin-2-yl	δ 1.46 - 1.36 (2H, m), 1.91 - 1.87 (2H, m), 2.18 - 2.05 (1H, m), 3.11 - 3.04 (2H, m), 4.24 (2H, d), 4.34 - 4.31 (2H, m), 6.95 (1H, dd), 7.63 (1H, d), 8.03 (1H, d), 8.15 (1H, d), 8.23 (1H, d)	458

Examples 560-561

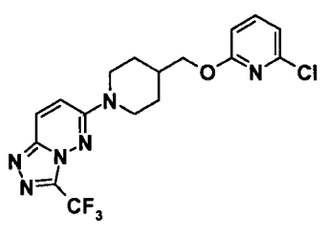
The following compounds were prepared in 30-37% yield by an analogous method to Example 294, starting from 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate pyridinol:-



Ex.	R	1H NMR (400.1 MHz, DMSO-d6)	m/z [M+H]+
560	pyridin-3-yl	1.38 (2H, ddd), 1.93 - 1.90 (2H, m), 2.16 - 2.10 (1H, m), 3.11 - 3.04 (2H, m), 3.96 (2H, d), 4.33 - 4.30 (2H, m), 7.32 (1H, dd), 7.39 (1H, ddd), 7.63 (1H, d), 8.16 (1H, dd), 8.23 (1H, d), 8.30 (1H, d)	379
561	pyridin-4-yl	δ 1.38 (2H, ddd), 1.91 - 1.88 (2H, m), 2.21 - 2.11 (1H, m), 3.11 - 3.04 (2H, m), 3.97 (2H, d), 4.33 - 4.30 (2H, m), 6.97 - 6.96 (2H, m), 7.62 (1H, d), 8.23 (1H, d), 8.38 - 8.37 (2H, m)	379

Example 562

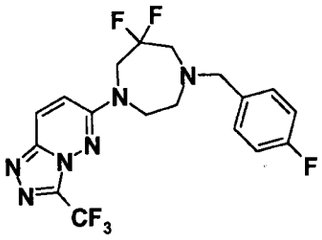
Preparation of 6-[4-[[(6-chloropyridin-2-yl)oxy]methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 75% yield by an analogous method to Example 447, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) and 6-chloropyridin-2-ol. 1H NMR (400.1 MHz, DMSO-d6) δ 1.37 (2H, ddd), 1.89 - 1.87 (2H, m), 2.14 - 2.08 (1H, m), 3.06 (2H, t), 4.14 (2H, d), 4.33 - 4.30 (2H, m), 6.84 (1H, d), 7.08 (1H, d), 7.62 (1H, d), 7.76 (1H, t), 8.22 (1H, d); m/z = 413 [M+H]+.

Example 563

Preparation of 6-[6,6-difluoro-4-(4-fluorobenzyl)-1,4-diazepan-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Sodium cyanotrihydroborate (58.5 mg, 0.93 mmol) was added to a stirred mixture of 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (200 mg, 0.62 mmol), 4-fluorobenzaldehyde (93 mg, 0.75 mmol) and acetic acid (71.1 µl, 1.24 mmol) in methanol (10 mL) at room temperature. The resulting mixture was stirred at 21°C for 20 hours. The reaction mixture was concentrated to dryness, diluted with methanol and a few drops of 7M ammonia in methanol were added. The mixture was concentrated to dryness, the residue was diluted with DCM and the salts were filtered off. The filtrate was concentrated and purified by flash chromatography on silica gel eluting with 0 to 20% acetonitrile in DCM. Product-containing fractions were concentrated to give to give 6-[6,6-difluoro-4-(4-fluorobenzyl)-1,4-diazepan-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (154 mg, 55%).

1H NMR (500 MHz, DMSO-d6) δ 2.82-2.88 (m, 2H), 3.02-3.11 (m, 2H), 3.73 (s, 2H), 3.79-3.84 (m, 2H), 4.28-4.36 (m, 2H), 6.95 (dd, 2H), 7.23 (dd, 2H), 7.61 (d, 1H), 8.32 (d, 1H); m/z = 431[M+H]+.

The 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

Preparation of tert-butyl 6,6-difluoro-1,4-diazepane-1-carboxylate

Di-tert-butyl dicarbonate (5.29 ml, 23.0 mmol) in DCM (50 mL) was added dropwise to a ice-cooled mixture of 6,6-difluoro-1,4-diazepane (3.6 g, 26.4 mmol, obtained as described in Synthesis, 2003, 223) and DIPEA (2.30 mL, 13.2 mmol) in DCM (100 mL) . The resulting mixture was stirred at room temperature for 15 hours. The mixture was concentrated to dryness and diluted with water and ethyl acetate. Insoluble material was removed by filtration and the organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography

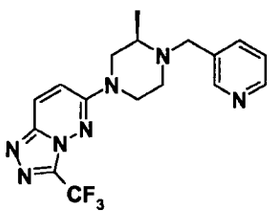
on silica gel eluting with 0 to 4% methanol in DCM. Product-containing fractions were concentrated to afford tert-butyl 6,6-difluoro-1,4-diazepane-1-carboxylate (3.45 g, 55.2%) as a white solid. 1H NMR (500 MHz, CDCl3) δ 1.47 (s, 9H), 2.90-3.00 (m, 2H), 3.05-3.15 (m, 2H), 3.41-3.54 (m, 2H), 3.78-3.94 (m, 2H).

Preparation of 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

A mixture of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1 g, 4.49 mmol), tert-butyl 6,6-difluoro-1,4-diazepane-1-carboxylate (1.06 g, 4.49 mmol) and DIPEA (1.56 ml, 8.99 mmol) in DMA (15 mL) was stirred at 135°C for 6 hours. The reaction mixture was concentrated to dryness and DCM (30 mL) was added. The solution was cooled in an ice bath and TFA (15 mL) was added. The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to dryness, diluted with water, basified with 6M aqueous sodium hydroxide and extracted with DCM. The organic phase was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0 to 4% methanol in DCM to give 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.820 g, 56.6%) as a beige solid.
1H NMR (500 MHz, DMSO-d6) δ 2.80 (bs, 1H), 2.94-3.07 (m, 4H), 3.74-3.81 (m, 2H), 4.24-4.31 (m, 2H), 7.58 (d, 1H), 8.30 (d, 1H); m/z = 323 [M+H]+.

Example 564

Preparation of 6-[(3R)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of pyridine-3-carboxaldehyde and 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5, to give 6-[(3R)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 58% yield.

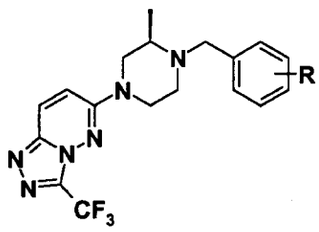
1H NMR (399.9 MHz, DMSO-d_6) δ 1.16 (3H, d), 2.24 - 2.30 (1H, m), 2.53 - 2.63 (1H, m), 2.72 - 2.76 (1H, m), 3.09 - 3.14 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.35 (1H, d), 3.84 - 3.89 (1H, m), 3.92 - 4.00 (2H, m), 7.36 - 7.39 (1H, m), 7.61 (1H, d), 7.74 - 7.77 (1H, m), 8.25 (1H, d), 8.47 - 8.49 (1H, m), 8.54 (1H, d); m/z = 378 [M+H]+.

The 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 75% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3R)-tert-butyl 2-methylpiperazine-1-carboxylate.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.04 (3H, d), 2.37 (1H, s), 2.54 - 2.60 (1H, m), 2.68 - 2.75 (2H, m), 2.87 - 3.00 (2H, m), 4.07 - 4.11 (2H, m), 7.61 (1H, d), 8.23 (1H, d).

Examples 565-569

The following compounds were prepared in 29-45% yield by General Synthetic Method 5, starting from 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 564, preparation of starting materials) and the appropriate aldehyde:-

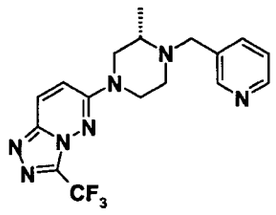


Ex.	R	1H NMR (399.9 MHz, DMSO-d_6)	m/z [M+H]+
565	4-CN	δ 1.13 (3H, d), 2.26 - 2.32 (1H, m), 2.61 - 2.65 (1H, m), 2.70 - 2.75 (1H, m), 3.10 - 3.15 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.41 (1H, d), 3.85 - 3.89 (1H, m), 3.93 - 3.97 (1H, m), 4.03 (1H, d), 7.58 (2H, d), 7.60 - 7.63 (1H, m), 7.80 - 7.83 (2H, m), 8.26 (1H, d)	402
566	3,4-di-F	δ 1.13 (3H, d), 2.24 - 2.29 (1H, m), 2.59 - 2.63 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.15 (1H, m), 3.28 – 3.32 (2H + H_2O, m), 3.84 – 3.89 (2H, m), 3.93 (1H, d), 7.18 - 7.21 (1H, m), 7.36 - 7.42 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	413

567	3,5-di-F	δ 1.12 (3H, d), 2.27 - 2.32 (1H, m), 2.59 – 2.62 (1H, m), 2.74 - 2.78 (1H, m), 3.11 - 3.16 (1H, m), 3.33 - 3.38 (2H, m), 3.86 - 3.97 (3H, m), 7.08 - 7.13 (3H, m), 7.62 (1H, d), 8.26 (1H, d)	413
568	4-F	δ 1.14 (3H, d), 2.20 - 2.26 (1H, m), 2.56 - 2.61 (1H, m), 2.70 - 2.75 (1H, m), 3.08 - 3.14 (1H, m), 3.26 – 3.33 (2H, m), 3.84 - 3.96 (3H, m), 7.14 - 7.18 (2H, m), 7.36 - 7.40 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	395
569	3-CN, 4-F	δ 1.13 (3H, d), 2.24 - 2.30 (1H, m), 2.60 - 2.65 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.16 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.36 (1H, d), 3.85 - 3.98 (3H, m), 7.49 - 7.53 (1H, m), 7.61 (1H, d), 7.75 - 7.79 (1H, m), 7.86 - 7.88 (1H, m), 8.26 (1H, d)	420

Example 570

Preparation of 6-[(3S)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of pyridine-3-carboxaldehyde and 6-[(3S)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(3S)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 62% yield.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.16 (3H, d), 2.24 - 2.30 (1H, m), 2.53 - 2.63 (1H, m), 2.72 - 2.76 (1H, m), 3.09 - 3.14 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.35 (1H, d), 3.84 - 3.89 (1H, m), 3.92 - 4.00 (2H, m), 7.36 - 7.39 (1H, m), 7.61 (1H, d), 7.74 - 7.77 (1H, m), 8.25 (1H, d), 8.47 - 8.49 (1H, m), 8.54 (1H, d); m/z = 378 [M+H]+.

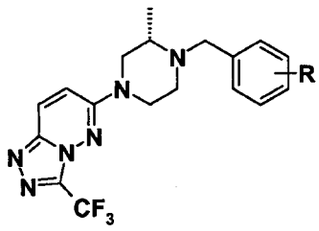
The 6-[(3S)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 71.5% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-

chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3S)-tert-butyl 2-methylpiperazine-1-carboxylate.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.04 (3H, d), 2.37 (1H, s), 2.54 - 2.60 (1H, m), 2.68 - 2.75 (2H, m), 2.87 - 3.00 (2H, m), 4.07 - 4.11 (2H, m), 7.61 (1H, d), 8.23 (1H, d).

Examples 571-575

The following compounds were prepared in 36-55% yield by General Synthetic Method 5, starting from 6-[(3S)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 570, preparation of starting materials) and the appropriate aldehyde:-

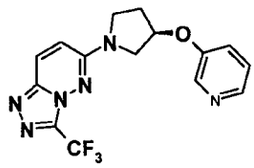


Ex.	R	1H NMR (399.9 MHz, DMSO-d_6)	m/z [M+H]+
571	4-CN	δ 1.13 (3H, d), 2.26 - 2.32 (1H, m), 2.61 - 2.65 (1H, m), 2.70 - 2.75 (1H, m), 3.10 - 3.15 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.41 (1H, d), 3.85 - 3.89 (1H, m), 3.93 - 3.97 (1H, m), 4.03 (1H, d), 7.58 (2H, d), 7.60 - 7.63 (1H, m), 7.80 - 7.83 (2H, m), 8.26 (1H, d)	402
572	3,4-di-F	δ 1.13 (3H, d), 2.24 - 2.29 (1H, m), 2.59 - 2.63 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.15 (1H, m), 3.28 – 3.32 (2H + H_2O, m), 3.84 – 3.89 (2H, m), 3.93 (1H, d), 7.18 - 7.21 (1H, m), 7.36 - 7.42 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	413
573	3,5-di-F	δ 1.12 (3H, d), 2.27 - 2.32 (1H, m), 2.59 – 2.62 (1H, m), 2.74 - 2.78 (1H, m), 3.11 - 3.16 (1H, m), 3.33 - 3.38 (2H, m), 3.86 - 3.97 (3H, m), 7.08 - 7.13 (3H, m), 7.62 (1H, d), 8.26 (1H, d)	413
574	4-F	δ 1.14 (3H, d), 2.20 - 2.26 (1H, m), 2.56 - 2.61 (1H, m), 2.70 - 2.75 (1H, m), 3.08 - 3.14 (1H, m), 3.26 – 3.33 (2H, m), 3.84 - 3.96 (3H, m), 7.14 - 7.18 (2H,	395

		m), 7.36 - 7.40 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	
575	3-CN, 4-F	δ 1.13 (3H, d), 2.24 - 2.30 (1H, m), 2.60 - 2.65 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.16 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.36 (1H, d), 3.85 - 3.98 (3H, m), 7.49 - 7.53 (1H, m), 7.61 (1H, d), 7.75 - 7.79 (1H, m), 7.86 - 7.88 (1H, m), 8.26 (1H, d)	420

Example 576

Preparation of 6-[(3R)-3-(pyridin-3-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 68% yield by an analogous procedure to Example 216, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3R)-3-(pyridin-3-yloxy)pyrrolidine.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.27 - 2.38 (2H, m), 3.63 - 3.88 (4H, m), 5.30 - 5.34 (1H, m), 7.32 (1H, d), 7.35 - 7.39 (1H, m), 7.47 - 7.50 (1H, m), 8.21 - 8.23 (1H, m), 8.25 (1H, d), 8.34 (1H, d); m/z = 351 [M+H]+.

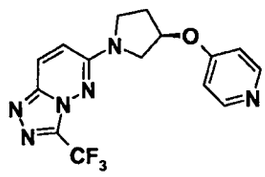
The (3R)-3-(pyridin-3-yloxy)pyrrolidine used as starting material was prepared as follows:-

DIAD (0.631 mL, 3.20 mmol) in DCM (5 ml) was added dropwise to a mixture of (S)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (500 mg, 2.67 mmol), pyridin-3-ol (305 mg, 3.20 mmol) and triphenylphosphine (840 mg, 3.20 mmol) in DCM (20 ml), cooled in an ice bath. The mixture was allowed to warm to room temperature, stirred for 1 hour and then concentrated. The residue was dissolved in dioxan (15 mL) and 4M HCl in dioxan (15 mL) was added. The mixture was stirred for 1 hour and concentrated. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford (3R)-3-(pyridin-3-yloxy)pyrrolidine (405 mg, 92%) as a colourless oil.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.72 - 1.79 (1H, m), 1.99 - 2.08 (1H, m), 2.75 - 2.81 (1H, m), 2.84 - 2.95 (2H, m), 3.05 - 3.09 (1H, m), 4.90 - 4.95 (1H, m), 7.30 - 7.37 (2H, m), 8.15 - 8.16 (1H, m), 8.25 (1H, d); m/z = 165 [M+H]+.

Example 577

Preparation of 6-[(3R)-3-(pyridin-4-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 60% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3R)-3-(pyridin-4-yloxy)pyrrolidine.

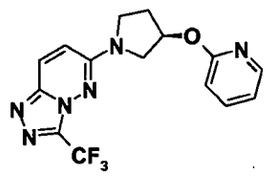
1H NMR (399.9 MHz, DMSO-d_6) δ 2.25 - 2.30 (1H, m), 2.34 - 2.41 (1H, m), 3.61 - 3.90 (4H, m), 5.34 - 5.38 (1H, t), 7.03 - 7.04 (2H, m), 7.32 (1H, d), 8.25 (1H, d), 8.41 - 8.43 (2H, m); m/z = 351 [M+H]+.

The (3R)-3-(pyridin-4-yloxy)pyrrolidine used as starting material was prepared in 61% yield by an analogous method to Example 576, preparation of starting materials, starting from (3S)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate and pyridin-4-ol.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.71 - 1.79 (1H, m), 2.01 - 2.10 (1H, m), 2.75 - 2.81 (1H, m), 2.86 - 2.93 (2H, m), 3.05 - 3.14 (1H, m), 4.93 - 4.97 (1H, m), 6.91 - 6.93 (2H, m), 8.36 - 8.38 (2H, m); m/z = 165 [M+H]+.

Example 578

Preparation of 6-[(3R)-3-(pyridin-2-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 63% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3R)-3-(pyridin-2-yloxy)pyrrolidine.

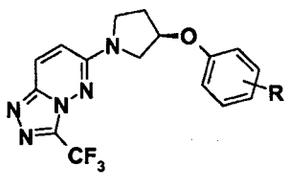
1H NMR (399.9 MHz, DMSO-d_6) δ 2.25 - 2.30 (1H, m), 2.33 - 2.42 (1H, m), 3.65 - 3.76 (3H, m), 3.89 (1H, d), 5.69 - 5.72 (1H, m), 6.82 - 6.84 (1H, m), 7.00 - 7.04 (1H, m), 7.29 - 7.32 (1H, m), 7.71 - 7.75 (1H, m), 8.21 - 8.24 (2H, m); m/z = 351 [M+H]+.

The (3R)-3-(pyridin-2-yloxy)pyrrolidine used as starting material was prepared in 65% yield by an analogous method to Example 576, preparation of starting materials, starting from tert-butyl (3S)-3-hydroxypyrrolidine-1-carboxylate and pyridin-2-ol.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.72 - 1.80 (1H, m), 1.97 - 2.06 (1H, m), 2.75 - 2.84 (2H, m), 2.87 - 2.94 (1H, m), 3.05 - 3.10 (1H, m), 5.34 - 5.38 (1H, m), 6.75 - 6.77 (1H, m), 6.93 - 6.96 (1H, m), 7.66 - 7.70 (1H, m), 8.15 - 8.17 (1H, m); m/z = 165 [M+H]+.

Examples 579-586

The following compounds were prepared in 29-45% yield by an analogous method to Example 447, starting from (3S)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol and the appropriate phenol:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d_6)	m/z [M+H]+
579	4-CF3	δ 2.26 - 2.42 (2H, m), 3.63 - 3.90 (4H, m), 5.33 – 5.37 (1H, m), 7.20 (2H, d), 7.32 (1H, d), 7.69 (2H, d), 8.25 (1H, d)	418
580	4-CN	δ 2.25 - 2.29 (1H, m), 2.33 - 2.41 (1H, m), 3.62 - 3.90 (4H, m), 5.35 – 5.38 (1H, s), 7.17 - 7.21 (2H, m), 7.31 (1H, d), 7.79 - 7.82 (2H, m), 8.25 (1H, d)	375
581	4-F	δ 2.22 - 2.34 (2H, m), 3.61 - 3.84 (4H, m), 5.17 - 5.20 (1H, m), 7.00 - 7.05 (2H, m), 7.12 - 7.18 (2H, m), 7.31 (1H, d), 8.24 (1H, d)	368
582	4-OMe	δ 2.20 - 2.34 (2H, m), 3.54 - 3.89 (7H, m), 5.10 – 5.13 (1H, m), 6.87 - 6.90 (2H, m), 6.93 - 6.95 (2H, m), 7.31 (1H, d), 8.24 (1H, d)	380
583	3-CF3	δ 2.28 - 2.37 (2H, m), 3.63 - 3.86 (4H, m), 5.35 - 5.39 (1H, m), 7.31 - 7.34 (4H, m), 7.55 - 7.59 (1H, m), 8.25	418

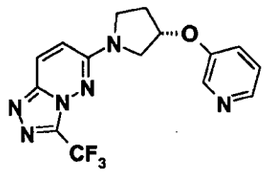
		(1H, d)	
584	3-CN	δ 2.23 – 2.29 (1H, m), 2.31 - 2.38 (1H, m), 3.62 - 3.89 (4H, m), 5.31 – 5.35 (1H, m), 7.32 (1H, d), 7.34 - 7.37 (1H, m), 7.45 (1H, d), 7.51 - 7.55 (2H, m), 8.25 (1H, d)	375
585	3-F	δ 2.23 - 2.36 (2H, m), 3.61 - 3.87 (4H, m), 5.24 – 5.28 (1H, m), 6.78 - 6.86 (2H, m), 6.89 - 6.93 (1H, m), 7.30 - 7.38 (2H, m), 8.25 (1H, d)	368
586	3-OMe	δ 2.23 - 2.37 (2H, m), 3.56 - 3.92 (7H, m), 5.20 - 5.24 (1H, m), 6.54 - 6.60 (3H, m), 7.22 (1H, t), 7.32 (1H, d), 8.24 (1H, d)	380

The (3S)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol used as starting material was prepared in 77% yield by an analogous method to Example 216, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (S)-pyrrolidin-3-ol.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.93 - 1.98 (1H, m), 2.03 - 2.08 (1H, m), 3.42 (1H, d), 3.55 - 3.62 (3H, m), 4.43 - 4.45 (1H, m), 5.07 (1H, d), 7.26 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]+.

Example 587

Preparation of 6-[(3S)-3-(pyridin-3-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 74% yield by an analogous procedure to Example 447, starting from (3R)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol and pyridin-3-ol.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.27 - 2.38 (2H, m), 3.63 - 3.88 (4H, m), 5.31 - 5.34 (1H, m), 7.32 (1H, d), 7.35 - 7.39 (1H, m), 7.47 - 7.50 (1H, m), 8.21 - 8.23 (1H, m), 8.25 (1H, d), 8.34 (1H, d); m/z = 351 [M+H]+.

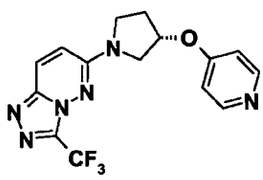
The (3R)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol used as starting material was prepared in 81% yield by an analogous method to Example

216, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (R)-pyrrolidin-3-ol.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.93 - 1.98 (1H, m), 2.03 - 2.08 (1H, m), 3.42 (1H, d), 3.55 - 3.62 (3H, m), 4.43 - 4.45 (1H, m), 5.07 (1H, d), 7.26 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]+.

Example 588

Preparation of 6-[(3S)-3-(pyridin-4-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 75% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3S)-3-(pyridin-4-yloxy)pyrrolidine.

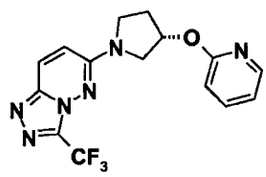
1H NMR (399.9 MHz, DMSO-d_6) δ 2.25 - 2.30 (1H, m), 2.34 - 2.43 (1H, m), 3.61 - 3.90 (4H, m), 5.34 - 5.37 (1H, m), 7.03 - 7.04 (2H, m), 7.32 (1H, d), 8.25 (1H, d), 8.41 - 8.43 (2H, m); m/z = 351 [M+H]+.

The (3S)-3-(pyridin-4-yloxy)pyrrolidine used as starting material was prepared in 61% yield by an analogous method to Example 576, preparation of starting materials, starting from tert-butyl (3R)-3-hydroxypyrrolidine-1-carboxylate and pyridin-4-ol.

1H NMR (399.9 MHz, DMSO-d_6) δ 1.71 - 1.79 (1H, m), 2.01 - 2.10 (1H, m), 2.75 - 2.81 (1H, m), 2.86 - 2.93 (2H, m), 3.05 - 3.14 (1H, m), 4.93 - 4.97 (1H, m), 6.91 - 6.93 (2H, m), 8.36 - 8.38 (2H, m); m/z = 165 [M+H]+.

Example 589

Preparation of 6-[(3S)-3-(pyridin-2-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



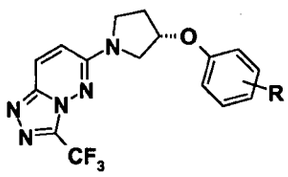
Obtained in 62% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3S)-3-(pyridin-2-yloxy)pyrrolidine.

1H NMR (399.9 MHz, DMSO-d_6) δ 2.25 - 2.30 (1H, m), 2.33 - 2.42 (1H, m), 3.65 - 3.76 (3H, m), 3.89 (1H, d), 5.70 - 5.72 (1H, m), 6.82 - 6.84 (1H, m), 7.01 - 7.04 (1H, m), 7.31 (1H, d), 7.71 - 7.75 (1H, m), 8.21 - 8.25 (2H, m); m/z = 351 [M+H]+.

The (3S)-3-(pyridin-2-yloxy)pyrrolidine used as starting material was prepared in 62% yield by an analogous method to Example 576, preparation of starting materials, starting from tert-butyl (3R)-3-hydroxypyrrolidine-1-carboxylate and pyridin-2-ol.
1H NMR (399.9 MHz, DMSO-d_6) δ 1.72 - 1.80 (1H, m), 1.97 - 2.06 (1H, m), 2.75 - 2.84 (2H, m), 2.87 - 2.94 (1H, m), 3.05 - 3.10 (1H, m), 5.34 - 5.38 (1H, m), 6.75 - 6.77 (1H, m), 6.93 - 6.96 (1H, m), 7.66 - 7.70 (1H, m), 8.15 - 8.17 (1H, m); m/z = 165 [M+H]+.

Examples 590-592

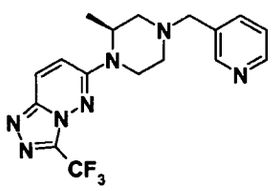
The following compounds were prepared in 22-51% yield by an analogous method to Example 447, starting from (3R)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol (obtained as described in Example 587, preparation of starting materials) and the appropriate phenol:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d_6)	m/z [M+H]+
590	3-CN	δ 2.24 - 2.29 (1H, m), 2.31 - 2.39 (1H, m), 3.62 - 3.89 (4H, m), 5.33 (1H, s), 7.32 (1H, d), 7.34 - 7.37 (1H, m), 7.43 - 7.46 (1H, m), 7.51 - 7.55 (2H, m), 8.24 - 8.26 (1H, m)	375
591	4-CN	δ 2.27 - 2.30 (1H, m), 2.33 - 2.39 (1H, m), 3.62 - 3.90 (4H, m), 5.37 (1H, s), 7.17 - 7.21 (2H, m), 7.31 (1H, d), 7.79 - 7.83 (2H, m), 8.25 (1H, d)	375
592	4-CF3	δ 2.26 - 2.31 (1H, m), 2.33 - 2.40 (1H, m), 3.63 - 3.90 (4H, m), 5.35 (1H, s), 7.20 (2H, d), 7.32 (1H, d), 7.69 (2H, d), 8.25 (1H, d)	418

Example 593

Preparation of 6-[(2S)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

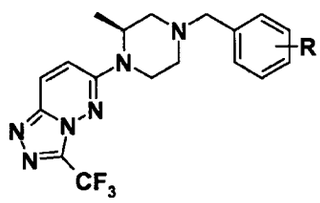


A mixture of pyridine-3-carboxaldehyde and 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 358, preparation of starting materials) was allowed to react by General Synthetic Method 5, to give 6-[(2S)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 76% yield.

1H NMR (500.1MHz, DMSO-d6, 373K) δ 1.31 (3H, d), 2.42 (1H, m), 2.56 (1H, m), 2.88 (1H, m), 3.04 (1H, m), 3.33 (1H, m), 3.77 (2H, m), 4.05 (1H, m), 4.51 (1H, m), 7.47 (2H, m), 7.91 (1H, m), 8.15 (1H, d), 8.56 (1H, m), 8.63 (1H, m); m/z = 378 [M+H]+.

Examples 594-598

The following compounds were prepared in 43-89% yield by General Synthetic Method 5, starting from 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

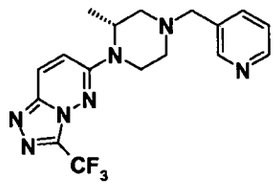


Ex.	R	1H NMR (400.1 MHz, CDCl3)	m/z [M+H]+
594	4-CN	δ 1.47 (3H, d), 2.70 (1H, m), 2.86 (1H, m), 3.20 (1H, m), 3.50 (1H, m), 3.63 (1H, m), 4.01 (1H, d), 4.15 (2H, m), 4.55 (1H, m), 7.05 (1H, d), 7.60 (2H, d), 7.73 (2H, d), 8.05 (1H, d)	402
595	3,4-di-F	δ 1.35 (3H, d), 2.22 (1H, m), 2.36 (1H, m), 2.76 (1H, m), 2.95 (1H, m), 3.33 (1H, m), 3.44 (1H, d), 3.55	413

		(1H, d), 3.98 (1H, m), 4.33 (1H, m), 7.04 - 7.16 (3H, m), 7.23 (1H, m), 7.93 (1H, d)	
596	3,5-di-F	δ 1.48 (3H, d), 2.73 (1H, m), 2.90 (1H, m), 3.28 (1H, m), 3.57 (1H, m), 3.67 (1H, m), 4.00 (1H, d), 4.15 (2H, m), 4.58 (1H, m), 6.89 (1H, m), 7.01 (2H, m), 7.05 (1H, d), 8.06 (1H, d)	413
597	4-F	δ 1.51 (3H, d), 2.83 (1H, m), 3.02 (1H, m), 3.41 (1H, m), 3.77 (2H, m), 4.18 (2H, m), 4.35 (1H, d), 4.64 (1H, m), 7.03 (1H, d), 7.15 (2H, m), 7.45 (2H, m), 8.05 (1H, d)	395
598	3-CN, 4-F	δ 1.36 (3H, d), 2.25 (1H, m), 2.41 (1H, m), 2.74 (1H, m), 2.92 (1H, m), 3.33 (1H, m), 3.49 (1H, d), 3.58 (1H, d), 3.99 (1H, m), 4.34 (1H, m), 7.06 (1H, d), 7.21 (1H, m), 7.63 (2H, m), 7.94 (1H, d)	420

Example 599

Preparation of 6-[(2R)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



A mixture of pyridine-3-carboxaldehyde and 6-[(2R)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2R)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in quantitative yield.

1H NMR (500.1MHz, DMSO-d6, 373K) δ 1.30 (3H, d), 2.37 (1H, m), 2.55 (1H, m), 2.85 (1H, m), 3.02 (1H, m), 3.32 (1H, m), 3.73 (2H, m), 4.04 (1H, m), 4.50 (1H, m), 7.45 (2H, m), 7.87 (1H, m), 8.15 (1H, d), 8.54 (1H, m), 8.61 (1H, m); m/z = 378 [M+H]+.

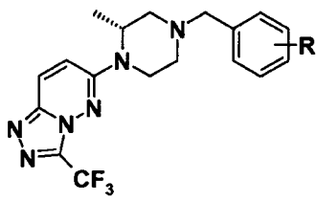
The 6-[(2R)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 74% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-

chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3R)-tert-butyl 3-methylpiperazine-1-carboxylate.

1H NMR (399.1 MHz, DMSO-d6) δ 1.23 (3H, d), 2.43 (1H, m), 2.65 (1H, m), 2.85 (2H, m), 3.04 (2H, m), 3.91 (1H, m), 4.35 (1H, m), 7.56 (1H, d), 8.23 (1H, d); m/z = 287 [M+H]+.

Examples 600-604

The following compounds were prepared in 56-93% yield by by General Synthetic Method 5, starting from 6-[(2R)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

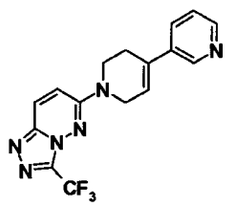


Ex.	R	1H NMR (400.1 MHz, CDCl3)	m/z [M+H]+
600	4-CN	δ 1.46 (3H, d), 2.68 (1H, m), 2.84 (1H, m), 3.18 (1H, m), 3.48 (1H, m), 3.62 (1H, m), 3.99 (1H, d), 4.14 (2H, m), 4.54 (1H, m), 7.05 (1H, d), 7.59 (2H, d), 7.72 (2H, d), 8.04 (1H, d)	402
601	3,4-di-F	δ 1.47 (3H, d), 2.70 (1H, m), 2.87 (1H, m), 3.25 (1H, m), 3.56 (1H, m), 3.66 (1H, m), 3.97 (1H, d), 4.14 (2H, m), 4.57 (1H, m), 7.02 - 7.33 (4H, m), 8.04 (1H, d)	413
602	3,5-di-F	δ 1.47 (3H, d), 2.68 (1H, m), 2.85 (1H, m), 3.23 (1H, m), 3.52 (1H, m), 3.64 (1H, m), 3.95 (1H, d), 4.12 (2H, m), 4.56 (1H, m), 6.88 (1H, m), 7.00 (2H, m), 7.05 (1H, d), 8.05 (1H, d)	413
603	4-F	δ 1.50 (3H, d), 2.82 (1H, m), 3.00 (1H, m), 3.39 (1H, m), 3.75 (2H, m), 4.17 (2H, m), 4.33 (1H, d), 4.63 (1H, m), 7.02 (1H, d), 7.15 (2H, m), 7.45 (2H, m), 8.05 (1H, d)	395
604	3-CN, 4-	δ 1.35 (3H, d), 2.25 (1H, m), 2.41 (1H, m), 2.74 (1H,	420

	F	m), 2.93 (1H, m), 3.33 (1H, m), 3.49 (1H, d), 3.58 (1H, d), 3.99 (1H, m), 4.35 (1H, m), 7.06 (1H, d), 7.21 (1H, m), 7.63 (2H, m), 7.94 (1H, d)	

Example 605

Preparation of 1'-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1',2',3',6'-tetrahydro-3,4'-bipyridine



Sodium carbonate (114 mg, 1.08 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (150 mg, 0.36 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (81 mg, 0.40 mmol) in a mixture of DME (2 mL) and water (0.5 mL). The mixture was bubbled with nitrogen for 10 minutes then tetrakis(triphenylphosphine)palladium(0) (20.77 mg, 0.02 mmol) was added and the mixture was stirred at 80°C for 3 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc (3 mL) and water (2 mL). The organic layer was separated and dried, and the solvent was evaporated to give crude product. Purification by flash silica chromatography, elution gradient 0 to 3% MeOH in DCM, gave 1'-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1',2',3',6'-tetrahydro-3,4'-bipyridine (100 mg, 80%).

1H NMR (399.1 MHz, DMSO-d6) δ 2.70 (2H, m), 3.91 (2H, m), 4.29 (2H, m), 6.44 (1H, m), 7.41 (1H, m), 7.69 (1H, d), 7.89 (1H, m), 8.30 (1H, d), 8.50 (1H, m), 8.74 (1H, m); m/z = 347 [M+H]+.

The 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate used as starting material was prepared as follows:-

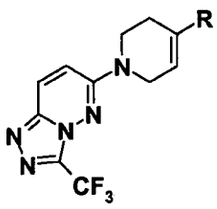
A solution of 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-one (obtained as described in Example 310, preparation of starting materials) (11.08 g, 38.85 mmol) in THF (200 mL) was added dropwise to 1M lithium bis(trimethylsilyl)amide

in THF (42.7 mL, 42.73 mmol) at -78 °C, over a period of 30 minutes under nitrogen. The resulting suspension was stirred at -78°C for 20 minutes, then a solution of N-phenyltrifluoromethanesulfonimide (15.27 g, 42.73 mmol) in THF (150 ml) was added dropwise over a period of 10 minutes. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL), then concentrated and diluted with DCM (500 mL), washed with water (300 mL) then brine (300 mL) and evaporated to afford crude product. DCM (100 mL) was added to the crude product, the precipitate was collected by filtration and the filtrate was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness and combined with the previously collected precipitate to afford 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (12.91 g, 80%).

1H NMR (399.9 MHz, DMSO-d6) δ 2.63 (2H, m), 3.90 (2H, m), 4.25 (2H, m), 6.19 (1H, m), 7.67 (1H, d), 8.33 (1H, d); m/z = 418 [M+H]+.

Examples 606-609

The following compounds were prepared in 54-77% yield by an analogous method to Example 605, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate and the appropriate heteroaryl boronic acid or boronic acid pinacol ester:-

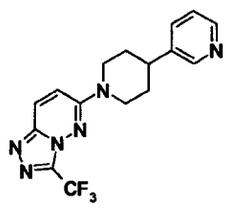


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
606	3-fluoropyridin-4-yl	δ 2.68 (2H, m), 3.90 (2H, m), 4.31 (2H, m), 6.47 (1H, m), 7.49 (1H, m), 7.68 (1H, d), 8.31 (1H, d), 8.44 (1H, m), 8.57 (1H, d)	365
607	5-fluoropyridin-3-yl	δ 2.71 (2H, m), 3.91 (2H, m),	365

		4.30 (2H, m), 6.55 - 6.57 (1H, m), 7.70 (1H, d), 7.84 - 7.88 (1H, m), 8.30 (1H, d), 8.50 (1H, m), 8.63 (1H, m)	
608	5-(ethoxycarbonyl)pyridin-3-yl	δ 1.36 (3H, t), 2.75 (2H, m), 3.92 (2H, m), 4.31 (2H, m), 4.38 (2H, q), 6.56 (1H, m), 7.69 (1H, d), 8.29 - 8.32 (2H, m), 8.98 - 9.00 (2H, m)	419
609	5-fluoro-6-methoxypyridin-3-yl	δ 2.66 (2H, m), 3.89 (2H, m), 3.97 (3H, s), 4.26 - 4.27 (2H, m), 6.38 (1H, m), 7.69 (1H, d), 7.87 - 7.91 (1H, m), 8.11 (1H, d), 8.29 (1H, d)	395

Example 610

Preparation of 6-(4-pyridin-3-ylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

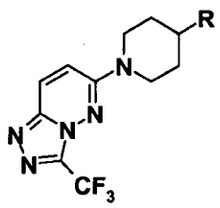


A mixture of 1'-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1',2',3',6'-tetrahydro-3,4'-bipyridine (obtained as described in Example 605) (82 mg, 0.24 mmol) and 10% palladium on carbon (25.2 mg, 0.02 mmol) in MeOH (10 mL) was stirred under an atmosphere of hydrogen at atmospheric pressure for 3 days. The catalyst was removed by filtration and the solvent evaporated to give crude product, which was purified by flash silica chromatography, elution gradient 0 to 3% MeOH in DCM. Fractions containing the desired product were evaporated to dryness to give 6-(4-pyridin-3-ylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (24 mg, 29%).

1H NMR (399.1 MHz, DMSO-d6) δ 1.75 (2H, m), 1.93 (2H, m), 2.94 (1H, m), 3.14 (2H, m), 4.44 (2H, m), 7.33 (1H, m), 7.69 (2H, m), 8.26 (1H, d), 8.43 (1H, m), 8.53 (1H, d); m/z = 349 [M+H]+.

Examples 611-614

The following compounds were prepared in 13-57% yield by an analogous method to Example 610, starting from the appropriate tetrahydro bipyridine (obtained as described in Examples 606-609):-



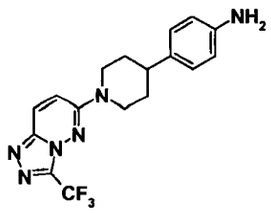
Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
611	3-fluoropyridin-4-yl	δ 1.79 (2H, m), 1.91 (2H, m), 3.21 (3H, m), 4.44 (2H, m), 7.44 (1H, m), 7.67 (1H, d), 8.26 (1H, d), 8.38 (1H, d), 8.51 (1H, d)	367
612	5-fluoropyridin-3-yl	δ 1.75 - 1.79 (2H, m), 1.94 (2H, m), 2.98 - 3.17 (3H, m), 4.43 - 4.46 (2H, m), 7.66 - 7.72 (2H, m), 8.26 (1H, d), 8.43 (2H, m)	367
613	5-(ethoxycarbonyl)pyridin-3-yl	δ 1.34 (3H, t), 1.78 - 1.82 (2H, m), 1.96 (2H, m), 3.08 - 3.17 (3H, m), 4.36 (2H, q), 4.46 (2H, m), 7.67 (1H, d), 8.16 (1H, m), 8.26 (1H, d), 8.79 (1H, m), 8.96 (1H, m)	462 [1]
614	5-fluoro-6-methoxypyridin-3-yl	δ 1.70 - 1.74 (2H, m), 1.90 (2H, m), 2.92 (1H, m), 3.08 - 3.14 (2H, m), 3.92 (3H, s), 4.43 (2H, m), 7.65 - 7.69 (2H, m), 7.91	397

		(1H, m), 8.25 (1H, d)	

[1] Detected as adduct with acetonitrile used as solvent in mass spectral determination

Example 615

Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline



DIPEA (1.631 mL, 9.36 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1.389 g, 6.24 mmol) and 4-(piperidin-4-yl)aniline (1.21 g, 6.86 mmol) in DMF (30 mL). The resulting solution was stirred at 80°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and purified by flash chromatography on silica gel, elution gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to give 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (1.910 g, 84%) as a solid.

1H NMR (399.9 MHz, CDCl3) δ 1.72 - 1.79 (2H, m), 1.96 - 2.00 (2H, m), 2.70 - 2.73 (1H, m), 3.06 - 3.14 (2H, m), 3.60 (2H, s), 4.33 - 4.38 (2H, m), 6.65 (2H, d), 7.01 (2H, d), 7.12 (1H, d), 7.91 (1H, d); m/z = 363 [M+H]+.

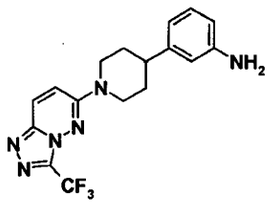
The 4-(piperidin-4-yl)aniline used as starting material was prepared as follows;

TFA (5 mL) was added to tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (1.9 g, 6.87 mmol, CAS 170011-57-1) in DCM (5 mL). The resulting solution was stirred at ambient temperature for 2 hours then added to an SCX column. The desired product was eluted from the column using 2M ammonia in methanol and the solvent evaporated to dryness to give 4-(piperidin-4-yl)aniline (1.210 g, 100%) as a solid.

m/z = 177 [M+H]+.

Example 616

Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline

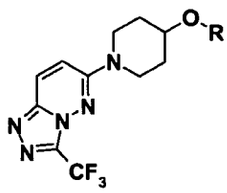


Obtained in 78% yield by an analogous procedure to Example 615, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-(piperidin-4-yl)aniline.
1H NMR (399.9 MHz, CDCl3) δ 1.76 - 1.80 (2H, m), 2.00 (2H, m), 2.74 (1H, m), 3.07 - 3.14 (2H, m), 3.64 (2H, s), 4.34 - 4.39 (2H, m), 6.54 - 6.63 (3H, m), 7.11 (2H, m), 7.92 (1H, d); m/z = 363 [M+H]+.

The 3-(piperidin-4-yl)aniline used as starting material was prepared in 97% yield by an analogous procedure to Example 616, preparation of starting materials, starting from tert-butyl 4-(3-aminophenyl)piperidine-1-carboxylate (CAS 387827-19-2).
m/z = 177 [M+H]+.

Examples 617-622

The following compounds were prepared in 9-67% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate hydroxy heterocycle:-

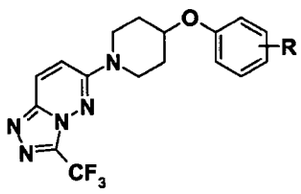


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
617	5-chloropyridin-3-yl	δ 1.75 (2H, m), 2.10 (2H, m), 3.52 (2H, m), 3.99 (2H, m), 4.85 (1H, m), 7.65 (1H, d), 7.74 (1H, m), 8.25 (2H, m), 8.33 (1H, d)	399
618	5-chloropyridin-2-yl	δ 1.73 - 1.81 (2H, m), 2.08 - 2.14	399

		(2H, m), 3.49 - 3.56 (2H, m), 3.96 - 4.02 (2H, m), 5.25 - 5.28 (1H, m), 6.88 (1H, d), 7.65 (1H, d), 7.80 - 7.83 (1H, m), 8.22 - 8.27 (2H, m)	
619	pyrimidin-4-yl	δ 1.78 - 1.83 (2H, m), 2.12 - 2.17 (2H, m), 3.51 - 3.58 (2H, m), 3.97 - 4.03 (2H, m), 5.41 (1H, m), 6.95 - 6.97 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.53 - 8.55 (1H, m), 8.80 (1H, m)	366
620	5-bromopyrimidin-2-yl	δ 1.80 - 1.86 (2H, m), 2.12 - 2.16 (2H, m), 3.51 - 3.58 (2H, m), 3.96 - 4.02 (2H, m), 5.22 - 5.25 (1H, m), 7.66 (1H, d), 8.26 (1H, d), 8.78 (2H, s)	444
621	4-trifluoromethylpyridin-2-yl	δ 1.76 - 1.85 (2H, m), 2.11 - 2.16 (2H, m), 3.53 - 3.60 (2H, m), 3.97 - 4.03 (2H, m), 5.37 - 5.41 (1H, m), 7.20 (1H, d), 7.33 - 7.34 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.46 (1H, d)	433
622	4-methylpyrimidin-2-yl	δ 1.78 - 1.82 (2H, m), 2.10 - 2.15 (2H, m), 2.41 (3H, s), 3.53 - 3.59 (2H, m), 3.95 - 4.01 (2H, m), 5.26 (1H, m), 7.02 (1H, d), 7.66 (1H, d), 8.26 (1H, d), 8.45 (1H, d)	380

Examples 623-627

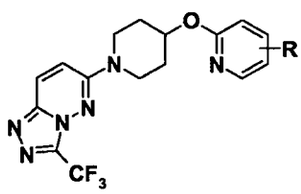
The following compounds were prepared in 12-29% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate phenol:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
623	3-CN	δ 1.72 - 1.75 (2H, m), 2.08 - 2.13 (2H, m), 3.48 - 3.55 (2H, m), 3.96 - 4.01 (2H, m), 4.80 (1H, m), 7.35 - 7.38 (1H, m), 7.40 - 7.43 (1H, m), 7.49 - 7.56 (2H, m), 7.65 (1H, d), 8.26 (1H, d)	389
624	4-CF3	δ 1.75 - 1.78 (2H, m), 2.09 - 2.11 (2H, m), 3.52 - 3.58 (2H, m), 3.96 - 4.00 (2H, m), 4.84 (1H, m), 7.21 (2H, d), 7.64 - 7.68 (3H, m), 8.27 (1H, d)	432
625	4-F	δ 1.69 - 1.76 (2H, m), 2.03 - 2.09 (2H, m), 3.49 - 3.55 (2H, m), 3.93 - 3.99 (2H, m), 4.62 - 4.65 (1H, m), 7.02 - 7.06 (2H, m), 7.11 - 7.15 (2H, m), 7.64 (1H, d), 8.25 (1H, d)	382
626	3-CF3	δ 1.73 - 1.78 (2H, m), 2.07 - 2.12 (2H, m), 3.52 - 3.59 (2H, m), 3.95 - 4.00 (2H, m), 4.84 (1H, m), 7.30 - 7.35 (3H, m), 7.53 - 7.57 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	432
627	4-CN	δ 1.74 - 1.77 (2H, m), 2.09 (2H, m), 3.51 - 3.56 (2H, m), 3.96 - 4.00 (2H, m), 4.86 (1H, m), 7.20 (2H, d), 7.65 (1H, d), 7.79 (2H, d), 8.26 (1H, d)	389

Examples 628-629

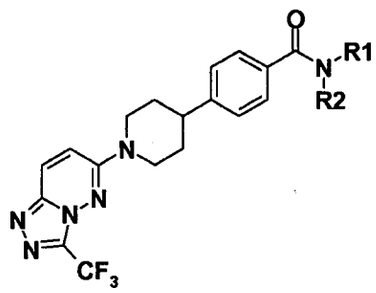
The following compounds were prepared in 23-48% yield by an analogous method to Example 448, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate chloropyridine:-

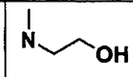
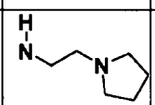
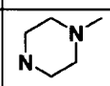


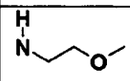
Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
628	5-CN	δ 1.78 - 1.84 (2H, m), 2.13 - 2.16 (2H, m), 3.51 - 3.57 (2H, m), 3.97 - 4.03 (2H, m), 5.39 - 5.42 (1H, m), 7.01 (1H, d), 7.66 (1H, d), 8.16 - 8.18 (1H, m), 8.27 (1H, d), 8.71 (1H, d)	390
629	4-CN	δ 1.78 - 1.81 (2H, m), 2.11 (2H, m), 3.51 - 3.57 (2H, m), 3.98 - 4.02 (2H, m), 5.35 (1H, m), 7.38 (1H, m), 7.41 - 7.43 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.42 - 8.43 (1H, m)	390

Examples 630-635

The following compounds were prepared in 10-90% yield by an analogous method to Example 512, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid and the appropriate amine:-

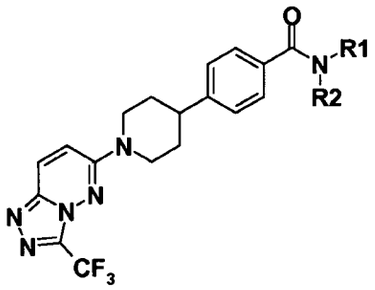


Ex.	NR1R2	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
630		δ 1.76 - 1.86 (2H, m), 2.03 (2H, m), 2.84 - 2.90 (1H, m), 3.08 - 3.17 (5H, m), 3.72 - 3.90 (4H, m), 4.37 - 4.41 (2H, m), 7.13 (1H, d), 7.26 (2H, d), 7.42 (2H, d), 7.94 (1H, d)	449
631		δ 1.77 - 1.84 (6H, m), 2.02 - 2.05 (2H, m), 2.54 - 2.57 (4H, m), 2.70 (2H, m), 2.89 (1H, m), 3.10 - 3.18 (2H, m), 3.52 - 3.57 (2H, m), 4.38 - 4.41 (2H, m), 6.79 (1H, t), 7.13 (1H, d), 7.29 (2H, d), 7.75 (2H, d), 7.94 (1H, d)	488
632		δ 1.81 (2H, m), 2.02 (2H, m), 2.33 (3H, s), 2.43 (4H, m), 2.87 (1H, m), 3.13 (2H, m), 3.48 - 3.78 (4H, m),	474

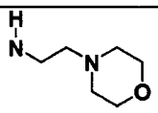
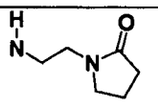
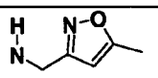
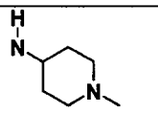
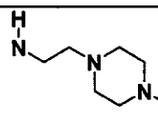
		4.39 (2H, m), 7.13 (1H, d), 7.26 (2H, d), 7.37 (2H, d), 7.94 (1H, d)	
633		δ 1.76 - 1.87 (2H, m), 2.01 - 2.05 (2H, m), 2.87 - 2.93 (1H, m), 3.10 - 3.18 (2H, m), 3.38 (3H, s), 3.56 (2H, m), 3.63 - 3.67 (2H, m), 4.38 - 4.41 (2H, m), 6.48 (1H, t), 7.14 (1H, d), 7.29 (2H, d), 7.75 (2H, d), 7.95 (1H, d)	449
634	NMe2	δ 1.79 - 1.86 (2H, m), 2.00 - 2.04 (2H, m), 2.85 (1H, s), 2.98 - 3.17 (8H, m), 4.37 - 4.41 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.38 (2H, d), 7.94 (1H, d)	419
635		δ 1.79 - 1.83 (2H, m), 2.00 - 2.04 (2H, m), 2.87 (1H, m), 3.10 - 3.17 (2H, m), 3.69 (8H, m), 4.37 - 4.41 (2H, m), 7.13 (1H, d), 7.27 (2H, d), 7.38 (2H, d), 7.95 (1H, d)	461

Examples 636-642

The following compounds were prepared in 5-85% yield by an analogous method to Example 512, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid and the appropriate amine:-

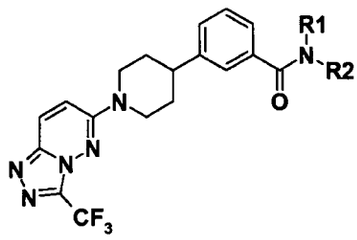


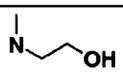
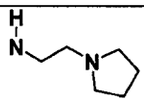
Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
636		δ 1.68 - 1.78 (2H, m), 1.92 - 1.97 (2H, m), 2.65 (4H, m), 2.89 - 2.97 (1H, m), 3.09 - 3.16 (2H, m), 3.44 - 3.52 (4H, m), 4.47 (2H, m), 7.38 (2H, d), 7.67 (1H, d), 7.81 (2H, d), 8.26 (1H, d)	460
637	NHEt	δ 1.14 (3H, t), 1.68 - 1.79 (2H, m), 1.92 (2H, m), 2.91 - 2.97 (1H, m), 3.10 - 3.16 (2H, m), 4.44	419

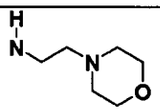
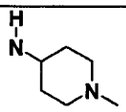
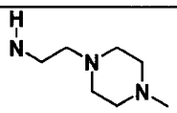
		(2H, d), 7.36 (2H, d), 7.67 (1H, d), 7.78 (2H, d), 8.25 (1H, d), 8.36 (1H, t), (2H obscured by water)	
638		δ 1.74 (2H, m), 1.92 (2H, m), 2.94 (1H, m), 3.14 (2H, m), 3.40 (2H, m), 3.60 (4H, m), 4.44 (2H, m), 7.37 (2H, d), 7.67 (1H, d), 7.78 (2H, d), 8.26 (1H, d), 8.33 (1H, t), (2H obscured by water, 4H obscured by DMSO)	504
639		δ 1.72 - 1.79 (2H, m), 1.87 - 1.94 (4H, m), 2.16 - 2.20 (2H, m), 2.91 - 2.97 (1H, m), 3.10 - 3.16 (2H, m), 3.33 - 3.43 (6H, m), 4.44 (2H, d), 7.37 (2H, d), 7.67 (1H, d), 7.75 (2H, d), 8.25 (1H, d), 8.43 (1H, t)	502
640		δ 1.72 - 1.78 (2H, m), 1.92 (2H, m), 2.37 (3H, s), 2.96 (1H, m), 3.11 - 3.17 (2H, m), 4.42 - 4.46 (4H, m), 6.14 (1H, s), 7.39 (2H, d), 7.67 (1H, d), 7.83 (2H, d), 8.26 (1H, d), 8.97 (1H, t)	486
641		δ 1.54 - 1.78 (6H, m), 1.92 (2H, m), 2.00 - 2.10 (2H, m), 2.21 (3H, s), 2.81 (2H, m), 2.91 - 2.98 (1H, m), 3.10 - 3.16 (2H, m), 3.72 - 3.76 (1H, m), 4.44 (2H, m), 7.36 (2H, d), 7.67 (1H, d), 7.79 (2H, d), 8.14 (1H, d), 8.25 (1H, d)	488
642		δ 1.74 (2H, m), 1.92 (2H, m), 2.17 (3H, s), 2.32 - 2.48 (10H, m), 2.94 (1H, m), 3.13 (2H, m), 3.36 (2H, m), 4.44 (2H, m), 7.36 (2H, d), 7.67 (1H, d), 7.77 (2H, d), 8.27 (2H, m)	517

Examples 643-652

The following compounds were prepared in 16-73% yield by an analogous method to Example 512, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid and the appropriate amine:-



Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
643		δ 1.69 - 1.77 (2H, m), 1.93 (2H, m), 2.89 - 2.97 (4H, m), 3.10 - 3.16 (2H, m), 3.49 - 3.61 (4H, m), 4.43 (2H, m), 4.75 (1H, t), 7.23 - 7.24 (1H, m), 7.30 - 7.35 (3H, m), 7.67 (1H, d), 8.25 (1H, d)	449
644		δ 1.64 - 1.71 (4H, m), 1.73 - 1.80 (2H, m), 1.94 (2H, m), 2.46 - 2.49 (4H, m), 2.56 (2H, m), 2.91 - 2.97 (1H, m), 3.11 - 3.17 (2H, m), 3.35 - 3.39 (2H, m), 4.45 (2H, m), 7.37 - 7.44 (2H, m), 7.67 - 7.69 (2H, m), 7.74 (1H, s), 8.26 (1H, d), 8.38 (1H, t)	488
645		δ 1.73 (2H, m), 1.93 (2H, m), 2.19 (3H, s), 2.30 (4H, m), 2.94 (1H, m), 3.13 (2H, m), 3.33 - 3.66 (4H, m), 4.43 (2H, m), 7.21 (1H, m), 7.27 (1H, s), 7.38 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	474
646		δ 1.68 - 1.78 (2H, m), 1.92 - 1.97 (2H, m), 2.69 (4H, m), 2.89 - 2.97 (1H, m), 3.09 - 3.16 (2H, m), 3.44 - 3.52 (4H, m), 4.43 (2H, m), 7.19 - 7.22 (1H, m), 7.26 (1H, s), 7.31 - 7.40 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	460
647	NMe2	δ 1.68 - 1.79 (2H, m), 1.93 (2H, m), 2.88 - 2.97 (7H, m), 3.09 - 3.16 (2H, m), 4.42 - 4.45 (2H, m), 7.22 - 7.25 (1H, m), 7.29 (1H, s), 7.34 - 7.39 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	419
648		δ 1.69 - 1.78 (2H, m), 1.93 (2H, m), 2.90 - 2.96 (1H, m), 3.10 - 3.16 (2H, m), 3.60 (8H, m), 4.43	461

		(2H, m), 7.23 - 7.26 (1H, m), 7.31 (1H, s), 7.36 - 7.41 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	
649	NHMe	δ 1.75 (2H, m), 1.94 (2H, m), 2.78 (3H, d), 2.94 (1H, m), 3.14 (2H, m), 4.45 (2H, m), 7.40 (2H, m), 7.68 (2H, m), 7.74 (1H, s), 8.26 (1H, d), 8.38 (1H, m)	405
650		δ 1.75 (2H, m), 1.94 (2H, m), 2.44 (6H, m), 2.95 (1H, m), 3.14 (2H, m), 3.38 (2H, m), 3.57 (4H, m), 4.46 (2H, m), 7.41 (2H, m), 7.68 (2H, m), 7.73 (1H, s), 8.26 (1H, d), 8.36 (1H, t)	504
651		δ 1.58 (2H, m), 1.76 (4H, m), 1.94 (4H, m), 2.16 (3H, s), 2.77 (2H, m), 2.94 (1H, m), 3.13 (2H, m), 3.73 (1H, m), 4.46 (2H, m), 7.40 (2H, m), 7.68 (2H, m), 7.74 (1H, s), 8.18 (1H, d), 8.26 (1H, d)	488
652		δ 1.75 (2H, m), 1.94 (2H, m), 2.14 (3H, s), 2.30 (4H, m), 2.43 (4H, m), 2.56 (2H, m), 2.95 (1H, m), 3.14 (2H, m), 3.36 (2H, m), 4.45 (2H, m), 7.41 (2H, m), 7.68 (2H, m), 7.73 (1H, s), 8.26 (1H, d), 8.33 (1H, t)	517

The 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid used as starting material was prepared as follows:-

Preparation of ethyl 3-(pyridin-4-yl)benzoate

Obtained in 92% yield by an analogous procedure to Example 605, starting from 4-bromopyridine hydrochloride and 3-(ethoxycarbonyl)phenylboronic acid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.37 (3H, t), 4.38 (2H, q), 7.71 (1H, m), 7.76 (2H, d), 8.08 (2H, m), 8.30 (1H, s), 8.69 (2H, d); m/z = 228 [M+H]+.

Preparation of ethyl 3-(piperidin-4-yl)benzoate

Ethyl 3-(pyridin-4-yl)benzoate (1.46 g, 6.42 mmol), 5% palladium on carbon (50% wet) (0.301 g, 0.07 mmol) and citric acid monohydrate (0.601 g, 2.86 mmol) in a mixture of isopropanol (50 mL) and water (5 mL) were stirred under an atmosphere of hydrogen at 20 atmosphere and 70°C for 15 hours. The reaction was cooled to room temperature, the

catalyst removed by filtration and the solvent evaporated to give the crude product, which was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol to give ethyl 3-(piperidin-4-yl)benzoate (1.190 g, 79%) as a liquid.

m/z = 275 [M+H]+ (acetonitrile adduct).

Preparation of ethyl 3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]benzoate

Ethyl 3-(piperidin-4-yl)benzoate (1.195 g, 5.12 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1 g, 4.49 mmol) and DIPEA (1.174 mL, 6.74 mmol) in DMA (10 mL). The resulting solution was stirred at 125°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and purified by flash silica chromatography, eluting with 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to give a beige solid, which was triturated with ether to give ethyl 3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]benzoate (0.805 g, 42.7%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.33 (3H, t), 1.74 (2H, m), 1.94 (2H, m), 2.99 (1H, m), 3.14 (2H, m), 4.32 (2H, q), 4.44 (2H, m), 7.47 (1H, m), 7.59 (1H, m), 7.67 (1H, d), 7.83 (2H, m), 8.25 (1H, d); m/z = 420 [M+H]+.

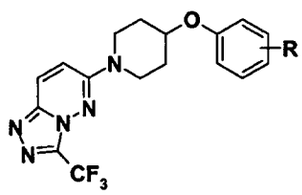
Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid

Obtained in 100% yield by an analogous procedure to Example 512, preparation of starting materials, starting from ethyl 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate.

1H NMR (399.9 MHz, DMSO-d6) δ 1.69 - 1.79 (2H, m), 1.94 (2H, m), 2.95 - 3.01 (1H, m), 3.14 (2H, m), 4.44 (2H, m), 7.45 (1H, m), 7.54 - 7.56 (1H, m), 7.67 (1H, d), 7.79 - 7.82 (1H, m), 7.84 (1H, m), 8.25 (1H, d), 12.78 (1H, s); m/z = 392 [M+H]+.

Examples 653-654

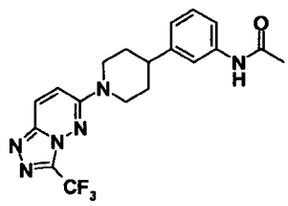
The following compounds were prepared in 25-37% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate phenol:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
653	2-CF3	δ 1.81 (2H, m), 2.08 (2H, m), 3.69 (2H, m), 3.80 (2H, m), 4.94 (1H, m), 7.11 (1H, m), 7.40 (1H, m), 7.64 (3H, m), 8.26 (1H, d)	432
654	2-CN	δ 1.82 (2H, m), 2.11 (2H, m), 3.65 (2H, m), 3.90 (2H, m), 4.94 (1H, m), 7.12 (1H, m), 7.41 (1H, m), 7.68 (2H, m), 7.75 (1H, m), 8.27 (1H, d)	389

Example 655

Preparation of N-[3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide

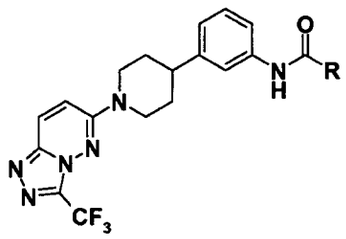


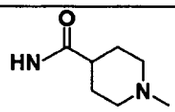
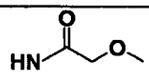
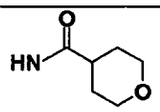
DIPEA (123 µl, 0.70 mmol) was added to 3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]aniline (obtained as described in Example 616) (85 mg, 0.23 mmol), acetic acid (16 µl, 0.28 mmol) and HATU (107 mg, 0.28 mmol) in DMA (2 mL). The resulting solution was stirred at ambient temperature for 2 hours then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents. Fractions containing the desired compound were evaporated to dryness to give N-[3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide (89 mg, 94%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.66 (2H, m), 1.91 (2H, m), 2.02 (3H, s), 2.84 (1H, m), 3.13 (2H, m), 4.42 (2H, m), 6.95 (1H, m), 7.22 (1H, m), 7.41 (1H, m), 7.49 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.84 (1H, s); m/z = 405 [M+H]+.

Examples 656-658

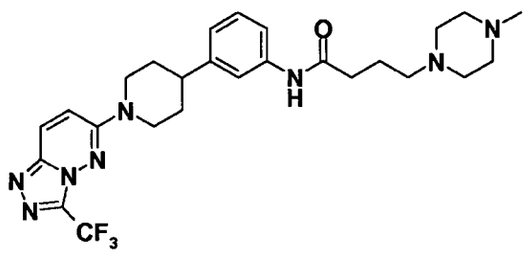
The following compounds were prepared in 71-86% yield by an analogous method to Example 655, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline and the appropriate carboxylic acid:-



Ex.	NHCOR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
656		δ 1.68 (6H, m), 1.88 (4H, m), 2.17 (3H, s), 2.25 (1H, m), 2.83 (3H, m), 3.13 (2H, m), 4.42 (2H, m), 6.94 (1H, m), 7.21 (1H, m), 7.42 (1H, m), 7.56 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.77 (1H, s)	488
657		δ 1.67 (2H, m), 1.92 (2H, m), 2.85 (1H, m), 3.14 (2H, m), 3.38 (3H, s), 3.98 (2H, s), 4.43 (2H, m), 6.99 (1H, m), 7.24 (1H, m), 7.53 (1H, m), 7.59 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.64 (1H, s)	435
658		δ 1.66 (6H, m), 1.91 (2H, m), 2.58 (1H, m), 2.84 (1H, m), 3.13 (2H, m), 3.35 (2H, m), 3.91 (2H, m), 4.42 (2H, m), 6.95 (1H, m), 7.22 (1H, m), 7.43 (1H, m), 7.56 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.80 (1H, s)	475

Example 659

Preparation of 4-(4-methylpiperazin-1-yl)-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide



1-Methylpiperazine (152 µl, 1.37 mmol) was added to 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide (160 mg, 0.343 mmol) and sodium iodide (10 mg, 0.069 mmol) in a mixture of THF (2 mL) and DMA (0.5 mL). The resulting solution was heated at 60°C for 16 hours, then cooled and evaporated to give the crude product, which was purified by flash chromatography on silica, eluting with a gradient of 0 – 10% 2M ammonia in methanol in DCM. The solvents were evaporated, then the resulting gum triturated with ether and the precipitate filtered and dried to give 4-(4-methylpiperazin-1-yl)-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide (87 mg, 48%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.60 - 1.76 (4H, m), 1.91 (2H, m), 2.12 (3H, s), 2.25 - 2.35 (12H, m), 2.84 (1H, m), 3.13 (2H, m), 4.42 (2H, m), 6.94 (1H, m), 7.21 (1H, m), 7.42 (1H, m), 7.52 (1H, m), 7.67 (1H, d), 8.25 (1H, d), 9.77 (1H, s); m/z = 531 [M+H]+.

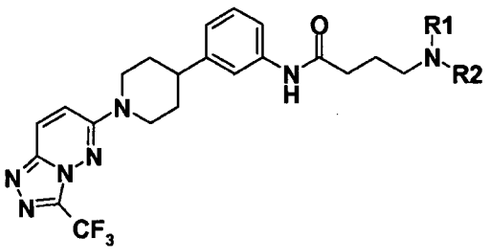
The 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide used as starting material was prepared as follows:-

A solution of 4-chlorobutyryl chloride (175 mg, 1.24 mmol) in DCM (2 mL) was added dropwise to a stirred suspension of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 616) (375 mg, 1.03 mmol) and pyridine (164 mg, 2.07 mmol) in DCM (3 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with DCM (5 mL), washed with saturated sodium bicarbonate (10 mL), dried and the solvents evaporated to a yellow gum, which was triturated with ether to give 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide (480 mg, 99%) as a solid.

m/z = 467 [M+H]+.

Examples 660-661

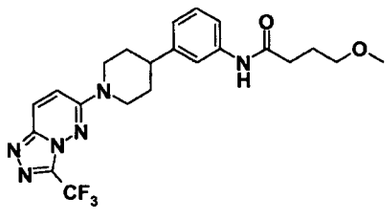
The following compounds were prepared in 5-34% yield by an analogous method to Example 659, starting from 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide and the appropriate amine:-



Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
660		δ 1.66 (2H, m), 1.85 - 1.95 (8H, m), 2.40 (2H, t), 2.85 (1H, m), 2.98 - 3.19 (8H, m), 4.43 (2H, m), 6.97 (1H, m), 7.24 (1H, m), 7.43 (1H, m), 7.51 (1H, m), 7.67 (1H, d), 8.26 (1H, d), 9.90 (1H, s)	502
661		δ 1.61 - 1.77 (4H, m), 1.86 (2H, m), 2.27 - 2.40 (8H, m), 2.84 (1H, m), 3.13 (2H, m), 3.59 (4H, m), 4.45 (2H, m), 6.92 (1H, m), 7.22 (1H, m), 7.46 (1H, m), 7.54 (1H, m), 7.69 (1H, d), 8.26 (1H, d), 9.78 (1H, s)	518

Example 662

Preparation of 4-methoxy-N-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]phenyl]butanamide



Obtained in 68% yield by an analogous procedure to Example 655, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline and 4-methoxybutanoic acid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.66 (2H, m), 1.80 (2H, m), 1.91 (2H, m), 2.34 (2H, t), 2.84 (1H, m), 3.13 (2H, m), 3.24 (3H, s), 3.35 (2H, t), 4.42 (2H, m), 6.94 (1H, d), 7.22 (1H, m), 7.42 (1H, d), 7.53 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.81 (1H, s); m/z = 463 [M+H]+.

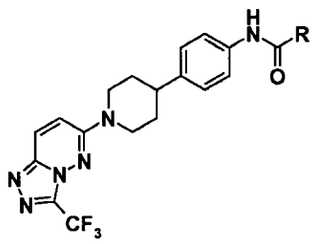
The 4-methoxybutanoic acid used as starting material was prepared as follows:-

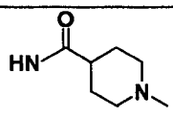
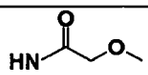
Lithium hydroxide monohydrate (0.381 g, 9.08 mmol) was added to methyl 4-methoxybutanoate (1g, 7.57 mmol) in a mixture of MeOH (20 mL) and water (10 mL). The resulting suspension was stirred at 50°C for 16 hours. The reaction was cooled to room temperature, the MeOH evaporated and the aqueous residues diluted with water (50 mL) and washed with EtOAc (2 x 50 mL). The aqueous layer was then acidified to pH 4 with 1M citric acid and extracted with EtOAc (2 x 50 mL). The combined extracts were dried over $MgSO_4$ and the solvent evaporated to afford 4-methoxybutanoic acid (0.709 g, 79%) as a liquid.

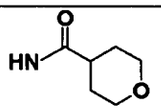
1H NMR (399.9 MHz, CDCl3) δ 1.91 (2H, m), 2.46 (2H, t), 3.34 (3H, s), 3.44 (2H, t), 10.92 (1H, br s).

Examples 663-665

The following compounds were prepared in 22-68% yield by an analogous method to Example 655, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 615) and the appropriate carboxylic acid:-

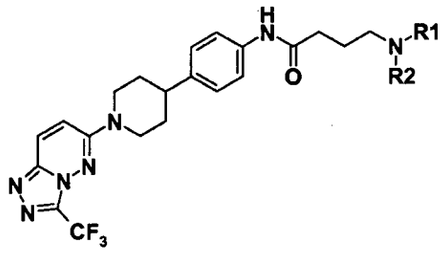


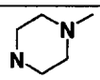
Ex.	NHCOR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
663		δ 1.60 - 1.75 (6H, m), 1.88 (4H, m), 2.18 (3H, s), 2.26 (1H, m), 2.83 (3H, m), 3.10 (2H, m), 4.41 (2H, m), 7.18 (2H, d), 7.52 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.75 (1H, s)	488
664		δ 1.68 (2H, m), 1.89 (2H, m), 2.83 (1H, m), 3.11 (2H, m), 3.38 (3H, s), 3.98 (2H, s), 4.42 (2H, m), 7.21 (2H, d), 7.58 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.66 (1H, s)	435

665		δ 1.67 (6H, m), 1.89 (2H, m), 2.82 (1H, m), 3.11 (2H, m), 3.36 (2H, m), 3.91 (2H, m), 4.41 (2H, m), 7.19 (2H, d), 7.53 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.79 (1H, s), (1H obscured by DMSO)	475

Examples 666-668

The following compounds were prepared in 27-68% yield by an analogous method to Example 659, starting from 4-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]phenyl]butanamide and the appropriate amine:-



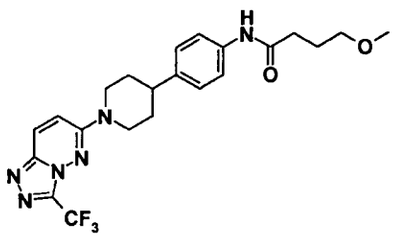
Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
666		δ 1.62 - 1.76 (4H, m), 1.88 (2H, m), 2.13 (3H, s), 2.26 - 2.37 (12H, m), 2.81 (1H, m), 3.11 (2H, m), 4.41 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.76 (1H, s)	531
667		δ 1.62 - 1.79 (8H, m), 1.89 (2H, m), 2.33 (2H, m), 2.41 - 2.50 (6H, m), 2.82 (1H, m), 3.11 (2H, m), 4.42 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.80 (1H, s)	502
668		δ 1.62 - 1.78 (4H, m), 1.89 (2H, m), 2.27 - 2.40 (8H, m), 2.82 (1H, m), 3.11 (2H, m), 3.56 (4H, m), 4.41 (2H, m), 7.19 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.78 (1H, s)	518

The 4-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]phenyl]butanamide used as starting material was obtained in 80% yield by an analogous procedure to Example 659, preparation of starting materials, starting from 4-[1-[3-

(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 615).

m/z = 467 [M+H]+.

Example 669

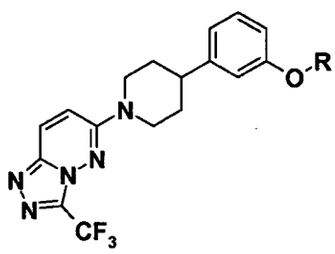


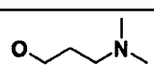
Obtained in 38% yield by an analogous procedure to Example 655, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 615) and 4-methoxybutanoic acid (obtained as described in Example 662, preparation of starting materials).

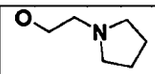
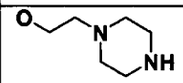
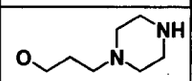
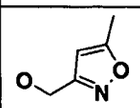
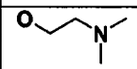
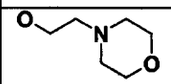
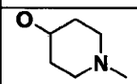
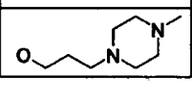
1H NMR (399.9 MHz, DMSO-d6) δ 1.68 (2H, m), 1.80 (2H, m), 1.89 (2H, m), 2.34 (2H, t), 2.82 (1H, m), 3.11 (2H, m), 3.24 (3H, s), 3.35 (2H, t), 4.41 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.80 (1H, s); m/z = 463 [M+H]+.

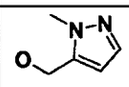
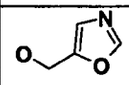
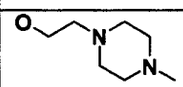
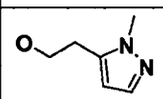
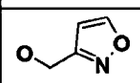
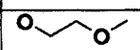
Examples 670-684

The following compounds were prepared in 17-64% yield by an analogous method to Example 513, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol and the appropriate alcohol:-



Ex.	OR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
670		δ 1.71 (2H, m), 1.85 (4H, m), 2.14 (6H, s), 2.35 (2H, t), 2.84 (1H, m), 3.10 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 6.76 (1H, m), 6.83 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	449

671		δ 1.66 - 1.77 (6H, m), 1.90 (2H, m), 2.59 (4H, m), 2.85 (3H, m), 3.11 (2H, m), 4.07 (2H, t), 4.42 (2H, m), 6.78 (1H, m), 6.85 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	461
672		δ 1.72 (2H, m), 1.90 (2H, m), 2.38 (4H, m), 2.65 (6H, m), 2.84 (1H, m), 3.10 (2H, m), 4.05 (2H, t), 4.42 (2H, m), 6.77 (1H, m), 6.84 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	476
673		δ 1.71 (2H, m), 1.86 (4H, m), 2.29 (4H, m), 2.36 (2H, m), 2.67 (4H, m), 2.84 (1H, m), 3.10 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 6.76 (1H, m), 6.83 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	490
674		δ 1.72 (2H, m), 1.91 (2H, m), 2.41 (3H, s), 2.85 (1H, m), 3.11 (2H, m), 4.42 (2H, m), 5.12 (2H, s), 6.32 (1H, s), 6.85 - 6.94 (3H, m), 7.24 (1H, m), 7.67 (1H, d), 8.25 (1H, d)	459
675		δ 1.71 (2H, m), 1.90 (2H, m), 2.21 (6H, s), 2.61 (2H, t), 2.84 (1H, m), 3.10 (2H, m), 4.03 (2H, t), 4.42 (2H, m), 6.78 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	435
676		δ 1.71 (2H, m), 1.90 (2H, m), 2.47 (4H, m), 2.68 (2H, t), 2.84 (1H, m), 3.11 (2H, m), 3.57 (4H, m), 4.07 (2H, t), 4.42 (2H, m), 6.78 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	477
677		δ 1.65 - 1.76 (4H, m), 1.88 - 2.01 (4H, m), 2.42 (3H, s), 2.86 (3H, m), 3.10 (2H, m), 4.44 (3H, m), 6.83 (3H, m), 7.21 (1H, m), 7.66 (1H, d), 8.25 (1H, d), (2H obscured by DMSO)	461
678		δ 1.71 (2H, m), 1.87 (4H, m), 2.14 (3H, s), 2.25 -	504

		2.42 (10H, m), 2.84 (1H, m), 3.10 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 6.76 (1H, m), 6.83 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	
679		δ 1.72 (2H, m), 1.91 (2H, m), 2.86 (1H, m), 3.11 (2H, m), 4.43 (2H, m), 5.22 (2H, s), 6.69 (1H, d), 6.89 (2H, m), 6.95 (1H, m), 7.24 (1H, m), 7.67 (1H, d), 8.25 (1H, d), 8.94 (1H, d)	445
680		δ 1.72 (2H, m), 1.91 (2H, m), 2.86 (1H, m), 3.11 (2H, m), 4.43 (2H, m), 5.17 (2H, s), 6.89 (2H, m), 6.94 (1H, m), 7.24 (1H, m), 7.32 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 8.40 (1H, s)	445
681		δ 1.72 (2H, m), 1.90 (2H, m), 2.14 (3H, s), 2.30 (4H, m), 2.47 (4H, m), 2.66 (2H, t), 2.84 (1H, m), 3.10 (2H, m), 4.05 (2H, t), 4.42 (2H, m), 6.77 (1H, m), 6.84 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	490
682		δ 1.71 (2H, m), 1.90 (2H, m), 2.81 - 2.88 (3H, m), 3.10 (2H, m), 3.78 (3H, s), 4.07 (2H, t), 4.42 (2H, m), 6.79 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.33 (1H, s), 7.56 (1H, s), 7.66 (1H, d), 8.24 (1H, d)	472
683		δ 1.72 (2H, m), 1.91 (2H, m), 2.86 (1H, m), 3.11 (2H, m), 3.83 (3H, s), 4.43 (2H, m), 5.16 (2H, s), 6.36 (1H, d), 6.90 (2H, m), 6.96 (1H, m), 7.24 (1H, m), 7.37 (1H, d), 7.67 (1H, d), 8.25 (1H, d)	458
684		δ 1.72 (2H, m), 1.90 (2H, m), 2.84 (1H, m), 3.10 (2H, m), 3.31 (3H, s), 3.65 (2H, m), 4.08 (2H, m), 4.42 (2H, m), 6.78 (1H, m), 6.85 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	422

The 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol used as starting material was prepared as follows:-

Preparation of 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl]phenol

Obtained in 72% yield by an analogous procedure to Example 605, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate and 3-hydroxyphenylboronic acid.

1H NMR (399.9 MHz, DMSO-d6) δ 2.63 (2H, m), 3.88 (2H, m), 4.25 (2H, m), 6.24 (1H, m), 6.70 (1H, m), 6.86 (1H, m), 6.92 (1H, m), 7.17 (1H, m), 7.67 (1H, d), 8.29 (1H, d), 9.38 (1H, s); m/z = 362 [M+H]+.

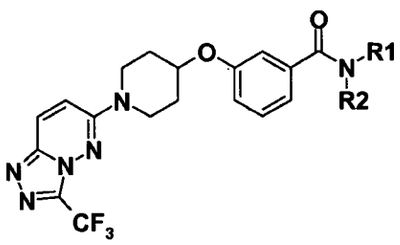
Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol

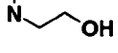
Obtained in 73% yield by an analogous procedure to Example 610, starting from 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl]phenol.

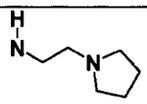
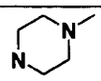
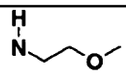
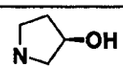
1H NMR (399.9 MHz, DMSO-d6) δ 1.64 - 1.71 (2H, m), 1.89 (2H, m), 2.75 - 2.79 (1H, m), 3.07 - 3.14 (2H, m), 4.39 - 4.42 (2H, m), 6.59 - 6.70 (3H, m), 7.09 (1H, m), 7.66 (1H, d), 8.24 (1H, d), 9.24 (1H, s); m/z = 364 [M+H]+.

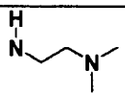
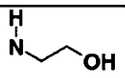
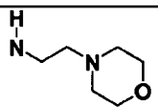
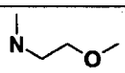
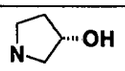
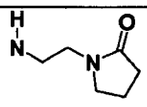
Examples 685-707

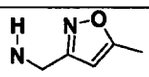
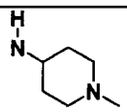
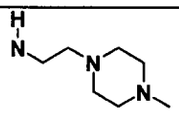
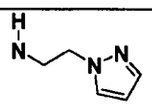
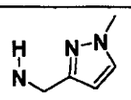
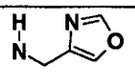
The following compounds were prepared in 31-95% yield by an analogous method to Example 512, starting from 3-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid and the appropriate amine:-



Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
685		δ 1.74 (2H, m), 2.09 (2H, m), 2.96 (3H, m), 3.46 - 3.65 (6H, m), 3.97 (2H, m), 4.75 (2H, m), 6.96 (1H, m), 7.05 (2H, m), 7.34 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	465

686		δ 1.66 - 1.80 (6H, m), 2.10 (2H, m), 2.48 (4H, m), 2.57 (2H, t), 3.38 (2H, m), 3.56 (2H, m), 3.96 (2H, m), 4.75 (1H, m), 7.17 (1H, m), 7.36 - 7.44 (3H, m), 7.65 (1H, d), 8.26 (1H, d), 8.39 (1H, t)	504
687		δ 1.74 (2H, m), 2.09 (2H, m), 2.27 (3H, s), 2.37 - 2.47 (4H, m), 3.37 - 3.70 (6H, m), 3.97 (2H, m), 4.75 (1H, m), 6.94 (1H, m), 7.00 (1H, m), 7.09 (1H, m), 7.37 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	490
688		δ 1.73 (2H, m), 2.08 (2H, m), 2.60 - 2.75 (4H, m), 3.28 (2H, m), 3.54 (4H, m), 3.98 (2H, m), 4.75 (1H, m), 6.92 (1H, m), 6.98 (1H, m), 7.07 (1H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	476
689		δ 1.76 (2H, m), 2.09 (2H, m), 3.28 (3H, s), 3.44 (4H, m), 3.57 (2H, m), 3.96 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.39 (1H, m), 7.45 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.48 (1H, t)	465
690	NMe2	δ 1.73 (2H, m), 2.08 (2H, m), 2.91 (3H, s), 2.98 (3H, s), 3.53 (2H, m), 3.97 (2H, m), 4.75 (1H, m), 6.95 (1H, m), 7.02 (1H, m), 7.07 (1H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	435
691		δ 1.70 - 1.97 (4H, m), 2.08 (2H, m), 3.39 (1H, m), 3.55 (5H, m), 3.96 (2H, m), 4.28 (1H, m), 4.76 (1H, m), 4.95 (1H, m), 7.08 (3H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	477
692		δ 1.69 - 1.89 (6H, m), 2.08 (2H, m), 3.37 (2H, m), 3.47 (2H, m), 3.54 (2H, m), 3.97 (2H, m), 4.75 (1H, m), 7.08 (3H, m), 7.35 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	461
693		δ 1.74 (2H, m), 2.09 (2H, m), 3.32 - 3.67 (10H, m), 3.97 (2H, m), 4.75 (1H, m), 6.97 (1H, m), 7.02 (1H, m), 7.09 (1H, m), 7.37 (1H, m), 7.65	477

		(1H, d), 8.26 (1H, d)	
694	NHMe	δ 1.75 (2H, m), 2.10 (2H, m), 2.79 (3H, d), 3.56 (2H, m), 3.97 (2H, m), 4.75 (1H, m), 7.16 (1H, m), 7.36 - 7.44 (3H, m), 7.66 (1H, d), 8.26 (1H, d), 8.39 (1H, q)	421
695	NHEt	δ 1.13 (3H, t), 1.75 (2H, m), 2.09 (2H, m), 3.28 (2H, m), 3.57 (2H, m), 3.96 (2H, m), 4.76 (1H, m), 7.17 (1H, m), 7.38 (1H, m), 7.44 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.42 (1H, t)	435
696		δ 1.76 (2H, m), 2.09 (2H, m), 2.22 (6H, s), 2.45 (2H, t), 3.37 (2H, m), 3.57 (2H, m), 3.96 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.37 - 7.44 (3H, m), 7.66 (1H, d), 8.26 (1H, d), 8.36 (1H, t)	478
697		δ 1.76 (2H, m), 2.09 (2H, m), 3.33 (2H, m), 3.55 (4H, m), 3.96 (2H, m), 4.70 (1H, t), 4.76 (1H, m), 7.17 (1H, m), 7.38 (1H, m), 7.45 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.39 (1H, t)	451
698		δ 1.76 (2H, m), 2.10 (2H, m), 2.45 (4H, m), 3.40 (2H, m), 3.57 (6H, m), 3.96 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.41 (3H, m), 7.65 (1H, d), 8.26 (1H, d), 8.38 (1H, t), (2H obscured by DMSO)	520
699		δ 1.74 (2H, m), 2.08 (2H, m), 2.95 (3H, m), 3.21 (2H, m), 3.33 - 3.62 (7H, m), 3.97 (2H, m), 4.74 (1H, m), 6.94 (1H, m), 7.00 (1H, m), 7.06 (1H, m), 7.35 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	479
700		δ 1.70 - 1.96 (4H, m), 2.08 (2H, m), 3.38 (1H, m), 3.54 (5H, m), 3.97 (2H, m), 4.28 (1H, m), 4.76 (1H, m), 4.95 (1H, m), 7.08 (3H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	477
701		δ 1.76 (2H, m), 1.91 (2H, m), 2.10 (2H, m), 2.19 (2H, m), 3.39 (6H, m), 3.56 (2H, m), 3.98 (2H,	518

		m), 4.75 (1H, m), 7.17 (1H, m), 7.39 (3H, m), 7.66 (1H, d), 8.26 (1H, d), 8.47 (1H, t)	
702		δ 1.76 (2H, m), 2.10 (2H, m), 2.38 (3H, s), 3.57 (2H, m), 3.96 (2H, m), 4.46 (2H, d), 4.76 (1H, m), 6.16 (1H, s), 7.20 (1H, m), 7.41 (1H, m), 7.48 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 9.03 (1H, t)	502
703		δ 1.60 (2H, m), 1.76 (4H, m), 1.97 (2H, m), 2.09 (2H, m), 2.19 (3H, s), 2.79 (2H, m), 3.57 (2H, m), 3.73 (1H, m), 3.95 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.38 (1H, m), 7.44 (2H, m), 7.65 (1H, d), 8.19 (1H, d), 8.26 (1H, d)	504
704		δ 1.75 (2H, m), 2.10 (2H, m), 2.24 (3H, s), 2.40 - 2.51 (10H, m), 3.38 (2H, m), 3.56 (2H, m), 3.96 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.40 (3H, m), 7.65 (1H, d), 8.26 (1H, d), 8.35 (1H, t)	533
705		δ 1.75 (2H, m), 2.09 (2H, m), 3.56 (2H, m), 3.64 (2H, m), 3.97 (2H, m), 4.31 (2H, t), 4.74 (1H, m), 6.23 (1H, m), 7.18 (1H, m), 7.39 (3H, m), 7.46 (1H, m), 7.66 (1H, d), 7.70 (1H, m), 8.27 (1H, d), 8.53 (1H, t)	501
706		δ 1.76 (2H, m), 2.09 (2H, m), 3.57 (2H, m), 3.79 (3H, s), 3.96 (2H, m), 4.41 (2H, d), 4.76 (1H, m), 6.13 (1H, d), 7.17 (1H, m), 7.38 (1H, m), 7.48 (2H, m), 7.58 (1H, d), 7.65 (1H, d), 8.26 (1H, d), 8.85 (1H, t)	501
707		δ 1.75 (2H, m), 2.10 (2H, m), 3.57 (2H, m), 3.96 (2H, m), 4.38 (2H, d), 4.76 (1H, m), 7.18 (1H, m), 7.39 (1H, m), 7.48 (2H, m), 7.65 (1H, d), 7.97 (1H, s), 8.26 (1H, d), 8.32 (1H, s), 8.90 (1H, t)	488

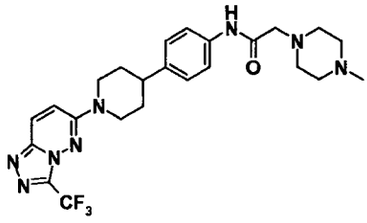
The 3-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid used as starting material was prepared in 2 steps in 38% overall yield

by an analogous method to Example 412, preparation of starting materials, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol and methyl 4-hydroxy benzoate.

1H NMR (399.9 MHz, DMSO-d6) δ 1.74 - 1.78 (2H, m), 2.06 - 2.11 (2H, m), 3.54 - 3.60 (2H, m), 3.93 - 3.99 (2H, m), 4.78 (1H, m), 7.27 - 7.30 (1H, m), 7.44 (1H, m), 7.51 - 7.57 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 12.97 (1H, s); m/z = 408 [M+H]+.

Example 708

Preparation of 2-(4-methylpiperazin-1-yl)-N-[4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide



1-Methylpiperazine (140 µl, 1.27 mmol) was added to 2-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide (139 mg, 0.317 mmol) and sodium iodide (10 mg, 0.063 mmol) in a mixture of THF (2 mL) and DMA (0.5 mL). The resulting solution was heated at 60°C for 2 hours, then cooled and evaporated to give the crude product which was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 2-(4-methylpiperazin-1-yl)-N-[4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide (111 mg, 70%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.68 (2H, m), 1.89 (2H, m), 2.17 (3H, s), 2.37 (4H, m), 2.83 (1H, m), 3.11 (4H, m), 4.42 (2H, m), 7.21 (2H, d), 7.54 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.58 (1H, s), (4H obscured by DMSO); m/z = 503 [M+H]+.

The 2-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide used as starting material was prepared as follows:-

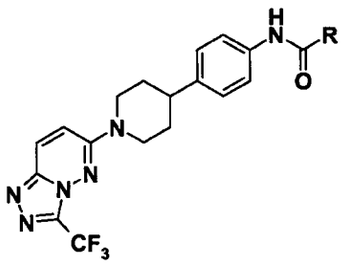
A solution of chloroacetyl chloride (140 mg, 1.24 mmol) in DCM (2 mL) was added dropwise to a stirred suspension of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 615) (375 mg,

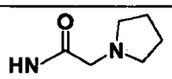
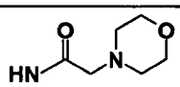
1.03 mmol) and pyridine (164 mg, 2.07 mmol) in DCM (3 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 2 hours. The resulting precipitate was collected by filtration, washed with DCM (2 mL) and dried under vacuum to give 2-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide (418 mg, 92%) as a solid.

m/z = 439 [M+H]+.

Examples 709-710

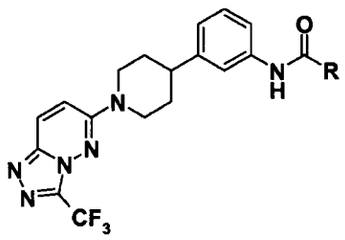
The following compounds were prepared in 41-61% yield by an analogous method to Example 708, starting from 2-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide and the appropriate amine:-

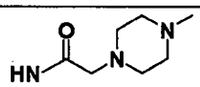
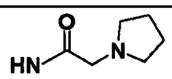
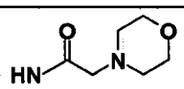


Ex.	NHCOR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
709		δ 1.63 - 1.76 (6H, m), 1.89 (2H, m), 2.59 (4H, m), 2.83 (1H, m), 3.11 (2H, m), 3.22 (2H, s), 4.42 (2H, m), 7.20 (2H, d), 7.56 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.60 (1H, s)	474
710		δ 1.68 (2H, m), 1.89 (2H, m), 2.55 (4H, m), 2.83 (1H, m), 3.11 (4H, m), 3.64 (4H, m), 4.42 (2H, m), 7.21 (2H, d), 7.55 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.64 (1H, s)	490

Examples 711-713

The following compounds were prepared in 26-33% yield by an analogous method to Example 708, starting from 2-chloro-N-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide and the appropriate amine:-



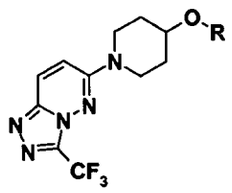
Ex.	NHCOR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
711		δ 1.68 (2H, m), 1.92 (2H, m), 2.17 (3H, s), 2.37 (4H, m), 2.85 (1H, m), 3.12 (4H, m), 4.43 (2H, m), 6.98 (1H, m), 7.24 (1H, m), 7.50 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 9.58 (1H, s), (4H obscured by DMSO)	503
712		δ 1.63 - 1.77 (6H, m), 1.92 (2H, m), 2.58 (4H, m), 2.85 (1H, m), 3.13 (2H, m), 3.22 (2H, s), 4.43 (2H, m), 6.97 (1H, m), 7.23 (1H, m), 7.53 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 9.59 (1H, s)	474
713		δ 1.68 (2H, m), 1.91 (2H, m), 2.56 (4H, m), 2.85 (1H, m), 3.13 (4H, m), 3.64 (4H, m), 4.43 (2H, m), 6.98 (1H, m), 7.24 (1H, m), 7.52 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 9.64 (1H, s), (4H partially obscured by DMSO)	490

The 2-chloro-N-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide used as starting material was prepared in 100% yield by an analogous method to Example 708, preparation of starting materials, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 616) and chloroacetyl chloride.

m/z = 439 [M+H]+.

Examples 714-723

The following compounds were prepared in 15-48% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate hydroxy heterocycle:-

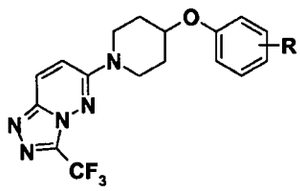


Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
714	5-chloropyrimidin-2-yl	δ 1.82 (2H, m), 2.14 (2H, m), 3.55 (2H, m), 3.99 (2H, m), 5.24 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.73 (2H, s)	400
715	2-chloropyridin-3-yl	δ 1.81 (2H, m), 2.09 (2H, m), 3.64 (2H, m), 3.89 (2H, m), 4.88 (1H, m), 7.41 (1H, m), 7.65 (1H, d), 7.75 (1H, m), 8.01 (1H, m), 8.26 (1H, d)	399
716	6-chloropyridin-2-yl	δ 1.78 (2H, m), 2.12 (2H, m), 3.56 (2H, m), 3.97 (2H, m), 5.24 (1H, m), 6.84 (1H, m), 7.10 (1H, m), 7.65 (1H, d), 7.78 (1H, m), 8.26 (1H, d)	399
717	2-bromopyridin-3-yl	δ 1.83 (2H, m), 2.07 (2H, m), 3.69 (2H, m), 3.85 (2H, m), 4.90 (1H, m), 7.42 (1H, m), 7.67 (2H, m), 8.00 (1H, m), 8.27 (1H, d)	443
718	pyridin-3-yl	δ 1.75 (2H, m), 2.10 (2H, m), 3.53 (2H, m), 3.98 (2H, m), 4.78 (1H, m), 7.35 (1H, m), 7.49 (1H, m), 7.65 (1H, d), 8.19 (1H, m), 8.26 (1H, d), 8.35 (1H, m)	365
719	5-trifluoromethylpyridin-2-yl	δ 1.81 (2H, m), 2.14 (2H, m), 3.55 (2H, m), 4.00 (2H, m), 5.40 (1H, m), 7.02 (1H, d), 7.66 (1H, d), 8.07 (1H, m), 8.26 (1H, d), 8.59 (1H, m)	433

720	6-chloropyridin-3-yl	δ 1.74 (2H, m), 2.10 (2H, m), 3.52 (2H, m), 3.97 (2H, m), 4.78 (1H, m), 7.45 (1H, d), 7.59 (1H, m), 7.65 (1H, d), 8.19 (1H, d), 8.26 (1H, d)	399
721	5-bromopyridin-2-yl	δ 1.76 (2H, m), 2.11 (2H, m), 3.52 (2H, m), 3.99 (2H, m), 5.26 (1H, m), 6.84 (1H, d), 7.65 (1H, d), 7.91 (1H, m), 8.26 (1H, d), 8.30 (1H, d)	443
722	5-bromopyridin-3-yl	δ 1.74 (2H, m), 2.10 (2H, m), 3.52 (2H, m), 3.99 (2H, m), 4.85 (1H, m), 7.65 (1H, d), 7.85 (1H, m), 8.25 - 8.36 (3H, m)	443
723	3-bromopyridin-2-yl	δ 1.82 (2H, m), 2.10 (2H, m), 3.67 (2H, m), 3.89 (2H, m), 5.40 (1H, m), 6.97 (1H, m), 7.65 (1H, d), 8.05 (1H, m), 8.18 (1H, m), 8.26 (1H, d)	443

Examples 724-725

The following compounds were prepared in 18-26% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate phenol:-

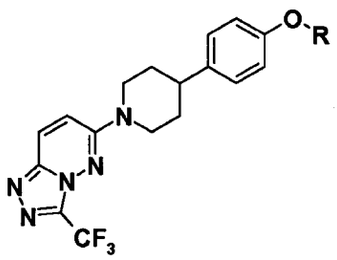


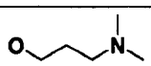
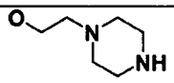
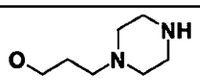
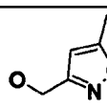
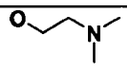
Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
724	4-Cl	δ 1.72 (2H, m), 2.07 (2H, m), 3.52 (2H, m), 3.96 (2H, m), 4.68 (1H, m), 7.05 (2H, d), 7.34 (2H, d), 7.64 (1H, d), 8.25 (1H, d)	398
725	3-Cl	δ 1.72 (2H, m), 2.08 (2H, m), 3.53 (2H, m), 3.96 (2H, m), 4.75 (1H, m), 7.00 (2H, m), 7.12 (1H, m), 7.32 (1H, m),	398

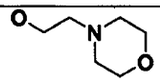
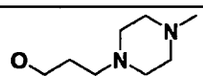
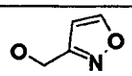
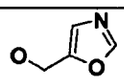
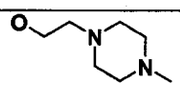
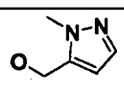
		7.64 (1H, d), 8.25 (1H, d)	

Examples 726-736

The following compounds were prepared in 7-51% yield by an analogous method to Example 513, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol and the appropriate alcohol:-

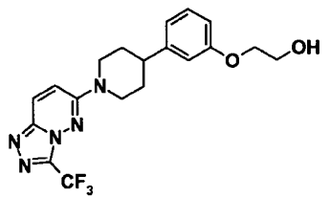


Ex.	OR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
726		δ 1.66 (2H, m), 1.79 - 1.91 (4H, m), 2.14 (6H, s), 2.34 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 3.96 (2H, t), 4.41 (2H, m), 6.85 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	449
727		δ 1.66 (2H, m), 1.88 (2H, m), 2.39 (4H, m), 2.63 (2H, t), 2.68 (4H, m), 2.81 (1H, m), 3.10 (2H, m), 4.03 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	476
728		δ 1.66 (2H, m), 1.85 (4H, m), 2.38 (6H, m), 2.78 - 2.84 (5H, m), 3.10 (2H, m), 3.97 (2H, t), 4.41 (2H, m), 6.85 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	490
729		δ 1.67 (2H, m), 1.88 (2H, m), 2.41 (3H, s), 2.82 (1H, m), 3.10 (2H, m), 4.41 (2H, m), 5.11 (2H, s), 6.31 (1H, s), 6.95 (2H, d), 7.20 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	459
730		δ 1.66 (2H, m), 1.88 (2H, m), 2.22 (6H, s), 2.61 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 4.01 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	435

731		δ 1.66 (2H, m), 1.88 (2H, m), 2.47 (4H, m), 2.68 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 3.58 (4H, m), 4.06 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	477
732		δ 1.66 (2H, m), 1.80 - 1.90 (4H, m), 2.15 (3H, s), 2.25 - 2.42 (10H, m), 2.81 (1H, m), 3.10 (2H, m), 3.96 (2H, t), 4.41 (2H, m), 6.85 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	504
733		δ 1.67 (2H, m), 1.89 (2H, m), 2.82 (1H, m), 3.10 (2H, m), 4.41 (2H, m), 5.20 (2H, s), 6.68 (1H, d), 6.97 (2H, d), 7.21 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 8.94 (1H, d)	445
734		δ 1.67 (2H, m), 1.89 (2H, m), 2.82 (1H, m), 3.10 (2H, m), 4.41 (2H, m), 5.15 (2H, s), 6.97 (2H, d), 7.20 (2H, d), 7.32 (1H, s), 7.66 (1H, d), 8.24 (1H, d), 8.40 (1H, s)	445
735		δ 1.66 (2H, m), 1.88 (2H, m), 2.15 (3H, s), 2.31 (4H, m), 2.46 (4H, m), 2.66 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 4.03 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	490
736		δ 1.68 (2H, m), 1.89 (2H, m), 2.82 (1H, m), 3.10 (2H, m), 3.83 (3H, s), 4.42 (2H, m), 5.14 (2H, s), 6.36 (1H, d), 6.99 (2H, d), 7.21 (2H, d), 7.37 (1H, d), 7.66 (1H, d), 8.24 (1H, d)	458

Example 737

Preparation of 2-[3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]ethanol

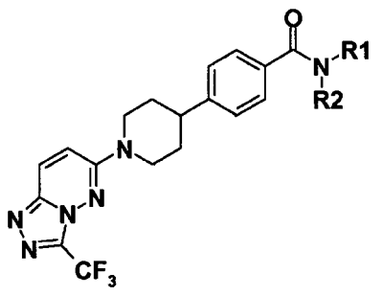


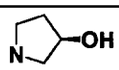
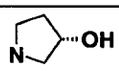
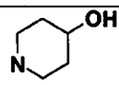
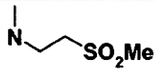
DIAD (0.081 mL, 0.41 mmol) was added dropwise to 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (obtained as described in Example 670, preparation of starting materials) (125 mg, 0.34 mmol), triphenylphosphine (108 mg, 0.41 mmol) and 2-(tetrahydro-2H-pyran-2-yloxy)ethanol (60.4 mg, 0.41 mmol) in THF (3 mL) under nitrogen. The resulting mixture was stirred at ambient temperature for 4 hours, then added to an SCX column. The crude product was eluted from the column using 2M ammonia in methanol and the solvents were evaporated. The crude product was purified by flash silica chromatography, elution gradient 80 to 100% EtOAc in isohexane. Fractions containing product were evaporated then further purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 2-(3-(1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl)phenoxy)ethanol (74 mg, 53%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.71 (2H, m), 1.91 (2H, m), 2.85 (1H, m), 3.11 (2H, m), 3.70 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 4.80 (1H, t), 6.78 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.24 (1H, d); m/z = 408 [M+H]+.

Examples 738-741

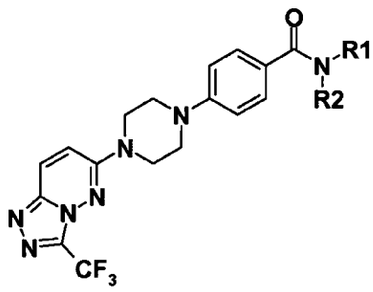
The following compounds were prepared in 78-89% yield by an analogous method to Example 512, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid and the appropriate amine:-

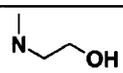
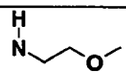
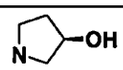
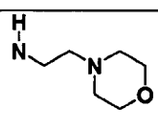


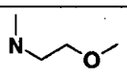
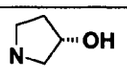
Ex.	NR1R2	1H NMR (399.1 MHz, DMSO-d6)	m/z [M+H]+
738		δ 1.68 - 1.95 (6H, m), 2.93 (1H, m), 3.13 (2H, m), 3.33 - 3.42 (1H, m), 3.47 - 3.62 (3H, m), 4.22 - 4.32 (1H, m), 4.44 (2H, m), 4.88 - 4.98 (1H, m), 7.34 (2H, d), 7.46 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	461
739		δ 1.68 - 1.96 (6H, m), 2.93 (1H, m), 3.13 (2H, m), 3.35 - 3.42 (1H, m), 3.47 - 3.62 (3H, m), 4.22 - 4.32 (1H, m), 4.44 (2H, m), 4.88 - 4.98 (1H, m), 7.34 (2H, d), 7.46 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	461
740		δ (373K) 1.38 (2H, m), 1.75 (4H, m), 1.97 (2H, m), 3.18 (4H, m), 3.75 (3H, m), 4.39 (3H, m), 7.31 (4H, m), 7.56 (1H, d), 8.14 (1H, d)	475
741		δ 1.73 (2H, m), 1.94 (2H, m), 2.90 - 3.17 (9H, m), 3.48 (2H, t), 3.85 (2H, m), 4.44 (2H, m), 7.36 (4H, s), 7.67 (1H, d), 8.25 (1H, d)	511

Examples 742-752

The following compounds were prepared in 39-84% yield by an analogous method to Example 512, starting from 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]benzoic acid and the appropriate amine:-



Ex.	NR1R2	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
742		δ 2.67 (4H, m), 3.41 (8H, m), 3.78 (4H, m), 7.02 (2H, d), 7.30 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	461
743		δ 2.98 (3H, s), 3.41 (6H, m), 3.55 (2H, m), 3.78 (4H, m), 4.79 (1H, t), 7.02 (2H, d), 7.35 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	450
744		δ 2.20 (3H, s), 2.30 (4H, m), 3.42 (4H, m), 3.49 (4H, m), 3.78 (4H, m), 7.03 (2H, d), 7.31 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	475
745		δ 3.27 (3H, s), 3.39 - 3.47 (8H, m), 3.78 (4H, m), 7.03 (2H, d), 7.69 (1H, d), 7.78 (2H, d), 8.27 (1H, t), 8.31 (1H, d)	450
746	NMe2	δ 2.97 (6H, s), 3.42 (4H, m), 3.78 (4H, m), 7.02 (2H, d), 7.34 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	420
747		δ 1.77 - 1.95 (2H, m), 3.29 (1H, m), 3.42 - 3.66 (7H, m), 3.78 (4H, m), 4.27 (1H, m), 4.95 (1H, m), 7.02 (2H, d), 7.46 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	462
748		δ 1.83 (4H, m), 3.43 (8H, m), 3.78 (4H, m), 7.01 (2H, d), 7.47 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	446
749		δ 3.42 (4H, m), 3.50 (4H, m), 3.59 (4H, m), 3.78 (4H, m), 7.03 (2H, d), 7.34 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	462
750		δ 2.39 - 2.46 (6H, m), 3.36 (2H, m), 3.46 (4H, m), 3.57 (4H, m), 3.78 (4H, m), 7.03 (2H, d), 7.69 (1H,	505

		d), 7.76 (2H, d), 8.16 (1H, t), 8.31 (1H, d)	
751		δ 2.97 (3H, s), 3.24 (3H, s), 3.41 (4H, m), 3.50 (4H, m), 3.78 (4H, m), 7.02 (2H, d), 7.32 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	464
752		δ 1.76 - 1.95 (2H, m), 3.29 (1H, m), 3.42 - 3.66 (7H, m), 3.78 (4H, m), 4.27 (1H, m), 4.96 (1H, m), 7.02 (2H, d), 7.46 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	462

The 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]benzoic acid used as starting material was prepared as follows:-

Preparation of ethyl 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]benzoate

DIPEA (2.348 mL, 13.48 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2 g, 8.99 mmol) and ethyl 4-(piperazin-1-yl)benzoate (2.316 g, 9.89 mmol, CAS 80518-57-6) in DMF (20 mL). The resulting solution was stirred at 80°C for 2 hours. The reaction mixture was cooled to room temperature, then evaporated to dryness and redissolved in DCM (150 mL) and washed with water (100 mL). The organic layer was dried over MgSO4, filtered and evaporated to afford crude product which was triturated with ether. The solid was collected by filtration and dried under vacuum to give ethyl 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]benzoate (3.40 g, 90%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.30 (3H, t), 3.54 (4H, m), 3.79 (4H, m), 4.26 (2H, q), 7.04 (2H, d), 7.66 (1H, d), 7.83 (2H, d), 8.30 (1H, d); m/z = 421 [M+H]+.

Preparation of 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]benzoic acid

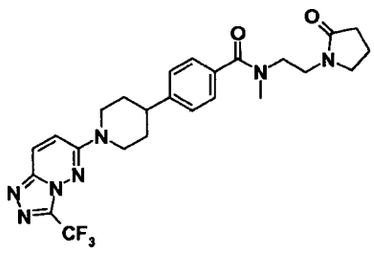
Lithium hydroxide monohydrate (0.373 g, 8.90 mmol) was added to ethyl 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]benzoate (3.40 g, 8.09 mmol) in a mixture of MeOH (60 mL) and water (30 mL). The resulting suspension was stirred at 50°C for 16 hours. Further lithium hydroxide monohydrate (0.373 g, 8.90 mmol) was added, the temperature was increased to 65 °C and the suspension was stirred for a further 6 hours. The reaction mixture was cooled to room temperature and the MeOH evaporated. The residues were dissolved in water (200 mL) and filtered. The filtrate was

acidified with 1M citric acid until precipitation ceased, and the precipitate was collected by filtration, washed with water and dried under vacuum to afford 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]benzoic acid (3.17 g, 100%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.52 (4H, m), 3.79 (4H, m), 7.03 (2H, d), 7.67 (1H, d), 7.81 (2H, d), 8.30 (1H, d), 12.20 (1H, s); m/z = 393 [M+H]+.

Example 753

Preparation of N-methyl-N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide

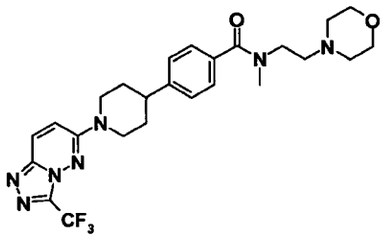


A solution of N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide (obtained as described in Example 639) (150 mg, 0.30 mmol) in DMF (2 mL) was added dropwise to a stirred suspension of sodium hydride (60% in mineral oil) (13.16 mg, 0.33 mmol) in DMF (1 mL) under nitrogen. The resulting suspension was stirred at ambient temperature for 5 minutes, then iodomethane (0.028 mL, 0.45 mmol) was added and the mixture was stirred at ambient temperature for a further 10 minutes. The reaction was quenched with MeOH (0.5 mL) and purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-methyl-N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide (84 mg, 55%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.67 - 1.94 (6H, m), 2.17 (2H, m), 2.87 - 2.98 (4H, m), 3.12 (2H, m), 3.44 (4H, m), 3.62 (2H, m), 4.44 (2H, m), 7.25 - 7.35 (4H, m), 7.68 (1H, d), 8.26 (1H, d); m/z = 516 [M+H]+.

Example 754

Preparation of N-methyl-N-(2-morpholin-4-ylethyl)-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide

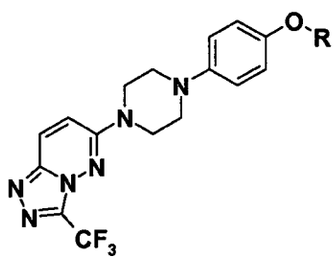


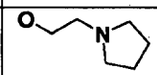
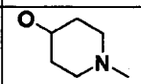
Obtained in 74% yield by an analogous method to Example 753, starting from N-(2-morpholin-4-ylethyl)-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide (obtained as described in Example 638).

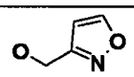
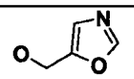
1H NMR (399.9 MHz, DMSO-d6) δ 1.72 (2H, m), 1.92 (2H, m), 2.14 (2H, m), 2.41 (4H, m), 2.88 - 2.97 (4H, m), 3.13 (2H, m), 3.43 - 3.59 (6H, m), 4.44 (2H, m), 7.33 (4H, m), 7.68 (1H, d), 8.26 (1H, d); m/z = 518 [M+H]+.

Examples 755-758

The following compounds were prepared in 9-24% yield by an analogous method to Example 514, starting from 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol and the appropriate alcohol:-

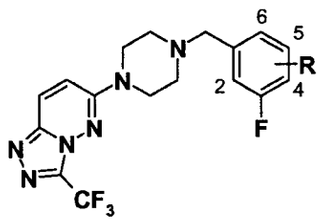


Ex.	OR	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
755		δ 1.70 (4H, m), 2.58 (4H, m), 2.82 (2H, m), 3.17 (4H, m), 3.76 (4H, m), 4.02 (2H, m), 6.87 (2H, d), 6.97 (2H, d), 7.69 (1H, d), 8.30 (1H, d)	462
756		δ 1.61 (2H, m), 1.89 (2H, m), 2.19 (5H, m), 2.64 (2H, m), 3.17 (4H, m), 3.75 (4H, m), 4.23 (1H, m), 6.87 (2H, d), 6.96 (2H, d), 7.69 (1H, d), 8.30 (1H, d)	462

757		δ 3.19 (4H, m), 3.76 (4H, m), 5.17 (2H, s), 6.69 (1H, d), 6.97 (4H, m), 7.69 (1H, d), 8.30 (1H, d), 8.95 (1H, d)	446
758		δ 3.19 (4H, m), 3.76 (4H, m), 5.11 (2H, s), 6.97 (4H, m), 7.31 (1H, s), 7.69 (1H, d), 8.30 (1H, d), 8.41 (1H, s)	446

Examples 759-768

The following compounds were prepared in 15-49% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

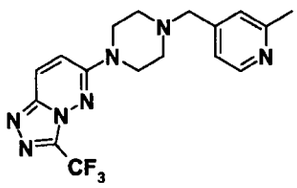


Ex.	R	1H NMR (400.1 MHz, DMSO-d6)	m/z [M+H]+
759	5-Cl	δ 2.52 - 2.56 (4H, m), 3.59 (2H, s), 3.62 - 3.66 (4H, m), 7.18 - 7.22 (1H, m), 7.29 (1H, s), 7.32 - 7.36 (1H, m), 7.59 (1H, d), 8.26 (1H, d)	415
760	5-CF3	δ 2.53 - 2.57 (4H, m), 3.62 - 3.66 (4H, m), 3.68 (2H, s), 7.56 - 7.61 (4H, m), 8.26 (1H, d)	449
761	2-CF3	δ 2.54 - 2.58 (4H, m), 3.60 - 3.64 (4H, m), 3.73 (2H, s), 7.38 - 7.44 (1H, m), 7.58 - 7.61 (2H, m), 7.69 - 7.72 (1H, m), 8.27 (1H, d)	449
762	6-CF3	δ 2.57 - 2.61 (4H, m), 3.65 - 3.69 (4H, m), 3.72 (2H, s), 7.32 - 7.36 (1H, m), 7.61 (1H, d), 7.64 - 7.67 (1H, m), 7.80 - 7.83 (1H, m), 8.27 (1H, d)	449
763	2,5-F	δ 2.55 - 2.58 (4H, m), 3.62 - 3.65 (4H, m), 3.67 (2H, d), 7.17 - 7.20 (1H, m), 7.45 - 7.48 (1H, m), 7.59 (1H, d), 8.26 (1H, d)	417
764	2,6-F	δ 2.55 - 2.59 (4H, m), 3.59 - 3.63 (4H, m), 3.71 (2H, s), 7.15 - 7.18 (1H, m), 7.48 - 7.53 (1H, m), 7.57 (1H,	417

		d), 8.24 (1H, d)	
765	6-SO2Me	δ 2.59 - 2.63 (4H, m), 3.42 (3H, s), 3.62 - 3.66 (4H, m), 3.96 (2H, s), 7.43 - 7.47 (1H, m), 7.56 - 7.59 (1H, m), 7.62 (1H, d), 8.04 - 8.08 (1H, m), 8.28 (1H, d)	459
766	2,4-F	δ 2.54 - 2.58 (4H, m), 3.60 - 3.64 (6H, m), 7.30 - 7.34 (2H, m), 7.59 (1H, d), 8.25 (1H, d)	417
767	4,5-F	δ 2.53 - 2.56 (4H, m), 3.56 (2H, s), 3.61 - 3.65 (4H, m), 7.28 - 7.32 (2H, m), 7.60 (1H, d), 8.26 (1H, d)	417
768	2-Cl	δ 2.59 - 2.63 (4H, m), 3.62 - 3.66 (4H, m), 3.69 (2H, s), 7.35 - 7.42 (3H, m), 7.60 (1H, d), 8.26 (1H, d)	415

Example 769

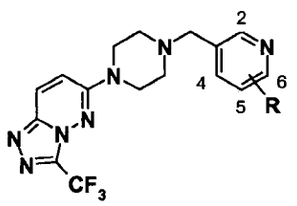
Preparation of 6-[4-[(2-methylpyridin-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 61% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 2-methylpyridine-4-carboxaldehyde 1H NMR (399.9 MHz, DMSO-d6) δ 2.47 (3H, s), 2.54 - 2.58 (4H, m), 3.55 (2H, s), 3.62 - 3.66 (4H, m), 7.15 - 7.17 (1H, m), 7.22 (1H, s), 7.59 (1H, d), 8.26 (1H, d), 8.39 - 8.40 (1H, m); m/z = 378 [M+H]+.

Examples 770-777

The following compounds were prepared in 19-69% yield by General Synthetic Method 5 starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

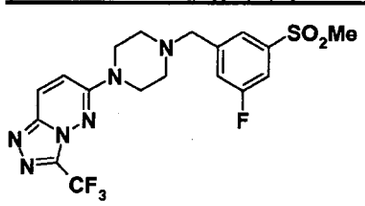


Ex.	R	1H NMR (400.1 MHz, DMSO-d6)	m/z [M+H]+

770	5-Cl	δ 2.54 - 2.58 (4H, m), 3.62 - 3.65 (6H, m), 7.59 (1H, d), 7.89 (1H, t), 8.26 (1H, d), 8.51 (1H, d), 8.56 (1H, d)	398
771	4-CF3	δ 2.56 - 2.60 (4H, m), 3.62 - 3.66 (4H, m), 3.76 (2H, s), 7.60 (1H, d), 7.74 (1H, d), 8.27 (1H, d), 8.78 (1H, d), 8.99 (1H, s)	432
772	2-Me	δ 2.53 - 2.57 (7H, m), 3.54 (2H, s), 3.60 - 3.64 (4H, m), 7.19 - 7.22 (1H, m), 7.60 (1H, d), 7.65 (1H, d), 8.26 (1H, d), 8.35 - 8.37 (1H, m)	378
773	4-Cl	δ 2.58 - 2.62 (4H, m), 3.61 - 3.65 (4H, m), 3.70 (2H, s), 7.56 (1H, d), 7.60 (1H, d), 8.26 (1H, d), 8.47 (1H, d), 8.66 (1H, s)	398
774	5-Br	δ 2.49 - 2.53 (4H, m), 3.60 - 3.90 (6H, m), 7.54 - 7.57 (1H, m), 7.63 (1H, d), 8.04 - 8.06 (1H, m), 8.34 (1H, d), 8.43 (1H, s)	442
775	2-OMe	δ 2.54 (2H, d), 2.56 (1H, t), 3.59 - 3.62 (3H, m), 3.64 (3H, d), 3.85 (3H, s), 7.33 (1H, q), 7.59 (1H, d), 8.14 (1H, d), 8.21 - 8.22 (1H, m), 8.26 (1H, d)	394
776	6-Me	δ 2.46 (3H, s), 2.52 - 2.55 (4H, m), 3.54 (2H, s), 3.60 - 3.63 (4H, m), 7.23 - 7.24 (1H, m), 7.57 - 7.63 (2H, m), 8.25 (1H, d), 8.39 (1H, s)	378
777	2-CF3	δ 2.56 - 2.60 (4H, m), 3.62 - 3.66 (4H, m), 3.75 (2H, s), 7.61 (1H, d), 7.73 - 7.76 (1H, m), 8.26 - 8.29 (2H, m), 8.65 - 8.66 (1H, m)	432

Example 778

Preparation of 6-[4-[3-fluoro-5-(methylsulfonyl)benzyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 45% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-fluoro-5-methylsulfonylbenzaldehyde.

1H NMR (399.9 MHz, DMSO-d6) δ 2.55 - 2.59 (4H, m), 3.30 (3H, s), 3.63 - 3.67 (4H, m), 3.70 (2H, s), 7.58 - 7.62 (2H, m), 7.70 - 7.73 (1H, m), 7.77 (1H, d), 8.26 (1H, d); m/z = 459 [M+H]+.

The 3-fluoro-5-methylsulfonylbenzaldehyde used as starting material was prepared as follows:-

Preparation of [3-fluoro-5-(methylsulfonyl)phenyl]methanol

Methanesulphinic acid sodium salt (748 mg, 7.33 mmol) was added to (3-bromo-5-fluorophenyl)methanol (501 mg, 2.44 mmol) and copper(I) iodide (0.248 mL, 7.33 mmol) in DMSO (12 mL) under nitrogen. The resulting mixture was stirred at 90°C for 3 days. The reaction mixture was diluted with EtOAc (300 mL), then filtered. The filtrate was washed sequentially with water (200 mL) and saturated brine (2 x 200 mL). The organic layer was dried over Na2SO4, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 70 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford [3-fluoro-5-(methylsulfonyl)phenyl]methanol (240 mg, 48.1%) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 2.49 (1H, t), 3.07 (3H, s), 4.79 (2H, d), 7.36 - 7.40 (1H, m), 7.51 - 7.54 (1H, m), 7.72 (1H, s); m/z = 203 [M-H]-.

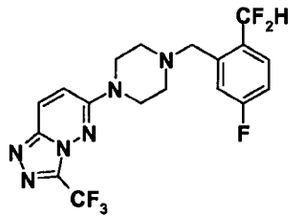
Preparation of 3-fluoro-5-methylsulfonylbenzaldehyde

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (530 mg, 1.21 mmol) was added in one portion to [3-fluoro-5-(methylsulfonyl)phenyl]methanol (225 mg, 1.10 mmol) in DCM (20 mL) at 22°C. The resulting solution was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with DCM (50 ml) and poured into saturated aqueous sodium bicarbonate (30 mL) containing sodium thiosulfate (1219 mg, 7.71 mmol). The resulting suspension was stirred for 10 minutes before separating the layers. The organic layer was washed with water (1 x 50 mL), dried over MgSO4 and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 30 to 40% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 3-fluoro-5-(methylsulfonyl)benzaldehyde (168 mg, 75%) as a white solid.

1H NMR (399.9 MHz, CDCl3) δ 3.13 (3H, s), 7.85 - 7.88 (1H, m), 7.91 - 7.93 (1H, m), 8.26 (1H, t), 10.07 (1H, d); m/z = 201 [M-H]-.

Example 779

Preparation of 6-[4-[2-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 61% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 2-difluoromethyl-5-fluorobenzaldehyde.

1H NMR (399.9 MHz, DMSO-d6) δ 2.55 - 2.59 (4H, m), 3.60 - 3.64 (4H, m), 3.70 (2H, s), 7.26 - 7.32 (1H, m), 7.36 (1H, t), 7.36 - 7.41 (1H, m), 7.60 (1H, d), 7.67 - 7.71 (1H, m), 8.26 (1H, d); m/z = 431 [M+H]+.

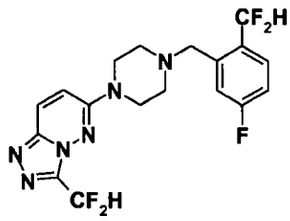
The 2-difluoromethyl-5-fluorobenzaldehyde used as starting material was prepared as follows:-

Isopropylmagnesium chloride - lithium chloride complex in THF (1M, 21.46 mL, 21.46 mmol) was added to 2-bromo-1-(difluoromethyl)-4-fluorobenzene (4.39 g, 19.51 mmol) in THF (120 mL) cooled to -20°C under nitrogen. The resulting solution was stirred at -20°C for 1 hour. N,N-Dimethylformamide (1.813 mL, 23.41 mmol) was added, and the mixture stirred for a further 1 hour, maintaining the temperature in the range -15 to -20 °C. The mixture was allowed to warm to ambient temperature, then 2M hydrochloric acid (100 mL) was added and the mixture was extracted with EtOAc (150 mL). The organic layer was washed with saturated sodium bicarbonate (120 mL) and concentrated to yield crude product. The crude product was purified by flash silica chromatography, elution gradient 5 to 10% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 2-(difluoromethyl)-5-fluorobenzaldehyde (1.250 g, 36.8%) as a colourless liquid.

1H NMR (399.9 MHz, CDCl3) δ 7.26 (1H, t), 7.37 - 7.43 (1H, m), 7.63 - 7.67 (1H, m), 7.78 - 7.82 (1H, m), 10.19 (1H, d); m/z = 173 [M-H]-.

Example 780

Preparation of 3-(difluoromethyl)-6-[4-[2-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

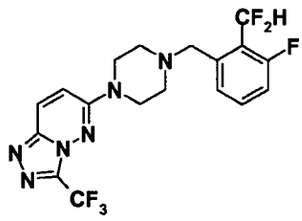


Obtained in 58% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and 2-difluoromethyl-5-fluorobenzaldehyde (obtained as described in Example 779, preparation of starting materials).

1H NMR (399.9 MHz, DMSO-d6) δ 2.54 - 2.57 (4H, m), 3.60 - 3.63 (4H, m), 3.70 (2H, s), 7.27 - 7.31 (1H, m), 7.36 (1H, t), 7.36 - 7.41 (1H, m), 7.51 - 7.53 (1H, m), 7.53 (1H, t), 7.67 - 7.71 (1H, m), 8.19 (1H, d); m/z = 413 [M+H]+.

Example 781

Preparation of 6-[4-[2-(difluoromethyl)-3-fluorobenzyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 33% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 2-difluoromethyl-3-fluorobenzaldehyde.

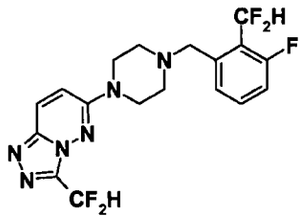
1H NMR (399.9 MHz, DMSO-d6) δ 2.57 - 2.57 (4H, m), 3.56 - 3.60 (4H, m), 3.73 (2H, s), 7.28 - 7.32 (2H, m), 7.42 (1H, t), 7.55 - 7.60 (2H, m), 8.26 (1H, d); m/z = 431 [M+H]+.

The 2-difluoromethyl-3-fluorobenzaldehyde used as starting material was obtained in 32% yield by an analogous method to Example 779, preparation of starting materials, starting from 1-bromo-2-(difluoromethyl)-3-fluorobenzene.

1H NMR (399.9 MHz, CDCl3) δ 7.20- 7.43 (2H, m), 7.61 - 7.67 (1H, m), 7.86 (1H, d), 10.38 - 10.48 (1H, m); m/z = 173 [M-H]-.

Example 782

Preparation of 3-(difluoromethyl)-6-[4-[2-(difluoromethyl)-3-fluorobenzyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

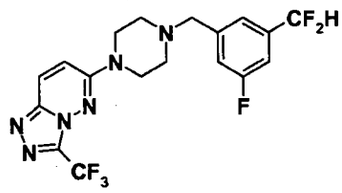


Obtained in 39% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and 2-difluoromethyl-3-fluorobenzaldehyde (obtained as described in Example 781, preparation of starting materials).

1H NMR (399.9 MHz, DMSO-d6) δ 2.52 - 2.56 (4H, m), 3.56 - 3.60 (4H, m), 3.73 (2H, s), 7.28 - 7.32 (2H, m), 7.34 - 7.57 (4H, m), 8.20 (1H, d); m/z = 413 [M+H]+.

Example 783

Preparation of 6-[4-[3-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 73% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-difluoromethyl-5-fluorobenzaldehyde.

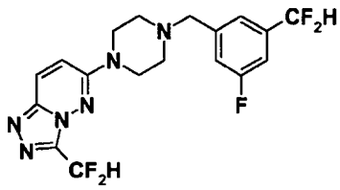
1H NMR (399.9 MHz, DMSO-d6) δ 2.53 - 2.58 (4H, m), 3.62 - 3.66 (6H, m), 7.07 (1H, t), 7.33 - 7.43 (3H, m), 7.60 (1H, d), 8.26 (1H, d); m/z = 431 [M+H]+.

The 3-difluoromethyl-5-fluorobenzaldehyde used as starting material was obtained in 44% yield by an analogous method to Example 779, preparation of starting materials, starting from 1-bromo-3-(difluoromethyl)-5-fluorobenzene.

1H NMR (399.9 MHz, CDCl3) δ 6.72 (1H, t), 7.49 - 7.52 (1H, m), 7.68 - 7.71 (1H, m), 7.83 (1H, d), 10.03 (1H, d); m/z = 173 [M-H]-.

Example 784

Preparation of 3-(difluoromethyl)-6-[4-[3-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine

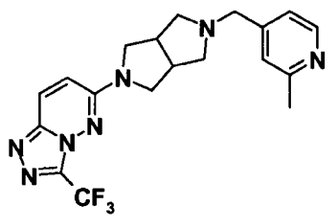


Obtained in 66% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and 3-difluoromethyl-5-fluorobenzaldehyde (obtained as described in Example 783, preparation of starting materials).

1H NMR (399.9 MHz, DMSO-d6) δ 2.53 - 2.57 (4H, m), 3.61 - 3.65 (6H, m), 7.07 (1H, t), 7.33 - 7.67 (5H, m), 8.19 (1H, d); m/z = 413 [M+H]+.

Example 785

Preparation of 6-[5-[(2-methylpyridin-4-yl)methyl]hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

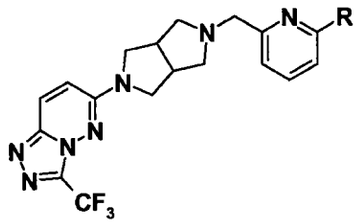


Obtained in 47% yield by General Synthetic Method 10, starting from 6-[(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)]-[1,2,4]triazolo[4,3-b]pyridazine and 2-methylpyridine-4-carboxaldehyde.

1H NMR (399.9 MHz, DMSO-d6) δ 2.43 (3H, s), 2.55 - 2.63 (4H, m), 2.97 – 2.99 (2H, m), 3.41 - 3.44 (2H, m), 3.57 (2H, s), 3.73 - 3.78 (2H, m), 7.10 (1H, d), 7.15 (1H, s), 7.32 (1H, d), 8.23 (1H, d), 8.34 (1H, d); m/z = 404 [M+H]+.

Examples 786-787

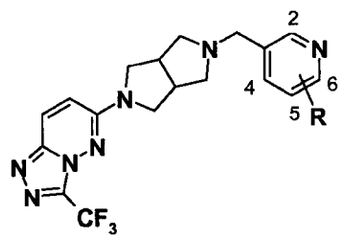
The following compounds were prepared in 22-57% yield by General Synthetic Method 10, starting from 6-[(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
786	H	δ 2.61 - 2.67 (4H, m), 2.96 – 3.00 (2H, m), 3.39 – 3.42 (2H, m), 3.71 (2H, s), 3.74 - 3.79 (2H, m), 7.23 - 7.26 (1H, m), 7.31 (1H, d), 7.39 (1H, d), 7.71 - 7.75 (1H, m), 8.22 (1H, d), 8.47 - 8.49 (1H, m)	390
787	Br	δ 2.62 - 2.68 (4H, m), 2.97 – 3.00 (2H, m), 3.40 – 3.44 (2H, m), 3.69 (2H, s), 3.75 - 3.79 (2H, m), 7.31 (1H, d), 7.45 (1H, d), 7.51 (1H, d), 7.71 (1H, t), 8.22 (1H, d)	469

Examples 788-805

The following compounds were prepared in 12-86% yield by General Synthetic Method 10, starting from 6-[hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



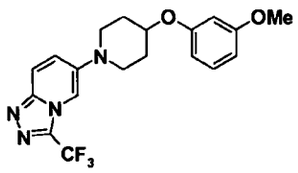
Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
788	2-OMe	δ 2.56 - 2.65 (4H, m), 2.95 - 2.99 (2H, m), 3.40 - 3.44 (2H, m), 3.56 (2H, s), 3.73 - 3.78 (2H, m), 3.86 (3H, s), 6.93 - 6.96 (1H, m), 7.32 (1H, d), 7.63 - 7.66 (1H, m), 8.04 - 8.05 (1H, m), 8.22 (1H, d)	420
789	5-F	δ 2.58 - 2.64 (4H, m), 2.96 - 3.00 (2H, m), 3.40 - 3.44 (2H, m), 3.67 (2H, s), 3.73 - 3.77 (2H, m), 7.31 (1H, d), 7.60 - 7.64 (1H, m), 8.22 (1H, d), 8.39 (1H, d), 8.46 (1H, d)	408
790	2-Cl	δ 2.63 - 2.70 (4H, m), 2.98 - 3.01 (2H, m), 3.41 - 3.44	424

		(2H, m), 3.70 (2H, s), 3.75 - 3.80 (2H, m), 7.32 (1H, d), 7.39 - 7.42 (1H, m), 7.88 - 7.90 (1H, m), 8.23 (1H, d), 8.29 - 8.31 (1H, m)	
791	6-Cl	δ 2.54 - 2.62 (4H, m), 2.96 - 2.98 (2H, m), 3.36 - 3.41 (2H, m), 3.62 (2H, s), 3.72 - 3.77 (2H, m), 7.30 (1H, d), 7.44 - 7.47 (1H, m), 7.76 - 7.78 (1H, m), 8.22 (1H, d), 8.32 (1H, d)	424
792	2-Cl, 5-F	δ 2.63 - 2.68 (4H, m), 2.98 - 3.01 (2H, m), 3.42 – 3.46 (2H, m), 3.70 (2H, s), 3.75 - 3.80 (2H, m), 7.32 (1H, d), 7.79 - 7.82 (1H, m), 8.23 (1H, d), 8.36 (1H, d)	442
793	6-OMe	δ 2.53 - 2.60 (4H, m), 2.95 – 2.98 (2H, m), 3.36 - 3.40 (2H, m), 3.52 (2H, s), 3.71 - 3.75 (2H, m), 3.83 (3H, s), 6.75 (1H, d), 7.30 (1H, d), 7.59 - 7.62 (1H, m), 8.05 (1H, d), 8.22 (1H, d)	420
794	5-Br	δ 2.53 - 2.56 (2H, m), 2.60 - 2.65 (2H, m), 2.95 – 2.99 (2H, m), 3.39 – 3.43 (2H, m), 3.63 (2H, s), 3.71 - 3.76 (2H, m), 7.31 (1H, d), 7.94 (1H, t), 8.22 (1H, d), 8.49 (1H, d), 8.59 (1H, d)	468
795	5-Br, 2-F	δ 2.53 - 2.59 (2H, m), 2.65 - 2.69 (2H, m), 2.96 – 2.99 (2H, m), 3.40 – 3.44 (2H, m), 3.64 (2H, s), 3.71 - 3.75 (2H, m), 7.31 (1H, d), 8.10 - 8.13 (1H, m), 8.22 (1H, d), 8.27 – 8.29 (1H, m)	486
796	2-Br	δ 2.62 - 2.68 (4H, m), 2.99 - 3.01 (2H, m), 3.40 – 3.44 (2H, m), 3.67 (2H, s), 3.76 - 3.80 (2H, m), 7.32 (1H, d), 7.41 - 7.44 (1H, m), 7.82 - 7.85 (1H, m), 8.22 (1H, d), 8.26 - 8.28 (1H, m)	468
797	5-OMe	δ 2.54 - 2.63 (4H, m), 2.97 – 2.99 (2H, m), 3.41 - 3.44 (2H, m), 3.61 (2H, s), 3.71 - 3.76 (2H, m), 3.79 (3H, s), 7.26 (1H, s), 7.31 (1H, d), 8.10 (1H, d), 8.17 - 8.18 (1H, m), 8.22 (1H, d)	420
798	6-Br	δ 2.53 - 2.62 (4H, m), 2.96 - 2.98 (2H, m), 3.36 - 3.41	468

		(2H, m), 3.59 (2H, s), 3.72 -3.75 (2H, m), 7.30 (1H, d), 7.57 - 7.60 (1H, m), 7.66 - 7.68 (1H, m), 8.22 (1H, d), 8.31 (1H, d)	
799	2-Me	δ 2.46 (3H, s), 2.56 - 2.62 (4H, m), 2.96 – 2.98 (2H, m), 3.38 - 3.41 (2H, m), 3.58 (2H, s), 3.73 - 3.77 (2H, m), 7.14 - 7.17 (1H, m), 7.30 (1H, d), 7.58 - 7.61 (1H, m), 8.22 (1H, d), 8.30 - 8.31 (1H, m)	404
800	4-Cl	δ 2.59 - 2.63 (2H, m), 2.66 - 2.70 (2H, m), 2.97 – 2.99 (2H, m), 3.39 - 3.43 (2H, m), 3.72 - 3.76 (4H, m), 7.31 (1H, d), 7.51 (1H, d), 8.22 (1H, d), 8.43 (1H, d), 8.58 (1H, s)	424
801	4-Br	δ 2.61 - 2.68 (4H, m), 2.97 - 2.99 (2H, m), 3.40 – 3.44 (2H, m), 3.73 - 3.76 (4H, m), 7.31 (1H, d), 7.67 (1H, d), 8.22 (1H, d), 8.31 (1H, d), 8.54 (1H, s)	469
802	4-CF3	δ 2.60 – 2.64 (4H, m), 2.97 – 3.00 (2H, m), 3.36 - 3.41 (3H, m), 3.75 - 3.78 (2H, m), 3.79 (2H, s), 7.31 (1H, d), 7.68 (1H, d), 8.22 (1H, d), 8.73 (1H, d), 8.89 (1H, s)	458
803	4-OMe	δ 2.53 - 2.68 (4H, m), 2.96 – 2.99 (2H, m), 3.41 – 3.44 (2H, m), 3.62 (2H, s), 3.71 - 3.75 (2H, m), 3.84 (3H, s), 7.02 (1H, d), 7.31 (1H, d), 8.22 (1H, d), 8.33 - 8.36 (2H, m)	420
804	5-Cl	δ 2.54 - 2.58 (2H, m), 2.60 - 2.65 (2H, m), 2.97 – 2.99 (2H, m), 3.41 – 3.44 (2H, m), 3.64 (2H, s), 3.72 - 3.76 (2H, m), 7.31 (1H, d), 7.82 (1H, t), 8.22 (1H, d), 8.46 - 8.47 (1H, m), 8.51 (1H, d)	424
805	2-CF3	δ 2.60 - 2.64 (4H, m), 2.97 - 3.00 (2H, m), 3.38 - 3.41 (2H, m), 3.76 - 3.79 (4H, m), 7.32 (1H, d), 7.66 - 7.69 (1H, m), 8.14 (1H, d), 8.23 (1H, d), 8.61 (1H, d)	458

Example 806

Preparation of 6-[4-(3-methoxyphenoxy)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridine

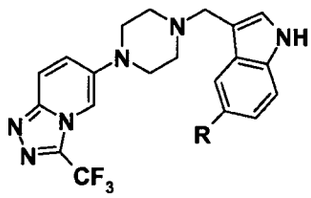


A mixture of 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (obtained as described in General Synthetic Method 9, preparation of starting materials) (100 mg, 0.38 mmol) and 4-(3-methoxyphenoxy)piperidine hydrochloride (110 mg, 0.45 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (17.56 mg, 0.03 mmol) and sodium tert-butoxide (0.161 mL, 1.32 mmol) was suspended in xylenes (5 mL), then de-gassed and purged with nitrogen. Bis(dibenzylideneacetone)palladium (11 mg, 0.02 mmol) was added, and the mixture was sealed into a microwave tube. The reaction was heated to 100°C for 20 minutes in the microwave reactor and cooled to ambient temperature. The reaction mixture was diluted with EtOAc (25 mL) and washed with water (25 mL). The organic layer was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-(3-methoxyphenoxy)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridine (45.0 mg, 30.5 %) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.77 - 1.83 (2H, m), 2.07 - 2.12 (2H, m), 3.11 - 3.17 (2H, m), 3.47 - 3.53 (2H, m), 3.74 (3H, s), 4.59 - 4.63 (1H, m), 6.51 - 6.55 (2H, m), 6.54 - 6.59 (1H, m), 7.20 (1H, t), 7.59 (1H, s), 7.75 - 7.78 (1H, m), 7.94 (1H, d); m/z = 393 [M+H]+.

Examples 807-809

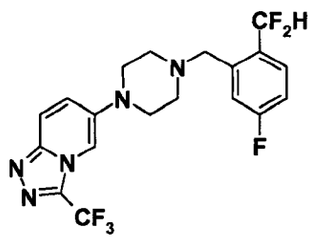
The following compounds were prepared in 61-70% yield by General Synthetic Method 9, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine and the appropriate indole-3-carboxaldehyde:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
807	H	δ 2.56 - 2.60 (4H, m), 3.16 - 3.19 (4H, m), 3.72 (2H, s), 6.97 - 7.01 (1H, m), 7.06 - 7.10 (1H, m), 7.28 (1H, d), 7.36 (1H, d), 7.51 (1H, s), 7.66 - 7.69 (1H, m), 7.71 - 7.74 (1H, m), 7.92 (1H, d), 10.96 (1H, s)	401
808	F	δ 2.55 - 2.59 (4H, m), 3.16 - 3.20 (4H, m), 3.69 (2H, s), 6.90 - 6.95 (1H, m), 7.34 - 7.37 (2H, m), 7.38 - 7.42 (1H, m), 7.51 (1H, s), 7.71 - 7.74 (1H, m), 7.92 (1H, d), 11.07 - 11.08 (1H, m)	419
809	CN	δ 2.56 - 2.60 (4H, m), 3.17 - 3.21 (4H, m), 3.76 (2H, s), 7.43 - 7.45 (1H, m), 7.51 - 7.56 (3H, m), 7.71 - 7.74 (1H, m), 7.92 (1H, d), 8.20 (1H, t), 11.57 (1H, d)	426

Example 810

Preparation of 6-[4-[2-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridine

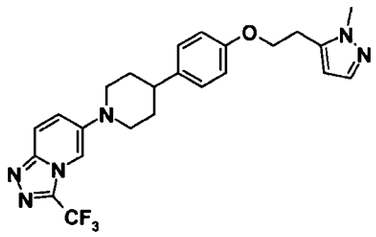


Obtained in 39% yield by General Synthetic Method 9, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine and 2-difluoromethyl-5-fluorobenzaldehyde (obtained as described in Example 779, preparation of starting materials).

1H NMR (399.9 MHz, DMSO-d6) δ 2.56 - 2.60 (4H, m), 3.18 - 3.22 (4H, m), 3.72 (2H, s), 7.28 - 7.32 (1H, m), 7.37 (1H, t), 7.37 - 7.41 (1H, m), 7.54 (1H, s), 7.68 - 7.75 (2H, m), 7.94 (1H, d); m/z = 430 [M+H]+.

Example 811

Preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridine



4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidine (69 mg, 0.24 mmol), 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (obtained as described in General Synthetic Method 9, preparation of starting materials) (65 mg, 0.24 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (11.41 mg, 0.02 mmol) and sodium tert-butoxide (0.060 mL, 0.49 mmol) were suspended in xylenes (5 mL), then de-gassed and purged with nitrogen. Bis(dibenzylideneacetone)palladium (7.02 mg, 0.01 mmol) was added, and the mixture was sealed into a microwave tube. The reaction was heated to 110°C for 30 minutes in the microwave reactor and cooled to ambient temperature. The reaction mixture was diluted with EtOAc (25 mL), and washed with water (25 mL). The aqueous layer was extraced with further EtOAc (25 mL). The combined organic layers were purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-a]pyridine (22.00 mg, 19.14 %) as a colourless gum. 1H NMR (399.9 MHz, DMSO-d6) δ 1.75 - 1.82 (2H, m), 1.84 - 1.90 (2H, m), 2.66 - 2.70 (1H, m), 2.80 - 2.85 (4H, m), 3.79 (3H, s), 3.80 - 3.83 (2H, s), 4.06 (2H, t), 6.90 (2H, d), 7.21 (2H, d), 7.34 (1H, s), 7.57 (2H, s), 7.77 - 7.80 (1H, m), 7.94 (1H, d); m/z = 471 [M+H]+.

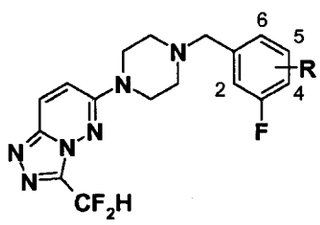
The 4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidine used as starting material was prepared as follows:-

DIAD (64.8 µl, 0.33 mmol) was added to 4-(piperidin-4-yl)phenol (CAS 263139-27-1, 53 mg, 0.30 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (obtained as described in PCT Int. Appl. WO 2007017222, Intermediate 1) (37.7 mg, 0.30 mmol) and triphenylphosphine (86 mg, 0.33 mmol) in DCM (3 mL) at 20°C under nitrogen. The resulting mixture was stirred at 22°C for 3 days. The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford 4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidine (85 mg, 96%) as a yellow oil.

m/z = 286 [M+H]+.

Examples 812-820

The following compounds were prepared in 11-72% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and the appropriate aldehyde:-

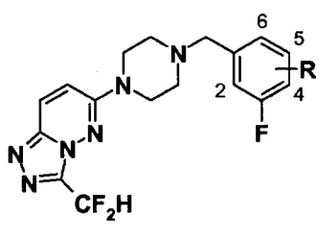


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
812	2-CF3	δ 2.54 (4H, t), 3.54 (4H, t), 3.66 (2H, s), 6.96 (1H, d), 7.02 - 7.07 (1H, m), 7.05 (1H, t), 7.39 - 7.45 (2H, m), 7.83 (1H, d)	432
813	5-Cl	δ 2.59 (4H, t), 3.54 (2H, s), 3.64 (4H, t), 7.00 - 7.26 (5H, m), 7.91 (1H, d)	398
814	5-CF3	δ 2.61 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.03 (1H, d), 7.13 (1H, t), 7.25 (1H, d), 7.31 (1H, d), 7.42 (1H, s), 7.91 (1H, dd)	432
815	6-Cl	δ 2.67 (4H, t), 3.64 - 3.67 (6H, m), 6.94 (1H, td), 7.04 (1H, d), 7.13 (1H, t), 7.26 - 7.35 (2H, m), 7.91 (1H, d)	398

816	6-CF3	δ 2.65 (4H, s), 3.66 (4H, s), 3.73 (2H, s), 7.03 - 7.07 (2H, m), 7.13 (1H, t), 7.59 (1H, d), 7.65 (1H, dd), 7.92 (1H, d)	432
817	2,6-F	δ 2.68 (4H, s), 3.63 (4H, t), 3.81 (2H, s), 6.83 - 6.89 (1H, m), 7.00 (1H, d), 7.08 - 7.16 (1H, m), 7.12 (1H, t), 7.89 (1H, d)	400
818	4,5-F	δ 2.59 (4H, s), 3.50 (2H, s), 3.64 (4H, s), 6.95 - 7.05 (3H, m), 7.15 (1H, t), 7.92 (1H, d)	399
819	6-SO2Me	δ 2.73 - 2.81 (4H, m), 3.31 (3H, s), 3.65 (4H, t), 4.07 (2H, s), 7.04 (1H, d), 7.12 (1H, t), 7.18 - 7.23 (1H, m), 7.36 (1H, s), 7.94 (1H, d), 8.15 (1H, dd)	441
820	2,5-F	δ 2.58 - 2.71 (4H, m), 3.56 - 3.72 (6H, m), 6.80 - 6.91 (1H, m), 6.95 - 7.03 (1H, m), 7.02 (1H, d), 7.13 (1H, t), 7.91 (1H, d)	400

Examples 821-823

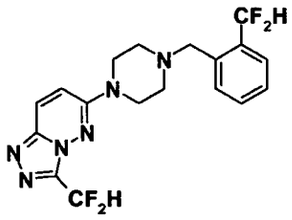
The following compounds were prepared in 19-45% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and the appropriate aldehyde:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
821	4,6-F	δ 3.18 - 3.80 (10H, m), 7.41 - 7.67 (4H, m), 8.21 (1H, d)	400
822	2-Cl	δ 3.38 - 4.41 (10H, m), 7.47 - 7.54 (4H, m), 7.56 (1H, t), 8.27 (1H, d)	397
823	2,4-F	δ 3.39 - 4.25 (10H, m), 7.34 - 7.69 (4H, m), 8.28 (1H, d)	399

Example 824

Preparation of 3-(difluoromethyl)-6-[4-[2-(difluoromethyl)benzyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine



Obtained in 70% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and 2-difluoromethylbenzaldehyde.

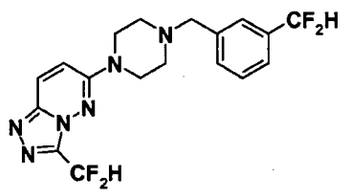
1H NMR (399.9 MHz, CDCl3) δ 2.51 (4H, t), 3.53 (4H, t), 3.62 (2H, s), 6.95 (1H, d), 7.05 (1H, t), 7.18 (1H, t), 7.27 - 7.37 (3H, m), 7.59 (1H, t), 7.83 (1H, d); m/z = 396 [M+H]+.

The 2-difluoromethylbenzaldehyde used as starting material was obtained in 19% yield by an analogous method to Example 779, preparation of starting materials, starting from 1-bromo-2-(difluoromethyl)benzene.

1H NMR (399.9 MHz, CDCl3) δ 7.36 (1H, t), 7.61 - 7.68 (2H, m), 7.75 (1H, d), 7.87 (1H, d), 10.12 (1H, s); m/z = 155 (M-H)-.

Example 825

Preparation of 3-(difluoromethyl)-6-[4-[3-(difluoromethyl)benzyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine



Obtained in 20% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-difluoromethylbenzaldehyde.

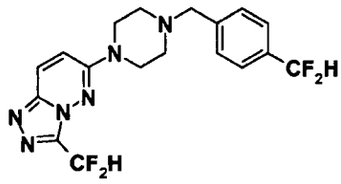
1H NMR (399.9 MHz, CDCl3) δ 2.53 (4H, t), 3.55 - 3.57 (6H, m), 6.58 (1H, t), 6.95 (1H, d), 7.06 (1H, t), 7.36 - 7.44 (4H, m), 7.83 (1H, d); m/z = 396 [M+H]+.

The 3-difluoromethylbenzaldehyde used as starting material was obtained in 10% yield by an analogous method to Example 779, preparation of starting materials, starting from 1-bromo-3-(difluoromethyl)benzene.

1H NMR (399.9 MHz, CDCl3) δ 6.66 (1H, t), 7.59 (1H, t), 7.72 (1H, d), 7.94 (1H, d), 7.97 (1H, s), 10.01 (1H, s)

Example 826

Preparation of 3-(difluoromethyl)-6-[4-[4-(difluoromethyl)benzyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine



Obtained in 20% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and 4-difluoromethylbenzaldehyde.

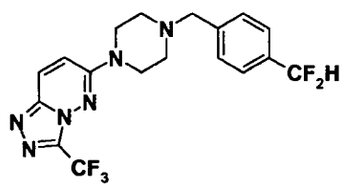
1H NMR (399.9 MHz, CDCl3) δ 2.54 - 2.69 (4H, m), 3.55 - 3.72 (6H, m), 6.65 (1H, t), 7.02 (1H, d), 7.12 (1H, t), 7.43 - 7.52 (4H, m), 7.91 (1H, d); m/z = 396 [M+H]+.

The 4-difluoromethylbenzaldehyde used as starting material was obtained in 34% yield by an analogous method to Example 779, preparation of starting materials, starting from 1-bromo-3-(difluoromethyl)benzene.

1H NMR (399.9 MHz, CDCl3) δ 6.71 (1H, t), 7.69 (2H, d), 7.98 (2H, d), 10.08 (1H, s); m/z = 155 [M-H]-.

Example 827

Preparation of 6-[4-[4-(difluoromethyl)benzyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

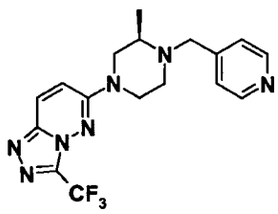


Obtained in 23% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 4-difluoromethylbenzaldehyde (obtained as described in Example 826, preparation of starting materials).

1H NMR (399.9 MHz, CDCl3) δ 2.57 - 2.70 (4H, m), 3.61 - 3.73 (6H, m), 6.65 (1H, t), 7.05 (1H, d), 7.45 - 7.51 (4H, m), 7.93 (1H, d); m/z = 414 [M+H]+.

Examples 828

Preparation of 6-[(3R)-3-methyl-4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

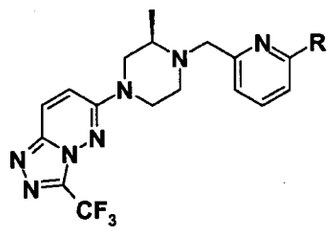


Obtained in 58% yield by General Synthetic Method 5, starting from 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 564, preparation of starting materials) and pyridine-4-carboxaldehyde.

1H NMR (399.9 MHz, CDCl3) δ 1.21 (3H, d), 2.34 (1H, ddd), 2.66 - 2.73 (1H, m), 2.81 (1H, ddd), 3.15 (1H, dd), 3.29 (1H, d), 3.37 (1H, ddd), 3.81 - 3.91 (2H, m), 4.04 (1H, d), 7.05 (1H, d), 7.32 (2H, d), 7.93 (1H, dd), 8.57 (2H, dd); m/z = 378 [M+H]+.

Examples 829-830

The following compounds were prepared in 19-28% yield by General Synthetic Method 5, starting from 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

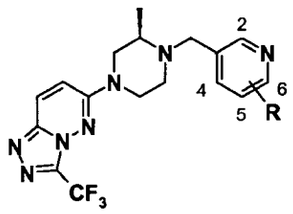


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
829	H	δ 1.22 - 1.33 (3H, m), 2.37 - 2.58 (1H, m), 2.66 - 2.84 (1H, m), 2.84 - 3.01 (1H, m), 3.08 - 3.27 (1H, m), 3.30 - 3.62 (2H, m), 3.84 - 3.94 (2H, m), 4.16 (1H, d), 7.05 (1H, d), 7.18 - 7.23 (1H, m), 7.44 - 7.52 (1H, m), 7.69 (1H, t), 7.92 (1H, d), 8.58 (1H, dd)	378
830	Br	δ 1.21 (3H, d), 2.42 - 2.52 (1H, m), 2.66 - 2.81 (1H, m), 2.89 - 2.91 (1H, m), 3.13 (1H, t), 3.37 (1H, t), 3.58 (1H, d), 3.87	456

		(2H, d), 4.07 (1H, d), 7.05 (1H, d), 7.38 (1H, d), 7.48 - 7.56 (2H, m), 7.93 (1H, d)	

Examples 831-836

The following compounds were prepared in 8-30% yield by General Synthetic Method 5, starting from 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

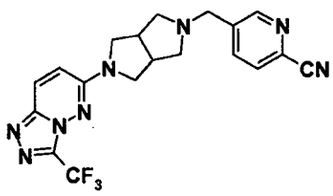


Ex.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
831	6-CF3	δ 1.24 (3H, d), 2.36 (1H, t), 2.67 - 2.81 (2H, m), 3.17 (1H, t), 3.34 - 3.40 (2H, m), 3.81 - 3.90 (2H, m), 4.11 (1H, d), 7.05 (1H, dd), 7.67 (1H, d), 7.86 - 7.92 (1H, m), 7.93 (1H, d), 8.71 (1H, s)	446
832	2-Cl	δ 1.22 (3H, d), 2.45 (1H, t), 2.71 - 2.87 (2H, m), 3.17 (1H, t), 3.39 (1H, t), 3.48 (1H, d), 3.86 (2H, t), 4.03 (1H, d), 7.06 (1H, d), 7.85 - 7.95 (2H, m), 8.26 - 8.36 (1H, m) (1H obscured by CHCl3)	412
833	6-Cl	δ 1.20 - 1.27 (3H, m), 2.25 - 2.41 (1H, m), 2.69 - 2.78 (2H, m), 3.09 - 3.20 (1H, m), 3.26 - 3.34 (2H, m), 3.80 - 3.88 (2H, m), 4.00 - 4.03 (1H, m), 7.04 (1H, d), 7.31 - 7.36 (1H, m), 7.64 - 7.71 (1H, m), 7.93 (1H, d), 8.35 (1H, d)	412
834	6-OMe	δ 1.24 (3H, d), 2.25 - 2.30 (1H, m), 2.59 - 2.69 (1H, m), 2.79 - 2.82 (1H, m), 3.12 (1H, t), 3.22 (1H, d), 3.27 - 3.35 (1H, m), 3.79 - 3.87 (2H, m), 3.94 (3H, s), 3.94 - 3.99 (1H, m), 6.74 (1H, d), 7.04 (1H, d), 7.57 - 7.59 (1H, m), 7.91 (1H, d), 8.07 (1H, s)	409
835	5-Br, 2-F	δ 1.21 - 1.24 (3H, m), 2.39 - 2.47 (1H, m), 2.68 - 2.80 (1H, m), 2.85 - 2.87 (1H, m), 3.11 - 3.20 (1H, m),	475

		3.39 - 3.42 (2H, m), 3.82 - 3.97 (3H, m), 7.06 (1H, d), 7.94 (1H, d), 7.99 - 8.08 (1H, m), 8.18 (1H, s)	
836	5-F	δ 1.16 (3H, d), 2.22 - 2.35 (1H, m), 2.65 - 2.76 (2H, m), 3.04 - 3.16 (1H, m), 3.25 - 3.34 (2H, m), 3.75 - 3.83 (2H, m), 3.99 (1H, d), 6.98 (1H, d), 7.34 - 7.49 (1H, m), 7.86 (1H, d), 8.33 (2H, s)	397

Example 837

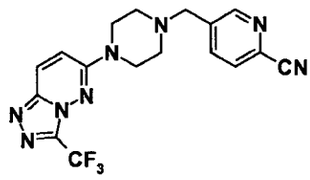
Preparation of 5-[[5-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]methyl]pyridine-2-carbonitrile



Obtained in 76% yield by an analogous method to Example 307, starting from 6-[5-[(6-bromopyridin-3-yl)methyl]hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 797). 1H NMR (399.9 MHz, CDCl3) δ 2.63 - 2.70 (4H, m), 3.43 (2H, dd), 3.45 (2H, s), 3.71 (2H, s), 3.83 (2H, dd), 6.87 (1H, d), 7.65 (1H, d), 7.78 (1H, d), 7.91 (1H, d), 8.65 (1H, s); m/z = 416 [M+H]+.

Example 838

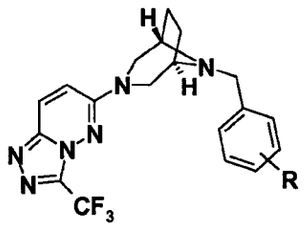
Preparation of 5-[[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]pyridine-2-carbonitrile



Obtained in 49% yield by an analogous method to Example 307, starting from 6-[4-[(6-bromopyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 374).
1H NMR (399.9 MHz, CDCl3) δ 2.58 - 2.69 (4H, m), 3.60 - 3.75 (6H, m), 7.06 (1H, d), 7.70 (1H, d), 7.83 - 7.90 (1H, m), 7.95 (1H, d), 8.71 (1H, s); m/z = 390 [M+H]+.

Examples 839-841

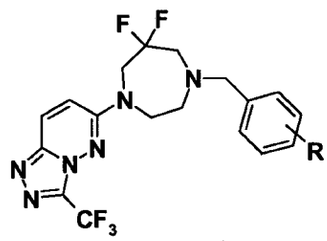
The following compounds were prepared in 62-77% yield by General Synthetic Method 5, starting from 6-[(1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 553, preparation of starting materials) and the appropriate aldehyde:-



Ex.	R	1H NMR (399.9 MHz, DMSO-d6)	m/z [M+H]+
839	4-F	δ 1.64 (2H, m), 2.00 - 2.04 (2H, m), 3.16 - 3.19 (2H, m), 3.58 (2H, s), 3.81 - 3.84 (2H, m), 7.14 - 7.18 (2H, m), 7.43 - 7.47 (2H, m), 7.50 (1H, d), 8.24 (1H, d)	407
840	3-CN	δ 1.65 - 1.67 (2H, m), 2.02 - 2.05 (2H, m), 3.20 - 3.23 (2H, m), 3.33 (2H, d), 3.67 (2H, s), 3.82 - 3.85 (2H, m), 7.51 (1H, d), 7.55 - 7.59 (1H, m), 7.73 - 7.76 (1H, m), 7.77 - 7.79 (1H, m), 7.86 (1H, s), 8.25 (1H, d)	414
841	4-CN	δ 1.65 - 1.68 (2H, m), 2.01 - 2.04 (2H, m), 3.19 - 3.22 (2H, m), 3.31 - 3.34 (2H, m, partially obscured by solvent peak), 3.71 (2H, s), 3.82 - 3.86 (2H, m), 7.51 (1H, d), 7.63 - 7.65 (2H, m), 7.80 - 7.83 (2H, m), 8.25 (1H, d)	414

Examples 842-844

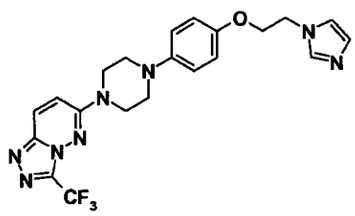
The following compounds were prepared in 42-55% yield by an analogous method to Example 563, starting from 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



Ex.	R	1H NMR (500 MHz, DMSO-d6)	m/z [M+H]+
842	3-F	δ 2.84-2.91 (m, 2H), 3.06-3.16 (m, 2H), 3.78 (s, 2H), 3.80-3.87 (m, 2H), 4.29-4.38 (m, 2H), 6.95-7.05 (m, 3H), 7.16-7.22 (m, 1H), 7.62 (d, 1H), 8.32 (d, 1H)	431
843	4-CN	δ 2.83-2.89 (m, 2H), 3.07-3.17 (m, 2H), 3.79-3.85 (m, 2H), 3.85 (s, 2H), 4.29-4.38 (m, 2H), 7.39 (d, 2H), 7.58 (d, 2H), 7.62 (d, 1H), 8.33 (d, 1H)	438
844	3-CN	δ 2.84-2.91 (m, 2H), 3.06-3.17 (m, 2H), 3.82 (s, 2H), 3.82-3.86 (m, 2H), 4.29-4.39 (m, 2H), 7.33 (dd, 1H), 7.53 (d, 1H), 7.59-7.66 (m, 2H), 7.68 (s, 1H), 8.32 (d, 1H)	438

Example 845

Preparation of 6-[4-[4-[2-(1H-imidazol-1-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

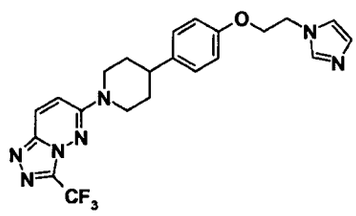


Obtained in 6% yield by an analogous method to Example 514, starting from 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol and 1-(2-hydroxyethyl)imidazole.

1H NMR (399.9 MHz, DMSO-d6) δ 3.18 (4H, t), 3.76 (1H, t), 4.18 (2H, t), 4.33 (2H, t), 6.82-6.99 (5H, m), 7.26 (1H, s), 7.53-7.72 (2H, m), 8.29 (1H, d); m/z = 459 [M+H]+.

Example 846

Preparation of 6-[4-[4-[2-(1H-imidazol-1-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

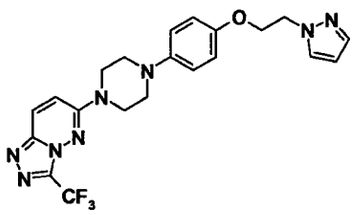


Obtained in 38% yield by an analogous method to Example 513, starting from 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-1-yl]phenol and 1-(2-hydroxyethyl)imidazole.

1H NMR (399.9 MHz, DMSO-d6) δ 1.58-1.73 (2H, m), 1.86 (2H, d), 2.76-2.88 (1H, m), 3.04-3.17 (2H, m), 4.18-4.29 (2H, m), 4.32-4.47 (4H, m), 6.83-6.93 (3H, m), 7.15-7.27 (3H, m), 7.62-7.70 (2H, m), 8.26 (1H, d); m/z = 458 [M+H]+.

Example 847

Preparation of 6-[4-[4-[2-(1H-pyrazol-1-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Sodium hydride (60% dispersion in oil, 16.97 mg, 0.42 mmol) was added to 1H-pyrazole (28.9 mg, 0.42 mmol) in DMF (2 mL) at 20°C under nitrogen. The resulting suspension was stirred at 20°C for 20 minutes. 6-[4-[4-(2-Bromoethoxy)phenyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (100 mg, 0.21 mmol) was added and the reaction stirred at 20°C for 1 hour. Water (25 mL) was then added and the resulting precipitate filtered off, washed with ether and dried overnight under vacuum at 50°C to give 6-[4-[4-[2-(1H-pyrazol-1-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (66.0 mg, 68 %) as a pale yellow solid.

1H NMR (399.9 MHz, DMSO-d6) δ 3.17 (4H, t), 3.73 (4H, t), 4.27 (2H, t), 4.46 (2H, t), 6.25 (1H, d), 6.84 (2H, d), 6.96 (2H, d), 7.48 (1H, d), 7.68 (1H, d), 7.79 (1H, d), 8.29 (1H, d); m/z = 459 [M+H]+.

The starting 6-[4-[4-(2-bromoethoxy)phenyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was prepared as follows:

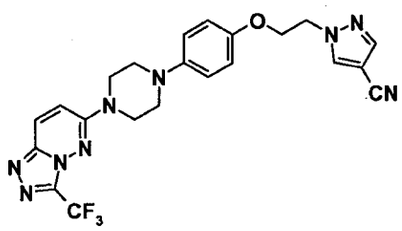
DIAD (1.625 mL, 8.25 mmol) was added to 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (obtained as described in Example 514, preparation of starting materials) (3.01 g, 8.25 mmol), 2-bromoethanol (0.645 mL, 9.08 mmol) and triphenylphosphine (2.165 g, 8.25 mmol) in THF (150 mL) at 20°C under nitrogen. The resulting solution was stirred at 20°C for 16 hours. The crude product was purified by flash

silica chromatography, elution gradient 0 to 3% MeOH in DCM to afford 6-[4-[4-(2-bromoethoxy)phenyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.765 g, 19.67 %) as a pale yellow solid.

1H NMR (399.9 MHz, $CDCl_3$) δ 3.22 (4H, t), 3.62 (2H, t), 3.79 (4H, t), 4.26 (2H, t), 6.87-6.96 (4H, m), 7.11 (1H, d),7.98 (1H, d); m/z = 473 [M+H]+

Example 848

Preparation of 1-[2-[4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenoxy]ethyl]-1H-pyrazole-4-carbonitrile

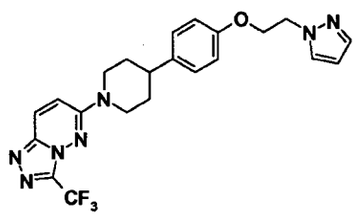


Obtained in 75% yield by an analogous method to Example 847, starting from 6-[4-[4-(2-bromoethoxy)phenyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 4-cyanopyrazole.

1H NMR (399.9 MHz, DMSO-d6) δ 3.19 (4H, t), 3.76 (4H, t), 4.32 (2H, t), 4.56 (2H, t), 6.85 (2H, d), 6.97 (2H, d), 7.67 (1H, d), 8.09 (1H, s), 8.29 (1H, d), 8.64 (1H, s); m/z = 484 [M+H]+.

Example 849

Preparation of 6-[4-[4-[2-(1H-pyrazol-1-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 67% yield by an analogous method to Example 847, starting from 6-[4-[4-(2-bromoethoxy)phenyl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and pyrazole.

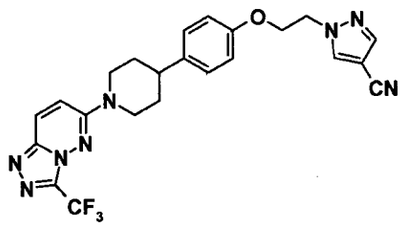
1H NMR (399.9 MHz, DMSO-d6) δ 1.59-1.74 (2H, m), 1.86 (2H, d), 2.76-2.86 (1H, m), 3.07 (2H, t), 4.31 (2H, t), 4.36-4.44 (2H, m), 4.47 (2H, t), 6.25 (1H, d), 6.85 (2H, d), 7.18 (2H, d), 7.46 (1H, d), 7.65 (1H, d), 7.79 (1H, d), 8.24 (1H, d); m/z = 458 [M+H]+.

The starting 6-[4-[4-(2-bromoethoxy)phenyl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was obtained in 29% yield by an analogous method to Example 847, preparation of starting materials, starting from 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-1-yl]phenol (obtained as described in Example 513, preparation of starting materials).

1H NMR (399.9 MHz, DMSO-d6) δ 1.61-1.74 (2H, m), 1.87 (2H, d), 2.77-2.88 (1H, m), 3.09 (2H, t), 3.79 (2H, t), 4.29 (2H, t), 4.40 (2H, d), 6.89 (2H, d), 7.19 (2H, d), 7.68 (1H, d) ,8.24 (1H, d); m/z = 472 [M+H]+.

Example 850

Preparation of 1-[2-[4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-1-yl]phenoxy]ethyl]-1H-pyrazole-4-carbonitrile

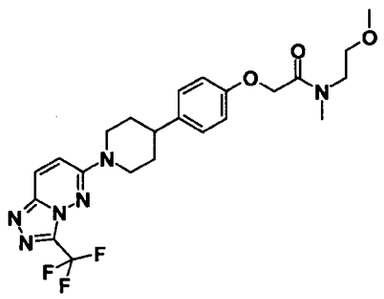


Obtained in 50% yield by an analogous method to Example 847, starting from 6-[4-[4-(2-bromoethoxy)phenyl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 849, preparation of starting materials) and 4-cyanopyrazole.

1H NMR (399.9 MHz, DMSO-d6) δ 1.58-1.74 (2H, m), 1.86 (2H, d), 2.76-2.87 (1H, m), 3.11 (2H, t), 4.31-4.47 (4H, m), 4.58 (2H, t), 6.86 (2H, d), 7.17 (2H, d), 7.68 (1H, d), 8.07 (1H, s), 8.23 (1H, d), 8.65 (1H, s); m/z = 484 [M+H]+.

Example 851

Preparation of N-(2-methoxyethyl)-N-methyl-2-[4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetamide



N-(2-methoxyethyl)methylamine (25 mg, 0.28 mmol) was added to 2-[4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid (100 mg, 0.24 mmol), HATU (108 mg, 0.28 mmol) and DIPEA (0.124 mL, 0.71 mmol) in DMF (2 mL). The resulting solution was stirred at ambient temperature for 3 hours then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give N-(2-methoxyethyl)-N-methyl-2-[4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetamide (26 mg, 22%).

1H NMR (499.8 MHz, DMSO-d6) δ 1.69 (2H, m), 1.93 (2H, m), 2.83 (1H, m), 3.14 (2H, m), 3.28 (3H, s), 3.48 (4H, m), 4.37 (2H, m), 4.72 (2H, s), 6.86 (2H, d), 7.16 (2H, d), 7.55 (1H, d), 8.13 (1H, d), 3H obscured by water peak; m/z = 493 [M+H]+.

The starting 2-[4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid was prepared as follows:

Preparation of methyl 2-[4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetate

Methyl 2-bromoacetate (0.418 mL, 4.42 mmol) was added to 4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (obtained as described in Example 513, preparation of starting materials) (1.07 g, 2.94 mmol) and potassium carbonate (0.814 g, 5.89 mmol) in DMF (20 mL). The resulting suspension was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated to dryness then water (50 mL) added and stirring continued for 20 minutes. The resulting precipitate was collected by filtration, washed with water then ether and dried to afford methyl 2-[4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetate (1.290 g, 100%).

1H NMR (399.9 MHz, DMSO-d6) δ 1.67 (2H, m), 1.88 (2H, m), 2.81 (1H, m), 3.09 (2H, m), 3.70 (3H, s), 4.42 (2H, m), 4.77 (2H, s), 6.86 (2H, d), 7.19 (2H, d), 7.67 (1H, d), 8.25 (1H, d); m/z = 436 [M+H]+.

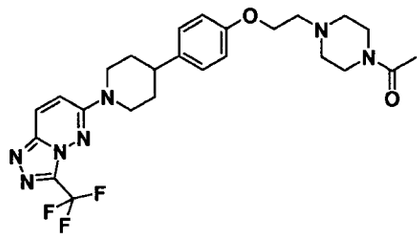
Preparation of 2-[4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid

Lithium hydroxide monohydrate (0.622 g, 14.81 mmol) was added to 2-[4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetate (1.29 g, 2.96 mmol) in a mixture of THF (20 mL), water (10 mL) and MeOH (5 mL). The resulting mixture was stirred at ambient temperature for 16 hours. The solvents were evaporated then the residues were suspended in water and acidified to pH 4 with 1M citric acid. The resulting precipitate was collected by filtration, washed with water and dried to afford 2-[4-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid (1.020 g, 82%).

1H NMR (399.9 MHz, DMSO-d6) δ 1.66 (2H, m), 1.88 (2H, m), 2.78 (1H, m), 3.09 (2H, m), 4.17 (2H, s), 4.41 (2H, m), 6.74 (2H, d), 7.12 (2H, d), 7.66 (1H, d), 8.23 (1H, d); m/z = 422 [M+H]+.

Example 852

Preparation of 6-[4-[4-[2-(4-acetylpiperazin-1-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



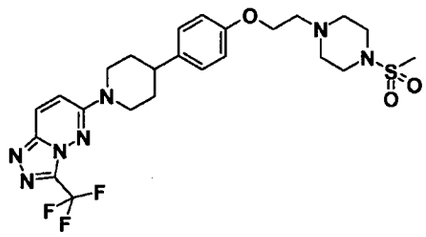
A solution of acetyl chloride (0.029 mL, 0.40 mmol) in DCM (0.5 mL) was added dropwise to 6-[4-[4-(2-piperazin-1-ylethoxy)phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 727) (160 mg, 0.34 mmol) and triethylamine (0.094 mL, 0.67 mmol) in DCM (1 mL) cooled to 0 °C under nitrogen. The resulting solution was stirred at 0°C for 5 minutes then allowed to warm to room temperature and stirred for 15 minutes. The reaction mixture was diluted with water (2 mL), passed through a phase separating cartridge and the organic layer evaporated to afford crude product. The crude product was purified by preparative HPLC

(Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammmonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[4-[2-(4-acetylpiperazin-1-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (60.0 mg, 35%).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 2.00 (2H, m), 2.08 (3H, s), 2.53 - 2.59 (4H, m), 2.75 - 2.84 (3H, m), 3.12 (2H, m), 3.48 (2H, m), 3.63 (2H, m), 4.10 (2H, t), 4.37 (2H, m), 6.87 (2H, d), 7.13 (3H, m), 7.92 (1H, d); m/z = 518 [M+H]+.

Example 853

Preparation of 6-[4-[4-[2-[4-(methylsulfonyl)piperazin-1-yl]ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

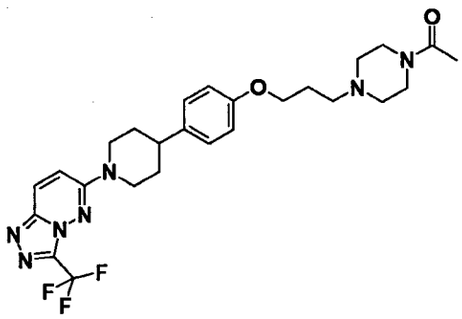


A solution of methanesulfonyl chloride (0.034 mL, 0.44 mmol) in DCM (0.5 mL) was added dropwise to 6-[4-[4-(2-piperazin-1-ylethoxy)phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 727) (175 mg, 0.37 mmol) and triethylamine (0.103 mL, 0.74 mmol) in DCM (1 mL) cooled to 0°C under nitrogen. The resulting solution was stirred at 0°C for 5 minutes then allowed to warm to room temperature and stirred for a further 15 minutes. The reaction mixture was diluted with water (2 mL), passed through a phase separating cartridge then the organic layer evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[4-[2-[4-(methylsulfonyl)piperazin-1-yl]ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (122 mg, 60%).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 2.00 (2H, m), 2.70 (4H, m), 2.75 - 2.83 (4H, m), 2.86 (2H, t), 3.12 (2H, m), 3.26 (4H, m), 4.09 (2H, t), 4.37 (2H, m), 6.86 (2H, d), 7.13 (3H, m), 7.92 (1H, d); m/z = 554 [M+H]+.

Example 854

Preparation of 6-[4-[4-[3-(4-acetylpiperazin-1-yl)propoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

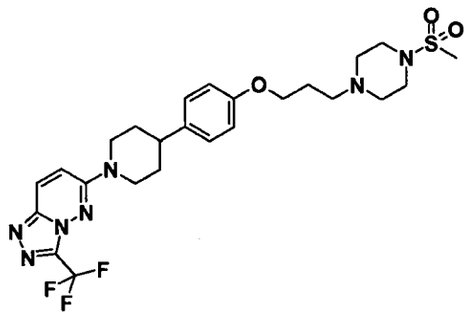


Obtained in 28% yield by an analogous method to Example 852, starting from 6-[4-[4-(3-piperazin-1-ylpropoxy)phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 728).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 1.92 - 2.02 (4H, m), 2.08 (3H, s), 2.44 (4H, m), 2.54 (2H, t), 2.78 (1H, m), 3.11 (2H, m), 3.46 (2H, m), 3.62 (2H, m), 4.01 (2H, t), 4.37 (2H, m), 6.86 (2H, d), 7.13 (3H, m), 7.92 (1H, d); m/z = 532 [M+H]+.

Example 855

Preparation of 6-[4-[4-[3-[4-(methylsulfonyl)piperazin-1-yl]propoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine

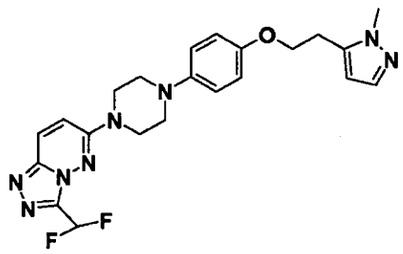


Obtained in 31% yield by an analogous method to Example 853, starting from 6-[4-[4-(3-piperazin-1-ylpropoxy)phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 728).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 1.92 - 2.01 (4H, m), 2.57 (6H, m), 2.74 - 2.82 (4H, m), 3.11 (2H, m), 3.25 (4H, m), 4.00 (2H, t), 4.37 (2H, m), 6.85 (2H, d), 7.12 (3H, m), 7.93 (1H, d); m/z = 568 [M+H]+.

Example 856

Preparation of 3-(difluoromethyl)-6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl]ethoxy]phenyl]piperazin-1-yl)[1,2,4]triazolo[4,3-b]pyridazine



Obtained in 32% yield by an analogous method to Example 514, starting from 4-[4-[3-(difluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol.

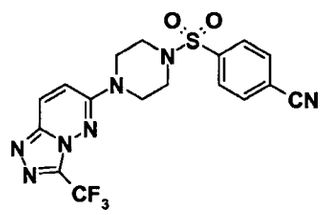
1H NMR (399.9 MHz, DMSO-d6) δ 3.07 (2H, t), 3.17 (4H, m), 3.75 (4H, m), 3.79 (3H, s), 4.15 (2H, t), 6.14 (1H, d), 6.88 (2H, d), 6.97 (2H, d), 7.31 (1H, d), 7.43 - 7.69 (2H, m), 8.22 (1H, d); m/z = 455 [M+H]+.

The 4-[4-[3-(difluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol used as starting material was prepared in 95% yield by an analogous method to Example 514, preparation of starting materials, starting from 3-(difluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in General Synthetic Method 1, preparation of starting materials).

1H NMR (399.9 MHz, DMSO-d6) δ 3.11 (4H, m), 3.74 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.43 - 7.69 (2H, m), 8.22 (1H, d), 8.87 (1H, s); m/z = 347 [M+H]+.

Example 857

Preparation of 4-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]piperazin-1-yl]sulfonylbenzonitrile

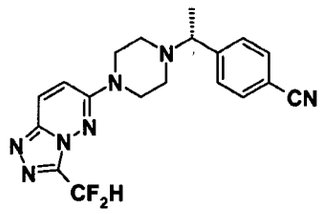


Obtained in 32% yield by an analogous procedure to Example 394, starting from 4-cyanobenzenesulfonyl chloride and 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (399.9 MHz, DMSO-d6) δ 3.07 (4H, m), 3.64 (4H, m), 7.46 (1H, d), 7.89 (2H, d), 8.06 (2H, d), 8.18 (1H, d); m/z = 438 [M+H]+.

Example 858

Preparation of 4-[(1R)-1-[4-[3-(difluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]piperazin-1-yl]ethyl]benzonitrile

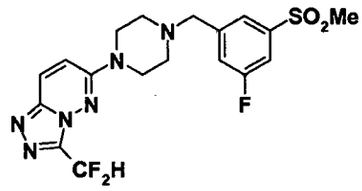


Obtained in 35% yield by an analogous procedure to Example 307, starting from 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 270).

1H NMR (399.9 MHz, CDCl3) δ 1.39 (3H, d), 2.48 - 2.53 (2H, m), 2.62 - 2.68 (2H, m), 3.49 (1H, q), 3.54 - 3.64 (4H, m), 7.00 (1H, d), 7.12 (1H, t), 7.47 - 7.49 (2H, m), 7.62 - 7.65 (2H, m), 7.89 (1H, d); m/z = 384 [M+H]+.

Example 859

Preparation of 3-(difluoromethyl)-6-{4-[3-fluoro-5-(methylsulfonyl)benzyl]piperazin-1-yl}[1,2,4]triazolo[4,3-b]pyridazine

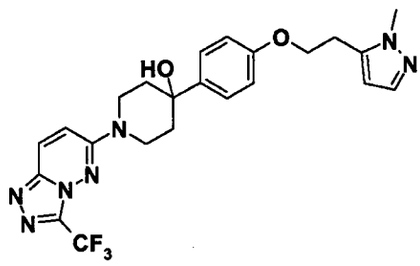


Obtained in 55% yield by General Synthetic Method 5, starting from 6-chloro-3-difluoromethyl-[1,2,4]triazolo[4,3-b]pyridazine and 3-fluoro-5-methylsulfonylbenzaldehyde (obtained as described in Example 778, preparation of starting materials).

1H NMR (399.9 MHz, DMSO) δ 2.53 - 2.57 (4H, m), 3.30 (3H, s), 3.62 - 3.66 (4H, m), 3.70 (2H, s), 7.51 - 7.54 (1H, m), 7.53 (1H, t), 7.58 - 7.60 (1H, m), 7.70 - 7.73 (1H, m), 7.77 (1H, d), 8.18 - 8.21 (1H, m); m/z = 441 [M+H]+.

Example 860

Preparation of 4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



DIAD (0.311 mL, 1.58 mmol) was added dropwise to 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (500 mg, 1.32 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (obtained as described in Example 513, preparation of starting materials) (249 mg, 1.98 mmol) and triphenylphosphine (519 mg, 1.98 mmol) in THF (10 mL) under nitrogen. The resulting suspension was stirred at ambient temperature for 16 hours then the solvents were evaporated to give crude product. The crude product was purified by flash silica chromatography, eluting with EtOAc then a gradient of 3 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to give a solid which was triturated with ether, filtered and dried to give 4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (464 mg, 72.2%) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.72 (2H, m), 1.99 (2H, m), 3.09 (2H, t), 3.43 (2H, m), 3.79 (3H, s), 4.18 (4H, m), 5.12 (1H, s), 6.13 (1H, d), 6.90 (2H, d), 7.30 (1H, d), 7.41 (2H, d), 7.65 (1H, d), 8.23 (1H, d); m/z = 488 [M+H]+.

The starting 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol was prepared as follows:-

Preparation of benzyl 4-[4-(benzyloxy)phenyl]-4-hydroxypiperidine-1-carboxylate

n-Butyllithium (1.6M in hexnae, 42.9 ml, 107.18 mmol) was added dropwise to 1-(benzyloxy)-4-bromobenzene (28.2 g, 107.18 mmol, CAS 6793-92-6) in THF (367 ml) at -78°C over a period of 15 minutes under nitrogen. The resulting solution was stirred at -78°C for 1 hour then benzyl 4-oxopiperidine-1-carboxylate (20 g, 85.74 mmol) in THF (122 ml) was added dropwise. The resulting mixture was stirred at -78°C for 10 minutes, then allowed to warm to room temperature and stirred for 16 hours. The reaction mixture

was evaporated to dryness and quenched with saturated ammonium chloride (50 mL), then then extracted with EtOAc (500 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 1 to 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford crude product. The crude product was further purified by flash silica chromatography, elution gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford benzyl 4-[4-(benzyloxy)phenyl]-4-hydroxypiperidine-1-carboxylate (13.49 g, 30.1%) as a gum.

1H NMR (399.9 MHz, DMSO-d6) δ 1.58 (2H, m), 1.80 (2H, m), 3.27 (2H, m), 3.71 (1H, m), 3.92 (2H, m), 5.10 (4H, m), 6.95 (2H, m), 7.39 (12H, m); m/z = 416 [M-H]+.

Preparation of 4-(4-hydroxyphenyl)piperidin-4-ol

10 % Palladium on carbon (3.44 g, 3.23 mmol) was added to benzyl 4-[4-(benzyloxy)phenyl]-4-hydroxypiperidine-1-carboxylate (13.49 g, 32.31 mmol) in MeOH (146 mL). The resulting mixture was stirred at room temperature for 20 hours under an atmosphere of hydrogen. The reaction mixture was filtered and evaporated to afford crude product. The crude material was triturated with DCM (100 mL) and MeOH (50 mL) to give a solid which was collected by filtration and dried under vacuum to give 4-(4-hydroxyphenyl)piperidin-4-ol (4.16 g, 66.6%).

1H NMR (399.9 MHz, DMSO-d6) δ 1.50 (2H, m), 1.73 (2H, m), 2.70 (2H, m), 2.90 (2H, m), 4.52 (1H, s), 6.69 (2H, m), 7.25 (2H, m), 9.21 (1H, s); m/z = 192 [M-H]+.

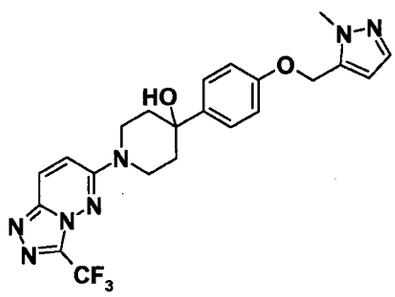
Preparation of 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol

DIPEA(1.174 mL, 6.74 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1 g, 4.49 mmol) and 4-(4-hydroxyphenyl)piperidin-4-ol (0.955 g, 4.94 mmol) in DMF (10 mL). The resulting solution was stirred at 80°C for 1 hour. The reaction mixture was cooled to room temperature then evaporated to dryness. The residues were triturated with water and the resulting solid collected by filtration, washed with further water followed by ether ,then dried under vacuum to afford 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (1.680 g, 99 %) as a solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.72 (2H, m), 1.95 (2H, m), 3.42 (2H, m), 4.17 (2H, m), 5.01 (1H, s), 6.70 (2H, d), 7.28 (2H, d), 7.65 (1H, d), 8.23 (1H, d), 9.20 (1H, s); m/z = 380 [M+H]+.

Example 861

Preparation of 4-[4-[(1-methyl-1H-pyrazol-5-yl)methoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol

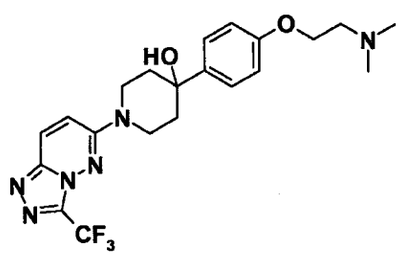


Obtained in 76% yield by an analogous method to Example 860, starting from 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol and 2-(1-methyl-1H-pyrazol-5-yl)methanol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.73 (2H, d), 1.95-2.07 (2H, m), 3.39-3.50 (2H, m), 3.83 (3H, s), 4.19 (2H, d), 5.13 (1H, s), 5.17 (2H, s), 6.37 (1H, d), 7.00 (2H, d), 7.38 (1H, d), 7.44 (2H, d), 7.66 (1H, d), 8.12 (1H, d); m/z = 474 [M+H]+.

Example 862

Preparation of 4-[4-[2-(dimethylamino)ethoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol

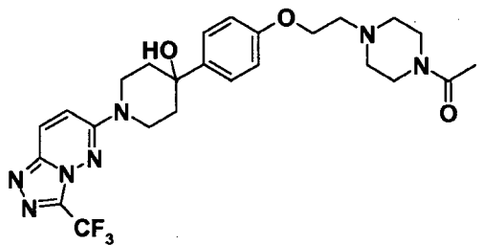


Obtained in 74% yield by an analogous method to Example 860, starting from 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol and 2-(dimethylamino)ethanol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.73 (2H, d), 1.95-2.06 (2H, m), 2.23 (6H, s), 2.61 (2H, t), 3.88-3.49 (2H, m), 4.04 (2H, t), 4.18 (2H, d), 5.11 (1H, s), 6.89 (2H, d), 7.39 (2H, d), 7.66 (1H, d), 8.23 (1H, d); m/z = 451 [M+H]+.

Example 863

Preparation of 4-[4-[2-(4-acetylpiperazin-1-yl)ethoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol

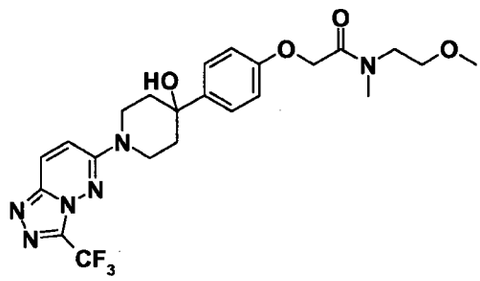


Obtained in 55% yield by an analogous method to Example 860, starting from 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol and 2-(4-acetylpiperazine-1-yl)ethanol (obtained as described in PCT Int. Appl. WO2003064413, Example 28, preparation of starting materials).

1H NMR (499.8 MHz, DMSO-d6, spectrum recorded at 100°C) δ 1.79 (2H, d), 1.97-2.07 (8H, m), 2.75 (2H, t), 3.39-3.48 (7H, m), 4.08-4.16 (4H, m), 6.89 (2H, d), 7.41 (2H, d), 7.55 (1H, d), 8.12 (1H, d); m/z = 534 [M+H]+.

Example 864

Preparation of 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]-N-(2-methoxyethyl)-N-methylacetamide



DIPEA (0.321 mL, 1.94 mmol) was added to 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid (283 mg, 0.65 mmol), N-(2-methoxyethyl)methylamine (63 mg, 0.71 mmol) and HATU (270 mg, 0.71 mmol) in DMF (5 mL) at 20°C under nitrogen. The resulting solution was stirred at 20°C for 4 hours. Water (50 mL) was then added and the mixture was extracted with DCM (2 x 50 mL). The combined organics were dried (Na_2SO_4), filtered and evaporated to give a orange oil. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in isohexane then 0 to 10% MeOH in EtOAc. Pure fractions were

evaporated to dryness then tritutated with isohexane, filtered and dried to afford 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]-N-(2-methoxyethyl)-N-methylacetamide (161 mg, 48.9%) as a white solid.
1H NMR (499.8 MHz, DMSO-d6, spectrum recorded at 100°C) δ 1.79 (2H, d), 1.98-2.06 (2H, m), 2.89-2.99 (6H, m), 3.47-3.54 (6H, m), 3.46-3.54 (6H, m), 4.12 (2H, d), 4.71-4.79 (3H, m), 6.87 (2H, d), 7.39 (2H, d), 7.54 (1H, d), 8.12 (1H, d); m/z = 509 [M+H]+.

The starting 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid was prepared as follows:-

Preparation of methyl 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetate

Methyl 2-bromoacetate (0.121 mL, 1.28 mmol) was added to 4-(4-hydroxyphenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (323 mg, 0.85 mmol) and potassium carbonate (235 mg, 1.70 mmol) in DMF (5 mL). The resulting suspension was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated to dryness, then water (50 mL) was added and the mixture was stirred for 20 minutes. The resulting precipitate was collected by filtration, washed with water then ether and dried to afford methyl 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetate (384 mg, 100%) as a beige solid.
1H NMR (399.9 MHz, $CDCl_3$) δ 1.93 (2H, d), 2.08-2.18 (2H, m), 3.58 (2H, t), 3.82 (3H, s), 4.14 (2H, d), 4.65 (2H, s), 6.91 (2H, d), 7.13 (1H, d), 7.42 (2H, d), 7.92 (1H, d); m/z = 452 [M+H]+.

Preparation of 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid

Lithium hydroxide monohydrate (177 mg, 4.21 mmol) was added to 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetate (380 mg, 0.84 mmol) in a mixture of THF (7 mL), water (3.5 mL) and MeOH (3.5 mL). The resulting mixture was stirred at ambient temperature for 16 hours. The solvents were evaporated, then the residues were suspended in water and acidified to pH 4 with 1M citric acid. The resulting precipitate was collected by filtration, washed with water and dried to afford 2-[4-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenoxy]acetic acid (297 mg, 81%) as a white solid.

1H NMR (399.9 MHz, DMSO-d6) δ 1.73 (2H, d), 1.95-2.06 (2H, m), 3.43 (2H, t), 4.18 (2H, d), 4.67 (2H, s), 5.14 (1H, s), 6.87 (2H, d), 7.42 (2H, d), 7.67 (1H, d), 8.23 (1H, d), 12.94 (1H, bs); m/z = 438 [M+H]+.

List of Figures

Figure 1: X-Ray Powder Diffraction Pattern for 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A when measured using CuKa radiation.

Figure 2: X-Ray Powder Diffraction Pattern for N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A when measured using CuKa radiation.

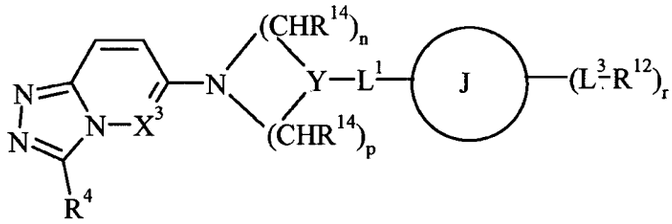
Figure 3: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuKa radiation.

Figure 4: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuKa radiation.

Figure 5: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate when measured using CuKa radiation.

Claims

1. A compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use as a medicament:



(Ic)

wherein

X^3 represents CH or N;

R^4 represents halo$C_{1\text{-}4}$alkyl;

Y represents CH, COH or N;

R^{14}, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$ or -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

L^3 represents a direct bond, -$(CR^9R^{10})_r$-, -C(O)N(R^{11})-$(CH_2)_q$-, -C(O)N(R^{11})-$(CH_2)_q$-S$(O)_2$-, -NR^{11}C(O)-$(CH_2)_q$-, -C(O)-$(CH_2)_q$-, -O-$(CH_2)_q$-, -O-$(CH_2)_q$-NR^{11}-$(CH_2)_q$-, –O-$(CH_2)_q$-C(O)NR^{11}-$(CH_2)_q$-, -S-, -S(O)- or –$S(O)_2$-;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

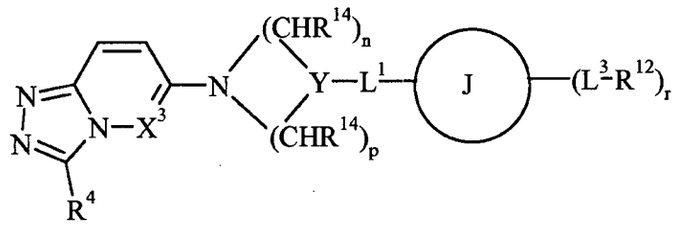
a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or –C(O)$NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

2. A compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer:



(Ic)

wherein

X^3 represents CH or N;

R^4 represents haloC_{1-4}alkyl;

Y represents CH, COH or N;

R^{14}, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$ or -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

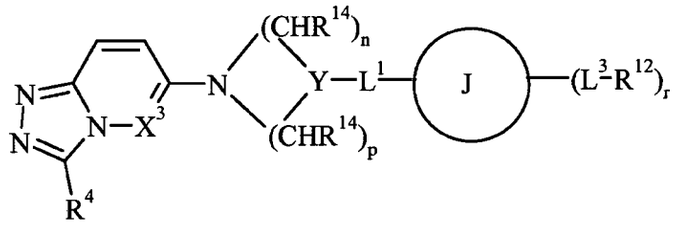
a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

3. A compound of Formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

wherein

X^3 represents CH or N;

R^4 represents haloC_{1-4}alkyl;

Y represents CH, COH or N;

R^{14}, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L^1 represents a direct bond, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$ or -S-, -S(O)- or $-S(O)_2-$;

R^9 and R^{10}, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl or thiadiazolyl; or

a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms , 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

L^3 represents a direct bond, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- or $-S(O)_2-$;

R^{11} represents hydrogen or methyl;

R^{12} represents:

halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, carboxy, C_{1-6}alkoxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, amino, N-C_{1-4}alkylamino or N,N-di-C_{1-4}alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

a monocylic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13}; or

a monocylic 4, 5, 6 or 7 membered heterocylic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{13};

R^{13} represents amino, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{2-6}alkanoyl, C_{1-6}alkoxyC_{1-6}alkyl, carboxy, cyano, oxo, fluoroC_{1-6}alkyl, hydroxy, hydroxyC_{1-6}alkyl, C_{1-6}alkylsulphanyl, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, N-C_{1-4}alkylamino, N,N-di-C_{1-4}alkylamino or $-C(O)NR^{14}R^{15}$ wherein R^{14} and R^{15} independently represent hydrogen or methyl;

r represents 1, 2 or 3 when J represents aryl;

r represents 0 when J represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

r represents 0, 1, 2 or 3 when J represents furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl, thiadiazolyl, or a bicyclic 9 membered heteroaryl ring system which

comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

with the proviso that the compound of Formula (Ic) is other than:

4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;

6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-fluorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(imidazo[1,2-*a*]pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3,4-dimethoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-{4-[2-(3,5-dimethoxyphenyl)ethyl]piperidin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-methoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-methylbenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-fluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

or

6-{4-[(2,6-difluorophenyl)sulfonyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.

4. A compound according to Claim 3, or a pharmaceutically acceptable salt thereof, wherein X^3 represents N.

5. A compound according to either of Claims 3 or 4, or a pharmaceutically acceptable salt thereof, wherein R^4 represents difluoromethyl, trifluoromethyl or chloro(difluoro)methyl.

6. A compound according to either of Claims 3 or 4, or a pharmaceutically acceptable salt thereof, wherein R^4 represents trifluoromethyl.

7. A compound according to any one of Claims 3 to 6, or a pharmaceutically acceptable salt thereof, wherein R^{14} represents hydrogen.

8. A compound according to any one of Claims 3 to 7, or a pharmaceutically acceptable salt thereof, wherein n and p both represent 2.

9. A compound according to any one of Claims 3 to 8, or a pharmaceutically acceptable salt thereof, wherein Y represents CH or COH.

10. A compound according to any one of Claims 3 to 9, or a pharmaceutically acceptable salt thereof, wherein Y represents N.

11. A compound according to any one of Claims 3 to 10, or a pharmaceutically acceptable salt thereof, wherein L^1 represents a direct bond.

12. A compound according to any one of Claims 3 to 11, or a pharmaceutically acceptable salt thereof, wherein J represents phenyl, pyridinyl, indolyl, indazolyl or pyrrolopyridinyl.

13. A compound according to any one of Claims 3 to 12, or a pharmaceutically acceptable salt thereof, wherein L^3 represents $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$ or $-O-(CH_2)_q-$.

14. A compound according to Claim 13, or a pharmaceutically acceptable salt thereof, wherein R^{11} represents methyl.

15. A compound according to any one of Claims 3 to 14, or a pharmaceutically acceptable salt thereof, wherein R^{12} represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, cyano, hydroxy, methylsulphonyl, dimethylamino, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or pyrazolyl.

16. A compound according to any one of Claims 3 to 15, or a pharmaceutically acceptable salt thereof, wherein R^{13} represents methyl, oxo or hydroxy.

17. A compound according to any one of Claims 3 to 16, or a pharmaceutically acceptable salt thereof, wherein r represents 1.

18. A compound according to any one of Claims 3 to 16, or a pharmaceutically acceptable salt thereof, wherein J does not represent aryl and r represents 0.

19. A compound according to Claim 3 selected from:
4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile;
3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine;
4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;
3-(difluoromethyl)-6-{4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl}[1,2,4]triazolo[4,3-b]pyridazine;
4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;
N-(2-methoxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;
N-(2-hydroxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-(4-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}piperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

N-(2-methoxyethyl)-N-methyl-3-({1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}oxy)benzamide;

2-morpholin-4-yl-N-(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}phenyl)acetamide;

6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-{4-[2-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-{4-[(6-methylpyridin-3-yl)methyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

1-[(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}phenyl)carbonyl]piperidin-4-ol;

N-methyl-N-[2-(methylsulfonyl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-[3-(4-methoxyphenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

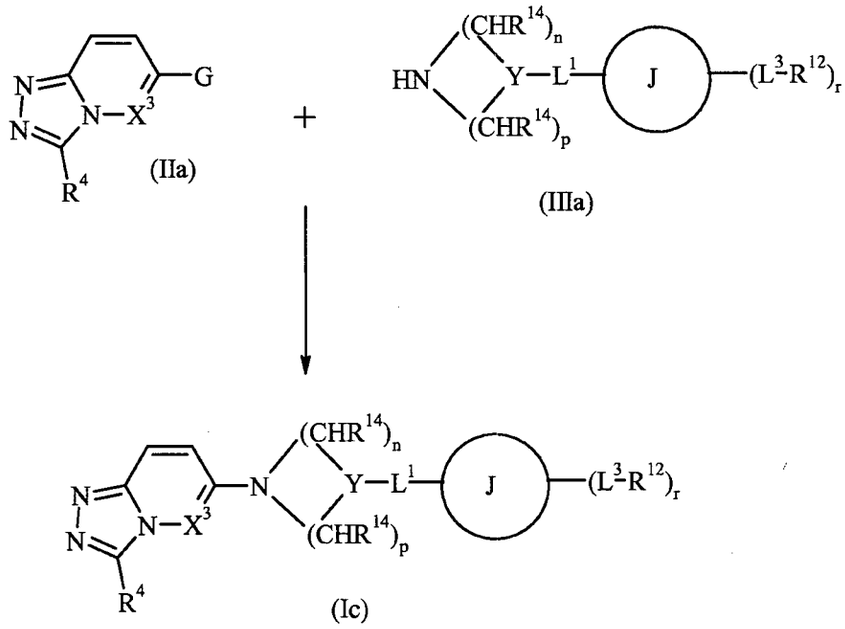
6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine; and

4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

and pharmaceutically acceptable salts thereof.

20. A pharmaceutical composition which comprises a compound according to any one of Claims 3 to 19, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

21. A process for the preparation of compounds of Formula (Ic) which comprises reacting a compound of Formula (IIa), wherein G represents halogen and R^4 and X^3 are as defined hereinbefore in relation to Fromula (Ic), with an amine of Formula (IIIa), wherein J, Y, L^1, L^3, R^{12}, R^{14}, n, p and r are as defined hereinbefore in relation to Formula (Ic):



(IIa) (IIIa) (Ic)

and thereafter, if necessary:

(i) converting a functional group of one compound of the invention into another functional group;

(ii) introducing a new functional group into one compound of the invention;

(iii) removing any protecting groups;

(iv) for compounds of the invention in the form of a single enantiomer separating a racemic compound of the invention into separate enantiomers;

(v) preparing a pharmaceutically acceptable salt thereof; and/or

(vi) preparing a crystalline form thereof.

Figure1: X-Ray Powder Diffraction Pattern for 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A when measured using CuKa radiation

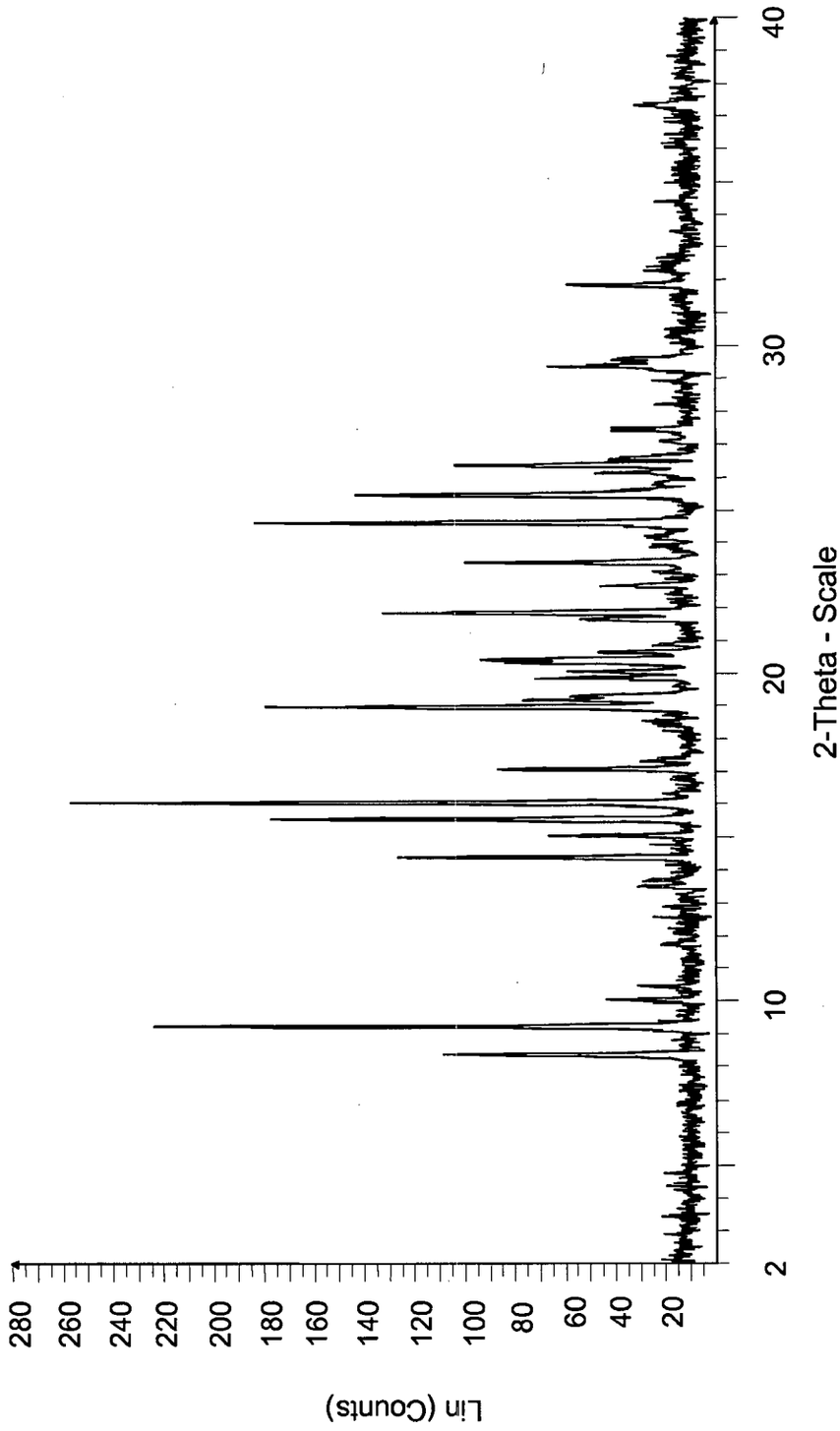


Figure 1

Figure 2: X-Ray Powder Diffraction Pattern for N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A when measured using CuKa radiation

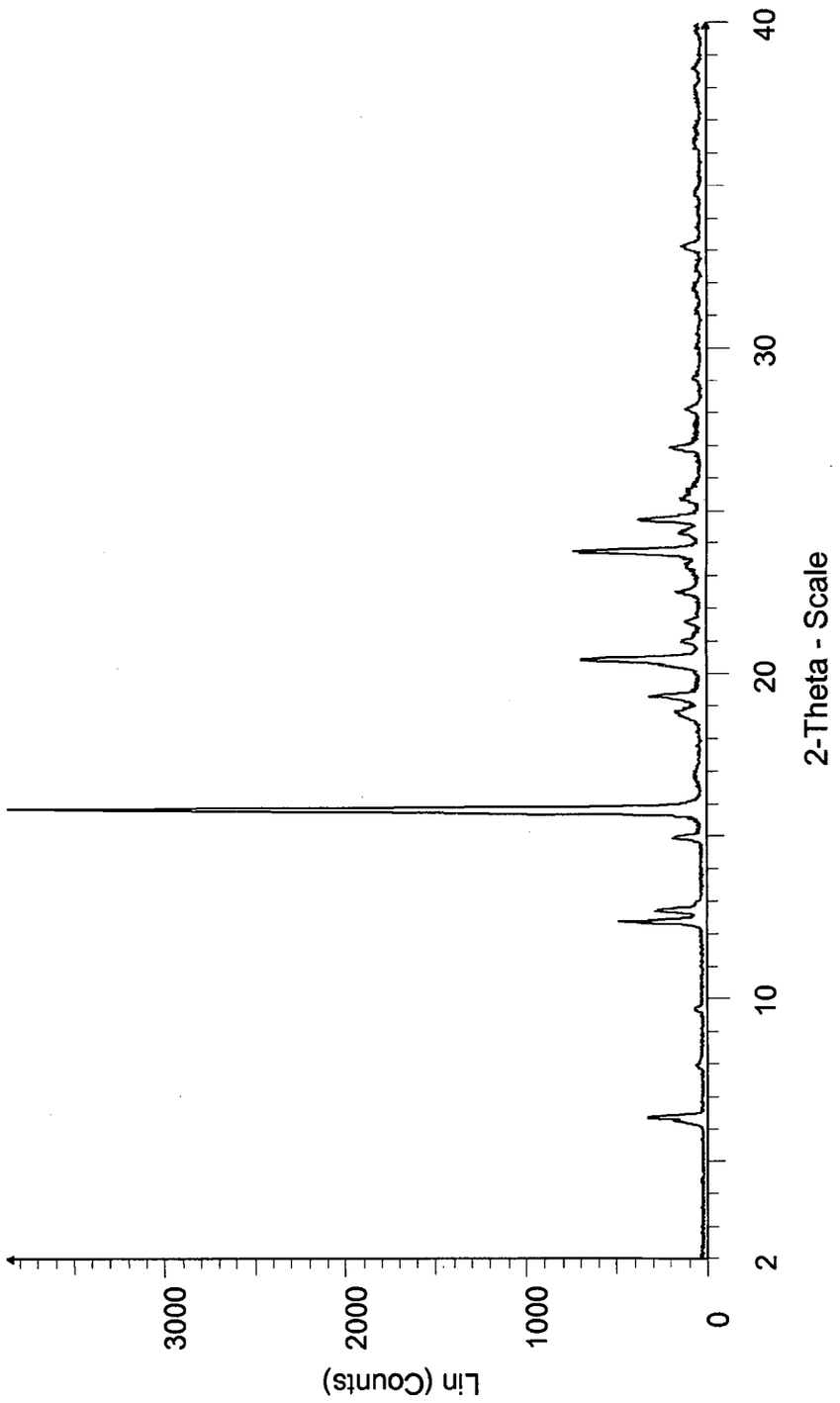


Figure 2

Figure 3: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuKa radiation

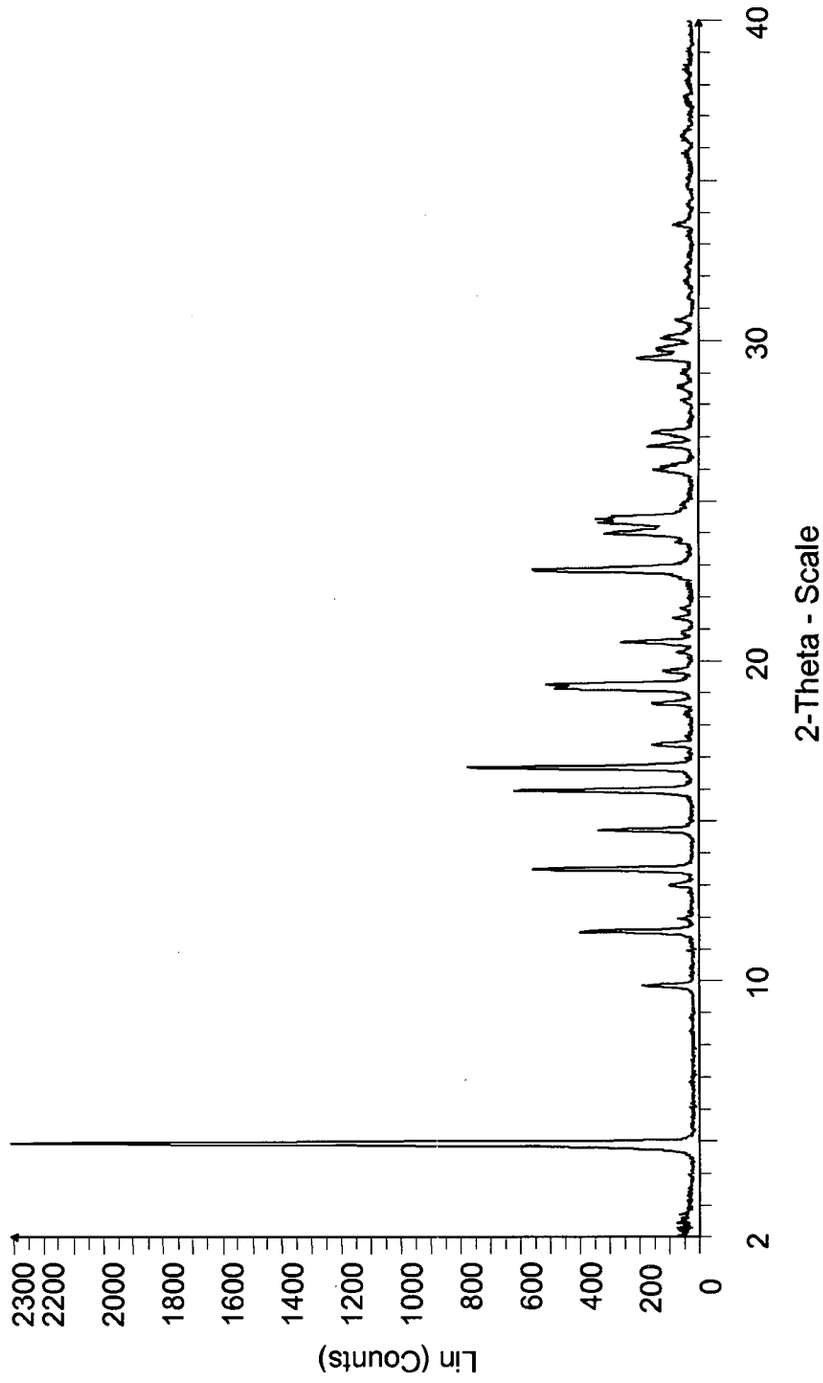


Figure 3

Figure 4: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuKa radiation

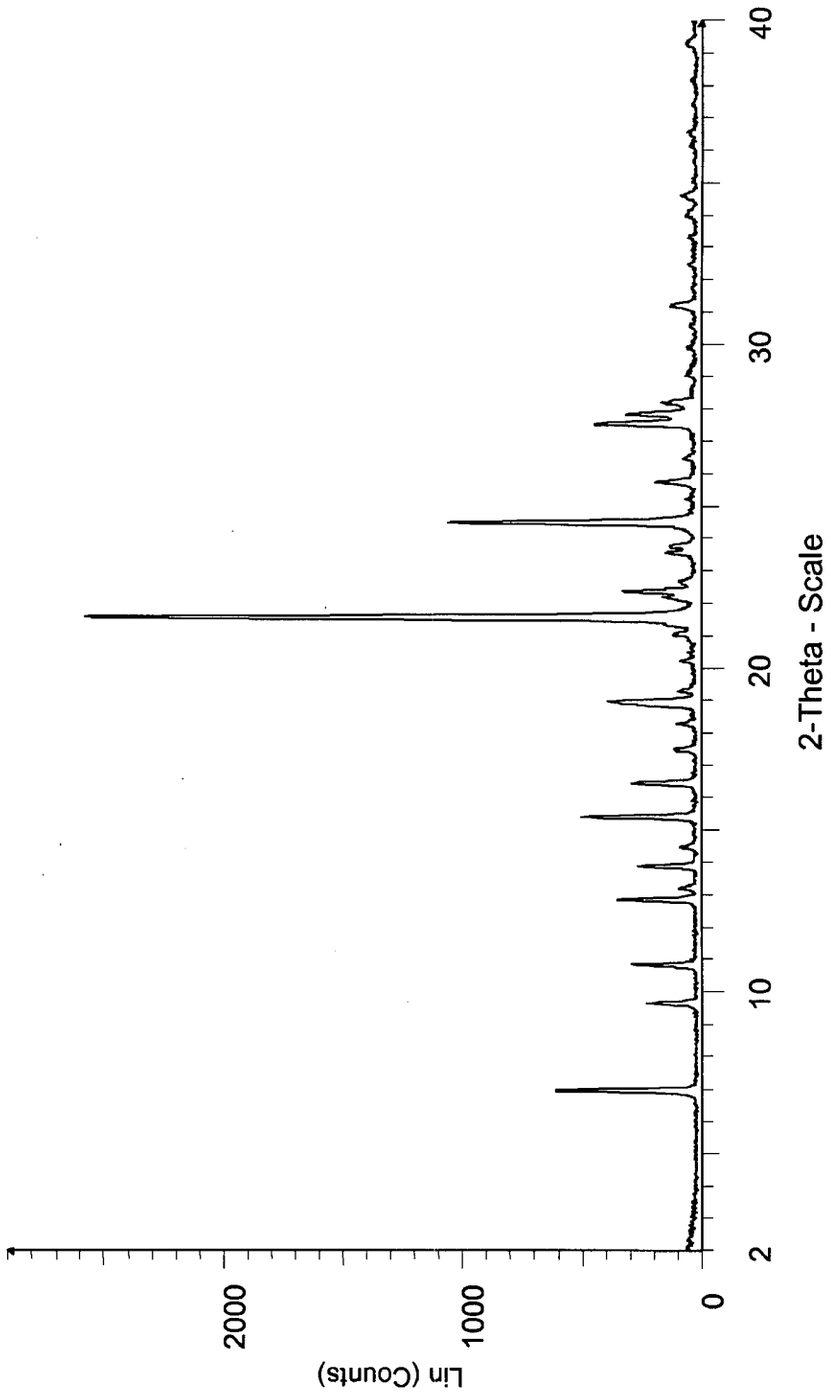


Figure 4

Figure 5: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate when measured using CuKa radiation

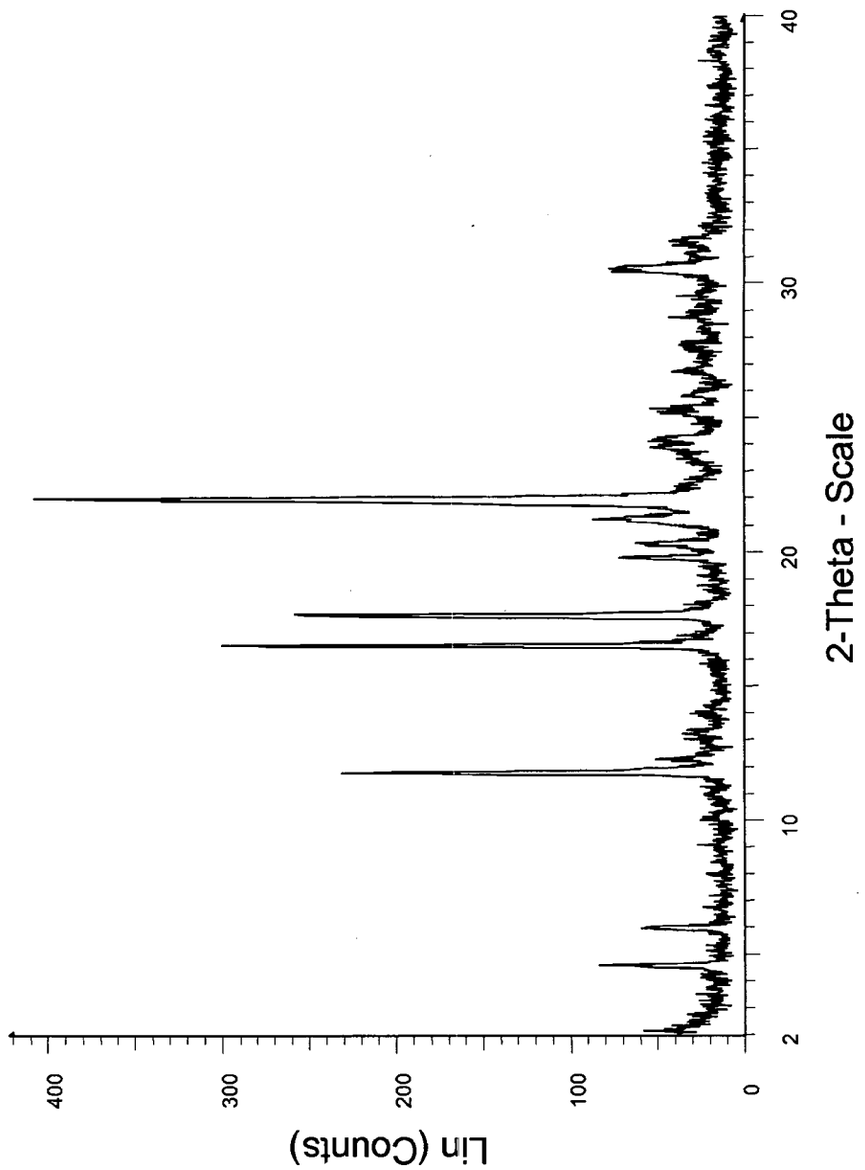


Figure 5

12) SOLICITUD INTERNACIONAL PUBLICADA EN VIRTUD DEL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

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(74) Mandatario: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

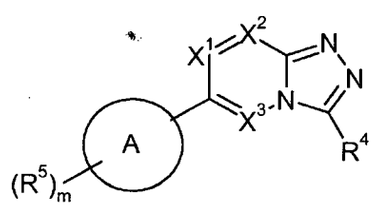
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(84) Estados designados *(a menos que se indique otra cosa, para toda clase de protección regional admisible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europea (AT, BE, 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).

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(54) **Title:** BICYCLIC DERIVATIVES FOR USE IN THE TREATMENT OF ANDROGEN RECEPTOR ASSOCIATED CONDITIONS

(54) **Título:** DERIVADOS BICÍCLICOS PARA USAR EN EL TRATAMIENTO DE AFECCIONES ASOCIADAS CON EL RECEPTOR DE ANDRÓGENO



(I)

(57) **Abstract:** The invention concerns bicyclic compounds of Formula (I), wherein the integers X^1, X^2, X^3, Ring A, R^4, R^5 and m are as defined in the description. The present invention also relates to processes for the preparation of such compounds, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use in the prevention or treatment of androgen-receptor associated conditions.

(57) **Resumen:** La invención se refiere a los compuestos bicíclicos de Fórmula I donde los números enteros X^1, X^2, X^3, el Anillo A, R^4, R^5 y m son como los definidos en la descripción. La presente invención también se relaciona con procesos para la preparación de tales compuestos, composiciones farmacéuticas que los contienen y su uso en la fabricación de un medicamento para su uso en la prevención o tratamiento de afecciones asociadas con el receptor de andrógeno.

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Derivados Bicíclicos para Usar en el Tratamiento de Afecciones Asociadas con el Receptor de Andrógeno

Esta invención se relaciona con nuevos derivados bicíclicos y, más particularmente, con derivados bicíclicos que actúan como ligandos del receptor de andrógeno (AR). Esta invención se relaciona también con los métodos de preparación de tales derivados bicíclicos, y nuevos productos intermedios en la preparación de los mismos, con composiciones farmacéuticas que contienen tales derivados bicíclicos, con el uso de tales derivados bicíclicos en la preparación de medicinas, y con el uso de tales derivados bicíclicos en el tratamiento de una afección asociada con el receptor de andrógeno tal como el cáncer de próstata.

El cáncer de próstata es la segunda causa más común de muerte por cáncer entre los hombres en los países desarrollados. Cuatro por ciento de las muertes entre los hombres mayores de 55 pueden ser atribuidas al cáncer de próstata. Aunque la tasa de muerte es relativamente baja, actualmente está aumentando anualmente a una tasa de alrededor del 14%. La proporción de hombres a los cuales el cáncer de próstata es probablemente diagnosticado se ha elevado en un 30% en los años recientes, aumento que es atribuible ampliamente a mejores métodos de diagnóstico y a un aumento general en la edad de la población, en lugar de una incidencia aumentada de nuevas enfermedades (E.J. Small, D.M. Reese, Curr. Opinion. Oncology, 2000, 12,265–272).

Las etapas tempranas del crecimiento del tumor cancerígeno de próstata son dependientes del andrógeno. Con la condición de que el tumor sea confinado a la propia próstata, el mismo puede usualmente ser tratado mediante la eliminación quirúrgica, terapia de radiación y/o mediante quimioterapia. En los casos más avanzados en los que el tumor no está solamente confinado a la próstata, sino que ha formado tumores metastáticos en cualquier parte del cuerpo, el tumor puede ser tratado paliativamente reduciendo los niveles de testosterona en sangre. Tal reducción en los niveles de testosterona en sangre puede ser lograda por castración quirúrgica (orquidectomía) o medicinalmente mediante tratamiento con antiandrógenos (Casodex, acetato de ciproterona, flutamida), Agonistas LHRH (Zoladex, Buserelin), antagonistas LHRH (Cetrorelix), o inhibidores de la 5α–reductasa (Finasteride). Debido a que la síntesis del andrógeno adrenal no se afecta por la castración quirúrgica, una tendencia reciente ha sido combinar el tratamiento quirúrgico y medicinal. Este tratamiento tiene solamente un éxito temporal ya que después de un

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intervalo de hasta 2 años el crecimiento renovado del tumor normalmente ocurre y este crecimiento renovado del tumor usualmente no es hormonalmente dependiente (L.J. Denis y K. Griffith, Seminars in Surg. Onc., 2000, 18, 52–74). A pesar de la amplia búsqueda en este tema durante los pasados 50 años no existe ningún tratamiento efectivo para las etapas avanzadas del cáncer de próstata. En los pacientes con cáncer de próstata avanzado la tasa de supervivencia de 5 años está por debajo de 15%.

Existe evidencia de que el receptor de andrógeno juega un papel importante en el desarrollo y crecimiento del cáncer de próstata no solamente en las etapas tempranas dependientes de la hormona sino también en las etapas avanzadas independientes de la hormona.

El receptor de andrógeno pertenece a la familia de los receptores de hormonas esteroides, los cuales funcionan como factores de transcripción. El enlace de un andrógeno al receptor de andrógeno resulta en la estabilización del receptor y lo protege de experimentar una rápida degradación proteolítica. El complejo de andrógeno y receptor de andrógeno es transportado al núcleo, donde el mismo regula la expresión de los genes sensibles al andrógeno mediante el enlace a sus elementos de ADN de respuesta al andrógeno en la región promotora de tales genes sensibles al andrógeno (D.J. Lamb *et.al.* Vitam. Horm. 2001, 62, 199–230).

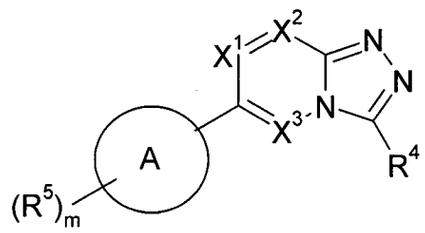
La investigación de los tumores de próstata muestra que en el 30% de los casos avanzados una amplificación del locus del gen receptor de andrógeno había ocurrido; en otros casos un rango de mutaciones del receptor de andrógeno fue encontrado en varios dominios del receptor de andrógeno y esto condujo al receptor de andrógenos con propiedades alteradas. Tales receptores mutados pueden tener una afinidad mayor que la normal por los andrógenos, pueden ser constitutivamente activos, pueden tener especificidad de ligandos alterada resultando en la activación por otras hormonas esteroides o incluso por los antiandrógenos, pueden ser activados mediante la interacción con las moléculas de otras rutas de transducción de la señal que promueven el crecimiento, pueden alterar las interacciones con otros cofactores, o pueden activar otros genes diana (J.P. Elo, T. Visakorpi, Ann. Med. 2001, 33, 130–141).

La identificación de los antiandrógenos que pudieran inhibir no solamente la forma natural del receptor de andrógeno sino también sus formas mutadas y por lo tanto alterar la molécula del receptor que se hace inestable pudiera ser muy útil en el tratamiento de los tumores de próstata en varias etapas del crecimiento. Tales compuestos pueden inhibir una recurrencia del crecimiento del tumor o al menos prolongar el intervalo libre de la

enfermedad. En el caso de los receptores de estrógeno, tales ligandos han sido identificados que desestabilizan el receptor y conducen a una reducción en el contenido del receptor tanto in vitro como in vivo (S. Dauvois y otros, Proc Natl. Acad. Sci. USA, 1992, 89, 4037–41; R.A. McClelland y otros Eur. J. Cancer, 1996, 32A, 413–416).

Los antiandrógenos no esteroides han sido descritos en US5411981 (derivados de fenilimidazolidina), en WO97/00071 (específicamente fenildimetil hidantoinas sustituidas y sus derivados imino y tio), en WO00/37430 (fenilalaninas, fenilhidantoinas, y fenilureas), en WO01/58855 (aminopropanilidas), y en EP1122242 (cianofenilpiperazinas sustituidas).

Se describe en la presente una serie de derivados bicíclicos capaces de inducir la regulación celular hacia abajo del receptor androgénico. De acuerdo con un primer aspecto de la presente invención se proporciona por lo tanto el uso de un compuesto de Fórmula (I) para el tratamiento de una afección asociada al receptor de andrógeno;



(I)

donde

X^1 es seleccionado de –N– y –C(R^1)–;

X^2 es seleccionado de –N– y –C(R^2)–;

X^3 es seleccionado de –N– y –C(R^3)–;

Donde al menos uno de X^1, X^2 y X^3 no es –N–;

El anillo A es seleccionado de un anillo mono, bicíclico o heterocíclico y un anillo carbocíclico;

R^1, R^2 y R^3 son independientemente seleccionados de hidrógeno, C_{1-6}alquil, C_{1-6}alcoxi, C_{1-6}alquiltio, halo y ciano donde una cadena alquil en R^1, R^2 y R^3 es opcionalmente sustituida por hasta tres grupos halo;

R^4 es seleccionado de hidrógeno, hidroxi, halo, ciano, amino, N–C_{1-6}alquilamino, N,N–di–C_{1-6}alquilamino, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{1-6}alquil–$S(O)_n$– donde n es un número entero de 0–2 y un anillo C_{3-4}carbocíclico, donde una cadena alquil, alquenil o alquinil dentro de R^4 puede opcionalmente estar sustituida por hasta 5 grupos seleccionados de ciano, halo, amino, C_{1-6}alcoxi, C_{1-4}alcoxiC_{1-4}alquil y C_{1-}

$_{6}$alquiltio y cuando R^4 comprende una cadena alquil la cadena puede estar perfluorada;

R^5 es seleccionado de oxo o el grupo $-L^1-J-L^2-K$

donde

L^1 y L^2 son independientemente seleccionados de un enlace directo, C_{1-6}alquileno, C_{2-6}alquenileno, C_{2-6}alquinileno, C_{1-6}alquilideno, donde una cadena alquil, alquenil, alquinil o alquilidenil dentro de L^1 y L^2 puede opcionalmente estar sustituida por hasta 3 grupos seleccionados de R^7 y donde L^1 y L^2 pueden también ser seleccionados de uno de los siguientes grupos o una cadena alquil, alquenil, alquinil o alquilidenil en la cual es insertado uno de los siguientes grupos, dichos grupos independientemente seleccionados de: $-O-$, $-C(O)-$, $-C(O)-O-$, $-O-C(O)-$, $-N(R^6)-$, $-N(R^6)-C(O)-$; $-C(O)-N(R^6)-$, $-N(R^6)-C(O)-O-$, $-O-C(O)-N(R^6)-$, $-C(O)-N(R^6)-O-$; $-O-N(R^6)-C(O)-$, $-N(R^6)-C(O)-N(R^6)-$, $-S(O)_{0-2}-$, $-O-S(O_2)-$, $S-(O_2)-O-$, $-N(R^6)-S(O)_2-$ y $-S(O)_2-N(R^6)-$;

J es seleccionado de un enlace directo, C_{1-4}alquileno, aril, heterociclil y heteroaril donde J está opcionalmente sustituido por hasta cinco grupos seleccionados de R^8;

K es seleccionado de C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, un anillo carbocíclico, aril, heterociclil y heteroaril donde K está opcionalmente sustituido por hasta cinco grupos seleccionados de R^8;

R^6 es seleccionado de hidrógeno y C_{1-6}alquil;

R^7 es seleccionado de hidroxi, carboxi, carbamoil, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{1-4}alquiloxiC_{1-4}alquil, C_{1-6}alcoxicarbonil, C_{1-6}alquil–$S(O)_n-$ donde n es un número entero de 0 a 2, aminosulfonil, carbamoil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino, N–C_{1-4}alquilaminocarbonil, N,N–di–C_{1-4}alquilaminocarbonil, N–C_{1-4}alquilaminosulfonil, N,N–di–C_{1-4}alquilaminosulfonil, oxo, C_{1-6}alquil(C_{1-6}alcoxi)oxofosfinil, diC_{1-6}alquiloxofosfinil, aril, carbociclil, heterociclil, heteroaril donde R^7 está opcionalmente sustituido por hasta tres grupos seleccionados de hidroxi, halo, ciano, C_{1-6}alquil, C_{1-6}alcoxi y un anillo carbocíclico y un grupo N,N–di–C_{1-4}alquilamino dentro de R^7 es opcionalmente ciclado para formar un anillo;

R^8 es seleccionado de hidroxi, oxo, ciano, halo, nitro, hidroxi, carboxi, C_{1-6}alquil, C_{1-6}alquenil, C_{1-6}alquinil, C_{1-6}alcoxi, C_{1-6}alcoxicarbonil, cianoC$_{1-6}$alcoxi, C_{1-6}alqueniloxi, C_{1-6}alcanoil, C_{1-4}alcoxicarbonil, C_{1-6}alquil–$S(O)_n-$ donde n es un

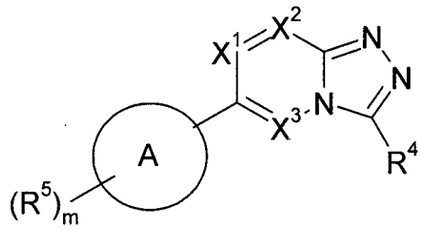
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número entero de 0 a 2, amino, C_{1-6}alquilsulfoniloxi, carbamoil, aminosulfonil, N–C_{1-4}alquilaminosulfonil, N,N–di–C_{1-4}alquilaminosulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino, carbamoil, N–C_{1-4}alquilaminocarbonil, N,N–di–C_{1-4}alquilaminocarbonil, aril, carbociclil, heterociclil y heteroaril donde un anillo o cadena alquil en R^8 está opcionalmente sustituido por hasta cinco grupos seleccionados de halo, amino, hidroxi, carboxi, C_{1-4}alcoxi, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino, carbamoil, N–C_{1-4}alquilaminocarbonil, N,N–di–C_{1-4}alquilaminocarbonil y oxo y un grupo N,N–di–C_{1-4}alquilamino dentro de R^8 es opcionalmente ciclado para formar un anillo; y

m es un número entero de 1 a 4;

o una sal farmacéuticamente aceptable del mismo.

De acuerdo con un segundo aspecto de la presente invención se proporciona el uso de un compuesto de Fórmula (Ia) como un medicamento;



(Ia)

donde X^1, X^2, X^3 , el anillo A, R^1, R^2, R^3, R^4 y R^5 son como los definidos anteriormente en la definición de un compuesto de Fórmula (I) con la condición de que

(i) cuando m es 1 entonces $(R^5)_m$ no puede ser hidroxi, oxo o C_{1-6}alquil y cuando m es 2 entonces $(R^5)_m$ no puede ser dihidroxi;

(ii) $-L^1-J-L^2-K$ no puede ser trifluorofenilpiperidin–1–il cuando el grupo piperidina está sustituido por amino o C_{1-4}alquilcarbonilamino;

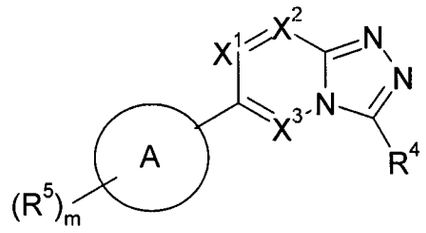
(iii) cuando el anillo A es pirrolidin–1–il, m es 2 y $(R^5)_m$ es piperidina–1–ilcarbonil sustituido y fenil sustituido o piperidina–1–ilcarbonil sustituido y piridil sustituido entonces el anillo fenil o piridil no puede ser sustituido por fluoro, cloro, ciano, trifluorometil o metoxi.

(iv) cuando el anillo A es indolina y m es 1 entonces R^5 no puede ser pirrolidinilcarbonil sustituido o no sustituido o piperidinilcarbonil sustituido o no sustituido;

o una sal farmacéuticamente aceptable del mismo.

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De acuerdo con un tercer aspecto de la presente invención se proporciona un compuesto de Fórmula (Ib);



(Ib)

donde X^1, X^2, X^3 , el anillo A, R^1, R^2, R^3, R^4 y R^5 son como los definidos anteriormente en la definición de un compuesto de Fórmula (I) con la condición de que

(i) cuando m es 1 entonces $(R^5)_m$ no puede ser hidroxi, C_{1-6}alquil, oxo, acetil, carbamoil, etoxicarbonil, metilsulfonil, metilsulfonilamino, isopropilaminocarbonilmetil o isobutilaminocarbonilmetil y cuando m es 2 $(R^5)_m$ no puede ser dihidroxi y no puede ser ciano y amino;

(ii) cuando R^4 es trifluorometil o metil y el anillo A es piperazin–1–il sustituido en la posición 4 por fenil, bencil fenetil, fenilsulfonil, fenilcarbonil o anilinocarbonil entonces el anillo de fenil no puede ser sustituido o no sustituido por 2–metil, 2,3–dimetil, 2,4–dimetil, 2,6–dimetil, 2–metoxi, 4–metoxi, 3–cloro, 4–cloro, 3–fluoro, 4–fluoro, 2,6–difluoro, 3–trifluorometil, 2–nitro, 4–nitro o 2,3,5,6–tetrafluoro–4–trifluorometil;

(iii) cuando R^4 es trifluorometil o metil y el anillo A es piperazinil sustituido por $–L^1–J–L^2–K$ en la posición 4 y m es 1 entonces $–L^1–J–L^2–K$ no puede ser α–carbamoilbencil no sustituido, α–fenilbencil, pirrolidin–1–ilcarbonil no sustituido, morfolinocarbonilmetil no sustituido, tien–3–ilmetil no sustituido, tiazol–2–il no sustituido, piridin–2–il no sustituido, piridin–4–ilmetil no sustituido, pirazin–2–il no sustituido, pirimidin–2–il no sustituido, tetrazolo[1,5–b]piridazin–6–il no sustituido, quinolin–8–ilmetil no sustituido, 1,3–benzodioxol–5ilmetil no sustituido, 2,6–difluorofenilsulfonil, 5–clorotien–2–ilsulfonil, 2–metiltiazol–4–ilmetil, 2–(4–metoxifenil)tiazol–4–ilmetil;

(iv) $–L^1–J–L^2–K$ no puede ser trifluorofenilpiperidin–1–il cuando el grupo piperidina está sustituido por amino o C_{1-4}alquilcarbonilamino; y

(v) cuando el anillo A es pirrolidin–1–il, m es 2 y $(R^5)_m$ es piperidina–1–ilcarbonil sustituido y fenil sustituido o piperidina–1–ilcarbonil sustituido y piridil sustituido

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entonces el anillo fenil o piridil no puede ser sustituido por fluoro, cloro, ciano, trifluorometil o metoxi;

(vi) cuando el anillo A es indolina y m es 1 entonces R^5 no puede ser pirrolidinilcarbonil sustituido o no sustituido o piperidinilcarbonil sustituido o no sustituido.

(vii) cuando R^4 es trifluorometil o metil y el anillo A es piperidinil sustituido por $-L^1-J-L^2-K$ en la posición 4 y m es 1 entonces $-L^1-J-L^2-K$ no puede ser carbamoil mono o disustituido;

(viii) Los siguientes compuestos están excluidos:

6–[2–(2,4–dimetoxifenil)–1–pirrolidinil]–3–(trifluorometil)–1,2,4–Triazolo[4,3–b]piridazina;

6–[4–(7–etil–1H–indol–3–il)–3,6–dihidro–1(2H)–piridinil]–3–(trifluorometil)–1,2,4–Triazolo[4,3–b]piridazina,

6–[4–(1H–indol–3–il)–3,6–dihidro–1(2H)–piridinil]–3–(trifluorometil)–1,2,4–Triazolo[4,3–b]piridazina;

6,7,8,9–tetrahidro–3–[1–[3–(trifluorometil)–1,2,4–triazolo[4,3–b]piridazin–6–il]–3–piperidinil]– 5H–1,2,4–triazolo[4,3–a]azepina;

6–[4–[2–(3,5–dimetoxifenil)etil]–1–piperidinil]–3–(trifluorometil)– 1,2,4–triazolo[4,3–b]piridazina;

2–tienil[4–[3–(trifluorometil)–1,2,4–triazolo[4,3–b]piridazin–6–il]–1–piperazinil]–metanona;

N–ciclopentil–N–metil–1–(3–metil–1,2,4–triazolo[4,3–b]piridazin–6–il)– 4–piperidinamina;

6–[4–(2–benzoxazolil)–1–piperidinil]–3–(trifluorometil)– 1,2,4–triazolo[4,3–b]piridazina

6–(3–fenilpirolidin–1il)–1,2,4–triazolo[4,3–b]piridazina; y

1–[[2,3–dihidro–1–(3–metil–1,2,4–triazolo[4,3–b]piridazin–6–il)–1H–indol–2–il]carbonil]–3–metil– piperidina;

o una sal de los mismos.

Aunque las sales farmacéuticamente aceptables de los compuestos de la invención son preferidas, otras sales no farmacéuticamente aceptables de los compuestos de la invención también pueden ser útiles, por ejemplo en la preparación de sales farmacéuticamente aceptables de los compuestos de la invención.

Debe ser entendido que, en la medida en que algunos de los compuestos de Fórmula (I) definido anteriormente pueda existir en formas ópticamente activas o racémicas en virtud de uno o más átomos de carbono asimétricos, la invención incluye en su definición cualquiera de tales formas ópticamente activas o racémicas que posee la actividad anteriormente mencionada. La síntesis de las formas ópticamente activas puede ser llevada a cabo mediante técnicas estándares de química orgánica bien conocidas en la materia, por ejemplo por la síntesis a partir de materiales de partida ópticamente activos o por resolución de una forma racémica. De manera similar, la actividad anteriormente mencionada puede ser evaluada usando las técnicas de laboratorio estándares referidas de aquí en lo adelante.

Ejemplos de métodos adecuados para separar los enantiómeros de un compuesto racémico incluye cromatografía usando una fase estacionaria quiral adecuada; o conversión de una mezcla racémica en derivados diastereoméricos, separación de la mezcla de derivados diastereoméricos en dos diastereómeros simples, y regeneración de un enantiómero simple separado de cada diastereómero simple separado.

Ejemplos de métodos adecuados para separar una mezcla de diastereómeros incluyen cristalización fraccional, cromatografía en fase normal, o cromatografía en fase inversa.

Debe ser entendido que algunos compuestos de Fórmula (I) definidos anteriormente pueden exhibir el fenómeno de tautomerismo. En particular, el tautomerismo puede afectar cualquiera de los grupos heterocíclicos que portan 1 ó 2 sustituyentes oxo. Debe ser entendido que la presente invención incluye en su definición cualquier forma tautomérica, o una mezcla de las mismas, que posea la actividad anteriormente mencionada y no está limitada meramente a cualquier forma tautomérica utilizada dentro de los dibujos de las Fórmulas o nombradas en los Ejemplos.

Debe ser entendido que algunos compuestos de Fórmula (I) anteriores pueden existir en formas no solvatadas así como formas solvatadas, tal como, por ejemplo, formas hidratadas. Debe ser entendido que la presente invención abarca todas esas formas solvatadas que poseen actividad ligando del receptor de andrógeno.

Debe ser entendido también que algunos compuestos de Fórmula (I) pueden exhibir polimorfismo, y que la presente invención abarca todas esas formas que poseen actividad ligando del receptor de andrógeno.

En esta descripción el término genérico "alquil", a menos que se especifique lo contrario, incluye tanto grupos alquil de cadena lineal y de cadena ramificada tales como

propil, isopropil y tert–butil. Sin embargo, referencias a grupos alquil individuales tales como "propil" son específicos para la versión de cadena lineal solamente, y referencias a grupos alquil de cadena ramificada individuales tales como "isopropil" son específicos para la versión de cadena ramificada solamente. El mismo principio también se aplica para los términos genéricos "alquenil" y "alquinil", a menos que se especifique lo contrario.

El término "fluoroC_{1-6}alquil" se pretende que signifique una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud la cual puede ser de cadena lineal o ramificada donde al menos uno de los átomos de hidrógeno han sido remplazados por flúor. Por ejemplo, "fluoroC_{1-6}alquil" incluye, pero no está limitado a, fluorometil, fluoroetil, fluoropropil, fluoroisopropil, fluorobutil, fluoroisobutil, fluoro–tert–butil, fluoropentil, fluoroisopentil, fluorohexil, fluoroisohexil, trifluorometil, pentafluoroetil, heptafluoropropil, nonafluorobutil, undecafluoropentil y tridecafluorohexil. El término "fluoroC_{1-4}alquil" se debe interpretar de acuerdo con lo anterior.

El término "C_{1-6} alcoxi" se pretende que signifique una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada, enlazada al oxígeno. Por ejemplo, "C_{1-6} alcoxi" incluye, pero no está limitado a, metoxi, etoxi, propoxi, butoxi, pentoxi y hexoxi.

El término "C_{2-6}alcanoil" se pretende que signifique una cadena de carbono saturada de 1 a 5 átomos de carbono de longitud de la cual puede ser de cadena lineal o ramificada, enlazada al carbonil. Por ejemplo, "C_{2-6}alcanoil" incluye, pero no está limitado a, etanoil, propanoil, butanoil, pentanoil y hexanoil.

El término "C_{1-6}alcoxiC_{1-6}alquil" se pretende que signifique una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada, enlazada a través del oxígeno a otra cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada. Por ejemplo, "C_{1-6}alcoxiC_{1-6}alquil" incluye, pero no está limitado a, metoxietil, metoxipropil, etoxipropil, propoxietil y butoxipropil.

El término "hidroxiC_{1-6}alquil" se pretende que signifique una cadena de carbono saturada de1 a 6 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada, que comprende un grupo hidroxilo simple. Por ejemplo "hidroxiC_{1-6}alquil" incluye, pero no está limitado a, hidroximetil, hidroxietil, 2–hidroxipropil, 3–hidroxipropil, 1–hidroxiisopropil, 4–hidroxibutil, hidroxipentil, hidroxihexil e hidroxiisohexil.

El término "C_{1-6}alquilsulfanil" se pretende que signifique una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser de cadena lineal o

ramificada, enlazada al azufre. Por ejemplo, "C_{1-6}alquilsulfanil" incluye, pero no está limitado a, metilsulfanil, etilsulfanil, propilsulfanil, isopropilsulfanil, butilsulfanil, isobutilsulfanil, *tert*–butilsulfanil, pentilsulfanil y hexilsulfanil.

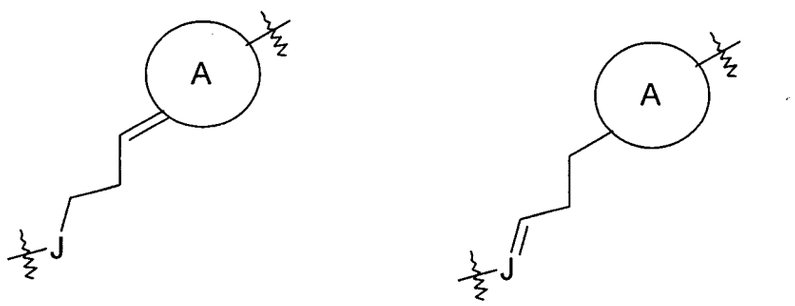
El término "C_{1-6}alquilsulfinil" se pretende que signifique una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada, enlazada al sulfóxido. Por ejemplo, "C_{1-6}alquilsulfinil" incluye, pero no está limitado a, metilsulfinil, etilsulfinil, propilsulfinil, isopropilsulfinil, butilsulfinil, isobutilsulfinil, *tert*–butilsulfinil, petilsulfinil y hexilsulfinil.

El término "C_{1-6}alquilsulfonil" se pretende que signifique una cadena de carbono saturada de 1 a 6 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada, enlazada al dióxido de azufre. Por ejemplo, "C_{1-6}alquilsulfonil" incluye, pero no está limitado a, metilsulfonil, etilsulfonil, propilsulfonil, isopropilsulfonil, butilsulfonil, isobutilsulfonil, *tert*–butilsulfonil, pentilsulfonil y hexilsulfonil.

El término "N–C_{1-4}alquilamino" se pretende que signifique una cadena de carbono saturada de 1 a 4 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada, enlazada a un grupo amino secundario. Por ejemplo, "N–C_{1-4}alquilamino" incluye, pero no está limitado a, metilamino, etilamino, propilamino y butilamino.

El término "N,N–di–C_{1-4}alquilamino" se pretende que signifique una cadena de carbono saturada de 1 a 4 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada, enlazada a un grupo amino terciario, el cual a su vez está enlazado a otra cadena de carbono saturada de la misma longitud. Por ejemplo, "N,N–di–C_{1-4}alquilamino" incluye, pero no está limitado a, N,N–dimetilamino, N,N–dietilamino, N,N–dipropilamino y N,N–dibutilamino.

El término "alquilideno" es usado para denotar una cadena de alquilideno la cual puede estar en cualquier orientación dentro de la molécula, así por ejemplo donde L^1 es propilideno esta podría cubrir las dos estructuras siguientes:



El término "halo" es usado aquí para denotar fluoro, cloro, bromo y yodo.

El término "haloC_{1-4}alquil" se pretende que signifique una cadena de carbono saturada de 1 a 4 átomos de carbono de longitud, la cual puede ser de cadena lineal o ramificada , en la que al menos uno de los átomos de hidrógeno ha sido sustituido por un átomo halo. Por ejemplo, "haloC_{1-4}alquil" incluye, pero no está limitado a, difluorometil, trifluorometil, cloro(difluoro)metil, difluoroetil y difluoropropil.

El término "aril" se refiere a fenil o naftil.

El término "carbamoil" se refiere al grupo $-C(O)NH_2$.

A menos que se indique lo contrario, el término "heteroaril" se refiere a un anillo mono o bicíclico, aromático de 4–10 miembros que contiene hasta 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre, enlazados a través de los átomos de carbono del anillo o de los átomos de nitrógeno del anillo donde un enlace desde un nitrógeno es permitido, por ejemplo ningún enlace es posible al nitrógeno de un anillo de piridina, pero un enlace es posible a través de 1–nitrógeno de un anillo de pirazol. En una realización el término "heteroaril" se refiere a un anillo mono o bicíclico aromático de 5–10 miembros que contiene hasta 5 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre, enlazados a través de los átomos de carbono del anillo o de los átomos de nitrógeno del anillo donde un enlace desde un nitrógeno es permitido, por ejemplo ningún enlace es posible al nitrógeno de un anillo de piridina, pero un enlace es posible a través de 1–nitrógeno de un anillo de pirazol. En otra realización el término "heteroaril" se refiere a un anillo monocíclico aromático de 5 ó 6 miembros que contiene hasta 4 heteroátomos independientemente seleccionados de nitrógeno, oxígeno o azufre, enlazado a través de los átomos de carbono del anillo o de los átomos de nitrógeno del anillo donde un enlace desde un nitrógeno es permitido, por ejemplo ningún enlace es posible al nitrógeno de un anillo de piridina, pero un enlace es posible a través de 1–nitrógeno de un anillo de pirazol. Ejemplos de anillos heteroaril de 5 ó 6 miembros incluyen pirrol, furano, imidazol, triazol, tetrazol, pirazina, pirazol, pirimidina, piridazina, pirrol, piridina, isoxazol, oxazol, 1,2,4 oxadiazol, isotiazol, tiazol, tiadiazol, 1,2,4–triazol y tiofeno. Ejemplos de sistemas de anillos bicíclicos 5/6 y 6/6 incluyen benzofurano, bencimidazol, benzotiofeno, benzotiazol, bencisotiazol, benzoxazol, bencisoxazol, 1,3–benzodioxol, indol, piridoimidazol, pirimidoimidazol, quinolina, isoquinolina, quinoxalina, quinazolina, ftalazina, cinolina y naftiridina. Esta definición comprende además anillos que contienen azufre donde el átomo de azufre ha sido oxidado a un grupo S(O) o $S(O_2)$.

A menos que se indique lo contrario, el término "heterociclil" se refiere a un anillo mono o bicíclico saturado o parcialmente saturado de 4–10 miembros que contiene hasta 5

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heteroátomos seleccionados de nitrógeno, oxígeno o azufre enlazado a través de los átomos de carbono del anillo o de los átomos de nitrógeno del anillo. Ejemplos de 'heterociclil' incluyen tetrahidrofuranil, 2,3–dihidro–4H–piranil, tetrahidro-2*H*-piranil, pirrolinil, pirrolidinil, 1,3–tiazolidina, morfolinil, oxetanil, piperidinil, piperazinil, dihidropiridinil, dihidropirimidinil y azepano. Ejemplos particulares de 'heterociclil' incluyen pirrolinil, pirrolidinil, morfolinil, piperidinil, piperazinil, dihidropiridinil y dihidropirimidinil. Esta definición comprende además anillos que contienen azufre donde el átomo de azufre ha sido oxidado a un grupo S(O) o $S(O_2)$.

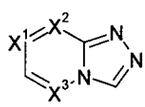
El término anillo "carbociclil" o carbocíclico se refiere a un anillo de carbono de 3–10 miembros mono, bicíclico, totalmente saturado o parcialmente saturado. Ejemplos de anillos carbocíclicos son ciclopropil, ciclobutil, ciclopentil, ciclohexil, biciclo[4,2,0]octano o 2,3–dihidroindeno.

Compuestos particularmente novedosos de la invención incluyen, por ejemplo, los compuestos de Fórmula (I), o sales farmacéuticamente aceptables de los mismos, donde, a menos que se indique lo contrario, cada uno de R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, A, J, K, L^1, L^2 y m tienen cualquiera de los significados definidos aquí anteriormente o en los párrafos (1) a (56) de aquí en adelante:

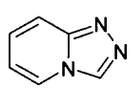
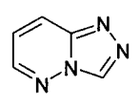
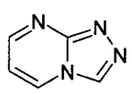
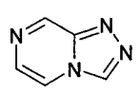
(1) X^1 y X^2 y X^3 son todos –C(H)–;

(2) X^1 es $–C(R^1)–$, X^2 es $–C(R^2)–$ y X^3 es $–C(R^3)–$;

(3) El anillo



es seleccionado de uno de los siguientes

;

(4) X^1 es $–C(R^1)–$, X^2 es $–C(R^2)–$ y X^3 es –N–;

(5) X^1 y X^2 son ambos C(H) y X^3 es –N–;

(6) El anillo A es seleccionado de pirrolidinil, piperidinil, 1,2–dihidropiridil, 1,2,5,6–tetrahidropiridil, morfolinil, tiomorfolinil, oxazepanil, tiazepanil, azepanil, 1,2,5,6–1H–tetrahidroazepinil, piperazinil, diazepanil, tetrahidroimidazolil, octahidro–1H–indolil, octahidro–2H–isoindolil, azabiciclo[2.2.1]heptanil, azabiciclo[3.3.0]octanil, azabiciclo[3.2.1]octanil,

triazaspirodecanil, octahidropirido[1,2–a]pirazinil, hexahidropirrolo[3,4–c]pirrolil, diazabiciclo[3.2.1]octanil y diazabicicloheptanil;

(7) En otra realización el anillo A es seleccionado de tetrahidrofuranil, tetrahidropiranil, y 5,6–dihidro–2H–piranil;

(8) El anillo A es seleccionado de piperidinil, pirrolidinil, piperazinil y diazepanil;

(9) El anillo A es seleccionado de piperidinil, piperazinil, diazepanil, 1,3,8–triazaspiro[4.5]decan–4–onil, 1,3,4,6,7,8,9,9a–octahidropirido[1,2–a]pirazinil, 3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrolil, 3,8–diazabiciclo[3.2.1]octanil y 2,5–diazabiciclo[2.2.1]heptanil.

(10) El anillo A es seleccionado de piperidinil, piperazinil, 3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrolil y diazepanil;

(11) El anillo A es seleccionado de piperazinil y 3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrolil;

(12) R^1 es C_{1-4}alquil y R^2 es C_{1-4}alquil;

(13) R^1 es hidrógeno y R^2 es C_{1-4}alquil;

(14) R^1 es C_{1-4}alquil y R^2 es hidrógeno;

(15) R^1 es seleccionado de metil y etil;

(16) R^1 es seleccionado de hidrógeno y metil;

(17) R^2 es seleccionado de hidrógeno y metil;

(18) R^3 es seleccionado de hidrógeno y metil;

(19) R^3 es hidrógeno;

(20) R^4 es seleccionado de halo, C_{1-6}alquil opcionalmente sustituido por hasta 5 susutituyentes halo, C_{1-6}alquilS(O)n– donde n es un número entero de 0 a 2 y amino;

(21) R^4 es seleccionado de halo, C_{1-4}alquil opcionalmente sustituido por hasta 5 susutituyentes halo, C_{1-4}alquiltio y amino;

(22) R^4 es seleccionado de cloro, difluorometil, trifluorometil, 1,1,2,2–tetrafluoroetil, metiltio o amino;

(23) R^5 es el grupo $–L^1–J–L^2–K$;

(24) R^5 es el grupo $–L^1–K$;

(25) R^5 es el group $–L^1–J–K$;

(26) R^5 es el grupo –K;

(27) R^5 es el grupo $–L^1–L^2–K$;

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(28) L^1 y L^2 son independientemente seleccionados de un enlace directo, C_{1-6}alquileno donde una cadena alquil dentro de L^1 y L^2 puede opcionalmente estar sustituida por hasta 3 grupos seleccionados de R^7 y donde L^1 y L^2 pueden también ser seleccionados de uno de los siguientes grupos o una cadena alquil en la cual es insertado uno de los siguientes grupos, dichos grupos independientemente seleccionados de: –O–, –C(O)–, –C(O)–O–, –O–C(O)–, – N(R^6)–, –N(R^6)–C(O)–; –C(O)–N(R^6)–, –N(R^6)–C(O)–O–, –O–C(O)–N(R^6)–, –C(O)–N(R^6)–O–; –O–N(R^6)–C(O)–, –N(R^6)–C(O)–N(R^6)–, –$S(O)_{0-2}$–, –O–$S(O_2)$–, S–(O_2) –O–, –N(R^6)–$S(O)_2$– y –$S(O)_2$–N(R^6)–;

(29) L^1 y L^2 son independientemente seleccionados de un enlace directo, C_{1-6}alquileno donde una cadena alquil dentro de L^1 y L^2 puede opcionalmente estar sustituida por hasta 3 grupos seleccionados de R^7 y donde L^1 y L^2 pueden también ser seleccionados de uno de los siguientes grupos o una cadena alquil en la cual es insertado uno de los siguientes grupos, dichos grupos independientemente seleccionados de: –O–, –C(O)– y –$S(O)_{0-2}$–;

(30) L^1 y L^2 son independientemente seleccionados de un enlace directo, C_{1-4}alquileno, –O–, –C(O)–, –OC(O)–, –C(O)O–, –N(R^6)–, –N(R^6)C(O)–, –C(O)N(R^6)–, –N(R^6)C(O)O–, –$S(O)_n$– donde n es un número entero de 0 a 2, –$OS(O)_2$–, –$S(O)_2$N(R^5)– y –N(R^5)$S(O)_2$–;

(31) L^1 y L^2 son independientemente seleccionados de un enlace directo, C_{1-4}alquileno, –O–, –C(O)–, –C(O)O–, –N(R^6)–, –N(R^6)C(O)–, –C(O)N(R^6)–, –N(R^6)C(O)O–, –S–, –$S(O)_2$–, –$OS(O)_2$–, –$S(O)_2$N(R^6)– y –N(R^6)$S(O)_2$–;

(32) L^1 y L^2 son independientemente seleccionados de un enlace directo, C_{1-2}alquileno, –O–, –$S(O)_2$N(R^6)– y –N(R^6)$S(O)_2$–;

(33) L^1 es independientemente seleccionado de un enlace directo, C_{1-2}alquileno, –O–, –$S(O)_2$N(R^6)– y –N(R^6)$S(O)_2$– y L^2 es un enlace directo;

(34) L^1 es seleccionado de un enlace directo, C_{1-4}alquileno, –C(O)–, –C(O)O–, –C(O)N(R^6)–, –$S(O)_2$– y –$S(O)_2$N(R^6)–;

(35) L^2 es seleccionado de un enlace directo, –O–, –C(O)O–, –N(R^6)–, –N(R^6)C(O)–, –C(O)N(R^6)–, –N(R^6)C(O)O–,–S–, –$S(O)_2$–, –$OS(O)_2$–, –(R^6)$S(O)_2$–;

(36) L^2 es un enlace directo;

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(37) J es seleccionado de un enlace directo, anillo aril y heteroaril donde J está opcionalmente sustituido por hasta cinco grupos seleccionados de R^8;

(38) J es seleccionado de un enlace directo, fenil, imidazolil y piridil;

(39) J es un enlace directo;

(40) K es seleccionado del anillo aril y heteroaril donde K está opcionalmente sustituido por hasta cinco grupos seleccionados de R^8;

(41) K es seleccionado de C_{1-6}alquil, C_{2-6}etenil, ciclohexil, fenil, naftil, , furanil, pirrolidinil, pirrolil, morfolinil, piperaziil, tienil, tiazolil, tiadiazolil, pirazolil, piperidinil, piridil, 2,3–dihidropiridil, pirazinil, pirimidinil, quinolinil, quinoxalinil, benzotiofenil, 1–benzofuranil, 2,3–dihidro–1–benzofuranil, 1,2,3,4–tetrahidroquinolinil, 1,4–dihidro–2H–3,1–benzoxazinil, 1,3–benzoxazolil, 2,3–dihidro–1,4–benzodioxinil, 1,3–benzodioxolil, 2,3–dihidro–1,4–benzodioxinil, 1,3–benzotiazolil y benzimidazolil;

(42) K es seleccionado de metil, etil, propil, butil, etenil, prop–2–enil, ciclohexil, fenil, naftil, furanil, pirrolidinil, pirrolil, morfolinil, piperazinil, tienil, tiazolil, tiadiazolil, pirazolil, piperidinil, piridil, 2,3–dihidropiridil, pirazinil, pirimidinil, quinolinil, quinoxalinil, benzotiofenil, 1–benzofuranil, 2,3–dihidro–1–benzofuranil, 1,2,3,4–tetrahidroquinolinil, 1,4–dihidro–2H–3,1–benzoxazinil, 1,3–benzoxazolil, 2,3–dihidro–1,4–benzodioxinil, 1,3–benzodioxolil, 2,3–dihidro–1,4–benzodioxinil, 1,3–benzotiazolil y benzimidazolil;

(43) K es seleccionado de fenil, naftil, furanil, pirrolil, , tienil, tiazolil, tiadiazolil, pirazolil, piperidinil, piridil, pirazinil, pirimidinil, quinolinil, quinoxalinil, benzotiofenil, 1–benzofuranil, 1,2,3,4–tetrahidroquinolinil, 1,4–dihidro–2H–3,1–benzoxazinil, 1,3–benzoxazolil, 2,3–dihidro–1,4–benzodioxinil, 1,3–benzodioxolil, 2,3–dihidro–1,4–benzodioxinil, 1,3–benzotiazolil y benzimidazolil;

(44) R^6 es seleccionado de hidrógeno y C_{1-4}alquil;

(45) R^6 es seleccionado de hidrógeno, metil;

(46) R^7 es seleccionado de C_{1-4}alquil, hidroxiC_{1-4}alquil y fenil;

(47) R^7 es seleccionado de fenil;

(48) R^8 es seleccionado de oxo, ciano, halo, C_{1-6}alquil, C_{1-6}alcoxi, C_{1-6}alcoxicarbonil, C_{1-6}alquil–$S(O)_n$– donde n es un número entero de 0 a 2,

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C_{1-6}alquilsulfoniloxi, carbamoil, aminosulfonil, N–C_{1-4}alquilaminosulfonil, N,N–di–C_{1-4}alquilaminosulfonil, N–C_{1-4}alquilaminocarbonil, N,N–di–C_{1-4}alquilaminocarbonil, aril, carbociclil, heterociclil y heteroaril donde un anillo o cadena alquil en R^8 está opcionalmente sustituido por hasta cinco grupos seleccionados de halo, carboxi, C_{1-4}alcoxi, N,N–di–C_{1-4}alquilamino, carbamoil, N–C_{1-4}alquilaminocarbonil, N,N–di–C_{1-4}alquilaminocarbonil y oxo y un grupo N,N–di–C_{1-4}alquilamino dentro de R^8 es opcionalmente ciclado para formar un anillo;

(49) R^8 es seleccionado de C_{1-6}alquil, C_{1-6}alquenil, C_{1-6}alquinil, C_{1-6}alcoxi, C_{1-6}alcoxicarbonil, hidroxi, carbamoil, ciano, halo, nitro, amino, N–C_{1-4}alquilamino, N,N–diC_{1-4}alquilamino y oxo donde una cadena alquil en R^8 es opcionalmente sustituida por hasta 5 grupos halo;

(50) R^8 es seleccionado de C_{1-6}alquil, C_{1-6}alquenil, C_{1-6}alquinil, C_{1-6}alcoxi, C_{1-6}alcoxicarbonil, hidroxi, carbamoil, ciano, halo, nitro, amino, N,N–diC_{1-4}alquilamino y oxo donde una cadena alquil en R^8 está opcionalmente sustituido por hasta 5 grupos halo;

(51) R^8 es seleccionado de metil, propil, isopropil, 2–metilpropil, t–butil, etinil, trifluorometil, metoxi, etoxi, butoxi, difluorometoxi, trifluorometoxi, etoxicarbonil, hidroxi, carbamoil, ciano, cloro, bromo, fluoro, amino, dimetilamino, dietilamino andoxo;

(52) m es un número entero de 0 a 3;

(53) m es 1;

(54) m es 2;

(55) m es 3;

(56) m es 4;

Compuestos particularmente novedosos de la invención incluyen cualquiera de los siguientes:

6–[4–(4–nitrofenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(3–bromofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–(naftalen–1–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(3–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

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6–[4–[3–cloro–5–(trifluorometil)piridin–2–il]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–(4–fenetilpiperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–(1–benzotiofen–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–a]piridina

6–[4–(3,5–dicloropiridin–4–il)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

4–[[5–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]benzonitrilo

3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina

4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo

6–[4–[(4–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo

6–[4–(tiofen–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(3–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(2–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–(1H–indol–6–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(2,2–difluoro–1,3–benzodioxol–4–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(2–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

5–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]isoquinolina

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6–[4–[(4–nitrofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(4–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–(2,6–dimetilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(4–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina

6–[4–[(3–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

3–[[5–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]benzonitrilo

6–[4–[(4–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(3–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(3–metilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(2–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–(1H–indol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(4–metilsulfonilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

3–(trifluorometil)–6–[4–[[2–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina

6–[4–(3–metilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(4–metilsulfanilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[[3–(difluorometoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(4,5–dimetilfuran–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[fenil–[4–(trifluorometil)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

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3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo

3–(trifluorometil)–6–[4–[[2–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(2–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)-[1,2,4]triazolo[4,3–b]piridazina

4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo

6–[4–[(4–metoxifenil)–fenilmetil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[4–[(3–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)-[1,2,4]triazolo[4,3–a]piridina

3–(trifluorometil)–6–[4–[[3–(trifluorometilsulfanil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina

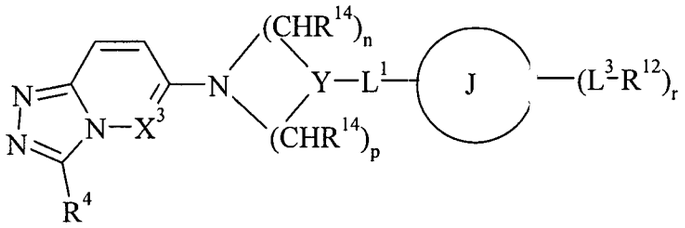
6–[4–[(4–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)-[1,2,4]triazolo[4,3–b]piridazina

6–[4–[4,4–bis(4–fluorofenil)butil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

6–[2–[(3–clorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

o sales farmacéuticamente aceptables de los mismos.

De acuerdo con un cuarto aspecto de la presente invención se proporciona un compuesto de Fórmula (Ic), o una sal farmacéuticamente aceptable del mismo, para su uso como un medicamento:



(Ic)

donde

X^3 representa CH o N;

R^4 representa haloC_{1-4}alquil;

Y representa CH, COH o N;

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R^{14}, de manera idéntica o diferente en cada aparición, representa hidrógeno o metil;

n y p independientemente representan 1 ó 2;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S;

un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O N o S; o

un sistema de anillos heteroaril de 9 ó 10 miembros bicíclico que comprende 1, 2, 3, 4 ó 5 heteroátomos independientemente seleccionados de O, N o S;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el

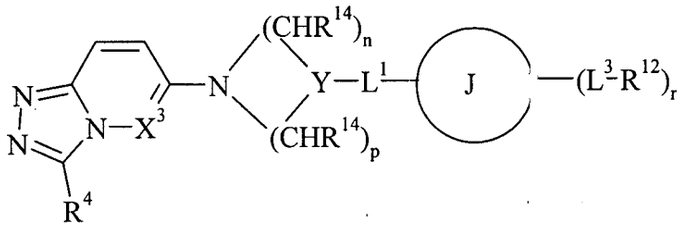
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anillo heterocíclico está opcionalmente sustituido por ., 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o –C(O)$NR^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil; y

r representa 0, 1, 2 ó 3.

De acuerdo con un quinto aspecto de la presente invención se proporciona un compuesto de Fórmula (Ic), o una sal farmacéuticamente aceptable del mismo, para su uso en el tratamiento del cáncer de próstata:



(Ic)

donde

X^3 representa CH o N;

R^4 representa haloC_{1-4}alquil;

Y representa CH, COH o N;

R^{14}, de manera idéntica o diferente en cada aparición, representa hidrógeno o metil;

n y p independientemente representan 1 ó 2;

L^1 representa un enlace directo, -$(CR^9R^{10})_t$-, -$(CR^9R^{10})_v$-O-$(CR^9R^{10})_v$-, –$N(R^{11})$-$(CH_2)_q$-, -S-, -S(O)- o –$S(O)_2$-;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S;

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un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S; o

un sistema de anillos heteroaril de 9 ó 10 miembros bicíclico que comprende 1, 2, 3, 4 ó 5 heteroátomos independientemente seleccionados de O, N o S;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

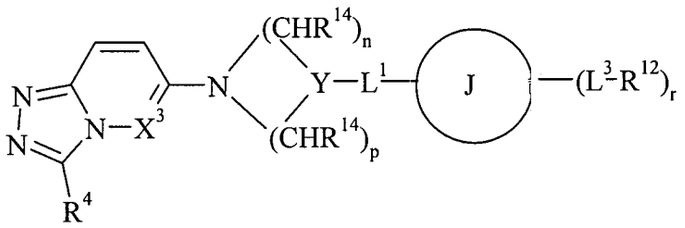
un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o $-C(O)NR^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil; y

r representa 0, 1, 2 ó 3.

De acuerdo con un sexto aspecto de la presente invención se proporciona un compuesto de Fórmula (Ic), o una sal farmacéuticamente aceptable del mismo:



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(Ic)

donde

X^3 representa CH o N;

R^4 representa halo C_{1-4}alquil;

Y representa CH, COH o N;

R^{14}, de manera idéntica o diferente en cada aparición, representa hidrógeno o metil;

n y p independientemente representan 1 ó 2;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

furanil, imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro-2*H*-piranil, pirazolil, piridazinil, piridinil, pirrolil o tiadiazolil; o

un sistema de anillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno, 1 ó 2 átomos de oxígeno, 1 átomo de azufre, o 1 átomo de nitrógeno y 1 átomo de azufre;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N-C_{1-4}alquilamino o N,N-di-C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S, y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monoc clico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados d e O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó l sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquir il, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alqu ilsulfonil, N-C_{1-4}alquilamino, N,N-di-C_{1-4}alquilamino o $-C(O)NR^{14}R^{15}$ londe R^{14} y R^{15} independientemente representan hidrógeno o metil;

r representa 1, 2 ó 3 cuando J representa aril;

r representa 0 cuando J representa un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado; y

r representa 0, 1, 2 ó 3 cuando J representa furanil, imid azolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro-2*H* piranil, pirazolil, piridazinil, piridinyl, pirrolil, tiadiazolil, o un sistema de anillos het eroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno, 1 ó 2 átomos de oxígeno, 1 átomo de azufre, o 1 átomo de nitrógeno y 1 átomo de a zufre;

con la condición de que el compuesto de Fórmula (Ic) sea dis into de:

4-{4-[3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazin-6-il]pip erazin-1-il}fenol;

6-[4-(piridin-3-ilmetil)piperazin-1-il]-3-(trifluorometil)[1,2,4] triazolo[4,3-*b*]piridazina;

6-[4-(2-fluorobencil)piperazin-1-il]-3-(trifluorometil)[1,2,4]tr iazolo[4,3-*b*]piridazina;

6-[4-(imidazo[1,2-*a*]piridin-2-ilmetil)piperazin-1-il]-3-(triflu orometil)[1,2,4]triazolo[4,3-*b*]piridazina;

6-[4-(3,4-dimetoxibencil)piperazin-1-il]-3-(trifluorometil)[1,2 ,4]triazolo[4,3-*b*]piridazina;

6-[4-(1*H*-indol-3-il)piperidin-1-il]-3-(trifluorometil)[1,2,4]tri azolo[4,3-*b*]piridazina;

6-{4-[2-(3,5-dimetoxifenil)etil]piperidin-1-il}-3-(trifluorome il)[1,2,4]triazolo[4,3-*b*]piridazina;

6-[4-(4-metoxibencil)piperazin-1-il]-3-(trifluorometil)[1,2,4]t riazolo[4,3-*b*]piridazina;

6-[4-(3-clorobencil)piperazin-1-yl]-3-(trifluorometil)[1,2,4]tr azolo[4,3-*b*]piridazina;

6-[4-(4-clorobencil)piperazin-1-yl]-3-(trifluorometil)[1,2,4]tr azolo[4,3-*b*]piridazina;

6-[4-(2-metilbencil)piperazin-1-yl]-3-(trifluorometil)[1,2,4]tr azolo[4,3-*b*]piridazina;

6-[4-(piridin-4-ilmetil)piperazin-1-il]-3-(trifluorometil)[1,2,4] triazolo[4,3-*b*]piridazina;

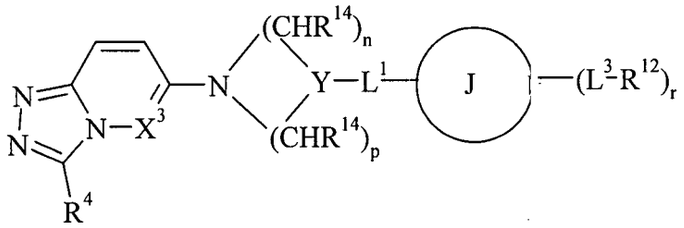
6-[4-(2,6-dimetilfenil)piperazin-1-il]-3-(trifluorometil)[1,2,4] riazolo[4,3-*b*]piridazina;

6-[4-(4-metoxifenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]tri azolo[4,3-*b*]piridazina;

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6-[4-(3-clorofenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina;
6-[4-(4-fluorofenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina; o
6-{4-[(2,6-difluorofenil)sulfonil]piperazin-1-il}-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina.

De acuerdo con una realización del sexto aspecto de la presente invención se estipula un compuesto de Fórmula (Ic) o una sal farmacéuticamente aceptable del mismo:



(Ic)

donde

X^3 representa CH o N;

R^4 representa difluorometil, trifluorometil o cloro(difluoro)metil;

Y representa CH, COH o N;

R^{14}, de manera idéntica o diferente en cada aparición, representa hidrógeno o metil;

n y p independientemente representan 1 ó 2;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ o $-N(R^{11})-(CH_2)_q-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ o $-N(R^{11})-(CH_2)_q-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q representa 0, 1, 2 ó 3;

t representa 1 ó 2;

v representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro–2*H*–piranil, pirazolil, piridazinil, piridinil;

un sistema de anillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno o un átomo de azufre simple;

L^3 representa un enlace directo, $-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$,

$-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-$, $-O-(CH_2)_q-C(O)NR^{11}-$, $-S-$, $-S(O)-$ o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino; un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o $-C(O)NR^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil;

r representa 1, 2 ó 3 cuando J representa aril;

r representa 0 cuando J representa un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado; y

r representa 0, 1, 2 ó 3 cuando J representa imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro–2*H*–piranil, pirazolil, piridazinil, piridinil o un sistema de anillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno o un átomo de azufre simple;

con la condición de que el compuesto de Fórmula (Ic) sea distinto de:

4–{4–[3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazin–6–il]piperazin–1–il}fenol;

6–[4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(2–fluorobencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(imidazo[1,2–*a*]piridin–2–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(3,4–dimetoxibencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

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6–[4–(1*H*–indol–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–{4–[2–(3,5–dimetoxifenil)etil]piperidin–1–il}–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(4–metoxibencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(3–clorobencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(4–clorobencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(2–metilbencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

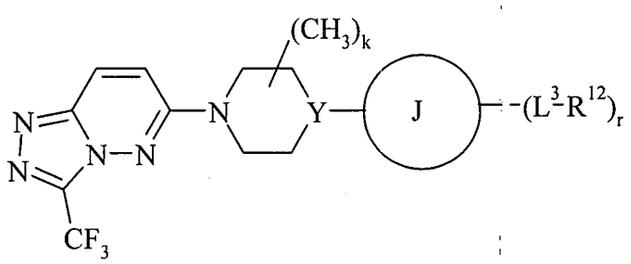
6–[4–(piridin–4–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(2,6–dimetilfenil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(4–metoxifenil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina; o

6–[4–(3–clorofenil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina.

De acuerdo con otra realización del sexto aspecto de la presente invención se proporciona un compuesto de Fórmula (If) o una sal farmacéuticamente aceptable del mismo:



(If)

donde

Y representa CH, COH o N;

k representa 0, 1 ó 2;

J representa:

arilo;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

furanilo, imidazolilo, isotiazolilo, morfolinilo, oxadiazolilo, oxazolilo, isoxazolilo, oxetanilo, tetrahidro-2*H*-piranilo, pirazolilo, piridazinilo, piridinilo, pirrolilo o tiadiazolilo; o

un sistema de anillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno, 1 ó 2 átomos de oxígeno, 1 átomo de azufre o 1 átomo de nitrógeno y 1 átomo de azufre;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metilo;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

R^{11} representa hidrógeno o metilo;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, fluoroC_{1-6}alquil, hidroxi, amino, N-C_{1-4}alquilamino o N,N-di-C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido con 1, 2 ó 3 sustituyentes seleccionados de R^{13};

un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O N o S y donde el anillo heteroaril está opcionalmente sustituido con 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos seleccionados independientemente de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido con 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N-C_{1-4}alquilamino, N,N-di-C_{1-4}alquilamino o $-C(O)NR^{14}R^{15}$, donde R^{14} y R^{15} independientemente representan hidrógeno o metilo;

r representa 1, 2 ó 3 cuando J representa arilo;

r representa 0 cuando J representa un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado; y

r representa 0, 1, 2 ó 3 cuando J representa furanil, imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro-2*H*-piranil, pirazolil, piridazinil, piridinil, pirrolil, tiadiazolil o un sistema de anillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno, 1 ó 2 átomos de oxígeno, 1 átomo de azufre o 1 átomo de nitrógeno y 1 átomo de azufre;

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siempre que el compuesto de Fórmula (If) no sea:

4-{4-[3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazin-6-il]piperazin-1-il}fenol;

6-[4-(1*H*-indol-3-il)piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina;

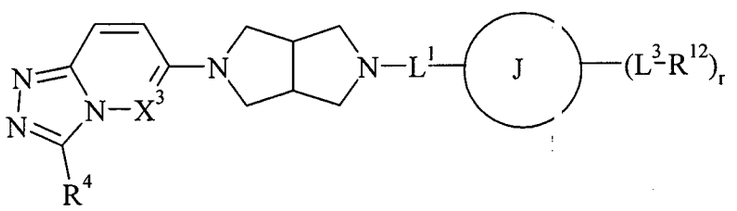
6-[4-(2,6-dimetilfenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina;

6-[4-(4-metoxifenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina;

6-[4-(3-clorofenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina; o

6-[4-(4-fluorofenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina.

De acuerdo con un séptimo aspecto de la presente invención se proporciona un compuesto de Fórmula (Id), o una sal farmacéuticamente aceptable del mismo:



(Id)

donde

X^3 representa CH o N;

R^4 representa haloC_{1-4}alquil;

L^1 representa un enlace directo, -$(CR^9R^{10})_t$-, -$(CR^9R^{10})_v$-O-$(CR^9R^{10})_v$-, –$N(R^{11})$-$(CH_2)_q$-, -S-, -S(O)- o –$S(O)_2$-;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S;

un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S; o

un sistema de anillos heteroaril de 9 ó 10 miembros bicíclico que comprende 1, 2, 3, 4 ó 5 heteroátomos independientemente seleccionados de O, N o S;

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L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o $-C(O)NR^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil; y

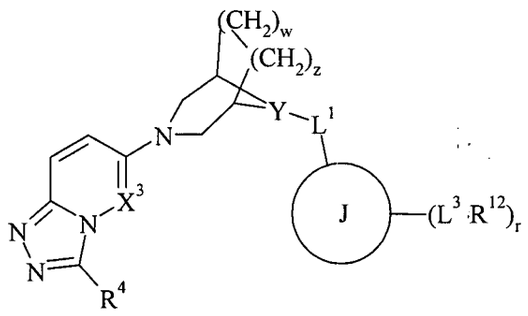
r representa 0, 1, 2 ó 3.

De acuerdo con un octavo aspecto de la presente invención se proporciona un compuesto de Fórmula (Id) como el definido aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, para su uso como un medicamento.

De acuerdo con un noveno aspecto de la presente invención se proporciona un compuesto de Fórmula (Id) como el definido aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, para su uso en el tratamiento del cáncer de próstata.

De acuerdo con un décimo aspecto de la presente invención se proporciona un compuesto de Fórmula (Ie), o una sal farmacéuticamente aceptable del mismo:

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(Ie)

donde

X^3 representa CH o N;

R^4 representa haloC_{1-4}alquil;

Y representa CH, COH o N;

w y z independientemente representan 0 ó 1;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S;

un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S; o

un sistema de anillos heteroaril de 9 ó 10 miembros bicíclico que comprende 1, 2, 3, 4 ó 5 heteroátomos independientemente seleccionados de O, N o S;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

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halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino; aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o –C(O)N$R^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil; y

r representa 0, 1, 2 ó 3.

De acuerdo con un décimo primer aspecto de la presente invención se proporciona un compuesto de Fórmula (Ie) como el definido aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, para su uso como un medicamento.

De acuerdo con un décimo segundo aspecto de la presente invención se proporciona un compuesto de Fórmula (Ie) como el definido aquí anteriormente, o una sal farmacéuticamente aceptable del mismo, para su uso en el tratamiento del cáncer de próstata.

En realizaciones adicionales del cuarto, quinto, sexto, séptimo, octavo, noveno, décimo, décimo primer y décimo segundo aspectos de la presente invención, cada uno de las siguientes definiciones de J, L^1, L^3, n, p, r, w, z, R^4, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, X^3 y Y en los párrafos (1) a (61) de aquí en adelante pueden ser usadas individualmente o en combinación con una o más de las siguientes otras definiciones para limitar las definiciones más amplias de las Fórmulas (Ic), (Id), (Ie) o (If).

(1) X^3 representa N;

(2) X^3 representa CH;

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(3) R^4 representa difluorometil, trifluorometil, cloro(difluoro)metil, difluoroetil o difluoropropil;

(4) R^4 representa difluorometil, trifluorometil o cloro(difluoro)metil;

(5) R^4 representa difluorometil

(6) R^4 representa trifluorometil;

(7) R^4 representa cloro(difluoro)metil;

(8) R^{14} representa hidrógeno;

(9) n y p ambos representan 2;

(10) n y p ambos representan 1;

(11) Y representa CH o COH;

(12) Y representa CH

(13) Y representa COH;

(14) Y representa N;

(15) L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_t-O-(CR^9R^{10})_v-$ o $-N(R^{11})-(CH_2)_q-$;

(16) L^1 representa un enlace directo, $-CH_2-$, $-CH(CH_3)-$ o –O-;

(17) L^1 representa un enlace directo;

(18) L^1 representa $-CH_2-$;

(19) J representa fenil, piridinil, indolil, indazolil o pirrolopiridinil;

(20) J representa fenil;

(21) J representa piridinil;

(22) J representa piridin-3-il;

(23) L^3 representa un enlace directo;

(24) L^3 representa un enlace directo, $-(CR^9R^{10})_+-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$ o $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$;

(25) L^3 representa $-(CR^9R^{10})_+-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$ o $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$;

(26) L^3 representa $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$ o $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$;

(27) L^3 representa $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $C(O)-(CH_2)_q-$ o $-O-(CH_2)_q-$;

(28) L^3 representa un enlace directo, $-C(O)N(R^{11})-(CH_2)_q-$ o $-O-(CH_2)_q-$;

(29) L^3 representa $-C(O)N(R^{11})-(CH_2)_q-$ o $-O-(CH_2)_q-$;

(30) L^3 representa $-O-(CH_2)_q-$;

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(31) L^3 representa -O-CH_2-CH_2-;

(32) R^9 y R^{10} representan hidrógeno;

(33) R^{11} representa hidrógeno;

(34) R^{11} representa metil;

(35) q representa 0, 1 o 2;

(36) R^{12} representa fluoro, cloro, metil, metoxi, difluorometil, trifluorometil, ciano, hidroxi, imidazolil, pirrolidinil, piperidinil, metilsulfonil, morfolinil, pirazolil o fenil;

(37) R^{12} representa fluoro, cloro, metil, metoxi, difluorometil, trifluorometil, hidroxi, imidazolil, pirrolidinil, piperidinil, metilsulfonil, morfolinil, pirazolil o fenil;

(38) R^{12} representa fluoro, cloro, metil, metoxi, difluorometil, trifluorometil, ciano, hidroxi, metilsulfonil, dimetilamino, pirrolidinil, piperidinil, piperazinil, morfolinil o pirazolil;

(39) R^{12} representa fluoro, cloro, metil, metoxi, difluorometil, trifluorometil, hidroxi, metilsulfonil, dimetilamino, pirrolidinil, piperidinil, piperazinil, morfolinil o pirazolil;

(40) R^{12} representa fluoro, cloro, metil, metoxi, difluorometil, trifluorometil, ciano o hidroxi;

(41) R^{12} representa fluoro, cloro, metil, metoxi, difluorometil, trifluorometil o hidroxi;

(42) R^{12} representa pirrolidinil, piperidinil, metilsulfonil, morfolinil o pirazolil;

(43) R^{12} representa pirazolil;

(44) R^{12} representa pirazol-5-il;

(45) R^{12} representa 1-metil-1H-pirazol-5-il

(46) r representa 1 ó 2 cuando J representa aril;

(47) r representa 1 cuando J representa aril;

(48) r representa 0 ó 1 cuando J representa imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolyl, isoxazolil, oxetanil, tetrahidro-2*H*-piranil, pirazolil, piridazinil, piridinil o un sistema debanillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno o un átomo de azufre simple;

(49) r representa 1 cuando J representa imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro-2*H*-piranil, pirazolil, piridazinil, piridinil o un sistema debanillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno o un átomo de azufre simple;

(50) r representa 0 cuando J representa imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro-2*H*-piranil, pirazolil, piridazinil, piridinil o o un sistema debanillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno o un átomo de azufre simple;

(51) r representa 1 cuando J representa pirazolil;

(52) L^3 representa -O-CH_2-CH_2-, R^{12} representa 1-metil-1H-pirazol-5-il y r representa 1;

(53) R^{13} representa metil, metoxi, oxo, hidroxi, ciano, acetil o metilsulfonil;

(54) R^{13} representa metil, metoxi, oxo, hidroxi, acetil o metilsulfonil;

(55) R^{13} representa metil, oxo o hidroxi;

(56) R^{13} representa metil;

(57) k representa 0;

(58) k representa 1;

(59) k representa 2;

(60) w y z ambos representan 1;

(61) w y z ambos representan 0.

Compuestos particularmente novedosos de Fórmula (I) incluyen, pero no están limitados a, los siguientes compuestos:

4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo;

3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina;

4–piridin–3–il–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol;

3–(difluorometil)–6–{4–[(1R)–1–(4–fluorofenil)etil]piperazin–1–il}[1,2,4]triazolo[4,3–b]piridazina;

4–(4–fluorofenil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol;

N–(2–metoxietil)–N–metil–4–{1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il}benzamida;

N–(2–hidroxietil)–N–metil–4–{1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il}benzamida;

6–(4–{4–[(4–metilpiperazin–1–il)carbonil]fenil}piperidin–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina;

N–[2–(2–oxopirrolidin–1–il)etil]–4–{1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il}benzamida;

6–[4–(1H–indazol–3–ilmetil)piperazin–1–il]–3–(trifluorometi)[1,2,4]triazolo[4,3–b]piridazina;

N–(2–metoxietil)–N–metil–3–({1–[3–(trifluorometil)[1,2,4]tr azolo[4,3–b]piridazin–6–il]piperidin–4–il}oxi)benzamida;

2–morfolin–4–il–N–(4–{1–[3–(trifluorometil)[1,2,4]triazolo[4 ,3–b]piridazin–6–il]piperidin–4–il}fenil)acetamida;

6–(4–{4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil}piperidin– –il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina;

6–{4–[2–(difluorometil)–5–fluorobencil]piperazin–1–il}–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina;

6–{4–[(6–metilpiridin–3–il)metil]piperazin–1–il}–3–(trifluor metil)[1,2,4]triazolo[4,3–b]piridazina;

6–[4–(1H–pirrolo[2,3–b]piridin–3–il)piperidin–1–il]–3–(triflu orometil)[1,2,4]triazolo[4,3–b]piridazina;

6–[4–(5–metoxi–1H–indol–3–il)piperidin–1–il]–3–(trifluoron etil)[1,2,4]triazolo[4,3–b]piridazina;

1–[(4–{1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6 -il]piperidin–4–il}fenil)carbonil]piperidin–4–ol;

N–metil–N–[2–(metilsulfonil)etil]–4–{1–[3–(trifluorometil)[1 ,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il}benzamida;

6–[3–(4–metoxifenoxi)azetidin–1–il]–3–(trifluorometil)[1,2,4 triazolo[4,3–b]piridazina;

6–(4–{4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil}piperazin– 1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina; y

4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]-1-[3-(trifluorome il)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol;

y sales farmacéuticamente aceptables de los mismos.

Las formas cristalinas de compuestos nuevos particula es de Fórmula (Ic) y una sal particular de estos también han sido identificadas.

De acuerdo con la presente invención se proporciona, por lo tanto, una forma cristalina de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con al menos un pico específico para un valor 2θ de aproximadamente 9.18°, 15.51°, 16.01°, 18.94° ó 24.59° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de más o menos 5° 2θ.

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De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de aproximadamente 9.18°, 15.51° 16.01°, 18.94° y 24.59° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de 8.30, 9.18, 9.96, 10.41, 14.35, 15.02, 15.51, 16.01, 17.03, 18.46, 18.94, 19.18, 19.82, 20.35, 20.61, 21.80, 22.65, 23.38, 24.15, 24.59, 25.43, 26.12, 26.35, 26.59, 27.43, 29.38, 31.83 y 37.33° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo que es sustancialmente igual al patrón de difracción de rayos X mostrado en la Figura 1 cuando se mide utilizando radiación CuKa.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con al menos un pico específico para un valor 2θ de aproximadamente 12.34°, 15.78°, 20.42°, 23.75° ó 24.73° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de aproximadamente 12.34°, 15.78°, 20.42°, 23.75° y 24.73° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de 6.23, 7.92, 9.65, 12.34, 12.69,

14.92, 15.78, 16.89, 18.78, 19.28, 20.42, 20.99, 21.57, 22.49, 23.31, 23.75, 24.34, 24.73, 25.38, 26.93, 28.14, 29.08, 31.16, 31.86, 32.50, 33.14, 34.79, 36.34, 36.78, 38.01 y 38.64° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo que es sustancialmente igual al patrón de difracción de rayos X mostrado en la Figura 2 cuando se mide utilizando radiación CuKa.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con al menos un pico específico para un valor 2θ de aproximadamente 4.90°, 13.47°, 15.93°, 16.64° ó 22.83° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de aproximadamente 4.90°, 13.47°, 15.93°, 16.64° y 22.83° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidra A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de 4.90, 9.784, 11.50, 11.94, 12.97, 13.47, 14.72, 15.93, 16.64, 17.36, 18.32, 18.67, 19.195, 19.67, 20.26, 20.58, 20.87, 21.33, 21.64, 22.83, 23.7, 24, 24.40, 25.99, 26.75, 27.15, 28.10, 28.55, 29.02, 29.46, 29.74, 30.12, 30.65, 31.37, 31.85, 33.66, 34.28, 35.85, 36.42, 37.62 y 38.53° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-

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(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidrato A, la cual tiene un patrón de difracción de rayos X en polvo que es sustancialmente igual al patrón de difracción de rayos X mostrado en la Figura 3 cuando se mide utilizando radiación CuKa.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidrato A, la cual tiene un patrón de difracción de rayos X en polvo con al menos un pico específico para un valor 2θ de aproximadamente 6.90°, 15.38°, 21.55°, 24.48° ó 27.56° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidrato A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de aproximadamente 6.90°, 15.38°, 21.55°, 24.48° y 27.56° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidrato A, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de 6.90, 9.6, 10.78, 12.82, 13.16, 13.85, 14.44, 15.38, 16.44, 17.46, 18.25, 18.92, 19.27, 20.18, 21.03, 21.55, 22.36, 22.63, 23.55, 23.76, 24.48, 25.2, 25.76, 26.47, 27.56, 27.83, 28.21, 29.10, 29.93, 30.59, 31.20, 32.49, 33.33, 34.04, 34.62, 36.18, 36.54, 37.45, 38.17 y 39.32° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de mas o menos 0.5° 2θ.

De acuerdo con la presente invención se estipula, por lo tanto, una forma cristalina de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, Forma Anhidrato A, la cual tiene un patrón de difracción de rayos X en polvo que es sustancialmente igual al patrón de difracción de rayos X mostrado en la Figura 4 cuando se mide utilizando radiación CuKa.

De acuerdo con la presente invención se proporciona, por lo tanto, una forma cristalina del fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, la cual tiene un patrón de difracción de

rayos X en polvo con al menos un pico específico para un valor 2θ de aproximadamente 11.72°, 16.46°, 17.58° o 21.89° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de más o menos 0.5° 2θ.

De acuerdo con la presente invención se proporciona, por lo tanto, una forma cristalina del fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de aproximadamente 11.72°, 16.46°, 17.58° y 21.89° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de más o menos 0.5° 2θ.

De acuerdo con la presente invención se proporciona, por lo tanto, una forma cristalina del fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina, la cual tiene un patrón de difracción de rayos X en polvo con picos específicos para valores 2θ de 4.5, 5.90, 11.72, 12.22, 13.23, 16.46, 17.58, 19.74, 20.26, 21.18, 21.89, 23.86, 24.17, 25.83, 26.75, 28.78, 30.54 y 31.51° cuando se mide utilizando radiación CuKa , más particularmente cuando dichos valores puedan ser de más o menos 0.5° 2θ.

De acuerdo con la presente invención se proporciona, por lo tanto, una forma cristalina del fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina la cual tiene un patrón de difracción de rayos X en polvo que es sustancialmente igual al patrón de difracción de rayos X en polvo mostrado en la Figura 5 cuando se mide utilizando radiación CuKa.

La referencia aquí a un compuesto de Fórmula (I) debe ser entendido que se refiere igualmente a un compuesto de Fórmula (Ic), (Id), (Ie) e (If).

Una sal farmacéuticamente aceptable adecuada de un compuesto de Fórmula (I) es, por ejemplo, una sal de adición ácida de un compuesto de Fórmula I, por ejemplo una sal de adición ácida con un ácido orgánico o inorgánico tal como ácido clorhídrico, bromhídrico, sulfúrico, trifluoroacético, cítrico o maleico; o, por ejemplo, una sal de un compuesto de Fórmula I el cual es suficientemente acídico, por ejemplo una sal de metal alcalino o alcalino térreo tal como una sal de calcio o magnesio, o una sal de amonio, o una sal con una base orgánica tal como metilamina, dimetilamina, trimetilamina, piperidina, morfolina o tris–(2–hidroxietil)amina. Una sal farmacéuticamente aceptable adecuada adicional de un compuesto de Fórmula I es, por ejemplo, una sal formada dentro del cuerpo humano o animal después de la administración de un compuesto de Fórmula I.

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Un solvato farmacéuticamente aceptable adecuado de un compuesto de Fórmula I es, por ejemplo, una hidrato tal como un semihidrato, un monohidrato, un dihidrato o un trihidrato o una cantidad alternativa del mismo.

Los compuestos de la invención pueden ser administrados en la forma de un profármaco, esto es un compuesto que se rompe en el cuerpo humano o animal para liberar un compuesto de la invención. Un profármaco puede ser usado para alterar las propiedades físicas y/o propiedades farmacocinéticas de un compuesto de la invención. Un profármaco puede formarse cuando el compuesto de la invención contiene un grupo o sustituyente adecuado al cual un grupo que modifica las propiedades puede estar unido. Ejemplos de profármacos incluyen derivados de ésteres escindibles *in vivo* que pueden ser formados en un grupo carboxi o un grupo hidroxi en un compuesto de Fórmula I y derivados de amidas escindibles *in vivo* que pueden ser formados en un grupo carboxi o un grupo amino en un compuesto de Fórmula I.

Por consiguiente, la presente invención incluye aquellos compuestos de Fórmula I como los definidos aquí anteriormente cuando se hacen disponibles por síntesis orgánica y cuando se hacen disponibles dentro del cuerpo humano o animal por medio de la escisión de un profármaco del mismo. Por consiguiente, la presente invención incluye aquellos compuestos de Fórmula I que son producidos por medios de síntesis orgánica y también compuestos tales que son producidos en el cuerpo humano o animal por medio del metabolismo de un compuesto precursor, es decir un compuesto de Fórmula I puede ser un compuesto sintéticamente producido o un compuesto metabólicamente producido.

Un profármaco farmacéuticamente aceptable adecuado de un compuesto de Fórmula I es uno que está basado en un veredicto médico razonable como siendo adecuado para la administración al cuerpo humano o animal sin actividades farmacológicas indeseables y sin toxicidad indebida.

Varias formas de profármacos han sido descritas, por ejemplo en los siguientes documentos :

a) Methods in Enzymology, Vol. 42, p. 309–396, editado por K. Widder y otros (Academic Press, 1985);

b) Design of Pro-Drugs, editado por H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, editado por Krogsgaard–Larsen y H. Bundgaard, Capítulo 5 "Design and Application of Pro-Drugs", de H. Bundgaard p. 113–191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1–38 (1992);

e) H. Bundgaard y otros, Journal of Pharmaceutical Sciences, 77, 285 (1988);

f) N. Kakeya y otros, Chem. Pharm. Bull., 32, 692 (1984);

g) T. Higuchi y V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium Series, Volumen 14; y

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

Un profármaco farmacéuticamente aceptable adecuado de un compuesto de Fórmula (I) que posee un grupo carboxi es, por ejemplo, un éster escindible *in vivo* del mismo. Un éster escindible *in vivo* de un compuesto de Fórmula (I) que contiene un grupo carboxi es, por ejemplo, un éster farmacéuticamente aceptable el cual es escindido en el cuerpo humano o animal para producir el ácido original. Ésteres farmacéuticamente aceptables adecuados para el carboxi incluyen los C_{1-6}alquil ésteres tal como metil, etil y *tert*–butil, C_{1-6}alcoximetil ésteres tal como metoximetil ésteres, C_{1-6}alcanoiloximetil ésteres tal como pivaloiloximetil ésteres, 3–ftalidil ésteres, C_{3-8}cicloalquilcarboniloxi– C_{1-6}alquil ésteres tal como ciclopentilcarboniloximetil y 1–ciclohexilcarboniloxietil ésteres, 2–oxo–1,3–dioxolenilmetil ésteres tal como 5–metil–2–oxo–1,3–dioxolen–4–ilmetil ésteres y C_{1-6}alcoxicarboniloxi– C_{1-6}alquil ésteres tal como metoxicarboniloximetil y 1–metoxicarboniloxietil ésteres.

Un profármaco farmacéuticamente aceptable adecuado de un compuesto de Fórmula (I) que posee un grupo hidroxi es, por ejemplo, un éster escindible *in vivo* o éter del mismo.

Un éster escindible *in vivo* o éter de un compuesto de Fórmula (I) que contiene un grupo hidroxi es, por ejemplo, un éster o éter farmacéuticamente aceptable el cual es escindido en el cuerpo humano o animal para producir el compuesto hidroxi original. Éster farmacéuticamente aceptable adecuado que forma grupos para un grupo hidroxi incluye los ésteres inorgánicos tales como ésteres fosfato (incluyendo los ésteres fosforamídicos cíclicos). Otro éster farmacéuticamente aceptable adecuado que forma grupos para un grupo hidroxi incluye grupos C_{1-10}alcanoil tal como acetil, benzoil, fenilacetil y grupos fenilacetil y benzoil sustituidos, grupos C_{1-10}alcoxicarbonil tal como etoxicarbonil, grupos *N*,*N*–[di–C_{1-4}alquil]carbamoil, 2–dialquilaminoacetil y 2–carboxiacetil. Ejemplos de sustituyentes del anillo en los grupos fenilacetil y benzoil incluyen aminometil, *N*–alquilaminometil, *N*,*N*–dialquilaminometil, morfolinometil, piperazin–1–ilmetil y 4–C_{1-4}alquilpiperazin–1–ilmetil. Grupos que forman éter farmacéuticamente aceptable adecuados para un grupo hidroxi incluyen grupos α–aciloxialquil tal como acetoximetil y pivaloiloximetil grupos.

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Un profármaco farmacéuticamente aceptable adecuado de un compuesto de Fórmula (I) que posee un grupo carboxi es, por ejemplo, una amida escindible *in vivo* del mismo, por ejemplo una amida formada con una amina tal como amoniaco, una C_{1-4}alquilamina tal como metilamina, una di–C_{1-4}alquilamina tal como dimetilamina, *N*–etil–*N*–metilamina o dietilamina, una C_{1-4}alcoxi–C_{2-4}alquilamina tal como 2–metoxietilamina, una fenil–C_{1-4}alquilamina tal como bencilamina y aminoácidos tal como glicina o un éster del mismo.

Un profármaco farmacéuticamente aceptable adecuado de un compuesto de Fórmula (I) que posee un grupo amino es, por ejemplo, un derivado amida escindible *in vivo* del mismo. Amidas farmacéuticamente aceptables adecuadas de un grupo amino incluyen, por ejemplo una amida formada con grupos C_{1-10}alcanoil tal como un acetil, benzoil, fenilacetil y grupos fenilacetil y benzoil sustituidos. Ejemplos de sustituyentes del anillo en los grupos fenilacetil y benzoil incluyen aminometil, *N*–alquilaminometil, *N*,*N*–dialquilaminometil, morfolinometil, piperazin–1–ilmetil y 4–(C_{1-4})alquilpiperazin–1–ilmetil.

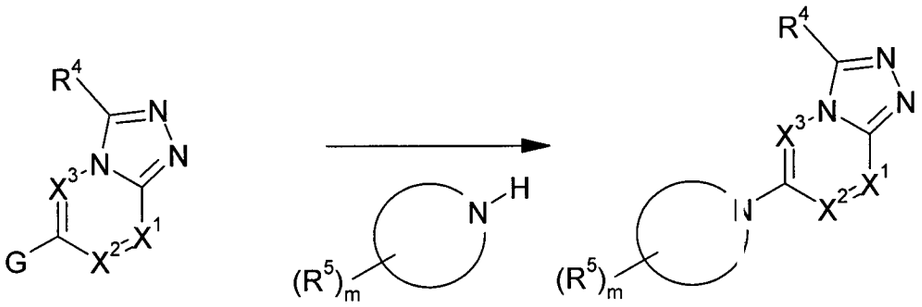
Los efectos *in vivo* de un compuesto de Fórmula (I) pueden ser ejercidos en parte por uno o más metabolitos que son formados dentro del cuerpo humano o animal después de la administración de un compuesto de Fórmula (I). Como se indicó aquí anteriormente, los efectos *in vivo* de un compuesto de Fórmula (I) también pueden ser ejercidos por medio del metabolismo de un compuesto precursor (un profármaco).

Un ejemplo de un metabolito de un compuesto de Fórmula (I) es 1-óxido de 3-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]piridina que es un metabolito de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol.

Los compuestos de Fórmula (I) pueden ser preparados por un proceso que comprende un paso seleccionado de (1) a (10) como sigue, estos procesos son proporcionados como una característica adicional de la invención:

Preparación de los compuestos de Fórmula (I)

1. Un proceso para la fabricación de los compuestos de Fórmula (I) comprende reaccionar un compuesto de Fórmula (II), donde G es un grupo saliente tal como halógeno, alcano sulfoniloxi, o arilsulfoniloxi y R^4, X^1, X^2, y X^3 son como los definidos anteriormente, con una amina monocíclica o bicíclica de Fórmula (III), donde R^5 y m son como los definidos anteriormente.

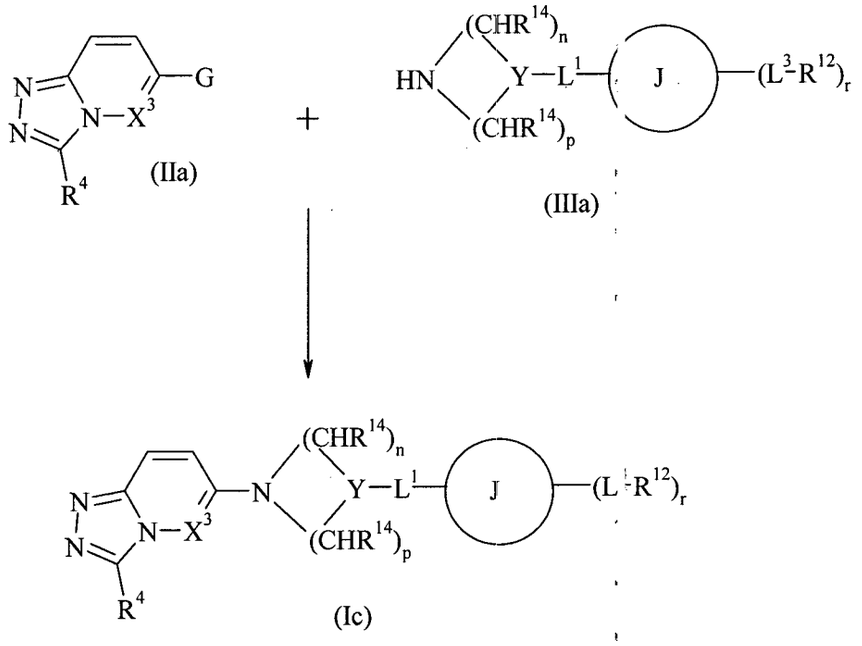


(II) (III)

La reacción puede ser llevada a cabo combinando los componentes en un solvente inerte tal como etanol, xileno, o N–metilpirrolidona a temperaturas entre 25°C y 250°C, preferiblemente entre 50°C y 150°C. La reacción puede ser ventajosamente catalizada por bases tal como bases orgánicas, por ejemplo diisopropiletilamina o por catalizadores de metal de transición de baja valencia tal como Pd(0), por ejemplo bis(dibencilidenoacetona) paladio(0). La reacción puede ser calentada por una fuente de calor convencional, tal como un baño de aceite o un bloque de calentamiento, o por calentamiento por microondas.

En una realización de la invención, se estipula un proceso para la preparación de compuestos de Fórmula (Ic) que comprende hacer reaccionar un compuesto de Fórmula (IIa), donde G es un grupo saliente adecuado tal como halógeno, por ejemplo, cloro, y R^4 y X^3 son tal como fueron definidos aquí anteriormente con relación a la Fórmula (Ic), con una amina de Fórmula (IIIa), donde J, Y, L^1, L^3, R^{12}, R^{14}, n, p y r son tal como fueron definidos aquí anteriormente en relación con la Fórmula (Ic):

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(IIa) (IIIa) (Ic)

y a partir de entonces, si fuera necesario:

(i) convertir un grupo funcional de un compuesto de la invención en otro grupo funcional;

(ii) introducir un grupo funcional nuevo en un compuesto de la invención;

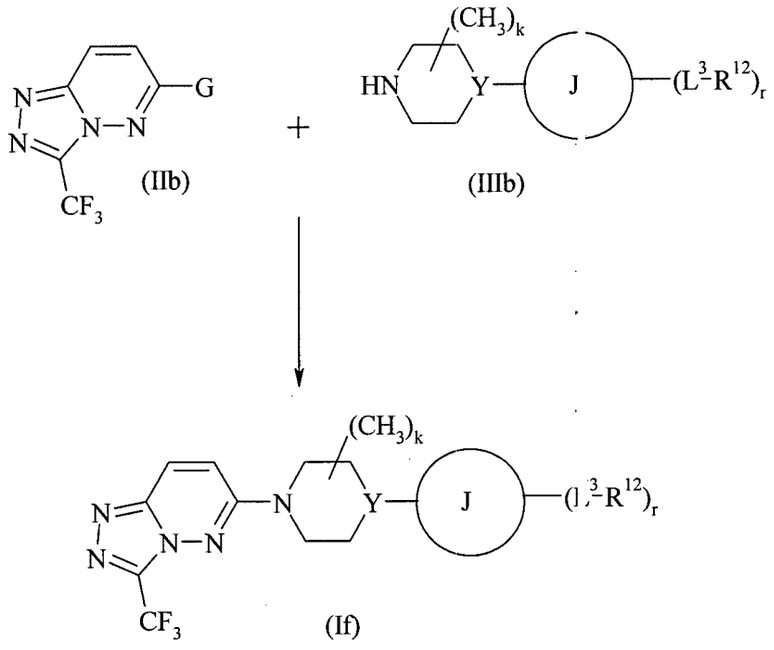
(iii) eliminar cualquiera de los grupos protectores;

(iv) para compuestos de la invención en forma de un enantiómero simple separar un compuesto racémico de la invención en enantiómeros separados;

(v) preparar una sal farmacéuticamente aceptable del mismo; y/o

(vi) preparar una forma cristalina del mismo.

En otra realización de la invención, se proporciona un proceso para la preparación de compuestos de Fórmula (If) que comprende hacer reaccionar un compuesto de Fórmula (IIb), donde G representa halógeno, con una amina de Fórmula (IIIb), donde Y, J, L^3, R^{12}, k y r son tal como fueron definidos aquí anteriormente con relación a la Fórmula (If):



y a partir de entonces, si fuera necesario:

(i) convertir un grupo funcional de un compuesto de la invención en otro grupo funcional;

(ii) introducir un nuevo grupo funcional en un compuesto de la invención;

(iii) eliminar cualquiera de los grupos protectores;

(iv) para compuestos de la invención en forma de un enantiómero simple separar un compuesto racémico de la invención en enantiómeros separados;

(v) preparar una sal farmacéuticamente aceptable del mismo; y/o

(vi) preparar una forma cristalina del mismo.

Las reacciones anteriores se pueden llevar a cabo combinando los componentes de Fórmula (IIa) y (IIIa) o (IIb) y (IIIb) en un solvente adecuado, por ejemplo, dimetilformamida o dimetilacetamida, a una temperatura adecuada, por ejemplo, entre 25°C y 250°C, más particularmente entre 50°C y 150°C, en presencia de una base adecuada, por ejemplo, diisopropiletilamina. La reacción puede ser calentada por una fuente de calor convencional, tal como un baño de aceite o un bloque de calentamiento, o mediante calentamiento por microondas.

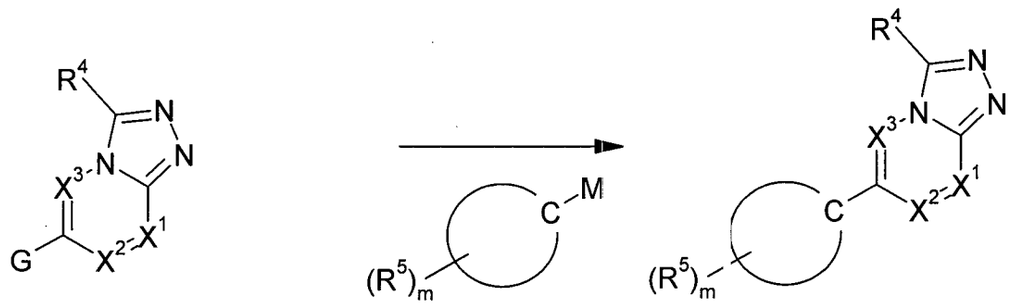
Los compuestos de Fórmula (II), (IIa) o (IIb) pueden sintetizarse por métodos bien conocidos por aquellos expertos en la materia incluyendo los métodos de acuerdo o análogos a métodos descritos en la literatura química, por ejemplo como se describió en W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Parte 1 y Parte 2, *Systems with Bridgehead Nitrogen*, Interscience, 1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27,

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Condensed Pyridazines, Wiley, 1973; y *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman y R.F. Cookson, Wiley, 1979 y las referencias ahí citadas.

Las aminas de Fórmula (III), (IIIa) o (IIIb) pueden sintetizarse por métodos bien conocidos por aquellos expertos en la materia incluyendo métodos de acuerdo a o análogos a métodos descritos en la literatura química, por ejemplo, J.R. Malpass, *Aliphatic and Cyclic Amines in Comprehensive Organic Chemistry*, Volumen 2, pág. 3, D. Barton y D. Ollis Eds, Pergamon, 1979, J.M.J. Gladych y D. Hartley, *Polyfunctional Amines in Comprehensive Organic Chemistry*, Volumen 2, pág. 61, D. Barton y D. Ollis Eds, Pergamon, 1979; *Houben–Weyl Methods of Organic Chemistry*, Vol E 23 e *Cyclic Compounds I* (1999) a Vol E 23 j *Cyclic Compounds VI* (2000) y las referencias ahí citadas y modificadas según se requiera por las transformaciones del grupo funcional bien conocidas por aquellos expertos en la materia incluyendo métodos de acuerdo a o análogos a métodos descritos en la literatura química, por ejemplo, *Comprehensive Functional Group Transformations,* A.R. Katritzky, O. Meth–Cohn y C.W. Rees Eds., Pergamon, 1995, y las referencias ahí citadas.

2. Un proceso para la fabricación de los compuestos de Fórmula (I) comprende reaccionar un compuesto de Fórmula (II), donde G es a grupo saliente tal como yoduro, bromuro, cloruro, alcanosulfoniloxi, o arilsulfoniloxi; y R^4, X^1, X^2 y X^3 son como los definidos anteriormente, con un compuesto organometálico monocíclico o bicíclico tal como un compuesto organozinc de Fórmula (IV) donde R^5 y m son como los definidos anteriormente y M es un metal adecuado tal como Zn–W donde W es uno o más ligandos inertes, tal como bromuro o yoduro.



b (II) (IV)

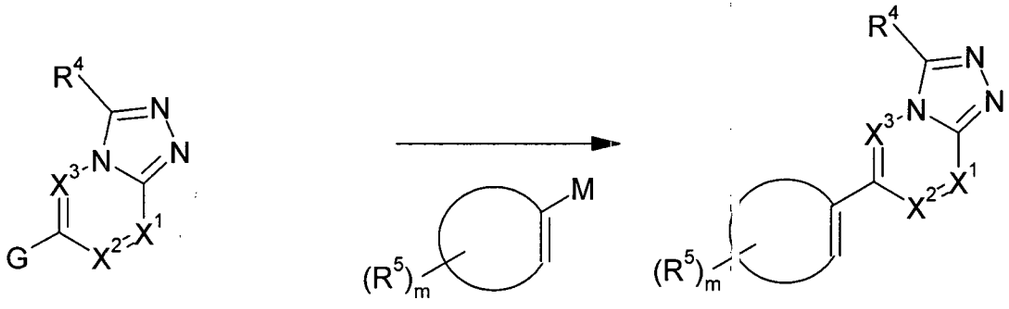
La reacción puede ser ventajosamente catalizada por catalizadores de metal de transición de baja valencia tal como Pd(0), por ejemplo, dicloruro de bis(difenilfosfinoferroceno)paladio(II) (dppf). La reacción puede ser llevada a cabo combinando los componentes en un solvente inerte tal como xileno o tetrahidrofurano a

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temperaturas entre 0°C y 150°C, preferiblemente entre 25°C y 100°C. La reacción puede ser calentada por una fuente de calor convencional, tal como un baño de aceite o un bloque de calentamiento, o por calentamiento por microondas.

Los reactivos organometálicos de Fórmula (IV) pueden sintetizarse por métodos bien conocidos por aquellos expertos en la materia incluyendo métodos de acuerdo a o análogos a métodos descritos en la literatura química, por ejemplo, E. Nakamura, *Organozinc Chemistry* p590 *in Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002 y las referencias ahí citadas.

3. Un proceso para la fabricación de los compuestos de Fórmula (I) comprende reaccionar un compuesto de Fórmula (II), donde G es un grupo saliente tal como yoduro, bromuro, cloruro, alcanosulfoniloxi o arilsulfoniloxi, y R^4, X^1, X^2 y X^3 son como los definidos anteriormente, con un compuesto organometálico monocíclico o bicíclico tal como un compuesto organoborano de Fórmula (V) donde M es un residuo organometálico tal como $B(OH)_2$ y donde R^5 y m son como los definidos anteriormente.



(II) (V)

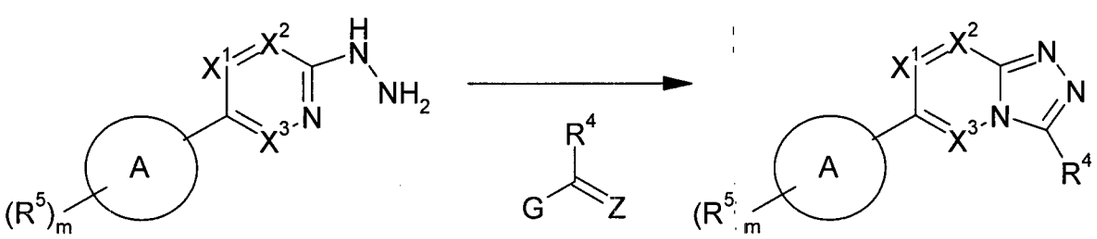
En cambio, M es un grupo saliente tal como yoduro, bromuro, cloruro, alcanosulfoniloxi, o arilsulfoniloxi, y R^4, X^1, X^2 y X^3 son como los definidos anteriormente y G es un compuesto organometálico tal como un organoestannano y donde R^5 y m son como los definidos anteriormente.

La reacción puede ser ventajosamente catalizada por catalizadores de metal de transición de baja valencia tal como Pd(0), por ejemplo, bis(dibencilidenoacetona)paladio/trifenilarsina. La reacción puede ser llevada a cabo combinando los componentes en un solvente inerte tal como xileno o tetrahidrofurano o N–metilpirrolidona a temperaturas entre 0°C y 150°C, preferiblemente entre 25°C y 100°C. La reacción puede ser calentada por una fuente de calor convencional, tal como un baño de aceite o un bloque de calentamiento, o por calentamiento por microondas.

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Para detalles adicionales de tales reacciones de acoplamiento ver, por ejemplo, *Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002, y las referencias ahí citadas. Los reactivos organometálicos de Fórmula (V) pueden sintetizarse por métodos bien conocidos por aquellos expertos en la materia incluyendo métodos de acuerdo a o análogos a métodos descritos en la literatura química, por ejemplo, *Comprehensive Organometallic Chemistry*, G. Wilkinson y F.G.A. Stone, Eds., Pergamon, 1982, y *Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002, y las referencias ahí citadas.

4. Un proceso para la fabricación de los compuestos de Fórmula (I) comprende reaccionar un compuesto de Fórmula VI con un agente de acilación, tal como un ácido carboxílico o un derivado reactivo del mismo donde R^4, X^1, X^2, X^3, R^5 y m son como los definidos anteriormente. Reactivos de acilación adecuados RC(=O)(Z)G son, por ejemplo, derivados de ácido carboxílico donde G = es seleccionado de Cl, O–C(=O)R, O–Alquil, S–Alquil y Z es seleccionado de O, S, N–Alquil o N–Aril, o donde Z y G tomados junto con el átomo de carbono al cual están unidos forman un nitrilo o un ortoéster o una ortoamida.



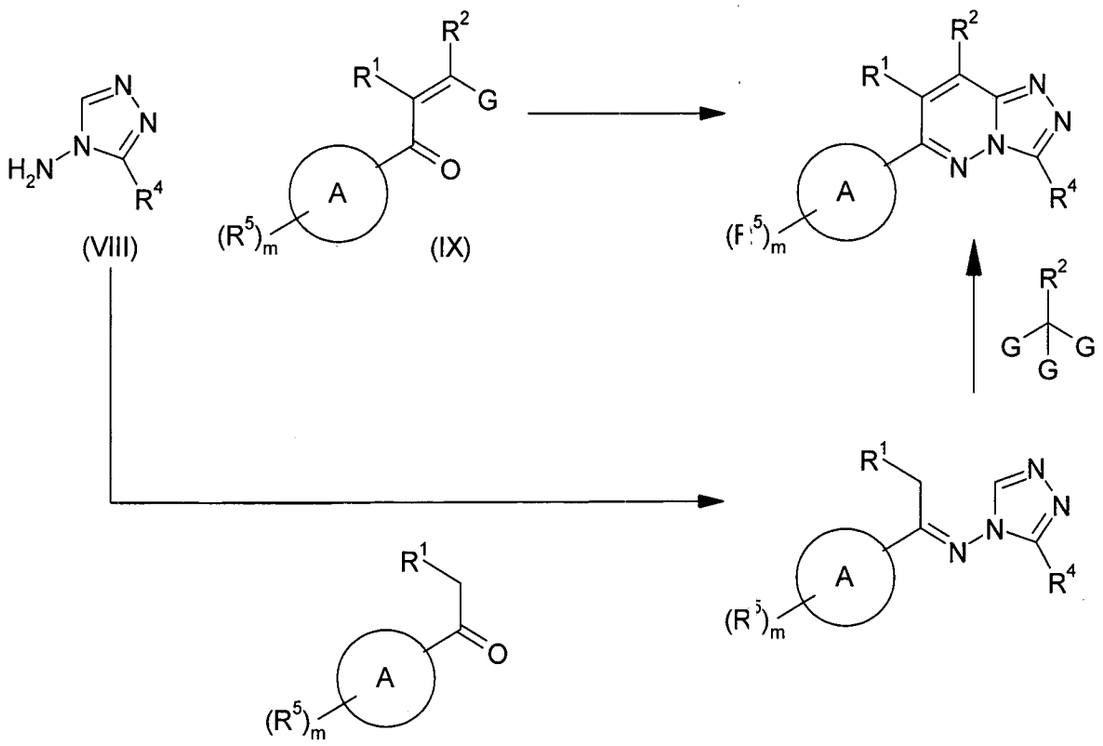
(VI) (VII)

La reacción puede ser llevada a cabo combinando los componentes en ausencia de un solvente o en un solvente inerte tal como orto–diclorobenceno a temperaturas entre 25°C y 250°C, preferiblemente entre 50°C y 150°C. La reacción puede ser calentada con una fuente de calor convencional, tal como un baño de aceite o un bloque de calentamiento, o por calentamiento por microondas.

Los compuestos de Fórmula (VI) pueden sintetizarse por métodos bien conocidos por aquellos expertos en la materia incluyendo los métodos de acuerdo o análogos a métodos descritos en la literatura química, por ejemplo, como se describió en W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Parte 1 y Parte 2, *Systems with Bridgehead Nitrogen*, Interscience, 1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; y *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman y R.F. Cookson, Wiley, 1979 y las referencias ahí citadas.

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5. Un proceso para la fabricación de los compuestos de Fórmula (I) ,donde X^1 y X^2 son $C(R^1)$ y $C(R^2)$ respectivamente y X^3 es nitrógeno, comprende reaccionar un N–amino–1,2,4–triazol (VIII) donde R^4 es como el definido anteriormente con una cetona no saturada o éster no saturado (IX) donde G es un grupo saliente tal como alcoxi o dialquilamino y R^1, R^2, R^5 y m son como los definidos anteriormente.



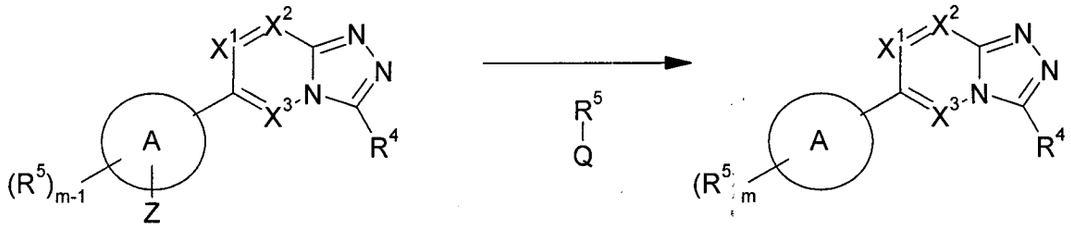
La reacción puede ser llevada a cabo en uno o dos pasos como es mostrado y el último paso tiene lugar en un solvente tal como ácido acético a temperaturas entre 25°C y 250°C, preferiblemente entre 50°C y 150°C ,por ejemplo, de acuerdo a procedimiento de D.F. Lieberman y J.D. Albright, *J. Het. Chem.*, **1988**, 827.

Otros procesos relacionados y útiles para la fabricación de los compuestos de Fórmula (I) o para la preparación de materiales de partida para la fabricación de los compuestos de Fórmula (I) son descritos en la literatura ,por ejemplo, en W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Parte 1 y Parte 2, *Systems with Bridgehead Nitrogen*, Interscience, 1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; y *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman y R.F. Cookson, Wiley, 1979 y las referencias ahí citadas.

6. Un proceso para la fabricación de los compuestos de Fórmula (I) que comprende introducir un grupo R^5 reaccionando un compuesto de Fórmula (X) donde Z es un grupo

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remplazable tal como un hidrógeno de una amina primaria o secundaria, o Z es un grupo saliente tal como halógeno o alquil o aril sulfoniloxi, o Z es una contraión tal como sodio(I) o magnesio(II) con un compuesto de Fórmula (XI) donde R^5 es como el definido anteriormente y Q es un grupo remplazable tal como un hidrógeno de una amina primaria o secundaria, o Q es a grupo saliente tal como halógeno o alquil o aril sulfoniloxi, o Q es un contraión tal como sodio(I) o magnesio(II).



(X) (XI)

Ejemplos de reacciones de este tipo incluyen alquilaciones, acilaciones, y sulfonilaciones. En cambio, si Z es el hidrógeno de una amina secundaria, preferiblemente una amina secundaria cíclica y R^5–Q es un aldehído, el m^{mo} grupo R^5 puede ser introducido por aminación reductiva, por ejemplo, reduciendo la mezcla de aldehído y la amina secundaria con cianoborohidruro de sodio.

7. Un proceso para la fabricación de los compuestos de Fórmula (I) que comprende convertir un grupo funcional de un compuesto de la invención en otro grupo funcional usando reacciones químicas estándares bien conocidas por aquellos expertos en la materia para producir otro compuesto de la invención. Tales métodos son descritos ,por ejemplo, en *Comprehensive Organic Chemistry*, Volumen 2, pág. 3, D. Barton y D. Ollis Eds, Pergamon, 1979, *Comprehensive Functional Group Transformations,* A.R. Katritzky, O. Meth–Cohn, y C.W. Rees Eds., Pergamon, 1995, y por varios autores en *Houben–Weil, Methods of Organic Chemistry*, Verlag Chemie, varios años, y las referencias ahí citadas.

8. Un proceso para la fabricación de compuestos de la invención comprende introducir un nuevo grupo funcional en un compuesto de la invención usando reacciones químicas estándares bien conocidas por aquellos expertos en la materia para producir otro compuesto de la invención. Tales métodos son descritos, por ejemplo, en *Comprehensive Organic Chemistry*, Volumen 2, pág. 3, D. Barton y D. Ollis Eds, Pergamon, 1979, *Comprehensive Functional Group Transformations,* A.R. Katritzky, O. Meth–Cohn, y C.W. Rees Eds., Pergamon, 1995, y por varios autores en *Houben–Weyl, Methods of Organic Chemistry*, Verlag Chemie, varios años, y las referencias ahí citadas.

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9. Un proceso para la fabricación de compuestos de la invención en forma de un enantiómero simple comprende separarar un compuesto racémico de la invención en enantiómeros separados.

Ejemplos de métodos adecuados para separar los enantiómeros de un compuesto racémico incluyen la cromatografía usando una fase estacionaria quiral adecuada; o la conversión de una mezcla racémica en derivados diastereoméricos, la separación de la mezcla de derivados diastereoméricos en dos diastereómeros simples, y la regeneración de un enantiómero simple separado de cada diastereómero simple separado; o la reacción química selectiva de uno de los enantiómeros de un compuesto racémico (resolución cinética) usando una reacción diastereoselectiva catalizada por un agente microbiológico o una enzima.

Ejemplos de métodos adecuados para separar una mezcla de diastereómeros incluyen la cristalización fraccional, cromatografía en fase normal o cromatografía en fase inversa.

Ejemplos de derivados diastereoméricos adecuados donde R^5 contiene un grupo hidroxi o amino incluyen ésteres formados por acilación de R usando un derivado activado de un enantiómero simple de un ácido carboxílico. Un ejemplo de un ácido carboxílico adecuado es ácido camfánico.

Ejemplos de derivados diastereoméricos adecuados donde R^5 contiene un ácido carboxílico incluyen ésteres o amidas formadas por acilación de un enantiómero simple de un alcohol o amina usando un derivado activado de un compuesto de Fórmula (I) donde al menos uno de R^5 contiene un ácido carboxílico. Un ejemplo de una amina adecuada es 1–feniletilamina y un ejemplo de un alcohol adecuado es mentol

Ejemplos de agentes adecuados para llevar a cabo una resolución cinética de una mezcla racémica de compuestos de la invención incluyen Esterasa de Hígado de Cerdo y Levadura de Pan.

10. Un proceso para la fabricación de un compuesto de la invención en forma de un enantiómero simple comprende llevar a cabo uno de los procesos descritos en las secciones precedentes usando productos intermedios quirales en forma resuelta.

Será apreciado por una persona experta en la materia que puede ser necesario/deseable proteger cualquier grupo sensible en los compuestos en algunos de los procesos/ reacciones mencionadas aquí. Los ejemplos donde la protección es necesaria o deseable, y los métodos adecuados para proporcionar tal protección son conocidos por aquellos expertos en la materia. Los grupos de protección convencionales puedne ser

usados de acuerdo con la práctica estándar (para ilustración ver P.G.M. Wuts y T.W. Green, *Protective Groups in Organic Synthesis*, 4.ª Edición, John Wiley e hijos, 2002). De esta manera, si los reactivos incluyen grupos tal como amino, carboxi o hidroxi puede ser deseable proteger el grupo en algunas de las reacciones mencionadas aquí.

Cualquier grupo de protección utilizado en los procesos descritos aquí puede en general ser escogido de cualquiera de los grupos descritos en la literatura o conocidos por aquellos expertos en la química como apropiados para la protección del grupo en cuestión y puede ser introducido por métodos convencionales. Los grupos de protección pueden ser eliminadlos por cualquier método conveniente como es descrito en la literatura o conocido por aquellos expertos en la química como apropiado para la eliminación del grupo de protección en cuestión, tales métodos siendo escogidos de manera de efectuar la eliminación del grupo de protección con una mínima alteración de los grupos en cualquier lugar de la molécula.

Ejemplos específicos de grupos de protección son dados a continuación con propósitos de conveniencia, en los cuales "inferior", como en, por ejemplo, alquil inferior, significa que el grupo al cual es aplicado preferiblemente tiene 1–4 átomos de carbono. Será entendido que estos ejemplos no son exhaustivos. Donde los ejemplos específicos de métodos para la eliminación de los grupos de protección sean dados a continuación estos son igualmente no exhaustivos. El uso de los grupos de protección y de los métodos de protección no específicamente mencionados está por supuesto dentro del alcance de la invención.

Un grupo de protección adecuado para un grupo amino o alquilamino es, por ejemplo, un grupo acil, por ejemplo, un grupo alcanoil tal como trifluoroacetil, un grupo alcoxicarbonil, por ejemplo, un grupo metoxicarbonil, etoxicarbonil o *t*–butoxicarbonil, un grupo arilmetoxicarbonil, por ejemplo, un benciloxicarbonil, o un grupo aroil o heteroaroil, por ejemplo, picolinoil. Las condiciones de desprotección para los grupos de protección anteriores necesariamente varían con la selección del grupo de protección. De esta manera, por ejemplo, un grupo acil tal como un grupo alcanoil o alcoxicarbonil o un grupo aroil puede ser eliminado, por ejemplo, por hidrólisis con un ácido adecuado tal como ácido clorhídrico, sulfúrico, o fosfórico o ácido trifluoroacético o una base adecuada tal como un hidróxido de metal alcalino, por ejemplo, hidróxido de litio o de sodio. En cambio, un grupo acil tal como un grupo *t*–butoxicarbonil puede ser eliminado, por ejemplo, por tratamiento con un ácido adecuado como ácido clorhídrico, sulfúrico o fosfórico o ácido trifluoroacético y un grupo arilmetoxicarbonil tal como un grupo benciloxicarbonil puede

ser eliminado, por ejemplo, por hidrogenación sobre un catalizador tal como paladio sobre carbono, o por tratamiento con un ácido de Lewis, por ejemplo, tris(trifluoroacetato) de boro. Un grupo de protección alternativo adecuado para un grupo amino primario es, por ejemplo, un grupo ftaloil el cual puede ser eliminado por tratamiento con una alquilamina, por ejemplo, dimetilaminopropilamina, o con hidrazina.

Un grupo de protección adecuado para un grupo hidroxi es, por ejemplo, un grupo acil, por ejemplo, un grupo alcanoil tal como acetil, un grupo aroil, por ejemplo, benzoil, o un grupo arilmetil, por ejemplo, bencil. Las condiciones de desprotección para los grupos de protección anteriores necesariamente variarán con la selección del grupo de protección. De esta manera, por ejemplo, un grupo acil tal como un grupo alcanoil o un aroil puede ser eliminado, por ejemplo, por hidrólisis con una base adecuada tal como un hidróxido de metal alcalino, por ejemplo hidróxido de litio o de sodio. En cambio un grupo arilmetil tal como un grupo bencil puede ser eliminado, por ejemplo, por hidrogenación sobre un catalizador tal como paladio sobre carbono.

Un grupo de protección adecuado para un grupo carboxi es, por ejemplo, un grupo de esterificación, por ejemplo, un grupo metil o un etil el cual puede ser eliminado, por ejemplo, por hidrólisis con una base tal como hidróxido de sodio o ,por ejemplo, un grupo *t*–butil el cual puede ser eliminado, por ejemplo, por tratamiento con un ácido, por ejemplo, un ácido orgánico tal como ácido trifluoroacético o , por ejemplo, un grupo bencil el cual puede ser eliminado, por ejemplo, por hidrogenación sobre un catalizador tal como paladio sobre carbono.

Los grupos de protección pueden ser eliminados en cualquier etapa conveniente en la síntesis usando técnicas convencionales bien conocidas en la materia de la química.

Ensayos Biológicos

La capacidad de los compuestos para reducir los números del Receptor de Andrógeno (AR) fue evaluada en un ensayo de inmunofluorescencia de base celular usando la línea celular epitelial de la próstata LNCaP.

a) Ensayo celular de regulación hacia abajo del Receptor de Andrógeno LNCaP

Este ensayo de punto final de la inmunofluorescencia mide la capacidad de un compuesto de prueba para regular hacia abajo y reducir los niveles medidos del AR en la línea celular del carcinoma de próstata LNCaP (LNCaP clon FGC (CRL–1740) obtenido de la American Type Culture Collection (ATCC)).

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Las células LNCaP fueron cultivadas en Medio de Crecimiento (libre de rojo de fenol Roswell Park Memorial Institute (RPMI) 1640 (Invitrogen Código no. 11835–063) conteniendo 2mM de L–Glutamina (Invitrogen Código no. 25030–024) y 1% (v/v) de Penicilina/Estreptomicina (10000 unidades/ml Penicilina y 10000 µg/ml de Estreptomicina utilizando penicilina G (sal de sodio) y sulfato de estreptomicina: preparado en solución salina normal, Invitrogen Código no. 15140122) y 10% (v/v) de suero fetal de ternero (FBS) en un incubador de aire CO_2 5% a 37°C. Las células para el ensayo fueron cosechadas de frascos de reserva T175 lavando una vez en PBS (solución salina de buffer de fosfato, pH 7.4) (Invitrogen Código no. 14190–094) y cosechadas usando 5 ml de 1 x Tripsina / ácido etilaminadiaminatetraacético (EDTA) (10 x Tripsina–EDTA, 5.0 g/L Tripsina, 2.0 g/L de EDTA•4Na y 8.5 g/L de NaCl, sin Rojo de Fenol, Invitrogen Código no. 15400–054) diluido en Solución PBS. Un volumen de 5ml de Medio de Crecimiento fue añadido a cada frasco (como anteriormente excepto que 5% (v/v) de FBS despojado de carbón (HyClone Código no. SH30068.03) fue incluido en lugar de 10% (v/v) de FBS). Las células fueron inyectadas con jeringuilla al menos dos veces usando una aguja de ancho calibre estéril 18G x 1.5" (1.2 x 40mm) y la densidad celular fue medida usando un hemocitómetro. Las células fueron además diluidas en Medio de Crecimiento más 5% (v/v) de carbón despojado de FBS y sembradas a una densidad de $6.5x10^3$ células por pocillo (en 90ul) en placas de 96 pocillos, tratadas con un cultivo de tejidos, negras, transparentes (Packard, No. 6005182).

Los datos de la prueba reportados en la presente fueron generados empleados dos métodos de preparación y dosificación de compuestos diferentes. En el método (1), una solución patrón de compuesto 10mM en 100% (v/v) de DMSO se diluyó en serie con diluciones en pasos cuatro veces superiores en 100% (v/v) de DMSO empleando un Termo Scientific Matrix SerialMate. Posteriormente, los compuestos diluidos se diluyeron más de 1 a 30 en medio de ensayo empleando un Termo Scientific Matrix PlateMate y una alícuota de 10µl de esta dilución se administró a células manualmente empleando una pipeta multicanal. En el método (2), partiendo de una solución patrón de compuesto 10mM, se empleó el Labcyte Echo 550 para generar un set de respuesta a la concentración de compuesto diluido en 30µl de medio de ensayo. El Echo 550 es un manipulador de líquidos que emplea tecnología acústica para llevar a cabo transferencias entre microplacas directas de soluciones de compuesto en DMSO. El sistema se puede programar para transferir volúmenes bajos como de 2.5 nL en incrementos multiples entre microplacas y al hacer esto genera una dilución en serie del compuesto que se vuelve a introducir

posteriormente para normalizar la concentración en DMSO a lo largo del rango de dilución. Se administra un volumen de 10µl de compuesto diluido posteriormente a las células empleando un Termo Scientific Matrix PlateMate.

Las placas fueron incubadas toda la noche a 37°C, 5% CO_2. Los pocillos fueron entonces dosificados con compuesto preparado por uno de los 2 métodos anteriores e incubados adicionalmente durante 20–22 horas a 37°C, 5% CO_2. Las placas fueron fijadas por la adición de 20 µl de 10% (v/v) de solución de formaldehído (en PBS) a cada pocillo (conc. formaldehído final = 1.67% (v/v)) y se dejó a temperatura ambiente durante 10 min. Esta solución de fijación fue eliminada y las células fueron lavadas con 250µl de PBS/0.05% (v/v) Tween 20 (PBST) usando un lavador de placas automático. Este proceso fue entonces repetido dos veces más.

El inmunoteñido fue realizado a temperatura ambiente. Las células fueron permeabilizadas por la adición de 35 µl de PBS conteniendo 0.5% Tween 20 e incubadas durante 1 hora a temperatura ambiente. La solución de permeabilización fue eliminada y las células fueron lavadas con 250µl de PBST usando un lavador de placas automático. Este proceso fue entonces repetido dos veces más. 35 µl de Solución de Bloqueo (PBST conteniendo 3% (p/v) de leche descremada seca Marvel (Nestle)) fue añadida a cada pocillo y las placas fueron incubadas a temperatura ambiente durante un mínimo de 1 hora. Después de la eliminación de la Solución de Bloqueo con un lavador de placas, 35µl de anticuerpo monoclonal AR antihumano en ratón (clon AR441) (inmunogen – péptido sintético que corresponde a los aminoácidos 229–315 del AR humano acoplado a la hemocianina keyhole limpet, DAKO, Código No. M3562), diluidos 1:500 en Solución de Bloqueo, fueron añadidos a cada pocillo e incubados durante 1 hora. Entonces esta solución de anticuerpo primario fue eliminada de los pocillos seguido por lavados 3 x 100µl PBST usando un lavador de placas. Entonces 35µl de anticuerpo secundario de IgG de cabra antiratón Alexa–Fluor 488 (Invitrogen, Código No. A–11001), diluidos 1:500 en Solución de Bloqueo, fueron añadidos a cada pocillo. A partir de ahí, donde fue posible, las placas fueron protegidas de la exposición a la luz. Las placas fueron incubadas durante 1 hora y luego la solución de anticuerpo secundario fue eliminada de los pocillos seguido por lavados 3 x 100ul PBST usando un lavador de placas. Entonces 50µl de PBST fueron añadidos a cada pocillo y las placas fueron cubiertas con un material negro de sellado para placas y almacenadas a 4°C antes de ser leídas. Las placas fueron leídas dentro de seis horas del completamiento del inmunoteñido.

La señal asociada al AR de Fluorescencia Verde en cada pocillo fue medida usando un Lector Acumen Explorer HTS (TTP Labtech Ltd., Cambridge). La emisión de fluorescencia asociada al AR puede ser detectada a 530nm después de la excitación a 488nm. El instrumento es un citómetro de microplacas de fluorescencia por exploración con láser el cual muestrea el pocillo a intervalos regulares y usa algoritmos umbrales para identificar todas las intensidades de fluorescencia por encima del fondo de la solución sin necesidad de genera y analizar una imagen. Estos objetos fluorescentes pueden ser cuantificados y proporcionan una medida de los niveles del AR en las células. Los datos de respuesta a la dosis de fluorescencia obtenidos con cada compuesto fueron exportados a un paquete de software adecuado (tal como Origin) para realizar el análisis de ajuste de curvas. La regulación hacia abajo de los niveles del AR fue expresada como un valor CI50. Este fue determinado por el cálculo de la concentración del compuesto que fue requerido para dar un 50% de reducción de la señal del AR.

La siguiente tabla divulga los datos biológicos para los compuestos de la presente invención usando el ensayo de regulación hacia abajo mencionado anteriormente.

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$	Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$	Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
1	3.4	21	0.27	41	28
2	8.3	22	1.4	42	12.0
3	11	23	0.45	43	1.5
4	2.5	24	>26	44	1.3
5	1.6	25	1.1	45	1.4
6	7.5	26	1.0	46	1.3
7	18	27	1.2	47	1.5
8	1.7	28	2.8	48	1.5
9	1.7	29	4.2	49	3.2
10	14	30	0.38	50	1.4
11	2.5	31	2.1	51	8.4

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Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
12	4.3
13	8.4
14	0.69
15	2.5
16	0.77
17	2.5
18	1.2
19	0.52
20	1.8
61	7.4
62	0.72
63	1.5
64	2.5
65	0.76
66	0.33
67	1.0
68	1.20
69	1.4
70	0.64
71	1.4
72	1.0
73	12
74	5.6
75	2.3
76	2.3

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
32	1.6
33	0.68
34	20
35	3.0
36	0.99
37	1.4
38	1.2
39	5.0
40	3.3
86	1.2
87	5.2
88	1.5
89	23
90	3.2
91	1.2
92	12
93	1.3
94	0.93
95	0.67
96	>1.3
97	0.36
98	2.3
99	2.9
100	1.8
101	1.7

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
52	1.3
53	7.9
54	6.7
55	8.8
56	2.1
57	4.3
58	3.1
59	2.7
60	0.61
111	0.77
112	4.7
113	7.1
114	6.5
115	2.5
116	1.1
117	1.7
118	0.30
119	2.2
120	1.7
121	4.8
122	4.3
123	4.1
124	1.7
125	1.9
126	2.0

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Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
77	1.4
78	1.20
79	2.4
80	16
81	7.2
82	1.6
83	2.5
84	1.8
85	1.6
136	1.2
137	1.5
138	13
139	2.0
140	7.1
141	9.7
142	5.1
143	8.8
144	4.9
145	1.2
146	7.3
147	2.5
148	3.4
149	7.9
150	7.6
151	3.1

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
102	2.9
103	6.2
104	9.5
105	3.2
106	4.4
107	7.2
108	2.3
109	7.2
110	1.3
161	1.4
162	1.0
163	3.6
164	1.7
165	1.7
166	0.93
167	2.4
168	1.6
169	0.92
170	0.61
171	0.62
172	0.81
173	1.2
174	0.94
175	0.68
176	0.85

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
127	1.5
128	2.3
129	0.99
130	1.8
131	4.1
132	2.6
133	1.3
134	1.8
135	4.9
186	2.8
187	4.7
188	2.2
189	1.1
190	0.79
191	2.1
192	8.7
193	2.0
194	2.4
195	4.0
196	1.5
197	0.82
198	1.2
199	1.9
200	1.3
201	1.7

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
152	6.7
153	7.9
154	1.6
155	18
156	11
157	2.4
158	3.0
159	1.4
160	6.6
211	8.2
212	3.7
213	4.5
214	15
215	7.4
216	6.8
217	3.7
218	>7.3
219	3.5
220	3.6
221	3.1
222	2.6
223	4.7
224	12
225	9.2
226	11

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
177	0.77
178	0.88
179	0.59
180	1.2
181	2.1
182	1.2
183	1.2
184	14
185	0.68
236	5.3
237	5.3
238	5
239	2.8
240	3
241	13
242	7.4
243	3.7
244	15
245	17
246	23
247	12
248	1.7
249	6.3
250	4.9
251	9.3

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
202	11
203	1.7
204	1.5
205	0.53
206	2.0
207	7.6
208	13
209	12
210	1.8
261	7.9
262	25
263	11
264	0.95
265	3.8
266	0.63
267	0.85
268	0.91
269	2
270	10
271	1.8
272	1.8
273	10
274	6.1
275	6
276	15

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
227	13
228	15
229	1.9
230	2.1
231	2.1
232	3.6
233	1.5
234	2
235	1.9
286	8.5
287	2
288	3.3
289	2.7
290	5.8
291	>9.7
292	7
293	11
294	9.5
295	3.4
296	2.1
297	15
298	5.7
299	0.84
300	1
301	1.8

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
252	8.9
253	3.7
254	1.3
255	1.8
256	7.4
257	9
258	6.4
259	4.8
260	5.6
311	5
312	2.6
313	1.8
314	4.6
315	2
316	12
317	4.1
318	3.7
319	11
320	8.6
321	8
322	9.6
323	>8.1
324	5.9
325	>1.2
326	2

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
277	2
278	0.65
279	13
280	0.78
281	0.8
282	2.4
283	0.78
284	0.98
285	2.7
336	2.4
337	1.5
338	8.5
339	0.77
340	1.5
341	1.3
342	2.1
343	1.7
344	0.29
345	1.1
346	8.5
347	0.97
348	1
349	1.7
350	0.74
351	1.9

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
302	1.1
303	5.8
304	1.8
305	4
306	1.3
307	3.4
308	1.4
309	1.6
310	3.2
361	4.7
362	1
363	22
364	16
365	19
366	>33
367	4.1
368	3.4
369	8.7
370	11
371	6.2
372	1.3
373	4
374	0.93
375	11
376	3

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
327	1
328	0.75
329	3.6
330	3.7
331	16
332	16
333	2.7
334	1.1
335	1.5
386	2.4
387	1.1
388	1.6
389	1.5
390	1.7
391	2.7
392	4.5
393	1.9
394	5.6
395	10
396	1.8
397	3.9
398	1.9
399	3.7
400	1.8
401	1.6

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
352	0.57
353	0.69
354	2.7
355	0.72
356	2.2
357	2.1
358	6.7
359	2.6
360	1
411	2.2
412	9.1
413	1.9
414	>10
415	1.4
416	2.7
417	4.6
418	>14
419	4
420	5.9
421	4
422	4.2
423	7.4
424	2.2
425	3.6
426	2.2

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
377	5.9
378	11
379	18
380	4.2
381	2.1
382	1.8
383	1.3
384	2.9
385	2.1
436	0.75
437	0.53
438	1.6
439	0.48
440	2.3
441	0.22
442	0.44
443	1.5
444	1.2
445	1.6
446	0.7
447	16
448	6.3
449	4.8
450	8.2
451	9.7

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
402	2.8
403	4.8
404	2.7
405	3
406	6.3
407	5.7
408	1.7
409	3.9
410	2.1
461	13
462	7.7
463	0.98
464	1.4
465	4
466	>19
467	4.9
468	>11
469	1.8
470	4.6
471	2
472	3.9
473	3.2
474	0.96
475	>15
476	3.5

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
427	4.3
428	15
429	2.6
430	1.7
431	1.5
432	1.2
433	0.9
434	0.83
435	0.98
486	>13
487	16
488	3.1
489	3.6
490	5.9
491	7.2
492	>30
493	18
494	0.43
495	0.35
496	11
497	2.8
498	2.4
499	1.7
500	>18
501	1.2

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
452	16
453	5.7
454	9.2
455	10
456	21
457	11
458	21
459	15
460	5.1
511	10
512	0.87
513	0.24
514	0.87
515	1.4
516	1.4
517	1.5
518	11
519	1.2
520	1.4
521	5.4
522	3.9
523	1
524	3.2
525	5.2
526	2.5

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
477	6.3
478	1.3
479	17
480	9.6
481	6.6
482	1.8
483	>30
484	>14
485	10
536	1.4
537	3
538	2.3
539	1.5
540	1.5
541	4
542	2.6
543	3.2
544	2.9
545	3.6
546	1.7
547	1.2
548	2.2
549	1.6
550	7.2
551	4

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
502	2.2
503	4.3
504	1.9
505	>19
506	9.8
507	0.53
508	2.2
509	1.8
510	3.7
561	2.9
562	2
563	1.3
564	6.7
565	3.5
566	16
567	>16
568	3.3
569	2.7
570	4.5
571	0.96
572	3.4
573	10
574	4
575	2.5
576	5

511

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
527	0.67
528	2.2
529	1.9
530	1.6
531	1.8
532	0.98
533	2.3
534	2.3
535	1.9
586	2.1
587	>17
588	5.3
589	4.8
590	22
591	20
592	9.6
593	7.2
594	22
595	6.8
596	4.2
597	2.9
598	4.2
599	5.8
600	0.85
601	2.2

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
552	7.8
553	2.6
554	4.9
555	1.4
556	4.4
557	3.1
558	2.6
559	2
560	8.8
611	1.6
612	>13
613	3.3
614	>12
615	0.88
616	1.7
617	4.3
618	>4
619	4.5
620	>13
621	2.3
622	7.4
623	0.89
624	3.1
625	1.4
626	1.1

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
577	5
578	2.5
579	4.1
580	2
581	3.3
582	2.4
583	4.1
584	2.8
585	1.5
636	20
637	1.8
638	0.9
639	1.2
640	0.92
641	1.4
642	1.4
643	6
644	1.5
645	2.3
646	6.1
647	1.7
648	2.1
649	2.3
650	3.1
651	1.9

SR

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
602	1.6
603	3.5
604	1.7
605	5
606	2.7
607	7.4
608	2.7
609	6.6
610	3.2
661	0.65
662	5.4
663	2.7
664	3.6
665	0.82
666	0.94
667	1
668	1.1
669	0.6
670	0.67
671	1.6
672	0.58
673	0.73
674	1.1
675	1.5
676	0.56

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
627	1.7
628	2.7
629	1.3
630	2.4
631	1.1
632	1.2
633	1.9
634	1.1
635	2.9
686	4.2
687	3.8
688	6.6
689	4.1
690	17
691	>28
692	4.2
693	2.3
694	3.2
695	3.3
696	4.2
697	>22
698	5.6
699	2.1
700	7.1
701	14

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
652	3.1
653	1
654	2.6
655	1.1
656	1.1
657	3.2
658	0.94
659	1
660	0.63
711	2.5
712	3
713	0.81
714	>9.9
715	1.2
716	0.81
717	2.9
718	3.6
719	3.5
720	2.7
721	2.9
722	4.1
723	0.9
724	0.69
725	1.2
726	1.4

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Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
677	4.5
678	15
679	0.58
680	0.6
681	1.3
682	0.58
683	0.49
684	0.69
685	5.7
736	0.4
737	0.74
738	3.3
739	3.2
740	2
741	2.2
742	17
743	14
744	9.6
745	3.4
746	3.3
747	23
748	5.6
749	>22
750	2.6
751	6.3

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
702	>12
703	5.5
704	4.2
705	5.3
706	2.9
707	7.9
708	6.2
709	1.7
710	2.1
761	1.5
762	1.2
763	>9.8
764	2.5
765	8.8
766	>17
767	>12
768	4.7
769	11
770	6.3
771	3.1
772	14
773	3.1
774	8
775	6.8
776	6.9

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
727	1.2
728	1.5
729	0.92
730	0.72
731	1.1
732	1.1
733	0.6
734	2.5
735	1.9
786	8.4
787	1.3
788	2.2
789	2.1
790	2
791	0.96
792	16
793	1.6
794	1.1
795	2.4
796	0.63
797	2.4
798	1
799	1.6
800	1.1
801	1.3

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Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
752	18
753	2.1
754	2.5
755	2.2
756	3.2
757	>12
758	1.3
759	3.9
760	>3.1
811	1.2
812	2.1
813	6.8
814	1.8
815	>17
816	9.3
817	5.6
818	3.8
819	>18
820	4
821	2
822	1.7
823	4.7
824	1.9
825	1.9
826	1.4

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
777	4.6
778	2.6
779	0.54
780	0.51
781	0.82
782	2
783	0.84
784	2.2
785	1.7
829	13
830	0.85
831	3.1
832	1.4
833	>12
834	4.4
835	20
837	1.6
838	7.6
839	1.1
840	2.6
841	2.9
842	1.1
843	0.93
844	0.78
845	0.9

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
802	1.2
803	7
804	1.3
805	1
806	2.3
807	7.5
808	1
809	
810	1.9
848	3.5
849	0.68
850	0.56
851	0.92
852	0.29
853	1.3
854	No realizado
855	0.44
856	2.2
857	>33
858	>33
859	>33
860	0.8
861	No realizado
862	No realizado
863	No realizado

Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$	Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$	Ejemplo Número	Ensayo de Regulación hacia abajo del Receptor de Andrógeno(a) $CI_{50}/\mu M$
827	1	846	0.27	864	No realizado
828	9.5	847	3.1		

b) Ensayo de unión competitivo del dominio de unión al ligando – Receptor de Andrógeno

La capacidad de los compuestos para unirse al dominio de unión del ligando al Receptor de Andrógeno aislado (AR–LBD) fue evaluada en ensayos de competencia empleando la detección del punto final por polarización por fluorescencia (FP) o por transferencia de energía fluorescente por resonancia con resolución temporal LantaScreen™ (TR-FRET).

Para el ensayo de polarización por fluorescencia, un kit de prueba de ensayo fue comprado a Invitrogen y usado para medir la unión del compuesto al AR–LBD de rata aislado el cual comparte 100% de identidad de la secuencia con el AR–LBD humano. El Ensayo de Competencia del Receptor de Andrógeno, Rojo de Invitrogen PolarScreen™ (Producto Código No. PV4293), es un ensayo de competencia basado en la polarización por fluorescencia (FP) el cual mide si el compuesto de prueba puede desplazar un compuesto trazador fluorescentemente marcado. Si el compuesto de prueba se une al AR–LBD éste prevendrá la formación del complejo receptor/trazador, el cual resultará en un bajo valor de polarización. Si el compuesto de prueba no se une al receptor, éste no tendrá ningún efecto en la formación del complejo receptor/trazador, y el valor de la polarización medida del trazador permanecerá alto. El ensayo fue realizado como se describió esencialmente en el método de Invitrogen con la excepción de que el volumen del ensayo final fue 12µl y esto requirió una placa de microtítulo de 384 pocillos negra de bajo volumen apropiada. Los compuestos se administraron directamente desde una microplaca fuente de compuesto que contenía el compuesto diluido en serie (4 pocillos que contenían 10mM, 0.1mM, 1µM y 10nM del compuesto final respectivamente) a una microplaca de

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ensayo empleando el Labcyte Echo 550. El Echo 550 es un manipulador de líquidos que emplea tecnología acústica para llevar a cabo transferencias entre microplacas directas de soluciones de compuesto en DMSO y el sistema se puede programar para transferir pequeños volúmenes de nL múltiples de compuesto desde los diferentes pocillos de la placa fuente para obtener la dilución en serie deseada del compuesto en el ensayo la cual se vuelve a introducir posteriormente para normalizar la concentración en DMSO a lo largo del rango de dilución. Los datos de respuesta a dosis FP obtenidos con cada compuesto fueron exportados a un paquete de software adecuado (tal como Origin) para realizar el análisis de ajuste de curvas. La unión competitiva al AR fue expresada como un valor CI50. El mismo fue determinado por el cálculo de la concentración del compuesto que fue requerida para dar un 50% de reducción en la unión del compuesto trazador al AR–LBD.

La siguiente tabla divulga varios datos biológicos para una selección representativa de los compuestos de la presente invención usando el ensayo de FP de unión al ligando anteriormente mencionado.

Ejemplo Número	Ensayo de FP de Unión del Receptor de Andrógeno al Ligando CI50/μM
4	20.18
41	19.55
166	6.085
174	16.3
183	14.37
Otros Ejemplos dentro del rango del Ejemplo 1 – Ejemplo 215 mostraron una Unión del Receptor de Andrógeno al Ligando con un CI50 mayor de 20μM	

Para LantaScreen™ TR-FRET, se adquirieron un fluoróforo adecuado (código de producto PV4294) y AR-LBD marcado con GST de rata de Invitrogen, y se emplearon para medir la unión del compuesto. El principio del ensayo es que AR-LBD se agrega a un ligando fluorescente para formar un complejo receptor/fluoróforo. Se emplea un anticuerpo anti-GST marcado con terbio para marcar de forma indirecta el receptor al unirse a una marca GST, y se detecta la unión competitiva mediante la capacidad de un compuesto de prueba para desplazar el ligando fluorescente lo cual da lugar a una pérdida

de la señal TR-FRET entre el anticuerpo Tb-anti-GST y el trazador. El ensayo se llevó a cabo como se indica a continuación, realizando todas las adiciones de reactivos empleando el Termo Scientific Matrix PlateMate :-

1. Dispersar de forma acústica 120nl del compuesto de prueba en una placa de ensayo negra de 384 pocillos de bajo volumen.
2. Dispensar 6µl de 2x reactivo fluoróforo en cada pocillo de la placa de ensayo
3. Dispensar 6µl de 2x AR-LBD/Tb-anti-GST Ab en cada pocillo de la placa de ensayo
4. Cubrir la placa de ensayo para proteger los reactivos de la luz y la evaporación, e incubar a temperatura ambiente durante 1 hora.
5. Excitar a 340nM y medir la señal de emisión fluorescente de caca pocillo a 495nm y 570nm empleando el BMG FeraSTAR.

Los compuestos se administraron directamente desde una microplaca fuente de compuesto que contenía el compuesto diluido en serie (4 pocilos que contienen 10mM, 0.1mM, 1µM y 10nM de compuesto final respectivamente) a una microplaca de ensayo empleando el Labcyte Echo 550. El Echo 550 es un manipulador de líquidos que emplea tecnología acústica para llevar a cabo transferencias entre microplacas directas de soluciones de compuesto en DMSO y el sistema se puede programar para transferir volúmenes pequeños de nL múltiples de compuesto desde los diferentes pocillos de la placa fuente para obtener la dilución en serie deseada de compuesto en el ensayo la cual se vuelve a introducir posteriormente para normalizar la concentración en DMSO a lo largo del rango de dilución. En total se agregan 120nL del compuesto junto con DMSO a cada pocillo y los compuestos se probaron en un formato de respuesta frente a la concentración de 12 puntos frente a un rango de concentración de compuesto final de 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001, 0.0001µM, respectivamente. Los datos de respuesta a la dosis para TR-FRET obtenidos con cada compuesto se exportaron a un paquete informático adecuado (como el Origin) para llevar a cabo un análisis de ajuste de la curva. La unión competitiva al AR se expresó como un valor CI_{50}. Este se determinó calculando la concentración del compuesto requerida para obtener una reducción del 50% en la unión de un compuesto trazador a AR-LBD.

Tabla de resultados – Ensayo de unión a AR LantaScreen™

Número de ejemplo	511	51
CI_{50} (µM)	>100 (n=2)	1.3 (n=2)

De acuerdo con un aspecto adicional de la invención se proporciona una composición farmacéutica la cual comprende un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente en asociación con un portador o diluente farmacéuticamente aceptable.

La composición puede estar en una forma adecuada para la administración oral, por ejemplo, como una tableta o cápsula; para inyección parenteral (incluyendo intravenosa, subcutánea, intramuscular, intravascular o infusión) como una solución estéril, suspensión o emulsión; para la administración tópica como una pomada o crema; o para la administración rectal como un supositorio.

En general las composiciones anteriores pueden ser preparadas de una manera convencional usando excipientes convencionales. Para aplicaciones preclínicas *in vivo* se pueden emplear formulaciones y suspensiones simples. Por ejemplo, se pueden formular 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol como una suspensión acuosa simple en un 1%p/v de Polisorbato 80 ó 0.57%p/v de PVP (Polivinilpirrolidona)/0.33%p/v de Aerosol AOT (1,2-bis(2-etilhexoxicarbonil)etanosulfonato de sodio). Se pueden preparar formulaciones de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina y 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina como suspensiones con un tamaño de partícula reducido (tamaño de partícula medio menor de 1 micrómetro) como se indica a continuación. La cantidad requerida de compuesto se agita en un vórtex y/o con un agitador magnético en un vehículo (agua que contiene un 1%p/v de Pluronic F127) para dividir los agregados grandes, humedecer el compuesto y desplazar el aire de la superficie. La suspensión resultante se transfiere a un recipiente de molienda de circonia que contiene de aproximadamente un tercio con un diámetro de 0.6-0.8mm con microesferas de molienda de circonia. Se agregaron microesferas de molienda de circonia adicionales al recipiente hasta que el nivel de la suspensión y las microesferas es aproximadamente igual y se cierra el recipiente. El recipiente se sella posteriormente con un anillo de teflón y una tapa de circonia y se introdujo en un molino adecuado, por ejemplo, un micromolino planetario Fritsch P7. El recipiente gira en el molino durante 4 ciclos de 30 minutos a una velocidad de rotación de 800rpm con un periodo de enfriamiento de 15 minutos entre cada ciclo. Al final de los 4 ciclos, el recipiente se deja enfriar hasta temperatura ambiente. La suspensión molida se retira del recipiente empleando una pipeta adecuada y se transfiere a un matraz adecuado. Por último, se ajusta el volumen de la suspensión molida con el

vehículo (agua que contiene un 1%p/v de Pluronic F127) para obtener una suspensión a una concentración requerida.

El compuesto de Fórmula (I) normalmente será administrado a un animal de sangre caliente en una dosis unitaria dentro del rango de 5–5000 mg/m^2 de área corporal del animal, es decir aproximadamente de 0.1–100 mg/kg, y esto normalmente proporciona una dosis terapéuticamente efectiva. Una forma de dosificación unitaria tal como una tableta o cápsula usualmente contendrá, por ejemplo, 1–250 mg de ingrediente activo. Preferiblemente una dosis diaria en el rango de 1–50 mg/kg es empleada. Sin embargo la dosis diaria será necesariamente variada dependiendo del hospedero tratado, la ruta particular de administración, y la severidad de la enfermedad que está siendo tratada. Por consiguiente la dosificación óptima puede ser determinada por el especialista que está tratando a cualquier paciente particular. Por ejemplo, se puede administrar 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol a un paciente humano en una dosis de 500 a 1500 mg BID (dos veces al día), más particularmente aproximadamente 1000 mg BID, y se puede administrar 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina a un paciente humano en una dosis de 165 a 660 mg BID, más particularmente aproximadamente 430 mg BID. Las dosis previstas para humanos de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol y 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina se basan en un ser humano estándar con un peso de 70 kg y las dosis BID son por dosis (es decir, la mitad de la dosis diaria total).

Para más información sobre las Rutas de Administración y los Regímenes de Dosificación el lector debe referirse al Capítulo 25.3 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Jefe del Consejo Editorial), Pergamon Press 1990.

Hemos descubierto que los compuestos definidos en la presente invención, o una sal farmacéuticamente aceptable de los mismos, o las composiciones farmacéuticas que los contienen, son moduladores efectivos del receptor de andrógeno.

Por consiguiente, los compuestos de la presente invención se espera que sean agentes potencialmente útiles en el tratamiento de enfermedades o afecciones médicas mediadas sólo o en parte por el receptor de andrógeno. Los compuestos de la invención pueden inducir la regulación hacia abajo del receptor de andrógeno y/o ser agonistas selectivos, agonistas parciales, antagonistas o antagonistas parciales del Receptor de Andrógeno.

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Los compuestos de la invención son útiles en el tratamiento de las afecciones asociadas con el receptor de andrógeno. Una "afección asociada con el receptor de andrógeno", como es usado aquí, denota una afección o trastorno que puede ser tratado modulando la función o actividad de un receptor de andrógeno en un sujeto, donde el tratamiento comprende la prevención, alivio parcial o cura de la afección o trastorno. La modulación puede ocurrir localmente, por ejemplo, dentro de algunos tejidos del sujeto, o más extensivamente a través de un sujeto que está siendo tratado por tal afección o trastorno.

En una realización, los compuestos de la presente invención pueden ser administrados a animales, por ejemplo, humanos, para el tratamiento de una variedad de afecciones y trastornos, incluyendo, pero no limitados a, el tratamiento de enfermedades o trastornos sensibles al andrógeno cuyo progreso o aparición es ayudado por la activación del receptor de andrógeno o de los moduladores del receptor de andrógeno. Ejemplos de enfermedades o trastornos sensibles al andrógeno particulares incluyen, pero no están limitados a, cánceres sensibles al andrógeno tal como cáncer de próstata y otros cánceres compuestos de células tumorales malignas que contienen el receptor de andrógeno, tal como es el caso para los cánceres de mama, cerebro, piel, ovario, vejiga, linfático, hígado y riñón; cánceres de piel, páncreas, endometrio, pulmón y colon; osteosarcoma; hipercalcemia por malignidad; enfermedad metastásica ósea; y trastornos sensibles al andrógeno tal como la hiperplasia prostática benigna y prostatomegalia, acné (acne vulgaris), seborrea, hirsutismo (hipertricosis), alopecia androgénica y calvicie de patrón masculino, pubertad precoz, endometriosis, síndrome de ovarios poliquísticos, tratamiento de espermatogénesis, contrarrestar la preeclampsia, eclampsia de embarazadas y labor de parto, tratamiento del síndrome premenstrual, tratamiento de la resequedad vaginal, perversión sexual, virilización, y similares. Los compuestos de la invención también pueden ser usados para mejorar la ovulación en un animal doméstico.

En otra realización, los compuestos de la presente invención pueden ser administrados a animales, por ejemplo, humanos, para el tratamiento de una variedad de afecciones y trastornos, incluyendo, pero no limitados a, el mantenimiento de la fortaleza y de la función muscular (por ejemplo, en la vejez); prevención o inversión de la fragilidad o deterioro funcional relacionada con la edad ("ARFD") en la vejez (por ejemplo, sarcopenia); tratamiento de efectos secundarios catabólicos de los glucocorticoides; prevención y/o tratamiento de la reducción en el crecimiento o densidad de la masa ósea, (por ejemplo, osteoporosis y osteopenia); tratamiento del síndrome de fatiga crónica

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(CFS); mialgia crónica; tratamiento del síndrome de fatiga aguda y pérdida muscular a continuación de la cirugía electiva (por ejemplo, rehabilitación postquirúrgica); aceleración de la curación de heridas; aceleración de la reparación de la fractura ósea (tal como aceleración de la recuperación de los pacientes con fractura de cadera); aceleración de la curación de fracturas complicadas, por ejemplo, osteogénesis por distracción; en el reemplazo de articulaciones; prevención de la formación de la adhesión postquirúrgica; aceleración de la reparación o crecimiento dental; mantenimiento de la función sensorial (por ejemplo, oído, vista, olfato y gusto); tratamiento de la enfermedad periodontal; tratamiento del debilitamiento secundario a las fracturas y del debilitamiento en relación con la enfermedad pulmonar obstructiva crónica (COPD), enfermedad crónica del hígado, SIDA, ingravidez, caquexia asociada al cáncer, recuperación de traumas y quemaduras, estado catabólico crónico (por ejemplo, coma), trastornos de la alimentación (por ejemplo, anorexia) y quimioterapia; tratamiento de cardiomiopatías; tratamiento de la trombocitopenia; tratamiento del retardo del crecimiento en relación con la enfermedad de Crohn; tratamiento del síndrome del intestino corto; tratamiento del síndrome del intestino irritable; tratamiento de la enfermedad inflamatoria del intestino; tratamiento de la enfermedad de Crohn y colitis ulcerativa; tratamiento de complicaciones asociadas con el transplante; tratamiento de la estatura fisiológica baja incluyendo los niños deficientes de la hormona del crecimiento y estatura baja asociada con enfermedades crónicas; tratamiento de la obesidad y retardo del crecimiento asociado con la obesidad; tratamiento de la anorexia (por ejemplo, asociado con la caquexia o envejecimiento); tratamiento del hipercortisolismo y síndrome de Cushing; enfermedad de Paget; tratamiento de la osteoartritis; inducción de la liberación pulsátil de la hormona de crecimiento; tratamiento de las osteocondrodisplasias; tratamiento de la depresión, nerviosismo, irritabilidad y estrés; tratamiento de energía mental reducida y baja autoestima (por ejemplo, motivación/firmeza); mejora de la función cognitiva (por ejemplo, el tratamiento de la demencia, incluyendo la enfermedad de Alzheimer y la pérdida de memoria a corto plazo); tratamiento del catabolismo en relación con la disfunción pulmonar y dependencia al ventilador; tratamiento de la disfunción cardiaca (por ejemplo asociada con la enfermedad valvular, infarto del miocardio, hipertrofia cardiaca o fallo cardiaco congestivo); disminución de la presión sanguínea; protección contra la disfunción ventricular–24 o prevención de los eventos de reperfusión; tratamiento de adultos en diálisis crónica; disminución o inversión del estado catabólico del envejecimiento; atenuación o inversión de las respuestas catabólicas de las proteínas a continuación del trauma (por ejemplo,

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inversión del estado catabólico asociado con la cirugía, fallo cardíaco congestivo, miopatía cardiaca, quemaduras, cáncer, COPD, etc.); reducción de la caquexia y la pérdida de proteínas debido a enfermedades crónicas tal como cáncer o SIDA; tratamiento de la hiperinsulinemia incluyendo la nesidioblastosis; tratamiento de pacientes inmunosuprimidos; tratamiento de debilitamiento en relación con la esclerosis múltiple u otros trastornos neurodegenerativos; promoción de la reparación de mielina; mantenimiento del espesor de la piel; tratamiento de la homeostasis metabólica y la homeostasis renal (por ejemplo, en los ancianos delicados); estimulación de osteoblastos, remodelación ósea y crecimiento de cartílagos; regulación de la absorción de los alimentos; tratamiento de resistencia a la insulina, incluyendo NIDDM, en mamíferos (por ejemplo, humanos); tratamiento de resistencia a la insulina en el corazón; mejora de la calidad del sueño y corrección del hiposomatotropismo relativo de senescencia debido al alto aumento en el sueño REM y una disminución en la latencia REM; tratamiento de la hipotermia; tratamiento del fallo cardíaco congestivo; tratamiento de la lipodistrofia (por ejemplo, en pacientes en tratamiento por VIH o SIDA tal como inhibidores de proteasa); tratamiento de la atrofia muscular (por ejemplo, debido a la inactividad física, reposo en cama o condiciones de soportar peso reducidas); tratamiento del deterioro musculoesquelético (por ejemplo, en los ancianos); mejora de la función pulmonar general; tratamiento de los trastornos del sueño; y el tratamiento del estado catabólico de enfermedades críticas prolongadas; niveles de testosterona disminuidos relacionados con la edad en los hombres, menopausia masculina, hipogonadismo, reemplazo de la hormona masculina, disfunción sexual masculina y femenina (por ejemplo, disfunción eréctil, deseo sexual disminuido, bienestar sexual, libido disminuida), incontinencia urinaria, anticoncepción masculina y femenina, pérdida de cabello, y la mejora del desempeño/fortaleza de músculos y huesos.

El término tratamiento también se pretende que incluya el tratamiento profiláctico.

Además, las afecciones, enfermedades, y dolencias colectivamente referidas como "Síndrome X" o Síndrome Metabólico como se detalló en Johannsson J. Clin. Endocrinol. Metab., 82, 727–34 (1997), pueden ser tratadas empleando los compuestos de la invención.

En una realización las afecciones asociadas al receptor de andrógeno incluyen cáncer de próstata, hiperplasia prostática benigna y prostamegalia, acné (acne vulgaris), seborrea, hirsutismo (hipertricosis), alopecia androgénica y calvicie de patrón masculino, pubertad precoz, síndrome de ovarios poliquísticos, perversión sexual, virilización, y similares. Los compuestos de la invención pueden ser también usados para mejorar la

ovulación en un animal doméstico.

Por consiguiente, la presente invención se relaciona con un método de tratamiento de cualquier afección asociada al receptor de andrógeno anteriormente mencionada en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente.

De acuerdo con un aspecto adicional la presente invención se relaciona con el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente en la fabricación de un medicamento para el tratamiento de cualquier afección asociada al receptor de andrógeno anteriormente mencionada.

De acuerdo con otro aspecto de la presente invención se proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable o profármaco del mismo, como el definido aquí anteriormente para uso en el tratamiento de cualquier afección asociada al receptor de andrógeno anteriormente mencionada.

De acuerdo con otro aspecto de la presente invención se proporciona un compuesto de Fórmula (Ia), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente para uso en un método de tratamiento del cuerpo humano o animal mediante terapia.

De acuerdo con un aspecto adicional de la invención se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable o profármaco del mismo, como el definido aquí anteriormente en la fabricación de un medicamento para uso en la producción de un efecto antiandrogénico en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para producir un efecto antiandrogénico en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente.

El término "efecto antiandrogénico" es usado aquí para significar la inhibición y/o regulación hacia abajo de los receptores de andrógeno.

De acuerdo con un aspecto adicional de la invención se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente en la fabricación de un medicamento para uso en la

producción de un efecto de antiproliferación celular en un animal de sangre caliente tal como el hombre.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método para producir un efecto de antiproliferación celular en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método de tratar cánceres sensibles al andrógeno en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente para uso en el tratamiento de cánceres sensibles al andrógeno.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente en la fabricación de un medicamento para uso en el tratamiento de cánceres sensibles al andrógeno.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método de tratamiento del cáncer de próstata en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente. En una realización de este aspecto de la invención, el cáncer de próstata es resistente al tratamiento hormonal.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente para su uso en el tratamiento del cáncer de próstata, más particularmente el cáncer de próstata resistente a hormonas.

De acuerdo con una característica adicional de la invención se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente en la fabricación de un medicamento para su uso en el

tratamiento del cáncer de próstata, más particularmente el cáncer de próstata resistente a hormonas.

El cáncer de próstata resistente al tratamiento hormonal (CPRH) aparece cuando el cáncer de próstata evoluciona hasta el estado hormonoindependiente de la enfermedad.

De acuerdo con una característica adicional de este aspecto de la invención se proporciona un método de tratamiento de cualquiera de las siguientes afecciones: hiperplasia prostática benigna, prostamegalia, acné (acne vulgaris), seborrea, hirsutismo (hipertricosis), alopecia androgénica y calvicie de patrón masculino, pubertad precoz, síndrome de ovarios poliquísticos, perversión sexual, o virilización; en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente.

De acuerdo con una característica adicional de la invención se proporciona un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente para uso en el tratamiento de cualquiera de las siguientes afecciones: hiperplasia prostática benigna, prostamegalia, acné (acne vulgaris), seborrea, hirsutismo (hipertricosis), alopecia androgénica y calvicie de patrón masculino, pubertad precoz, síndrome del ovario poliquístico, perversión sexual, o virilización.

De acuerdo con un característica adicional de la invención se proporciona el uso de un compuesto de Fórmula (I), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente en la fabricación de un medicamento para uso en el tratamiento de cualquiera de las siguientes afecciones: hiperplasia prostática benigna, prostamegalia, acné (acne vulgaris), seborrea, hirsutismo (hipertricosis), alopecia androgénica y calvicie de patrón masculino, pubertad precoz, síndrome del ovario poliquístico, perversión sexual, o virilización.

Como se declaró anteriormente el tamaño de la dosis requerida para el tratamiento terapéutico o profiláctico de una enfermedad de proliferación celular particular será necesariamente variada dependiendo del hospedero tratado, la ruta de administración y la severidad de la enfermedad que está siendo tratada. Una dosis unitaria en el rango de, por ejemplo, 1–100 mg/kg, preferiblemente de 1–50 mg/kg es considerada.

Los ligandos del receptor de andrógeno de la presente invención pueden ser aplicados como una terapia única o pueden incluir, además de un compuesto de la invención, uno o más otras sustancias y/o tratamientos. Tal tratamiento conjunto puede ser logrado por medio de la administración simultánea, secuencial o separada de los

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componentes individuales del tratamiento. En el campo de la oncología médica es una práctica normal usar una combinación de formas diferentes de tratamiento para tratar cada paciente con cáncer. En la oncología médica el(los) otro(s) componente(s) de tal tratamiento conjunto, además del tratamiento del ligando del receptor de andrógeno definido aquí anteriormente, puede ser: cirugía, radioterapia o quimioterapia. Tal quimioterapia puede incluir uno o más de las siguientes categorías de agentes antitumorales:

(i) otros fármacos antiproliferativos/antineoplásicos y combinaciones de los mismos, tal como se usa en oncología médica, tal como agentes alquilantes (por ejemplo cisplatino, oxaliplatino, carboplatino, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucil, busulfán, temozolamida y nitrosoureas); antimetabolitos (por ejemplo gemcitabina y antifolatos tal como fluoropirimidinas como el 5– fluorouracilo y tegafur, raltitrexed, metotrexato, citosina arabinosida e hidroxiurea); antibióticos antitumorales (por ejemplo antraciclinas como adriamicina, bleomicina, doxorrubicina, daunomicina, epirrubicina, idarrubicina, mitomicina C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo alcaloides vinca como vincristina, vinblastina, vindesina y vinorelbina y taxoides como taxol y taxotere e inhibidores de la poloquinasa); e inhibidores de la topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y tenipósida, amsacrina, topotecán y camptotecina);

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo, tamoxifeno, fulvestrant, toremifeno, raloxifeno, droloxifeno y yodoxifeno), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (por ejemplo goserelina, leuprorelina y buserelina), progestógenos (por ejemplo, acetato de megestrol), inhibidores de la aromatasa (por ejemplo como anastrozol, letrozol, vorazol y exemestano) y los inhibidores de la 5α–reductasa como finasteride;

(iii) agentes antiinvasión [por ejemplo inhibidores de la familia de la c–Src quinasa como 4–(6–cloro–2,3–metilenodioxianilino)–7–[2–(4–metilpiperazin–1–il)etoxi]–5–tetrahidropiran–4–iloxiquinazolina (AZD0530; Solicitud Internacional de Patente WO 01/94341) y *N*–(2–cloro–6–metilfenil)–2–{6–[4–(2–hidroxietil)piperazin–1–il]–2–metilpirimidin–4–ilamino}tiazol–5–carboxamida (dasatinib, BMS–354825; J. Med. Chem, 2004, 47, 6658–6661) y bosutinib (SKI–606), y los inhibidores de metaloproteínasas como marimastat, inhibidores de la función del receptor activador del plasminógeno de la uroquinasa o anticuerpos para la heparanasa];

(iv) inhibidores de la función del factor de crecimiento, por ejemplo tales inhibidores incluyen los anticuerpos del factor de crecimiento y los anticuerpos del receptor del factor de crecimiento (por ejemplo, el anticuerpo anti–erbB2 trastuzumab [Herceptin™], el anticuerpo anti–EGFR panitumumab, el anticuerpo anti–erbB1 cetuximab [Erbitux, C225], y cualquier inhibidor del receptor del factor de crecimiento o del factor de crecimiento descrito por Stern y otros. Critical reviews in oncology/haematology, 2005, Vol. 54, págs. 11–29); tales inhibidores también incluyen los inhibidores de la tirosina quinasa, por ejemplo inhibidores de la familia del factor de crecimiento epidérmico (por ejemplo inhibidores de la tirosina quinasa de la familia de EGFR tales como *N*–(3–cloro–4–fluorofenil)–7–metoxi–6–(3–morfolinopropoxi)quinazolin–4–amina (gefitinib, AZD1839), *N*–(3–etinilfenil)–6,7–bis(2–metoxietoxi)quinazolin–4–amina (erlotinib, OSI–774) y 6–acrilamido–*N*–(3–cloro–4–fluorofenil)–7–(3–morfolinopropoxi)quinazolin–4–amina (CI 1033), los inhibidores de la tirosina quinasa erbB2 tal como lapatinib, los inhibidores del factor de crecimiento de hepatocitos; los inhibidores de la familia del factor de crecimiento de tipo insulina; los inhibidores de la familia del factor de crecimiento derivado de las plaquetas tal como imatinib y/o nilotinib (AMN107); inhibidores de las serina/treonina quinasas (por ejemplo inhibidores de señales Ras/Raf tales como los inhibidores de la farnesil transferasa, por ejemplo sorafenib (BAY 43–9006), tipifarnib (R115777) y lonafarnib (SCH66336), inhibidores de señales celulares a través de MEK y/o AKT quinasas, inhibidores de c–kit, inhibidores de la abl quinasa, inhibidores de la PI3 quinasa, inhibidores de la Plt3 quinasa, inhibidores de la CSF–1R quinasa, inhibidores del receptor IGF quinasa (factor de crecimiento de tipo insulina); inhibidores de la aurora quinasa (por ejemplo AZD1152, PH739358, VX–680, MLN8054, R763, MP235, MP529, VX–528 y AX39459) e inhibidores de la quinasa dependiente de las ciclinas tales como los inhibidores CDK2 y/o CDK4;

(v) agentes antiangiogénicos tales como los que inhiben los efectos del factor de crecimiento endotelial vascular, [por ejemplo el anticuerpo del factor de crecimiento de células endoteliales antivascular bevacizumab (Avastin™) y por ejemplo, inhibidores de la tirosina quinasa del receptor del VEGF tal como vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG–013736), pazopanib (GW 786034), 4–(4–fluoro–2–metilindol–5–iloxi)–6–metoxi–7–(3–pirrolidin–1–ilpropoxi)quinazolina (AZD2171; Ejemplo 240 dentro de WO 00/47212), compuestos tales como aquellos descritos en las Solicitudes Internacionales de Patente WO 97/22596, WO 97/ 30035, WO

97/32856 y WO 98/13354 y compuestos que funcionan por otros mecanismos (por ejemplo linomida, inhibidores de la función de la integrina αvβ3 y angiostatina)];

(vi) agentes perjudiciales vasculares como Combretastatin A4 y compuestos divulgados en las Solicitudes Internacionales de Patente WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) un antagonista del receptor de endotelina, por ejemplo zibotentan (ZD4054) o atrasentan;

(viii) terapias antisentido, por ejemplo aquellas que son dirigidas a los objetivos listados anteriormente, tal como ISIS 2503, una antisentido antiras;

(ix) aproximaciones a la terapia génica, incluyendo por ejemplo aproximaciones para reemplazar los genes aberrantes tal como las aproximaciones aberrantes p53 o la BRCA1 o BRCA2, GDEPT aberrantes (terapia con profármacos de enzimas dirigidas a los genes) tal como aquellas que usan citosina deaminasa, timidina quinasa o una enzima nitroreductasa bacteriana y aproximaciones para aumentar la tolerancia del paciente a la quimioterapia o la radioterapia tal como la terapia génica resistente a múltiples fármacos; y

(x) aproximaciones de inmunoterapia, incluyendo por ejemplo aproximaciones ex vivo e in vivo para aumentar la inmunogenicidad de las células tumorales del paciente, tal como la transfección con citocinas como la interleucina 2, interleucina 4 o el factor estimulador de colonias de granulocitos macrófagos, aproximaciones para disminuir la anergia de células T, aproximaciones usando células inmunes transfectadas tal como las células dendríticas transfectadas de citoquinas, aproximaciones usando líneas celulares tumorales transfectadas de citoquinas y aproximaciones usando anticuerpos antiidiotípicos.

Aquí, donde el término "combinación" es usado debe entenderse que este se refiere a la administración simultánea, separada o secuencial . En un aspecto de la invención "combinación" se refiere a la administración simultánea. En otro aspecto de la invención "combinación" se refiere a la administración separada. En un aspecto adicional de la invención "combinación" se refiere a la administración secuencial. Donde la administración es secuencial o separada, el plazo de administración del segundo componente no debe ser tal que se pierda el efecto benéfico de la combinación.

De acuerdo con un aspecto adicional de la invención se proporciona una composición farmacéutica la cual comprende un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral

seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente, en asociación con un diluyente o portador farmacéuticamente aceptable.

De acuerdo con un aspecto adicional de la invención se proporciona una composición farmacéutica la cual comprende un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente, en asociación con un diluyente o portador farmacéuticamente aceptable para uso en el tratamiento de un trastorno sensible al andrógeno.

De acuerdo con un aspecto adicional de la invención se proporciona una composición farmacéutica la cual comprende un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente, en asociación con un diluyente o portador farmacéuticamente aceptable para uso en el tratamiento del cáncer, tal como el cáncer de próstata.

De acuerdo con otra característica de la invención se proporciona el uso de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente, en la fabricación de un medicamento para uso en el tratamiento de un trastorno sensible al andrógeno en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se proporciona el uso de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de un listado de acuerdo con (i) – (x) aquí anteriormente, en la fabricación de un medicamento para uso en el tratamiento del cáncer, tal como el cáncer de próstata, en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se proporciona un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de un listado de acuerdo con (i) – (x) aquí anteriormente para el uso en el tratamiento de un trastorno sensible al andrógeno en un animal de sangre caliente, tal como el hombre.

De acuerdo con otra característica de la invención se proporciona un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente para el uso en el tratamiento del cáncer, tal como el cáncer de próstata en un animal de sangre caliente, tal como el hombre.

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Por lo tanto en una característica adicional de la invención, se proporciona un método de tratamiento de un trastorno sensible al andrógeno en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente.

Por lo tanto en una característica adicional de la invención, se proporciona un método de tratamiento del cáncer, tal como el cáncer de próstata, en un animal de sangre caliente, tal como el hombre, en necesidad de tal tratamiento el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente.

De acuerdo con un aspecto adicional de la presente invención se proporciona un kit que comprende un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en combinación con un agente antitumoral seleccionado de uno listado de acuerdo con (i) – (x) aquí anteriormente.

De acuerdo con un aspecto adicional de la presente invención se proporciona un kit que comprende:

a) un compuesto de Fórmula (I) o una sal farmacéuticamente aceptable del mismo en una primera forma de dosificación unitaria;

b) un agente antitumoral seleccionado de un listado de acuerdo con (i) – (ix) aquí anteriormente; en una segunda forma de dosificación unitaria; y

c) un medio contenedor para contener dichas primera y segunda formas de dosificación.

En particular, los compuestos de la invención pueden ser usados para el tratamiento de varios cánceres dependientes de las hormonas incluyendo sin limitación el cáncer de próstata en combinación con uno o más de los siguientes agentes: agonistas de la gonadotrofina (GnRH) (agonistas LH–RH); inhibidores de la secreción de gonadotrofina; inhibidores de la 5–alfa reductasa; antiprogestinas; antiestrógenos; inhibidores de la aromatasa; progestinas; estrógenos; agentes citostáticos; agentes citotóxicos; inhibidores de las rutas de señalización del crecimiento celular, incluyendo sin limitación inhibidores de quinasa tal como inhibidores de quinasa VEGF; anticuerpos incluyendo sin limitación los anticuerpos dirigidos a los factores de señalización del crecimiento celular tal como anticuerpos EGF; oligonucleótidos antisentido; modificadores inmunológicos tal como

interferones, interleucinas, hormonas de crecimiento, y otras citoquinas; y otras terapias hormonales.

Los compuestos de la invención pueden también ser usados para el tratamiento de varias enfermedades y trastornos dependientes de las hormonas tal como el cáncer de próstata en combinación con uno o más de los siguientes agentes: antibióticos; agentes antiinflamatorios; abridores del canal de potasio; reemplazos de la hormona tiroides sintética; inhibidores de la proteína quinasa C (inhibidores PKC); e inhibidores o antagonistas de la inmunofilina.

De acuerdo a este aspecto de la invención se proporciona una composición farmacéutica que comprende un compuesto de Fórmula (I) como el definido aquí anteriormente y una sustancia antitumoral adicional como la definida aquí anteriormente para el tratamiento conjunto del cáncer.

Además a su uso en medicina terapéutica, los compuestos de Fórmula (I) y las sales farmacéuticamente aceptables de los mismos, también son útiles como herramientas farmacológicas en el desarrollo y estandardización de sistemas de prueba *in vitro* e *in vivo* para la evaluación de los efectos de los inhibidores de la actividad del ciclo celular en los animales de laboratorio tal como gatos, perros, conejos, monos, ratas y ratones, como parte de la búsqueda de nuevos agentes terapéuticos.

La invención será ahora ilustrada en los siguientes Ejemplos en los cuales, generalmente:

(i) las temperaturas son dadas en grados Celsio (°C); las operaciones fueron llevadas a cabo a temperatura del local o ambiente, o sea, a una temperatura en el rango de 18–25°C;

(ii) las soluciones orgánicas fueron secadas sobre sulfato de magnesio anhidro; la evaporación del solvente fue llevada a cabo usando un evaporador rotatorio a presión reducida (600–4000 Pascales; 4.5–30 mmHg) con una temperatura del baño de hasta 60°C;

(iii) cromatografía significa cromatografía flash en gel de sílice; la cromatografía de capa delgada (TLC) fue llevada a cabo en placas de gel de sílice;

(iv) en general, el curso de las reacciones fue seguido por TLC y/o LC–MS y los tiempos de reacción son dados para ilustración solamente;

(v) los productos finales tuvieron datos espectrales de masa y/o espectros de resonancia magnética (NMR) de protón satisfactorios;

(vi) los rendimientos son dados para ilustración solamente y no son necesariamente aquellos obtenidos por el desarrollo de procesos diligentes; las preparaciones fueron repetidas si más material era requerido;

(vii) cuando son dados, los datos de NMR están en forma de valores delta para los protones en diagnósticos importantes, dados en partes por millón (ppm) en relación con el tetrametilsilano (TMS) como un estándar interno, determinados a 500MHz usando perdeuterio dimetil sulfóxido (DMSO–d_6) como solvente a menos que se indique lo contrario; las siguientes abreviaturas han sido usadas: s, singlete; d, doblete; t, triplete; q, cuartete; m, multiplete; bs, singlete amplio;

(viii) los símbolos químicos tienen sus significados habituales; símbolos y unidades SI son usados;

(ix) los datos de los espectros de masa (MS) y LC–MS fueron generados en un sistema LC-MS donde el componente de la HPLC comprendió generalmente un equipamiento Agilent 1100, Waters Alliance HT (2790 & 2795) o una bomba HP1100 y Arreglo de Diodos con automuestreador CTC y fueron corridos en una columna Phenomenex Gemini C18 5 µm, 50 x 2 mm (o similar) eluyendo con eluente ácido (por ejemplo, usando un gradiente entre 0 – 95% agua / acetonitrilo con 5% de 1% ácido fórmico en una mezcla 50:50 agua:acetonitrilo (v/v)), o un eluente básico (por ejemplo, usando un gradiente entre 0 – 95% agua / acetonitrilo con 5% de una mezcla de 0.1% amoniaco 880 en acetonitrilo); y el componente de la MS comprendió generalmente un espectrómetro de masa Waters ZQ explorando sobre un rango de masa apropiado. Los cromatogramas para la Intensidad del Pico Base positivo y negativo por Electrospray (ESI), y Cromatograma de Absorción UV Total de 220–300nm, son generados y los valores para m/z son dados; generalmente, solamente los iones que indican la masa madre son reportados y a menos que se indique lo contrario el valor dado es el $(M+H)^+$ para el modo de ion positivo y (M–H)– para el modo de ion negativo;

(x) a menos que se indique lo contrario los compuestos que contienen un átomo de carbono y/o azufre asimétricamente sustituido no han sido resueltos;

(xi) cualquiera de las reacciones de microondas fueron llevadas a cabo en un microondas Biotage Optimizer EXP, o un CEM Explorer;

(xii) la cromatografía líquida de alta resolución preparativa (HPLC) fue realizada en un instrumento Gilson usando las siguientes condiciones:

Columna: C18 fase invertida sílice, por ejemplo, Waters 'Xbridge', 5 µm sílice, 19 x 100 mm, o 30 x 100 mm, usando mezclas de solventes decrecientemente polares como eluente (proporción de decrecimiento del Solvente A al Solvente B)

Solvente A: Agua con 1% hidróxido de amonio

Solvente B: Acetonitrilo

Tasa de flujo: 28 ml / min ó 61 ml / min

Gradiente: Ajustado para seguir cada compuesto – generalmente 7–10 min de longitud

Longitud de onda: 254 nm

(xiii) La cromatografía de intercambio catiónico fuerte (SCX) fue realizada en cartuchos preembasados (por ejemplo, cartuchos basados en ISOLUTE SCX–2 ácido propil sulfónico suministrado por International Sorbent Technology), usando un eluente básico (por ejemplo, amoniaco 2M en metanol);

(xiv) las siguientes abreviaturas han sido usadas aquí, donde sea necesario:

DMF	*N,N*-Dimetilformamida
DCM	Diclorometano
DME	1,2-Dimetoxietano
DMSO	Dimetilsulfóxido
THF	tetrahidrofurano
HATU	hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio
EDCI	1-(3-Dimetilaminopropil)-3-etilcarbodiimida
DCCI	1,3-Diciclohexilcarbodiimida
PYBOP	Hexafluorofosfato de benzotriazol-1-il-oxi-trispirrolidinofosfonio
DEAD	Azodicarboxilato de dietilo
DIAD	Azodicarboxilato de diisopropilo
DTAD	Azodicarboxilato de di-*tert*-butilo
DIPEA	N,N-Diisopropiletilamina
MeOH	Metanol
TFA	Ácido trifluoroacético
m-CPBA	Ácido m-cloroperoxibenzoico
AcOH	Ácido acético
DMA	*N,N*-Dimetilacetamida
EtOAc	Acetato de etilo
EtOH	Etanol
MeCN	Acetonitrilo
MTBE	Metil *tert*-butil éter
CAS	Chemical Abstracts Service

Difracción de Rayos X en Polvo (DRXP)

Los patrones de difracción de rayos X en polvo de las formas cristalinas fueron determinados colocando una muestra del material cristalino sobre soportes de obleas de

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monocristales de silicio (SSC) de Siemens, y extendiendo la muestra en una capa delgada con la ayuda de un portabjetos de microscopio. La muestra se hizo girar a 30 revoluciones por minute (para mejorar la estadística del recuento), y se irradió con rayos X generados mediante un tubo de cobre con foco largo y fino operado a 40 kV y 40 mA, con una longitud de onda de 1,5418 Angstroms utilizando un difractómetro de rayos X en polvo Bruker D5000 (Bruker AXS, Banner Lane Coventry CV4 9GH). La fuente de rayos X colimados se hizo pasar a través de una rendija automática de divergencia variable, ajustada a V20 y la radiación reflejada se dirigió a través de una rendija antidispersión de 2 mm y una rendija detectora de 0.2 mm. La muestra se expuso durante 1 segundo por incremento de 2-theta de 0.02 grados (modo de barrido continuo) a lo largo del intervalo de 2-theta de 2 grados a 40 grados en modo de barrido continuo theta-theta. El instrumento estaba equipado con un contador de centelleo como detector. El control y la captura de datos se realizaron por medio de un ordenador Dell Optiplex 6 6 NT 4.0 operando con software Diffrac+.

Un experto es consciente de que se puede obtener un patrón de difracción de rayos X en polvo que tiene uno o más errores de medida dependiendo de las condiciones de medida (tal como el equipamiento, la preparación de la muestra o el aparato utilizado). En particular, generalmente se sabe que las intensidades en los patrones de rayos X en polvo pueden fluctuar dependiendo de las condiciones de medida y la preparación de la muestra. Por ejemplo, un experto se dará cuenta de que la intensidad relativa de los picos puede verse afectada por, por ejemplo, granos de un tamaño mayor a 30 micrones y proporciones de aspecto no unitario, lo cual podría afectar al análisis de las muestras. Un experto también se dará cuenta de que la posición de la reflexión puede también verse afectada por la altura exacta a la que se coloca la muestra en el difractómetro y el calibrado cero del difractómetro. Puede que también tenga un pequeño efecto el cómo de plana sea la muestra. De ahí que un experto en la material apreciará que los datos para los patrones de difracción presentados aquí no deben interpretarse como absolutos (para más información ver Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996). Por lo tanto, se entenderá que la forma cristalina no está limitada a los cristales que proporcionen patrones de difracción de rayos X en polvo idénticos a los patrones de difracción de rayos X en polvo que se muestran en las Figuras A a D, y cualquier cristal que proporcione patrones de difracción de rayos X en polvo sustancialmente iguales a los que se muestran en las Figuras A a D entra dentro del alcance

de la presente invención. Un experto en el campo de la difracción de rayos X en plovo es capaz de judgar la identidad sustancial de patrones de difracción de rayos X en polvo.

Calorimetría Diferencial de Barrido (DSC, por sus siglas en inglés)

DSC fue regitrada utilizando un sistema Thermal Analysis Q1000. Típicamente, se calientan menos de 5mg de material, contenidos en un recipiente de aluminio con una tapa sellada, durante un intervalo de temperatua de 25°C a 300°C para una tasa de calentamiento constante de 10°C por minuto. Se utilizó nitrógeno como gas de purga con una velocidad de fujo de 50ml por minuto.

Método Sintético General 1

Procedimiento general para la reacción de una 6–cloro–3–(alquil–fluorado)–[1,2,4]–triazolo[4,3–b]piridazina con una amina cíclica

Una solución de la amina cíclica (1.47 mmol; 3 equivalentes) en etanol (1 mL) fue añadida a 6–cloro–3–(alquil–fluorado)–[1,2,4]–triazolo[4,3–b]piridazina (0.49 mmol) (ver abajo para la preparación de nuevos materiales de partida) y la reacción fue calentada y agitada a 70°C toda la noche. La mezcla de reacción fue evaporada hasta secarse y purificada por HPLC usando una columna Waters X Bridge C18 (5µ sílice, 19 mm diámetro, 100 mm longitud) eluida con mezclas decrecientemente polares de agua (conteniendo 5% amoniaco acuoso) y acetonitrilo para dar la 6–ciclicoamino–3–(alquil–fluorado)–[1,2,4]–triazolo[4,3–b]piridazina correspondiente.

La 6–cloro–3–difluorometil–[1,2,4]–triazolo[4,3–b]piridazina usada como material de partida para el Método Sintético General 1 fue preparada de acuerdo al siguiente procedimiento:

6–Cloro–3–difluorometil–[1,2,4]–triazolo[4,3–b]piridazina

Una mezcla de 3–cloropiridazin–6–il hidrazina (5.0g, 34.72 mmol) y ácido difluoroacético (21.93 mL; alrededor de 347 mmol) fue calentada a 100 °C durante 3 horas y entonces evaporada hasta secarse. El residuo no volátil fue disuelto en acetato de etilo (200 mL) y lavado secuencialmente con carbonato de sodio acuoso saturado y luego salmuera saturada. La fase orgánica fue secada sobre $MgSO_4$, filtrada, y evaporada para dar 6–cloro–3–difluorometil–[1,2,4]–triazolo[4,3–b]piridazina (6.0 g, 84.7%) como un sólido blanco que fue usado sin purificación adicional.

^{1}H NMR (300.13 MHz, DMSO–d_6) δ 7.68 (1H, t), 7.72 (1H, t, J_{HF} = 51.2 Hz), 8.59 – 8.62 (1H, m); m/z 205.38 $(M+1)^+$.

La 6–cloro–3–(3,3,3–trifluoroetil)–[1,2,4]–triazolo[4,3–b]piridazina usada como material de partida para el Método Sintético General 1 fue preparada de acuerdo al siguiente procedimiento:

6–Cloro–3–(3,3,3–trifluoroetil)–[1,2,4]–triazolo[4,3–b]piridazina

Una mezcla de 3–cloropiridazin–6–il hidrazina (5.0 g, 34.72 mmol) y ácido trifluoropropiónico (44.4 g, 347 mmol) fue calentada a 100 °C durante 3 horas y luego evaporada hasta secarse. El residuo no volátil fue extraído con acetato de etilo hirviendo (200 mL), el extracto de acetato de etilo caliente fue filtrado y se dejó enfriar a temperatura ambiente, y el producto fue aislado por filtración para dar 6–cloro–3–(3,3,3–trifluoroetil)–[1,2,4]–triazolo[4,3–b]piridazina (2.0 g, 24 %) como un sólido blanco hueso que fue usado sin purificación adicional.

^{1}H NMR (300.13 MHz, DMSO–d_6) δ 4.37 – 4.40 (2H, m), 7.56 – 7.59 (1H, m), 8.51 – 8.54 (1H, m); m/z 237.42 $(M+1)^+$.

La 6–cloro–3–(2,2,3,3–tetrafluoroetil)–[1,2,4]–triazolo[4,3–b]piridazina usada como material de partida para el Método Sintético General 1 fue preparada de acuerdo al siguiente procedimiento:

6–Cloro–3–(2,2,3,3–tetrafluoroetil)–[1,2,4]–triazolo[4,3–b]piridazina

Una mezcla de 3–cloropiridazin–6–il hidrazina (5.0 g, 34.72 mmol) y ácido tetrafluoropropiónico (32.5 mL; alrededor de 347 mmol) fue calentada a 100 °C durante 3 horas y luego evaporada hasta secarse. El residuo no volátil fue disuelto en acetato de etilo (200 mL) y lavado secuencialmente con carbonato de sodio acuoso saturado y luego con salmuera saturada. La fase orgánica fue secada sobre $MgSO_4$, filtrada, y evaporada para dar 6–cloro–3–(2,2,3,3–tetrafluoroetil)–[1,2,4]–triazolo[4,3–b]piridazina (4.2 g, 48.8%) como un sólido blanco que fue usado sin purificación adicional.

^{1}H NMR (300.13 MHz, DMSO–d_6) δ 7.21 (1H, t), 7.73 – 7.77 (1H, m), 8.65 – 8.68 (1H, m); m/z 255.28 $(M+1)^+$.

Método Sintético General 2

Procedimiento general para la reacción de una 6–cloro–3–(heteroátomo)–[1,2,4]–triazolo[4,3–b]piridazina con una amina cíclica

Una solución de la amina cíclica (1.10 mmol; 3 equivalentes) en etanol (2 mL) fue añadida a 6–cloro–3–(heteroátomo)–[1,2,4]–triazolo[4,3–b]piridazina (0.37 mmol) (ver abajo para la preparación de nuevos materiales de partida) y la reacción fue calentada y agitada a 70°C toda la noche. La mezcla de reacción fue evaporada hasta secarse y purificada por HPLC usando una columna Waters X Bridge C18 (5µ sílice, 19 mm diámetro, 100 mm longitud) eluida con mezclas decrecientemente polares de agua (conteniendo 5% amoniaco acuoso) y acetonitrilo para dar la 6–(ciclicoamino)–3–(heteroátomo)–[1,2,4]–triazolo[4,3–b]piridazina correspondiente.

Método Sintético General 3

Procedimiento general para la reacción de una 6–cloro–3–trifluorometil–[1,2,4]–triazolo[4,3–b]piridazina con una amina cíclica

Una solución de la amina cíclica (0.55 mmol) en etanol (1 mL) fue añadida a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (0.050 g, 0.22 mmol) y la mezcla fue calentada a 70°C durante 16 horas o hasta que el HPLC–MS analítico indicó que la reacción se completó. La mezcla de reacción fue evaporada para dejar un residuo no volátil que fue purificado por cromatografía de fase inversa preparativa para dar la 6–(ciclicoamino)–3–trifluorometil–[1,2,4]–triazolo[4,3–b]piridazina correspondiente.

Método Sintético General 4

Procedimiento general para la reacción de una 6–cloro–3–trifluorometil–[1,2,4]–triazolo[4,3–b]piridazina con la sal del ácido de una amina cíclica

Una solución de la sal del ácido de una amina cíclica (0.55 mmol) en etanol (1 mL) fue añadida a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (0.050 g, 0.22 mmol). La mezcla de reacción fue tratada con diisopropiletilamina (1 equivalente/sal del ácido) y la mezcla fue calentada a 70°C durante 16 horas o hasta que la HPLC–MS analítica indicó que la reacción se completó. La mezcla de reacción fue evaporada para dejar un residuo no volátil que fue purificado por cromatografía de fase inversa preparativa para dar la 6–(ciclicoamino)–3–trifluorometil–[1,2,4]–triazolo[4,3–b]piridazina correspondiente.

Método Sintético General 5

Procedimiento general para la aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con un aldehído

(Poliestirilmetil)trimetilamonio cianoborohidruro (4.1 mmol/g, 0.049 g, 0.2 mmol) fue añadido al aldehído (0.2 mmol) seguido por una solución de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.05 g, 0.184 mmol) en una mezcla de ácido acético y diclorometano (1:9; 2 mL). La mezcla fue agitada durante 40 horas y luego filtrada. El filtrado fue evaporado y el residuo no volátil fue purificado por cromatografía de fase inversa preparativa para producir la 6–(4–(metil–sustituido)–piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina correspondiente.

La 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de tert–butil 4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazina–1–carboxilato

Una mezcla de tert–butil piperazina–1–carboxilato (8.29 g, 44.5 mmol) y etanol (90 mL) fue añadida a una mezcla de diisopropiletilamina (9.16 mL, 52.6 mmol) y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (9.0 g, 40.4 mmol) en etanol (90 mL). La mezcla fue calentada a 70°C durante 11 horas y luego se dejó enfriar a temperatura ambiente para dar un precipitado. El precipitado fue recogido por filtración, lavado con etanol frío y luego con agua, y secado bajo vacío para producir tert–butil 4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazina–1–carboxilato (13.64 g, 90.6%) como un sólido blanco que fue usado sin purificación adicional.
1H NMR (300.132 MHz, DMSO) d 1.43 (s, 9H), 3.48 (m, 4H), 3.62 (m, 4H), 7.58 (d, 1H), 8.28 (d, 1H); m/z 373 $(M+H)^+$.

Preparación de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Ácido trifluoroacético (25 mL, 324.49 mmol) fue añadido a una mezcla de tert–butil 4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazina–1–carboxilato (6.7 g, 17.99 mmol) y diclorometano (100 mL) a temperatura ambiente y la solución resultante fue agitada a temperatura ambiente durante 1 hora. La mezcla de reacción fue evaporada para dar un residuo no volátil que fue tratado con solución de bicarbonato de sodio acuoso saturado (100 mL) y entonces extraído con diclorometano (4 x 200mL). Las fases orgánicas fueron combinadas y secadas sobre Na_2SO_4, filtradas, y evaporadas para dar 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (4.78 g, 98 %) como un sólido blanco que fue usado sin purificación adicional.

1H NMR (300.132 MHz, DMSO) δ 2.43 (s, 1H), 2.74 – 2.87 (m, 4H), 3.45 – 3.59 (m, 4H), 7.57 (d, 1H), 8.22 (d, 1H); m/z 273 $(M+H)^+$.

Método Sintético General 6

Procedimiento general para la aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con un aldehído

Una solución del aldehído (0.2 mmol) en diclorometano (0.5 mL) fue añadida a una mezcla de (Poliestirilmetil)trimetilamonio cianoborohidruro (4.1 mmol/g, 0.049 g, 0.2 mmol), 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.05 g, 0.184 mmol) y una mezcla de ácido acético y diclorometano (1:9; 2 mL). La mezcla de reacción fue agitada durante 16 horas y luego filtrada. El filtrado fue evaporado y el residuo no volátil fue purificado por cromatografía de fase inversa preparativa para producir la 6–(4–(metil–sustituido)–piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina correspondiente.

Método Sintético General 7

Procedimiento general para la aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con un aldehído

(Poliestirilmetil)trimetilamonio cianoborohidruro (4.1 mmol/g, 0.061 g, 0.25 mmol) fue añadido al aldehído (0.25 mmol) seguido por una solución de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.05 g, 0.184 mmol) en una mezcla de ácido acético y diclorometano (1:9; 2 mL). La mezcla fue agitada durante 4 días y luego filtrada. El filtrado fue evaporado y el residuo no volátil fue purificado por cromatografía de fase inversa preparativa para producir la 6–(4–(metil–sustituido)–piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina correspondiente.

Método Sintético General 8

Procedimiento general para la aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con un aldehído

(Poliestirilmetil)trimetilamonio cianoborohidruro (4.1 mmol/g, 0.049 g, 0.2 mmol) fue añadido al aldehído (0.2 mmol) seguido por una solución de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (0.053 g, 0.184 mmol) en una mezcla de ácido acético y diclorometano (1:9; 2 mL). La mezcla fue agitada durante 16 horas y luego filtrada. El filtrado fue evaporado y el residuo fue purificado por cromatografía de fase

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inversa preparativa para producir la 6–(4–(metil–sustituido)–1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina correspondiente.

La 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina usada como material de partida fue preparada como sigue:

Preparación de tert–butil 4–[3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazin–6–il]–1,4–diazepan–1–carboxilato

tert–Butil 1,4–diazepan–1–carboxilato (4.00 g, 20.0 mmol) fue añadido a una mezcla de diisopropiletilamina (4.11 mL, 23.7 mmol) y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (4.0 g, 18.2 mmol) en etanol (80 mL). La mezcla fue calentada bajo reflujo durante 6 horas y entonces se dejó enfriar a temperatura ambiente para dar un precipitado. El precipitado fue recogido por filtración, lavado con etanol, y secado bajo vacío para proporcionar tert–butil 4–[3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazin–6–il]–1,4–diazepan–1–carboxilato (5.94 g, 85.4 %) como un sólido blanco. 1H NMR (300.132 MHz, DMSO) δ 1.15 (9H, d), 1.72 – 1.93 (2H, m), 3.27 – 3.39 (2H, m), 3.50 – 3.63 (2H, m), 3.66 – 3.75 (2H, m), 3.83 (2H, t), 7.46 – 7.56 (1H, m), 8.19 – 8.31 (1H, m); aparentemente como una mezcla de rotámeros; m/z 387 $(M+H)^+$.

Preparación de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina

Ácido trifluoroacético (8 mL, 103.68 mmol) fue añadido a una mezcla de tert–butil 4–[3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazin–6–il]–1,4–diazepan–1–carboxilato (5.9 g, 15.3 mmol) y diclorometano (80 mL) a temperatura ambiente y la solución resultante fue agitada a temperatura ambiente durante 6 horas. La mezcla de reacción fue evaporada para dar un residuo no volátil que fue tratado con solución de bicarbonato de sodio acuosa saturada (100 mL) y luego extraída con diclorometano (4 x 200 mL). Las fases orgánicas fueron combinadas y secadas sobre Na_2SO_4, filtradas, y evaporadas para dar 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (3.8 g, 86.9 %) como un sólido blanco. 1H NMR (300.132 MHz, DMSO) δ 1.68 – 1.84 (m, 2H), 2.69 (t, 2H), 2.88 (t, 2H), 3.60 – 3.79 (m, 4H), 7.46 (d, 1H), 8.19 (d, 1H); m/z. 287 $(M+H)^+$.

Método Sintético General 9

Procedimiento general para la aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con un aldehído

(Poliestirilmetil)trimetilamonio cianoborohidruro (4.1 mmol/g, 0.061 g, 0.25 mmol) fue añadido al aldehído (0.25 mmol) seguido por una solución de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina (0.050 g, 0.184 mmol) en una mezcla de ácido acético y diclorometano (1:9; 2 mL). La mezcla fue agitada durante 40 horas y luego filtrada. El filtrado fue evaporado y el residuo no volátil fue purificado por cromatografía de fase inversa preparativa para producir la 6–(4–(metil–sustituido)–piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina correspondiente.

La 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina usada como material de partida fue preparada como sigue:

Preparación de 6–bromo–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina

Una mezcla de ácido polifosfórico (20 mL, 175 mmol) y N'–(5–bromopiridin–2–il)–2,2,2–trifluoroacetohidrazida (1.9 g, 6.69 mmol) fue agitada a 120 °C durante 20 horas y entonces vertida en agua. La mezcla fue entonces basificada con solución de bicarbonato de sodio acuosa saturada y extraído con diclorometano (3 x 250 mL). Las fases orgánicas fueron combinadas y lavadas con salmuera (1 x 100 mL), secadas con $MgSO_4$ y evaporadas para dar un residuo no volátil. El residuo fue purificado por cromatografía flash sobre gel de sílice usando un gradiente aumentado de acetato de etilo en isohexano como eluente para dar 6–bromo–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina (1.39 g, 78 %) como un sólido beige.

1H NMR (300.132 MHz, DMSO) δ 7.74 – 7.81 (m, 1H), 8.00 – 8.07 (m, 1H), 8.92 (s, 1H); m/z 266 y 268 ($M+H^+$).

Preparación de tert–butil 4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il)piperazina–1–carboxilato

Una solución de tert–butil piperazina–1–carboxilato (1.30 g, 6.99 mmol)], 6–bromo–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina (0.93 g, 3.50 mmol), bis(dibencilidenoacetona)paladio (0.101 g, 0.17 mmol), rac–2,2'–bis(difenilfosfino)–1,1'–binaftil (0.163 g, 0.26 mmol) y tert–butóxido de sodio (0.84g, 8.74 mmol) en xileno (30 mL) fue sellada en un tubo microondas y desgasificada durante 10 minutos. La mezcla de

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reacción fue calentada a 100 °C durante 30 minutos y luego enfriada a temperatura ambiente. La mezcla de reacción fue diluida con agua (20 mL) y luego extraída con acetato de etilo (2 x 40 mL). Las fases orgánicas fueron combinadas, secadas sobre Na_2SO_4, filtradas, y evaporadas para dar un residuo no volátil. El residuo fue purificado por cromatografía flash sobre gel de sílice usando un gradiente creciente de acetato de etilo en isohexano como eluente para dar tert–butil 4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il)piperazina–1–carboxilato (0.86 g, 66.2 %) como un sólido amarillo.
1H NMR (300.132 MHz, DMSO) δ 1.43 (s, 9H), 3.12 – 3.20 (m, 4H), 3.46 – 3.54 (m, 4H), 7.59 (s, 1H), 7.69 – 7.78 (m, 1H), 7.95 (d, 1H); m/z 372 ($M+H^+$).

Preparación de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina
Ácido trifluoroacético (5 mL, 64.90 mmol) fue añadido a una mezcla de tert–butil 4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il)piperazina–1–carboxilato (0.86 g, 2.32 mmol) y diclorometano (20 mL). La solución resultante fue agitada a 20 °C durante 90 minutos y luego evaporada para dejar un residuo no volátil. El residuo fue purificado por cromatografía de intercambio iónico en una columna SCX usando amoniaco acuoso (7M) en metanol como eluente para dar 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina (0.540 g, 86 %) como un sólido amarillo que fue usado sin purificación adicional.
1H NMR (300.132 MHz, DMSO) δ 2.79 – 2.92 (m, 4H), 3.03 – 3.13 (m, 4H), 7.49 (s, 1H), 7.67 – 7.76 (m, 1H), 7.91 (d, 1H); m/z 272 ($M+H^+$).

Método Sintético General 10

Procedimiento general para la aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con un aldehído
(Poliestirilmetil)trimetilamonio cianoborohidruro (4.1 mmol/g, 0.061 g, 0.25 mmol) fue añadido al aldehído (0.25 mmol) seguido por una solución de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.055 g, 0.184 mmol) en una mezcla de ácido acético y diclorometano (1:9; 2 mL). La mezcla fue agitada durante 16 horas y luego filtrada. El filtrado fue evaporado y el residuo no volátil fue purificado por cromatografía de fase inversa preparativa para producir la 6–(2–(metil–sustituido)–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina correspondiente.

La 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il) -3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Ácido trifluoroacético (15 mL, 194.70 mmol) fue añadido a una mezcla de tert–butil 5–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)hexahidropirrolo[3,4–c]pirrolo–2(1H)–carboxilato (3 g, 7.53 mmol) y diclorometano (60 mL). La solución resultante fue agitada a temperatura ambiente durante 1 hora y luego evaporada para dejar un residuo no volátil. El residuo fue purificado por cromatografía de intercambio iónico sobre una columna SCX usando amoniaco acuoso (7M) en metanol como eluente para dar 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (2.200 g, 98 %) como un sólido blanco que fue usado sin purificación adicional.

1H NMR (300.132 MHz, DMSO) δ 2.61 – 2.74 (m, 2H), 2.82 - 2.96 (m, 4H), 3.27 – 3.38 (m bajo H_2O, 2H), 3.67 – 3.80 (m, 2H), 7.27 (d, 1H), 8.20 (d, 1H); m/z 299 ($M+H^+$).

Ejemplo 1

Preparación de 6–(4–bencidrilpiperazin–1–il)–3–(1,1,2,2–tetrafluoroetil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencidrilpiperazina y 6–cloro–3–(2,2,3,3–tetrafluoroetil)–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 1 para dar 6–(4–bencidrilpiperazin–1–il)–3–(1,1,2,2–tetrafluoroetil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.46 (4H, t), 3.63 (4H, t), 4.39 (1H, s), 7.07 – 7.23 (3H, m), 7.33 (4H, t), 7.48 (4H, d), 7.51 – 7.52 (1H, m), 8.23 (1H, d); m/z = 471 [M+H]+.

Ejemplo 2

Preparación de 6–(4–bencil–1,4–diazepan–1–il)–3–(1,1,2,2–tetrafluoroetil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencil–1,4–diazepan y 6–cloro–3–(2,2,3,3–tetrafluoroetil)–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 1 para dar 6–(4–bencil–1,4–diazepan–1–il)–3–(1,1,2,2–tetrafluoroetil)–[1,2,4]triazolo[4,3–b]piridazina.

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1H NMR (700.03 MHz, DMSO–d6) δ 1.85 – 1.90 (2H, m), 2.61 (2H, t), 2.72 – 2.76 (2H, m), 3.63 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.05 – 7.21 (1H, m), 7.21 – 7.24 (1H, m), 7.24 – 7.27 (4H, m), 7.46 (1H, d), 8.19 (1H, d); m/z = 409 [M+H]+.

Ejemplo 3

Preparación de 6–piperidin–1–il–3–(2,2,2–trifluoroetil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de piperidina y 6–cloro–3–(3,3,3–trifluoroetil)–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 1 para dar 6–piperidin–1–il–3–(2,2,2–trifluoroetil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.59 – 1.62 (4H, m), 1.65 (2H, d), 3.60 (4H, t), 4.20 (2H, q), 7.43 (1H, d), 8.06 (1H, d); m/z = 286 [M+H]+.

Ejemplo 4

Preparación de 6–(4–bencidrilpiperazin–1–il)–3–(2,2,2–trifluoroetil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencidrilpiperazina y 6–cloro–3–(3,3,3–trifluoroetil)–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 1 para dar 6–(4–bencidrilpiperazin–1–il)–3–(2,2,2–trifluoroetil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.46 (4H, t), 3.62 (4H, s), 4.19 (2H, q), 4.39 (1H, s), 7.22 (2H, t), 7.33 (4H, t), 7.37 (1H, d), 7.48 (4H, d), 8.11 (1H, d); m/z = 453 [M+H]+.

Ejemplo 5

Preparación de 6–(4–bencidrilpiperazin–1–il)–3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencidrilpiperazina y 6–cloro–3–difluorometil–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 1 para dar 6–(4–bencidrilpiperazin–1–il)–3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.46 (4H, t), 3.63 (4H, s), 4.40 (1H, s), 7.21 – 7.23 (2H, m), 7.33 (4H, t), 7.28 – 7.57 (1H, m), 7.45 – 7.49 (5H, m), 8.18 – 8.19 (1H, m); m/z = 421 [M+H]+.

Ejemplo 6

Preparación de 6–(4–bencil–1,4–diazepan–1–il)–3–(difluor metil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencil–1,4–diazepan y 6–cloro–3–difluorom til–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 1 para dar 6–(4–bencil–1,4–diazepan–1–il)–3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.86 – 1.90 (2H, m), 2.01 (2H, t), 2.74 (2H, t), 3.63 (2H, s), 3.73 (2H, t), 3.75 (2H, t), 7.21 – 7.24 (1H, m), 7.26 (4H, t), 7.41 (1H, d), 7.40 – 7.55 (1H, m), 8.14 (1H, d); m/z = 359 [M+H]+.

Ejemplo 7

Preparación de 6–piperidin–1–il–[1,2,4]triazolo[4,3–b]piri lazin–3–amina

Una mezcla de piperidina y 3–amino–6–cloro–1,2,4–triazolo[,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 2 para dar 6– piperidin–1–il–[1,2,4]triazolo[4,3–b]piridazin–3–amina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.58 – 1.63 (6H, m), 3.53 (4H, t), 6.00 (2H, s), 7.07 (1H, d), 7.72 (1H, d); m/z = 219 [M+H]+.

Ejemplo 8

Preparación de 6–(4–bencidrilpiperazin–1–il)–3–cloro–[1, ,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencidrilpiperazina y 3,6–dicloro–1,2,4–tria zolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 2 para dar 6– (4–bencidrilpiperazin–1–il)–3–cloro–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.46 (4H, t), 3.63 (4H,), 4.40 (1H, s), 7.21 – 7.23 (2H, m), 7.33 (4H, t), 7.41 (1H, d), 7.47 (4H, d), 8.11 (1H, d); m/z = 405 [M+H]+.

Ejemplo 9

Preparación de 6–(4–bencidrilpiperazin–1–il)–3–metilsulf nil–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencidrilpiperazina y 6–cloro–3–metilsulfa il–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 2 para dar 6–(4–bencidrilpiperazin–1–il)–3–metilsulfanil–[1,2,4]triazolo[4,3–]piridazina.

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1H NMR (700.03 MHz, DMSO–d6) δ 2.46 (4H, t), 2.68 (3H, s), 3.58 (4H, t), 4.39 (1H, s), 7.21 – 7.23 (2H, m), 7.31 (1H, d), 7.33 (4H, t), 7.47 (4H, d), 8.05 (1H, d); m/z = 417 [M+H]+.

Ejemplo 10

Preparación de 6–(4–bencil–1,4–diazepan–1–il)–3–metilsulfanil–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencil–1,4–diazepan y 6–cloro–3–metilsulfanil–1,2,4–triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 2 para dar 6–(4–bencil–1,4–diazepan–1–il)–3–metilsulfanil–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.86 – 1.90 (2H, m), 2.50 (2H, t), 2.67 (3H, s), 2.74 (2H, t), 3.63 (2H, s), 3.72 (2H, t), 3.74 (2H, t), 7.22 – 7.24 (1H, m), 7.25 (1H, d), 7.26 – 7.28 (4H, m), 8.01 (1H, d); m/z = 355 [M+H]+.

Ejemplo 11

Preparación de 6–[4–(5–bromopiridin–2–il)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–(5–bromopiridin–2–il)piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina en etanol (7 mL) fue agitada a 80 °C durante 20 horas. La mezcla de reacción fue concentrada y particionada entre diclorometano (50 mL) y solución de bicarbonato de sodio acuoso saturado (25 mL). La fase acuosa fue extraída dos veces con diclorometano (2 x 50 mL). Las fases orgánicas fueron combinadas, lavadas con agua (100 mL), y concentradas para dar un residuo que fue purificado por cromatografía flash en gel de sílice usando acetato de etilo como eluente para dar 6–[4–(5–bromopiridin–2–il)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina 0.353 g, 73.4 %)

1H NMR (300.132 MHz, DMSO) δ 3.64 – 3.77 (8H, m), 6.90 (1H, d), 7.65 (1H, d), 7.71 – 7.76 (1H, m), 8.20 – 8.22 (1H, m), 8.29 (1H, d); m/z = 430 no asignado (Br).

Ejemplo 12

Preparación de 4–((4–(8–Metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)benzonitrilo

Una mezcla de 1–(4–cianobencil)–piperazina (0.158 g, 0.79 mmol) y 6–cloro–8–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina 0.062 g, 0.26 mmol) en etanol (5 mL) fue calentada hasta 70 °C durante 20 horas. La mezcla de reacción se dejó enfriar y luego fue

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concentrada para dar un residuo no volátil que fue purificado por cromatografía flash en gel de sílice usando un gradiente creciente de acetato de etilo en diclorometano para dar 4–((4–(8–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)benzonitrilo (0.0676 g, 64.3 %) como un sólido blanco; espectro 1H NMR ($CDCl_3$) δ 2.47 – 2.55 (4H, m), 2.61 (3H, d), 3.50 – 3.60 (6H, m), 6.72 – 6.76 (1H, m), 7.42 (2H, d), 7.57 (2H, d); m/z 402.69 (M+1)+.

La 6–cloro–8–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de una mezcla de 6–cloro–4–metilpiridazin–3–il hidrazina y 6–cloro–5–metilpiridazin–3–il hidrazina

Hidrazina hidrato (1.79 mL, 36.81 mmol) fue añadido a una suspensión agitada de 3,6–dicloro–4–metilpiridazina (0.50 g, 3.07 mmol) en agua (10 mL) y la mezcla de reacción fue calentada a 80 °C durante 4 horas. La mezcla de reacción se dejó enfriar y fue evaporada bajo presión reducida para dar una mezcla del compuesto de 3–cloro–6–hidrazinil–4–metilpiridazina y 6–cloro–3–hidrazinil–4–metilpiridazina (0.452 g) como un sólido color hueso que fue usado sin purificación adicional. m/z 159.41 (M+1)+.

Preparación de 6–cloro–7–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 6–cloro–8–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una suspensión de una mezcla del compuesto de 3–cloro–6–hidrazinil–4–metilpiridazina y 6–cloro–3–hidrazinil–4–metilpiridazina (0.200 g) en ácido trifluoroacético (10 mL) fue calentada bajo reflujo durante 20 horas. La mezcla de reacción se dejó enfriar y luego fue concentrada para dar un residuo no volátil que fue purificado por cromatografía flash en gel de sílice usando diclorometano como eluente para dar fracciones puras de:

6–cloro–8–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.0620 g) como un sólido blanco. 1H NMR ($CDCl_3$) δ 2.74 (3H, d), 7.05 (1H, q); m/z 237.37 (M+1)+; y

6–cloro–7–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.078 g) como un sólido blanco. 1H NMR ($CDCl_3$) δ 2.49 (3H, d), 7.97 (1H, q); m/z 237.37 (M+1)+.

Ejemplo 13

Preparación de 4–((4–(7–Metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)benzonitrilo

El método del ejemplo 12 fue repetido usando una mezcla de 6–cloro–7–metil–3–

(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.078 g, 0.33 mmol) y 1–(4–cianobencil)–piperazina (0.199 g, 0.99 mmol) para dar 4–((4–(7–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)benzonitrilo (0.099 g, 75%). 1H NMR ($CDCl_3$) δ 2.37 (3H, d), 2.53 – 2.63 (4H, m), 3.23 – 3.32 (4H, m), 3.57 (2H, s), 7.42 (2H, d), 7.57 (2H, d), 7.73 – 7.76 (1H, m); m/z 402.71 (M+1)+.

El 6–cloro–7–metil–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como se describió en el Ejemplo 12.

Ejemplo 14

Preparación de 6–[4–[(4–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–[(4–clorofenil)metil]piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina. 1H NMR (499.802 MHz, DMSO–d6) δ 2.48–2.51 (4H, m), 3.52 (2H, s), 3.56–3.62 (4H, m), 7.37 (4H, q), 7.57 (1H, d), 8.23 (1H, d) (Señal a 2.5 oscurecida por DMSO); m/z = 397 [M+H]+.

Ejemplo 15

Preparación de 6–[4–[(4–metoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–[(4–metoxifenil)metil]piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina. 1H NMR (499.802 MHz, DMSO–d6) δ 2.44–2.51 (4H, m), 3.47 (2H, s), 3.57–3.64 (4H, m), 3.75 (3H, s), 6.91 (2H, d), 7.25 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 393 [M+H]+.

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Ejemplo 16

Preparación de 6–[4–(2,6–dimetilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–(2,6–dimetilfenil)piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(2,6–dimetilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.
1H NMR (700.03 MHz, DMSO–d6) δ 2.31 (6H, s), 3.17 (4H, t), 3.73 (4H, t), 6.95 – 6.97 (1H, m), 7.00 (2H, d), 7.66 (1H, d), 8.27 (1H, d); m/z = 377 [M+H]+.

Ejemplo 17

Preparación de 1–[4–[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]fenil]etanona

Una mezcla de 1–(4–piperazin–1–ilfenil)etanona y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 1–[4–[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]fenil]etanona.
1H NMR (700.03 MHz, DMSO–d6) δ 2.47 (3H, s), 3.56 (4H, t), 3.79 (4H, t), 7.03 – 7.04 (2H, m), 7.66 (1H, d), 7.84 – 7.86 (2H, m), 8.30 (1H, d); m/z = 391 [M+H]+.

Ejemplo 18

Preparación de 6–[4–[4,4–bis(4–fluorofenil)butil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–[4,4–bis(4–fluorofenil)butil]piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–

[4,4–bis(4–fluorofenil)butil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.34 – 1.38 (2H, m), 2.02 (2H, q), 2.34 (2H, t), 2.42 (4H, t), 3.57 (4H, t), 4.01 (1H, t), 7.09 – 7.13 (4H, m), 7.32 – 7.35 (4H, m), 7.58 (1H, d), 8.23 (1H, d); m/z = 517 [M+H]+.

Ejemplo 19

Preparación de 6–[4–(3,5–dicloropiridin–4–il)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–(3,5–dicloropiridin–4–il)piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(3,5–dicloropiridin–4–il)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 3.45 – 3.46 (4H, m), 3.78 (4H, t), 7.67 (1H, d), 8.30 (1H, d), 8.50 (2H, s); m/z = 418 [M+H]+.

Ejemplo 20

Preparación de 1–fenil–8–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,8–triazaspiro[4.5]decan–4–ona

Una mezcla de 1–fenil–1,3,8–triazaspiro[4.5]decan–4–ona y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 1–fenil–8–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,8–triazaspiro[4.5]decan–4–ona.

1H NMR (700.03 MHz, DMSO–d6) δ 1.79 – 1.81 (2H, m), 2.55 (2H, d), 3.79 (2H, d), 4.19 – 4.22 (2H, m), 4.63 (2H, s), 6.67 (2H, d), 6.71 (1H, t), 7.07 - 7.09 (2H, m), 7.66 (1H, d), 8.29 (1H, d), 8.81 (1H, s); m/z = 418 [M+H]+.

Ejemplo 21

Preparación de 6–[4–(4–nitrofenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–(4–nitrofenil)piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(4–nitrofenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 3.66–3.74 (4H, m), 3.76–3.85 (4H, m), 7.06 (2H, d), 7.64 (1H, d), 8.10 (2H, d), 8.30 (1H, d); m/z = 394 [M+H]+.

Ejemplo 22

Preparación de 6–(4–bencidrilpiperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–bencidrilpiperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Phenomenex Luna C18 100A (10µ sílice, diámetro 21mm, longitud 150mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–(4–bencidrilpiperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.46 (4H, t), 3.63 (4H, t), 4.40 (1H, s), 7.21 – 7.23 (2H, m), 7.32 – 7.34 (4H, m), 7.46 – 7.48 (4H, m), 7.54 (1H, d), 8.25 (1H, d); m/z = 439 [M+H]+.

Ejemplo 23

Preparación de 6–(4–fenetilpiperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–fenetilpiperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–(4–fenetilpiperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

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1H NMR (700.03 MHz, DMSO–d6) δ 2.58 – 2.60 (6H, m), 2.79 (2H, t), 3.62 (4H, t), 7.18 – 7.21 (1H, m), 7.25 – 7.26 (2H, m), 7.28 – 7.30 (2H, m), 7.61 (1H, d), 8.25 (1H, d); m/z = 377 [M+H]+.

Ejemplo 24

Preparación de 1–piperidin–1–il–2–[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]etanona

Una mezcla de 2–piperazin–1–il–1–piperidin–1–iletanona y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 1–piperidin–1–il–2–[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]etanona.

1H NMR (700.03 MHz, DMSO–d6) δ 1.44 (2H, s), 1.53 (2H, s), 1.58 – 1.61 (2H, m), 2.58 (4H, t), 3.21 (2H, s), 3.42 (2H, t), 3.48 (2H, t), 3.61 (4H, t), 7.60 (1H, d), 8.26 (1H, d); m/z = 398 [M+H]+.

Ejemplo 25

Preparación de 6–[4–[(4–metoxifenil)–fenilmetil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–[(4–metoxifenil)–fenilmetil]piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metoxifenil)–fenilmetil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.45 (4H, t), 3.62 (4H, t), 3.72 (3H, s), 4.34 (1H, s), 6.88 – 6.90 (2H, m), 7.20 – 7.24 (1H, m), 7.31 – 7.33 (2H, m), 7.35 – 7.37 (2H, m), 7.44 – 7.45 (2H, m), 7.54 (1H, d), 8.25 (1H, d); m/z = 469 [M+H]+.

Ejemplo 26

Preparación de 6–[4–[fenil–[4–(trifluorometil)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–[fenil–[4–(trifluorometil)fenil]metil]piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[fenil–[4–(trifluorometil)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.45 – 2.49 (4H, m), 3.64 (4H, t), 4.57 (1H, s), 7.24 – 7.26 (1H, m), 7.35 (2H, t), 7.47 – 7.48 (2H, m), 7.54 (1H, d), 7.69 – 7.73 (4H, m), 8.26 (1H, d); m/z = 507 [M+H]+.

Ejemplo 27

Preparación de 6–[4–(6–bromonaftalen–2–il)sulfonilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–(6–bromonaftalen–2–il)sulfonilpiperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(6–bromonaftalen–2–il)sulfonilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 3.16 (4H, t), 3.72 (4H, t), 7.49 (1H, d), 7.81 – 7.83 (1H, m), 7.84 – 7.86 (1H, m), 8.16 (1H, d), 8.19 (1H, d), 8.21 (1H, d), 8.39 (1H, d), 8.52 (1H, d); m/z = 543 no asignado (Br).

Ejemplo 28

Preparación de N–[[(9aR)–2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,4,6,7,8,9,9a–octahidropirido[1,6–a]pirazin–7–il]metil]–2–metilquinolin–4–amina

Una mezcla de N–[[(9aR)–2,3,4,6,7,8,9,9a–octahidro–1H–pirido[1,6–a]pirazin–7–il]metil]–2–metilquinolin–4–amina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N–[[(9aR)–2–[3–

(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,4,6,7,8,9,9a–octahidropirido[1,6–a]pirazin–7–il]metil]–2–metilquinolin–4–amina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.06 – 1.10 (1H, m), 1.24 – 1.26 (1H, m), 1.69 – 1.71 (1H, m), 1.79 (1H, d), 1.91 – 1.94 (1H, m), 1.96 (1H, d), 2.09 – 2.12 (1H, m), 2.17 – 2.21 (1H, m), 2.47 (3H, s), 2.70 (1H, d), 2.85 – 2.87 (1H, m), 2.98 (1H, d), 3.02 – 3.06 (1H, m), 3.15 (2H, t), 4.13 (1H, d), 4.19 (1H, d), 6.37 (1H, s), 7.05 (1H, s), 7.33 – 7.36 (1H, m), 7.56 (1H, d), 7.62 (1H, d), 7.68 – 7.69 (1H, m), 8.19 (1H, d), 8.25 (1H, d); m/z = 497 [M+H]+.

Ejemplo 29

Preparación de 6–[4–(2,4–difluorofenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–(2,4–difluorofenil)piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(2,4–difluorofenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 3.13 (4H, t), 3.78 (4H, t), 7.01 – 7.04 (1H, m), 7.12 – 7.16 (1H, m), 7.22 – 7.25 (1H, m), 7.66 (1H, d), 8.29 (1H, d); m/z = 385 [M+H]+.

Ejemplo 30

Preparación de 6–[4–[3–cloro–5–(trifluorometil)piridin–2–il]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–[3–cloro–5–(trifluorometil)piridin–2–il]–1,4–diazepan y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[3–cloro–5–(trifluorometil)piridin–2–il]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.04 (2H, d), 3.76 (2H, t), 3.80 (2H, t), 3.96 (2H, d), 4.02 (2H, s), 7.52 (1H, d), 7.96 (1H, s), 8.20 (1H, d), 8.29 (1H, d); m/z = 466 [M+H]+.

Ejemplo 31

Preparación de 6–[4–[4–(4–fluorofenil)–5–(2–metoxipirimidin–4–il)imidazol–1–il]piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 4–[5–(4–fluorofenil)–3–piperidin–4–ilimidazol–4–il]–2–metoxipirimidina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[4–(4–fluorofenil)–5–(2–metoxipirimidin–4–il)imidazol–1–il]piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.07 – 2.13 (2H, m), 2.19 – 2.21 (2H, m), 3.13 (2H, d), 3.98 (3H, s), 4.43 – 4.45 (2H, m), 4.76 – 4.79 (1H, m), 6.96 (1H, d), 7.16 (2H, d), 7.42 – 7.44 (2H, m), 7.67 (1H, d), 8.17 (1H, s), 8.29 (1H, d), 8.56 (1H, d); m/z = 540 [M+H]+.

Ejemplo 32

Preparación de 6–[4–(2–metilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–(2–metilfenil)piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(2–metilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.32 (3H, s), 3.00 (4H, t), 3.77 (4H, t), 6.99 – 7.01 (1H, m), 7.06 (1H, d), 7.16 – 7.18 (1H, m), 7.20 (1H, d), 7.66 (1H, d), 8.28 (1H, d); m/z = 363 [M+H]+.

Ejemplo 33

Preparación de 6–[4–[(2–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 1–[(2–clorofenil)metil]–1,4–diazepan y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de

agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO–d6) δ 1.81–1.92 (2H, m), 2.65–2.70 (2H, m), 2.77–2.83 (2H, m), 3.70 (2H, s), 3.71–3.76 (2H, m), 3.76–3.80 (2H, m), 7.18–7.27 (2H, m), 7.34 (1H, d), 7.41 (1H, d), 7.49 (1H, d), 8.21 (1H, d); m/z = 411 [M+H]+.

Ejemplo 34

Preparación de 1–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]butan–1–ona

Una mezcla de 1–(2,3,3a,4,6,6a–hexahidro–1H–pirrolo[3,4–c]pirrol–5–il)butan–1–ona y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.2% amoniaco acuoso) y acetonitrilo como eluentes para dar 1–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]butan–1–ona.

1H NMR (300.132 MHz, DMSO–d6) δ 0.88 (3H, t), 1.51 (2H, sexteto), 2.16–2.25 (2H, m), 2.94–3.19 (2H, m), 3.25–3.34 (1H, m), 3.35–3.50 (3H, m), 3.54–3.64 (1H, m), 3.66–3.83 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Señal a 3.3 parcialmente oscurecida por agua); m/z = 369 [M+H]+.

Ejemplo 35

Preparación de tert–butil (1S,5R)–3–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–3,8–diazabiciclo[3.2.1]octano–8–carboxilato

Una mezcla de tert–butil (1S,5R)–3,8–diazabiciclo[3.2.1]octano–8–carboxilato y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 3. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar tert–butil (1S,5R)–3–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–3,8–diazabiciclo[3.2.1]octano–8–carboxilato.

1H NMR (300.132 MHz, DMSO–d6) δ 1.37 (9H, s), 1.59–1.69 (2H, m), 1.76–1.89 (2H, m), 3.00–3.10 (2H, m), 3.84–3.95 (2H, m), 4.18–4.25 (2H, m), 7.47 (1H, d), 8.20 (1H, d); m/z = 399 [M+H]+.

Ejemplo 36

Preparación de 6–[4–(3–metilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de dihidrocloruro de 1–(3–metilfenil)piperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 4. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(3–metilfenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 2.28 (3H, s), 3.76 (4H, t), 6.65 (1H, d), 6.80 – 6.81 (1H, m), 6.83 (1H, s), 7.13 (1H, t), 7.67 (1H, d), 8.29 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 363 [M+H]+.

Ejemplo 37

Preparación de 6–[4–(2–clorofenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de hidrocloruro de 1–(2–clorofenil)piperazina hidrato y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 4. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(2–clorofenil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 3.15 (4H, t), 3.79 (4H, t), 7.08 – 7.11 (1H, m), 7.21 – 7.22 (1H, m), 7.32 – 7.35 (1H, m), 7.45 – 7.47 (1H, m), 7.67 (1H, d), 8.30 (1H, d); m/z = 383 [M+H]+.

Ejemplo 38

Preparación de 6–[4–(6–cloronaftalen–2–il)sulfonilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de hidrocloruro de 1–(6–cloronaftalen–2–il)sulfonilpiperazina y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 4. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(6–cloronaftalen–2–il)sulfonilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 3.16 (4H, t), 3.72 (4H, t), 7.49 (1H, d), 7.71 – 7.72 (1H, m), 7.85 – 7.86 (1H, m), 8.16 (1H, d), 8.21 (1H, d), 8.23 (1H, d), 8.27 (1H, d), 8.53 (1H, d); m/z = 497 [M+H]+.

Ejemplo 39

Preparación de 1–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–4H–3,1–benzoxazin–2–ona

Una mezcla de hidrocloruro de 1–piperidin–4–il–4H–3,1–benzoxazin–2–ona y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 4. El producto crudo fue purificado por HPLC usando una columna Waters XTerra C18 (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 1–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–4H–3,1–benzoxazin–2–ona.

1H NMR (700.03 MHz, DMSO–d6) δ 1.95 – 1.97 (2H, m), 2.53 – 2.57 (2H, m), 3.22 (1H, d), 4.25 – 4.28 (1H, m), 4.41 – 4.43 (2H, m), 5.16 (2H, s), 7.12 – 7.15 (1H, m), 7.30 – 7.31 (1H, m), 7.37 (1H, d), 7.39 – 7.41 (1H, m), 7.67 (1H, d), 8.26 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 419 [M+H]+.

Ejemplo 40

Preparación de 1–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–3,4–dihidroquinolin–2–ona

Una mezcla de hidrocloruro de 1–piperidin–4–il–3,4–dihidroquinolin–2–ona y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 4. El producto crudo fue purificado por HPLC usando una columna Phenomenex Luna C18 100A (10µ sílice, diámetro 21mm, longitud 150mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y

acetonitrilo como eluentes para dar 1–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–3,4–dihidroquinolin–2–ona.

1H NMR (700.03 MHz, DMSO–d6) δ 1.83 – 1.85 (2H, m), 2.43 – 2.45 (2H, m), 2.61 – 2.67 (2H, m), 2.80 (2H, t), 3.15 – 3.18 (2H, m), 4.32 – 4.36 (1H, m), 4.39 – 4.41 (2H, m), 7.01 – 7.03 (1H, m), 7.23 – 7.26 (2H, m), 7.31 (1H, d), 7.66 (1H, d), 8.26 (1H, d); m/z = 417 [M+H]+.

Ejemplo 41

Preparación de 6–(5–bencil–2,5–diazabiciclo[2.2.1]heptan–2–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de (1R,4R)–6–bencil–3,6–diazabiciclo[2.2.1]heptano dihidrobromuro y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 4. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.2% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–(5–bencil–2,5–diazabiciclo[2.2.1]heptan–2–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.83 – 1.84 (1H, m), 2.00 (1H, d), 2.88 (1H, d), 3.63 (2H, s), 3.73 (2H, s), 7.23 (1H, d), 7.29 – 7.31 (2H, m), 7.32 (1H, t), 8.21 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 375 [M+H]+.

Ejemplo 42

Preparación de 6–[4–(piridin–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con piridina–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(piridin–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO–d6) δ 2.55–2.62 (4H, m), 3.61–3.66 (4H, m), 3.68 (2H, s), 7.26–7.32 (1H, m), 7.49 (1H, d), 7.59 (1H, d), 7.76–7.82 (1H, m), 8.25 (1H, d), 8.52 (1H, d); m/z = 364 [M+H]+.

Ejemplo 43

Preparación de 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo.

1H NMR (499.802 MHz, DMSO–d6) δ 2.51–2.57 (4H, m), 3.60–3.66 (6H, m), 7.54–7.62 (2H, m), 7.71 (1H, d), 7.76 (1H, d), 7.79 (1H, s), 8.26 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 388 [M+H]+.

Ejemplo 44

Preparación de 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo.

1H NMR (499.802 MHz, DMSO–d6) δ 2.51–2.56 (4H, m), 3.59–3.68 (6H, m), 7.53–7.62 (3H, m), 7.82 (2H, d), 8.26 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 388 [M+H]+.

Ejemplo 45

Preparación de 6–[4–[(4–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético

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General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO–d6) δ 2.48–2.52 (4H, m), 3.53 (2H, s), 3.58–3.66 (4H, m), 7.17 (2H, t), 7.34–7.41 (2H, m), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 381 [M+H]+.

Ejemplo 46

Preparación de 6–[4–[(2–metilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–metilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–metilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO–d6) δ 2.33 (3H, s), 2.49–2.53 (4H, m), 3.48 (2H, s), 3.56–3.61 (4H, m), 7.12–7.18 (3H, m), 7.25 (1H, d), 7.57 (1H, d), 8.23 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 377 [M+H]+.

Ejemplo 47

Preparación de 6–[4–[(4–metilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–metilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO–d6) δ 2.30 (3H, s), 2.45–2.51 (4H, m), 3.50 (2H, s), 3.56–3.65 (4H, m), 7.15 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 377 [M+H]+.

Ejemplo 48

Preparación de 6–[4–(1,3–benzotiazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1,3–benzotiazol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1,3–benzotiazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.73 (4H, t), 3.66 (4H, t), 4.04 (2H, s), 7.40 – 7.43 (1H, m), 7.46 – 7.51 (1H, m), 7.60 (1H, d), 7.94 (1H, d), 8.06 (1H, d), 8.25 (1H, d); m/z = 420 [M+H]+.

Ejemplo 49

Preparación de 6–[4–(1,3–benzoxazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1,3–benzoxazol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1,3–benzoxazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.72 (4H, t), 3.65 (4H, t), 3.97 (2H, s), 7.36 – 7.44 (2H, m), 7.59 (1H, d), 7.72 – 7.77 (2H, m), 8.25 (1H, d); m/z = 404 [M+H]+.

Ejemplo 50

Preparación de 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinolina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con quinolina–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 4–[[4–[3–(trifluorometil)–1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinolina.

1H NMR (499.802 MHz, DMSO) δ 2.65 (4H, t), 3.64 (4H, t), 4.04 (2H, s), 7.56 1H, d), 7.60 (1H, d), 7.63 – 7.67 (1H, m), 7.75 – 7.80 (1H, m), 8.05 (1H, d), 8.26 (1H, d), 8.33 (1H, d), 8.88 (1H, d); m/z = 414 [M+H]+.

Ejemplo 51

Preparación de 6–[4–(1,3–tiazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1,3–tiazol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1,3–tiazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.64 (4H, t), 3.63 (4H, t), 3.91 (2H, s), 7.58 (1H, d), 7.67 (1H, d), 7.73 (1H, d), 8.24 (1H, d); m/z = 370 [M+H]+.

Ejemplo 52

Preparación de 6–[4–(1–benzotiofen–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1–benzotiofeno–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1–benzotiofen–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.62 (4H, t), 3.65 (4H, t), 3.88 (2H, s), 7.30 – 7.38 (3H, m), 7.60 (1H, d), 7.78 (1H, d), 7.91 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]+.

Ejemplo 53

Preparación de 6–[4–(tiadiazol–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con tiadiazol–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(tiadiazol–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.62 (4H, t), 3.63 (4H, t), 4.13 (2H, s), 7.59 (1H, d), 8.25 (1H, d), 9.10 (1H, s); m/z = 371 [M+H]+.

Ejemplo 54

Preparación de 6–[4–[(1–metilbenzimidazol–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1–metilbenzimidazol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(1–metilbenzimidazol–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.62 (4H, t), 3.62 (4H, t), 3.85 – 3.89 (5H, m), 7.16 – 7.22 (1H, m), 7.22 – 7.28 (1H, m), 7.54 (1H, d), 7.57 – 7.62 (2H, m), 8.25 (1H, d); m/z = 417 [M+H]+.

Ejemplo 55

Preparación de 6–[4–(pirazin–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con pirazina–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(pirazin–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.61 (4H, t), 3.64 (4H, t), 3.75 (2H, s), 7.60 (1H, d), 8.26 (1H, d), 8.57 (1H, d), 8.60 – 8.62 (1H, m), 8.74 (1H, d); m/z = 365 [M+H]+.

Ejemplo 56

Preparación de 2–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinolina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con quinolina–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 2–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinolina.

1H NMR (499.802 MHz, DMSO) δ 2.61 (4H, t), 3.63 (4H, t), 3.83 (2H, s), 7.55 – 7.60 (2H, m), 7.67 (1H, d), 7.71 – 7.76 (1H, m), 7.96 (2H, t), 8.23 (1H, d), 8.34 (1H, d); m/z = 414 [M+H]+.

Ejemplo 57

Preparación de 6–[4–[(2–metilsulfonilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–metilsulfonilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–metilsulfonilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.60 (4H, t), 3.44 (3H, s), 3.62 (4H, t), 3.96 (2H, s), 7.58 – 7.67 (3H, m), 7.70 – 7.75 (1H, m), 7.99 – 8.02 (1H, m) 8.27 (1H, d); m/z = 441 [M+H]+.

Ejemplo 58

Preparación de 6–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinoxalina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con quinoxalina–6–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinoxalina.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.63 (4H, t), 3.81 (2H, s), 7.57 (1H, d), 7.86 – 7.89 (1H, m), 8.02 (1H, s), 8.07 (1H, d), 8.23 (1H, d), 8.91 (1H, d), 8.93 (1H, d); m/z = 415 [M+H]+.

Ejemplo 59

Preparación de 2–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 2–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzonitrilo.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.63 (4H, t), 3.74 (2H, s), 7.50 (1H, t), 7.60 (1H, d), 7.64 (1H, d), 7.69 – 7.74 (1H, m), 7.84 (1H, d), 8.26 (1H, d); m/z = 388 [M+H]+.

Ejemplo 60

Preparación de 6–[4–(1–benzotiofen–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1–benzotiofeno–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1–benzotiofen–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.62 (4H, t), 3.81 (2H, s), 7.36 – 7.44 (2H, m), 7.58 (1H, d), 7.63 (1H, s), 7.99 (1H, d), 8.03 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]+.

Ejemplo 61

Preparación de 6–[4–(1,3–tiazol–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1,3–tiazol–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1,3–tiazol–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.62 (4H, t), 3.75 (2H, s), 7.56 – 7.61 (2H, m), 8.25 (1H, d), 9.06 (1H, d); m/z = 370 [M+H]+.

Ejemplo 62

Preparación de 6–[4–[(2–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–clorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas

decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.59 (4H, t), 3.61 – 3.67 (6H, m), 7.30 – 7.34 (1H, m), 7.34 – 7.39 (1H, m), 7.44 – 7.47 (1H, m), 7.53 – 7.57 (1H, m), 7.60 (1H, d), 8.26 (1H, d); m/z = 397 [M+H]+.

Ejemplo 63

Preparación de 6–[4–(1H–indol–7–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–indol–7–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–indol–7–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.64 (4H, t), 3.82 (2H, s), 6.44 – 6.46 (1H, m), 6.94 – 7.03 (2H, m), 7.33 (1H, t), 7.48 (1H, d), 7.58 (1H, d), 8.25 (1H, d), 10.84 (1H, s); m/z = 402 [M+H]+.

Ejemplo 64

Preparación de 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinolina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con quinolina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinolina.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.63 (4H, t), 3.76 (2H, s), 7.55 – 7.62 (2H, m), 7.71 – 7.76 (1H, m), 7.97 (1H, d), 8.01 (1H, d), 8.21 - 8.26 (2H, m), 8.88 (1H, d); m/z = 414 [M+H]+.

Ejemplo 65

Preparación de 5–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]isoquinolina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con isoquinolina–5–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 5–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]isoquinolina.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.58 (4H, t), 3.95 (2H, s), 7.56 (1H, d), 7.61 – 7.66 (1H, m), 7.74 (1H, d), 8.06 (1H, d), 8.13 (1H, d), 8.23 (1H, d), 8.53 (1H, d), 9.31 (1H, s); m/z = 414 [M+H]+.

Ejemplo 66

Preparación de 6–[4–(naftalen–1–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con naftaleno–1–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(naftalen–1–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.58 (4H, t), 3.58 (4H, t), 3.94 (2H, s), 7.43 – 7.58 (5H, m), 7.83 – 7.88 (1H, m), 7.90 – 7.94 (1H, m), 8.23 (1H, d), 8.29 (1H, d); m/z = 413 [M+H]+.

Ejemplo 67

Preparación de 3–(trifluorometil)–6–[4–[[2–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método

Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[2–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina.
1H NMR (499.802 MHz, DMSO) δ 2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.50 (1H, t), 7.60 (1H, d), 7.67 – 7.75 (2H, m), 7.84 (1H, d), 8.26 (1H, d); m/z = 431 [M+H]+.

Ejemplo 68

Preparación de 6–[4–[(2,2–difluoro–1,3–benzodioxol–4–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2,2–difluoro–1,3–benzodioxol–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2,2–difluoro–1,3–benzodioxol–4–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.
1H NMR (499.802 MHz, DMSO) δ 2.56 (4H, t), 3.62 (4H, t), 3.67 (2H, s), 7.19 – 7.25 (2H, m), 7.32 – 7.35 (1H, m), 7.59 (1H, d), 8.25 (1H, d); m/z = 443 [M+H]+.

Ejemplo 69

Preparación de 6–[4–[(1–metilindol–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1–metilindol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(1–metilindol–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.
1H NMR (499.802 MHz, DMSO) δ 2.56 (4H, t), 3.59 (4H, t), 3.70 (2H, s), 3.78 (3H, s), 6.36 (1H, s), 6.99 (1H, t), 7.09 – 7.13 (1H, m), 7.40 (1H, d), 7 48 (1H, d), 7.57 (1H, d), 8.23 (1H, d); m/z = 416 [M+H]+.

Ejemplo 70

Preparación de 6–[4–(tiofen–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con tiofeno–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(tiofen–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.55 (4H, t), 3.62 (4H, t), 3.77 (2H, s), 6.98 – 7.02 (2H, m), 7.45 – 7.47 (1H, m), 7.59 (1H, d), 8.25 (1H, d); m/z = 369 [M+H]+.

Ejemplo 71

Preparación de 6–[4–[(1–metilindol–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1–metilindol–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(1–metilindol–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.55 (4H, t), 3.60 (4H, t), 3.70 (2H, s), 3.77 (3H, s), 7.04 (1H, t), 7.15 (1H, t), 7.26 (1H, s), 7.40 (1H, d), 7.56 (1H, d), 7.67 (1H, d), 8.23 (1H, d) (Señal a 2.55 parcialmente debajo de DMSO); m/z = 416 [M+H]+.

Ejemplo 72

Preparación de 6–[4–[(2–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters

XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.55 (4H, t), 3.59 – 3.65 (6H, m), 7.16 – 7.23 (2H, m), 7.32 – 7.38 (1H, m), 7.43 – 7.48 (1H, m), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.55 parcialmente debajo de DMSO); m/z = 381 [M+H]+.

Ejemplo 73

Preparación de 6–[4–(piridin–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con piridina–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(piridin–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.54 4H, t), 3.60 (2H, s), 3.64 (4H, t), 7.37 (2H, m), 7.59 (1H, d), 8.26 (1H, d), 8.52 – 8.55 (2H, m) (Señal a 2.54 parcialmente oscurecida por DMSO); m/z = 364 [M+H]+.

Ejemplo 74

Preparación de 6–[4–[(3–metilsulfonilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metilsulfonilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–metilsulfonilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

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1H NMR (499.802 MHz, DMSO) δ 2.53 (4H, t), 3.21 (3H, s), 3.62 (4H, t), 3.66 (2H, s), 7.57 (1H, d), 7.63 (1H, t), 7.69 (1H, d), 7.83 (1H, d), 7.88 (1H, s), 8.24 (1H, d); m/z = 441 [M+H]+.

Ejemplo 75

Preparación de 6–[4–[(2–metoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–metoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.52 (4H, t), 3.53 (2H, s), 3.60 (4H, t), 3.77 (3H, s), 6.90 – 6.95 (1H, m), 6.98 (1H, d), 7.21 – 7.26 (1H, m), 7.31 – 7.35 (1H, m), 7.56 (1H, d), 8.22 (1H, d); m/z = 393 [M+H]+.

Ejemplo 76

Preparación de 6–[4–(2,3–dihidro–1,4–benzodioxin–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2,3–dihidro–1,4–benzodioxina–5–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(2,3–dihidro–1,4–benzodioxin–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.52 (4H, t), 3.50 (2H, s), 3.59 (4H, t), 4.19 – 4.25 (4H, m), 6.73 – 6.80 (2H, m), 6.87 – 6.89 (1H, m), 7.56 (1H, d), 8.22 (1H, d); m/z = 421 [M+H]+.

Ejemplo 77

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Preparación de 6–[4–(1H–indol–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–indol–5–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–indol–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.52 – 2.54 (4H, m), 3.58 – 3.63 (6H, m), 6.38 – 6.41 (1H, m), 7.06 – 7.10 (1H, m), 7.32 (1H, t), 7.35 (1H, d), 7.47 (1H, s), 7.58 (1H, d), 8.24 (1H, d), 11.02 (1H, s) (Señal a 2.52 debajo de DMSO); m/z = 402 [M+H]+.

Ejemplo 78

Preparación de 6–[4–(1H–indol–6–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–indol–6–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–indol–6–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.51 – 2.55 (4H, m), 3.60 – 3.64 (6H, m), 6.38 – 6.41 (1H, m), 6.96 – 7.00 (1H, m), 7.31 (1H, t), 7.35 (1H, s), 7.49 (1H, d), 7.58 (1H, d), 8.24 (1H, d), 10.99 (1H, s) (Señal a 2.51 debajo de DMSO); m/z = 402 [M+H]+.

Ejemplo 79

Preparación de 6–[4–(furan–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con furan–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas

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decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(furan–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.51 – 2.55 (4H, m), 3.58 (2H, s), 3.61 (4H, t), 6.33 (1H, d), 6.40 – 6.44 (1H, m), 7.58 (1H, d), 7.60 – 7.62 (1H, m), 8.25 (1H, d) (Señal a 2.51 parcialmente oscurecida por DMSO); m/z = 353 [M+H]+.

Ejemplo 80

Preparación de 6–[4–(1H–pirazol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–pirazol–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–pirazol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.51 – 2.54 (4H, m), 3.51 – 3.65 (6H, m), 6.18 (1H, s), 7.41 (0H, s), 7.55 – 7.70 (2H, m), 8.24 (1H, d) (Señal a 2.51 oscurecida por DMSO); m/z = 353 [M+H]+.

Ejemplo 81

Preparación de 6–[4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con piridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.50 – 2.53 (4H, m), 3.57 (2H, s), 3.60 (4H, t), 7.34 – 7.39 (1H, m), 7.57 (1H, d), 7.71 – 7.76 (1H, m), 8.23 (1H, d), 8.46 – 8.49 (1H, m), 8.52 (1H, d) (Señal a 2.5 oscurecida por un pico de DMSO); m/z = 364 [M+H]+.

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Ejemplo 82

Preparación de 6–[4–[(3–metoxifenil)metil]piperazin–1–il] –3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–metoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.49 – 2.51 (4H, m), 3.50 (2H, s), 3.60 (4H, t), 3.74 (3H, s), 6.81 – 6.84 (1H, m), 6.87 – 6.91 (2H, m), 7.24 (1H, t), 7.56 (1H, d), 8.23 (1H, d) (Señal a 2.49 oscurecida por DMSO); m/z = 393 [M+H]+.

Ejemplo 83

Preparación de 6–[4–(1H–pirrol–2–ilmetil)piperazin–1–il] –3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–pirrol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–pirrol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.48 (4H, t), 3.48 (2H, s), 3.60 (4H, t), 5.89 – 5.92 (1H, m), 5.94 (1H, q), 6.64 – 6.67 (1H, m), 7.58 (1H, d), 8.24 (1H, d), 10.68 (1H, s) (Señal a 2.48 parcialmente oscurecida por DMSO); m/z = 352 [M+H]+.

Ejemplo 84

Preparación de 6–[4–(2,3–dihidro–1–benzofuran–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2,3–dihidro–1–benzofuran–5–carbaldehido fue llevada a cabo de acuerdo

al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(2,3–dihidro–1–benzofuran–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.47 – 2.51 (4H, m), 3.17 (2H, t), 3.45 (2H, s), 3.60 (4H, t), 4.51 (2H, t), 6.71 (1H, d), 7.02 (1H, d), 7.19 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.47 parcialmente oscurecida por DMSO); m/z = 405 [M+H]+.

Ejemplo 85

Preparación de 6–[4–(1,3–benzodioxol–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1,3–benzodioxol–5–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1,3–benzodioxol–5–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.47 – 2.50 (4H, m), 3.46 (2H, s), 3.61 (4H, t), 6.00 (2H, s), 6.77 – 6.80 (1H, m), 6.86 (1H, d), 6.90 (1H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.47 parcialmente oscurecida por DMSO); m/z = 407 [M+H]+.

Ejemplo 86

Preparación de 6–[4–(tiofen–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con tiofeno–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(tiofen–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.47 – 2.49 (4H, m), 3.54 (2H, s), 3.59 (4H, t), 7.05 – 7.08 (1H, m), 7.32 – 7.35 (1H, m), 7.47 – 7.50 (1H, m), 7.56 (1H, d), 8.23 (1H, d) (Señal a 2.47 parcialmente bajo DMSO); m/z = 369 [M+H]+.

Ejemplo 87

Preparación de 6–[4–[(1–metilpirrol–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1–metilpirrol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(1–metilpirrol–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.46 (4H, t), 3.44 (2H, s), 3.57 (4H, t), 3.60 (3H, s), 5.86 – 5.90 (2H, m), 6.67 (1H, t), 7.56 (1H, d), 8.23 (1H, d) (Señal a 2.46 parcialmente oscurecida por DMSO); m/z = 366 [M+H]+.

Ejemplo 88

Preparación de 6–[4–(2,3–dihidro–1,4–benzodioxin–6–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2,3–dihidro–1,4–benzodioxina–6–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(2,3–dihidro–1,4–benzodioxin–6–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.46 (4H, t), 3.40 (2H, s), 3.58 (4H, t), 4.21 (4H, s), 6.74 – 6.77 (1H, m), 6.78 (1H, s), 6.79 (1H, d), 7.56 (1H, d), 8.22 (1H, d) (Señal a 2.46 parcialmente debajo de DMSO); m/z = 421 [M+H]+.

Ejemplo 89

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Preparación de 6–[4–[(3–metilimidazol–4–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metilimidazol–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–metilimidazol–4–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.46 – 2.50 (4H, m), 3.49 (2H, s), 3.58 (4H, t), 3.62 (3H, s), 6.77 (1H, s), 7.55 (1H, s), 7.57 (1H, d), 8.23 (1H, d) (Señal a 2.46 debajo de DMSO); m/z = 367 [M+H]+.

Ejemplo 90

Preparación de 6–[4–(furan–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con furan–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(furan–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.46 – 2.49 (4H, m), 3.39 (2H, s), 3.59 (4H, t), 6.43 – 6.45 (1H, m), 7.56 (1H, s), 7.57 – 7.59 (1H, m), 7.61 (1H, t), 8.23 (1H, d) (Señal a 2.46 oscurecida por DMSO); m/z = 353 [M+H]+.

Ejemplo 91

Preparación de 6–[4–[(3–metilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas

decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–metilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.802 MHz, DMSO) δ 2.29 (3H, s), 2.47 (4H, t), 3.48 (2H, s), 3.59 (4H, t), 7.06 (1H, d), 7.10 (1H, d), 7.13 (1H, s), 7.21 (1H, t), 7.56 (1H, d), 8.22 (1H, d) (Señal a 2.29 oscurecida por DMSO); m/z = 377 [M+H]+.

Ejemplo 92

Preparación de 6–[4–(1H–benzimidazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–benzimidazol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–benzimidazol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 2.60–2.67 (4H, m), 3.61–3.69 (4H, m), 3.81 (2H, s), 7.09–7.21 (2H, m), 7.43–7.48 (1H, m), 7.53–7.62 (2H, m), 8.25 (1H, d), 12.33 (1H, s); m/z = 403 [M+H]+.

Ejemplo 93

Preparación de 6–[4–(1–benzofuran–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1–benzofuran–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1–benzofuran–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 2.58–2.67 (4H, m), 3.59–3.68 (4H, m), 3.76 (2H, s), 6.82 (1H, s), 7.18–7.32 (2H, m), 7.52–7.63 (3H, m), 8.24 (1H, d); m/z = 403 [M+H]+.

Ejemplo 94

Preparación de 6–[4–(1H–indol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–indol–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–indol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 2.51–2.59 (4H, m), 3.54–3.65 (4H, m), 3.71 (2H, s), 6.95–7.03 (1H, m), 7.04–7.12 (1H, m), 7.26 (1H, d), 7.36 (1H, d), 7.56 (1H, d), 7.66 (1H, d), 8.22 (1H, d), 10.94 (1H, s) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 402 [M+H]+.

Ejemplo 95

Preparación de 3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 2.50–2.57 (4H, m), 3.57–3.69 (6H, m), 7.54–7.71 (5H, m), 8.25 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 431 [M+H]+.

Ejemplo 96

Preparación de 6–[4–[(3–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético

General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, 21 mm diámetro, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 2.50–2.56 (4H, m), 3.57 (2H, s), 3.59–3.66 (4H, m), 7.05–7.21 (3H, m), 7.34–7.44 (1H, m), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 381 [M+H]+.

Ejemplo 97

Preparación de 6–[4–[(3–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–clorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 5. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, 21 mm diámetro, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 2.50–2.54 (4H, m), 3.56 (2H, s), 3.59–3.66 (4H, m), 7.27–7.43 (4H, m), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 397 [M+H]+.

Ejemplo 98

Preparación de 6–[4–[(4,5–dimetilfuran–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4,5–dimetilfuran–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 6. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4,5–dimetilfuran–2–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 1.88 (3H, s), 2.15 (3H, s), 3.45 (2H, s), 3.60 (4H, t), 6.07 (1H, s), 7.58 (1H, d), 8.24 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 381 [M+H]+.

Ejemplo 99

Preparación de 6–[4–(ciclohexilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con ciclohexanocarbaldehído fue llevada a cabo de acuerdo al Método Sintético General 6. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(ciclohexilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (700.03 MHz, DMSO–d6) δ 0.84 – 0.89 (2H, m), 1.15 – 1.18 (1H, m), 1.20 – 1.26 (2H, m), 1.51 – 1.54 (1H, m), 1.63 – 1.69 (3H, m), 1.76 (2H, d), 2.14 (2H, d), 2.46 (4H, t), 3.60 (4H, t), 7.59 (1H, d), 8.24 (1H, d); m/z = 369 [M+H]+.

Ejemplo 100

Preparación de 6–[4–[(2,2–difluoro–1,3–benzodioxol–5–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2,2–difluoro–1,3–benzodioxol–5–carbaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando a Phenomenex Luna C18 100A, 10m sílice, diámetro 21mm, longitud 150mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2,2–difluoro–1,3–benzodioxol–5–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.132 MHz, DMSO–d6) δ 2.50–2.55 (4H, m), 3.56 (2H, s), 3.58–3.65 (4H, m), 7.14–7.20 (1H, m), 7.33–7.40 (2H, m), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.5 oscurecida por DMSO); m/z = 443 [M+H]+.

Ejemplo 101

Preparación de 6–[4–(1H–indol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–indol–2–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, 21 mm diámetro, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–indol–2–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (500.133 MHz, DMSO–d6) δ 2.52–2.58 (4H, m), 3.58–3.65 (4H, m), 3.68 (2H, s), 6.29 (1H, s), 6.93 (1H, t), 7.02 (1H, t), 7.31 (1H, d), 7.44 (1H, d), 7.57 (1H, d), 8.22 (1H, d), 11.00 (1H, s); m/z = 402 [M+H]+.

Ejemplo 102

Preparación de 6–[4–(1,3–benzodioxol–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1,3–benzodioxol–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, 21 mm diámetro, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1,3–benzodioxol–4–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (500.133 MHz, DMSO–d6) δ 2.49–2.54 (4H, m), 3.51 (2H, s), 3.57–3.61 (4H, m), 5.98 (2H, s), 6.79–6.86 (3H, m), 7.56 (1H, d), 8.22 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 407 [M+H]+.

Ejemplo 103

Preparación de 5–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinoxalina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con quinoxalina–5–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, 21 mm diámetro, longitud 100 mm eluida con

mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 5–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]quinoxalina.

1H NMR (500.133 MHz, DMSO–d6) δ 2.60–2.66 (4H, m), 3.50–3.66 (4H, m), 4.24 (2H, s), 7.57 (1H, d), 7.85–7.90 (1H, m), 7.95 (1H, d), 8.03 (1H, s) 8.23 (1H, d), 8.96 (2H, s); m/z = 415 [M+H]+.

Ejemplo 104

Preparación de 6–[4–(1H–pirrol–3–ilmetil)piperazin–1–il] -3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 1H–pirrol–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, 21 mm diámetro, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–(1H–pirrol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (500.133 MHz, DMSO–d6) δ 2.43–2.48 (4H, m), 3.36 (2H, s), 3.54–3.60 (4H, m), 5.96 (1H, s), 6.63 (1H, s), 6.65–6.68 (1H, m), 7.56 (1H, d), 8.21 (1H, d), 10.57 (1H, s); m/z = 352 [M+H]+.

Ejemplo 105

Preparación de 6–[4–[[3–(4–metilfenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(4–metilfenoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[3–(4–metilfenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.30 (3H, s), 2.49 – 2.52 (4H, m), 3.53 (2H, s), 3.60 (4H, t), 6.86 – 6.88 (1H, m), 6.92 – 6.94 (2H, m), 6.96 (1H, s), 7.08 (1H, d), 7.21 (2H, d),

7.34 (1H, t), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 469 [M+H]+.

Ejemplo 106

Preparación de N,N–dimetil–4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]anilina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–dimetilaminobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N,N–dimetil–4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]anilina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.45 – 2.49 (4H, t), 2.88 (6H, s), 3.31 (2H, s), 3.60 (4H, t), 6.70 (2H, d), 7.13 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Señal de bencil oscurecida por agua); m/z = 406 [M+H]+.

Ejemplo 107

Preparación de N–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]acetamida

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con N–(4–formilfenil)acetamida fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]acetamida.

1H NMR (499.8 MHz, DMSO–d6) δ 2.04 (3H, s), 2.50 (4H, t), 3.48 (2H, s), 3.61 (4H, t), 7.24 (2H, d), 7.54 (2H, d), 7.58 (1H, d), 8.25 (1H, d), 9.90 (1H s) (Señal a 2.5 parcialmente oscurecida por DMSO); m/z = 420 [M+H]+.

Ejemplo 108

Preparación de 6–[4–[(4–etoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–etoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–etoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.33 (3H, t), 2.48 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 4.02 (2H, q), 6.89 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 407 [M+H]+.

Ejemplo 109

Preparación de 6–[4–[(4–butoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–butoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–butoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 0.94 (3H, t), 1.41 – 1.48 (2H, m), 1.67 – 1.73 (2H, m), 2.48 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 3.96 (2H, t), 6.89 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 435 [M+H]+.

Ejemplo 110

Preparación de 6–[4–[(3–nitrofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–nitrobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–nitrofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.57 (4H, t), 3.62 (4H, t), 3.71 (2H, s), 7.57 (1H, d), 7.64 (1H, t), 7.80 (1H, d), 8.12 – 8.15 (1H, m), 8.21 (1H, s), 8.24 (1H, d); m/z = 408 [M+H]+.

Ejemplo 111

Preparación de 6–[4–[(4–nitrofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–nitrobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–nitrofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.60 (1H, d), 7.65 (2H, d), 8.23 (2H, d), 8.26 (1H, d); m/z = 408 [M+H]+.

Ejemplo 112

Preparación de N,N–dimetil–3–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]propan–1–amina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(3–dimetilaminopropoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N,N–dimetil–3–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]propan–1–amina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.81 – 1.87 (2H, m), 2.15 (6H, s), 2.36 (2H, t), 2.49 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 3.98 (2H, t), 6.89 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 464 [M+H]+.

Ejemplo 113

Preparación de 6–[4–[(4–pirrolidin–1–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–pirrolidin–1–ilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando a Phenomenex Luna C18 100A, 10µ sílice, diámetro 21mm, longitud 150mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–pirrolidin–1–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.13 MHz, DMSO–d6) δ 1.92 – 1.97 (4H, m), 2.46 (4H, t), 3.21 (4H, t), 3.40 (2H, s), 3.59 (4H, t), 6.50 (2H, d), 7.10 (2H, d), 7.57 (1H, d), 8.23 (1H, d); m/z = 432 [M+H]+.

Ejemplo 114

Preparación de 6–[4–[[4–[(2–metilpropan–2–il)oxi]fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–[(2–metilpropan–2–il)oxi]benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[4–[(2–metilpropan–2–il)oxi]fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.30 (9H, s), 2.48 – 2.52 (4H, m), 3.50 (2H, s), 3.61 (4H, t), 6.94 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 435 [M+H]+.

Ejemplo 115

Preparación de 6–[4–[(4–propan–2–iloxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–propan–2–iloxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y

acetonitrilo como eluentes para dar 6–[4–[(4–propan–2–iloxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.27 (6H, d), 2.49 (4H, t), 3.46 (2H, s), 3.61 (4H, t), 4.56 – 4.61 (1H, m), 6.88 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 421 [M+H]+.

Ejemplo 116

Preparación de 3–(trifluorometil)–6–[4–[[3–(trifluorometilsulfanil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(trifluorometilsulfanil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[3–(trifluorometilsulfanil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.52 – 2.55 (4H, m), 3.63 (6H, d), 7.54 (1H, t), 7.59 (2H, d), 7.64 (1H, d), 7.70 (1H, s), 8.26 (1H, d) (Señal a 2.54 parcialmente oscurecida por DMSO); m/z = 463 [M+H]+.

Ejemplo 117

Preparación de 6–[4–[(4–piridin–3–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–piridin–3–ilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–piridin–3–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.56 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.48 – 7.51 (3H, m), 7.59 (1H, d), 7.72 (2H, d), 8.07 – 8.10 (1H, m), 8.26 (1H, d), 8.57 – 8.58 (1H, m), 8.91 (1H, d); m/z = 440 [M+H]+.

Ejemplo 118

Preparación de 6–[4–[(3–bromofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–bromobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–bromofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.50 – 2.54 (4H, m), 3.55 (2H, s), 3.63 (4H, t), 7.32 (1H, t), 7.35 – 7.37 (1H, m), 7.47 – 7.49 (1H, m), 7.55 (1H, s) 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.52 parcialmente oscurecida por DMSO); m/z = 441 no asignado (Br).

Ejemplo 119

Preparación de 6–[4–[[3–(4–clorofenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(4–clorofenoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[3–(4–clorofenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.53 (4H, m), 3.56 (2H, s), 3.61 (4H, t), 6.94 – 6.96 (1H, m), 7.03 – 7.06 (3H, m), 7.15 (1H, d), 7.38 (1H, d), 7.43 – 7.46 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.52 parcialmente oscurecida por DMSO); m/z = 489 [M+H]+.

Ejemplo 120

Preparación de 6–[4–[[3–(4–metoxifenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(4–metoxifenoxi)benzaldehído fue llevada a cabo de acuerdo al Método

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Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[3–(4–metoxifenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.49 – 2.51 (4H, m), 3.52 (2H, s), 3.60 (4H, t), 3.76 (3H, s), 6.81 – 6.83 (1H, m), 6.93 (1H, s), 6.96 – 6.98 (2H, m), 7.01 – 7.02 (2H, m), 7.05 (1H, d), 7.31 (1H, t), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 485 [M+H]+.

Ejemplo 121

Preparación de 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzoato de metilo

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–formilbenzoato de metilo fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzoato de metilo.

1H NMR (499.8 MHz, DMSO–d6) δ 2.53 (4H, t), 3.62 – 3.64 (6H, m), 3.86 (3H, s), 7.51 (2H, d), 7.59 (1H, d), 7.95 (2H, d), 8.25 (1H, d) (Señal a 2.53 parcialmente oscurecida por DMSO); m/z = 421 [M+H]+.

Ejemplo 122

Preparación de 6–[4–[(4–tert–butilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–tert–butilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–tert–butilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

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1H NMR (499.8 MHz, DMSO–d6) δ 1.29 (9H, s), 2.49 – 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.26 (2H, d), 7.37 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 419 [M+H]+.

Ejemplo 123

Preparación de 6–[4–[[4–(2–metilpropil)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(2–metilpropil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[4–(2–metilpropil)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 0.87 (6H, d), 1.81 – 1.86 (1H, m), 2.44 (2H, d), 2.48 – 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.13 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 419 [M+H]+.

Ejemplo 124

Preparación de 6–[4–[[6–(4–metilfenil)sulfanilpiridin–3–il]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–(4–metilfenil)sulfanilpiridina–3–carbaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[6–(4–metilfenil)sulfanilpiridin–3–il]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.38 (3H, s), 2.48 – 2.51 (4H, m), 3.51 (2H, s), 3.60 (4H, t), 6.89 (1H, d), 7.32 (2H, d), 7.48 (2H, d), 7.59 (2H, d), 8.25 (1H, d), 8.34 – 8.34 (1H, m) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 486 [M+H]+.

Ejemplo 125

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Preparación de 6–[4–[[3–(4–fluorofenil)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(4–fluorofenil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[3–(4–fluorofenil)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.56 (4H, t), 3.63 – 3.64 (6H, m), 7.28 – 7.32 (2H, m), 7.35 (1H, d), 7.45 (1H, t), 7.57 (3H, d), 7.70 – 7.73 (2H, m), 8.25 (1H, d); m/z = 457 [M+H]+.

Ejemplo 126

Preparación de 6–[4–[[4–(4–fluorofenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(4–fluorofenoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[4–(4–fluorofenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 6.97 (2H, d), 7.05 – 7.09 (2H, m), 7.21 – 7.26 (2H, m), 7.34 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Señal a 2.51 parcialmente oscurecida por DMSO); m/z = 473 [M+H]+.

Ejemplo 127

Preparación de 6–[4–[(4–bromofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–bromobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas

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decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–bromofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.49 – 2.52 (4H, m), 3.53 (2H, s), 3.62 (4H, t), 7.31 (2H, d), 7.54 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 443 no asignado (Br).

Ejemplo 128

Preparación de N,N–dietil–4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]anilina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–dietilaminobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N,N–dietil–4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]anilina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.09 (6H, t), 2.47 (4H, t), 3.39 (2H, s), 3.60 (4H, t), 6.62 (2H, d), 7.09 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Señales de aminometileno oscurecida por agua); m/z = 434 [M+H]+.

Ejemplo 129

Preparación de 6–[4–[(4–metilsulfanilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–metilsulfanilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metilsulfanilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.48 (3H, s), 2.49 – 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.25 (2H, d), 7.29 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 409 [M+H]+.

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Ejemplo 130

Preparación de 6–[4–[(4–propan–2–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–propan–2–ilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–propan–2–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.21 (6H, d), 2.48 – 2.51 (4H, m), 2.86 – 2.91 (1H, m), 3.50 (2H, s), 3.61 (4H, t), 7.21 (2H, d), 7.25 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 405 $[M+H]^+$.

Ejemplo 131

Preparación de 6–[4–[[4–(trifluorometoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(trifluorometoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[4–(trifluorometoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.54 (4H, m), 3.53 (2H, s), 3.62 (4H, t), 7.34 (2H, d), 7.48 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Señal a 2.52 parcialmente oscurecida por DMSO); m/z = 447 $[M+H]^+$.

Ejemplo 132

Preparación de 6–[4–[[4–(4–clorofenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(4–clorofenoxi)benzaldehído fue llevada a cabo de acuerdo al Método

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Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[4–(4–clorofenoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.54 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.01 – 7.04 (4H, m), 7.36 – 7.38 (2H, m), 7.42 – 7.45 (2H, m), 7.59 (1H, d), 8.26 (1H, d) (Señal a 2.52 parcialmente oscurecida por DMSO); m/z = 489 [M+H]+.

Ejemplo 133

Preparación de 6–[4–[(4–etinilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–etinilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–etinilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.50 – 2.53 (4H, m), 3.57 (2H, s), 3.62 (4H, t), 7.36 (2H, d), 7.46 (2H, d), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.52 oscurecida por DMSO); m/z = 387 [M+H]+.

Ejemplo 134

Preparación de 6–[4–[(4–piridin–2–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–piridin–2–ilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–piridin–2–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.56 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.34 – 7.37 (1H, m), 7.47 (2H, d), 7.60 (1H, d), 7.87 – 7.91 (1H, m), 7.96 (1H, d), 8.07 (2H, d), 8.25 (1H, d), 8.67 – 8.68 (1H, m); m/z = 440 [M+H]+.

Ejemplo 135

Preparación de 6–[4–[(4–etilsulfonilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–etilsulfonilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–etilsulfonilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.12 (3H, t), 2.55 (4H, t), 3.24 – 3.29 (2H, m), 3.64 (4H, t), 3.68 (2H, s), 7.59 (1H, d), 7.64 (2H, d), 7.87 (2H, d), 8.26 (1H, d) (Señal a 3.27 parcialmente oscurecida por agua); m/z = 455 [M+H]+.

Ejemplo 136

Preparación de 6–[4–[(3–prop–2–enoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–prop–2–enoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–prop–2–enoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.50 – 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 4.56 – 4.58 (2H, m), 5.25 – 5.28 (1H, m), 5.38 – 5.43 (1H, m), 6.02 – 6.09 (1H, m), 6.85 – 6.87 (1H, m), 6.92 (2H, d), 7.25 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.51 oscurecida por DMSO); m/z = 419 [M+H]+.

Ejemplo 137

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Preparación de 6–[4–[(6–cloropiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–cloropiridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(6–cloropiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.52 – 2.55 (4H, m), 3.60 (2H, s), 3.62 (4H, t), 7.51 (1H, d), 7.59 (1H, d), 7.82 – 7.84 (1H, m), 8.25 (1H, d), 8.37 (1H, d) (Señal a 2.53 parcialmente oscurecida por DMSO); m/z = 398 [M+H]+.

Ejemplo 138

Preparación de N–[3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]acetamida

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con N–(3–formilfenil)acetamida fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N–[3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]acetamida.

1H NMR (499.8 MHz, DMSO–d6) δ 2.04 (3H, s), 2.50 – 2.53 (4H, m), 3.51 (2H, s), 3.62 (4H, t), 7.00 (1H, d), 7.25 (1H, t), 7.51 (1H, d), 7.56 – 7.61 (2H, m), 8.25 (1H, d), 9.90 (1H, s) (Señal a 2.51 oscurecida por DMSO); m/z = 420 [M+H]+.

Ejemplo 139

Preparación de 6–[4–[(4–prop–2–enoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–prop–2–enoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con

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mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–prop–2–enoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.49 (4H, t), 3.47 (2H, s), 3.61 (4H, t), 4.55 – 4.57 (2H, m), 5.25 – 5.28 (1H, m), 5.38 – 5.42 (1H, m), 6.02 – 6.09 (1H, m), 6.92 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]+.

Ejemplo 140

Preparación de N,N–dimetil–2–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]etanamina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(2–dimetilaminoetoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N,N–dimetil–2–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]etanamina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.22 (6H, s), 2.47 – 2.51 (4H, m), 2.62 (2H, t), 3.47 (2H, s), 3.61 (4H, t), 4.04 (2H, t), 6.91 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.25 (1H, d); m/z = 450 [M+H]+.

Ejemplo 141

Preparación de N,N–dimetil–4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzamida

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–formil–N,N–dimetilbenzamida fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N,N–dimetil–4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzamida.

1H NMR (499.8 MHz, DMSO–d6) δ 2.52 – 2.55 (4H, m), 2.90 – 3.02 (6H, m), 3.59 (2H, s), 3.63 (4H, t), 7.37 – 7.41 (4H, m), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.53 parcialmente oscurecida por DMSO); m/z = 434 [M+H]+.

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Ejemplo 142

Preparación de 6–[4–[(6–metoxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–metoxipiridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(6–metoxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.49 – 2.52 (4H, m), 3.50 (2H, s), 3.61 (4H, t), 3.85 (3H, s), 6.81 (1H, d), 7.59 (1H, d), 7.66 – 7.68 (1H, m), 8.09 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 394 [M+H]+

Ejemplo 143

Preparación de 6–[4–[(6–morfolin–4–ilpiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–morfolin–4–ilpiridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(6–morfolin–4–ilpiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.47 – 2.51 (4H, m), 3.44 – 3.45 (6H, m), 3.60 (4H, t), 3.70 (4H, t), 6.83 (1H, d), 7.51 – 7.54 (1H, m), 7.58 (1H, d), 8.05 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO. Algunas señales distorsionadas por agua); m/z = 449 [M+H]+.

Ejemplo 144

Preparación de 6–[4–[(6–fenoxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

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La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–fenoxipiridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(6–fenoxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.54 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.02 (1H, d), 7.12 – 7.14 (2H, m), 7.20 – 7.23 (1H, m), 7.41 – 7.44 (2H, m), 7.59 (1H, d), 7.81 – 7.83 (1H, m), 8.09 (1H, d), 8.25 (1H, d) (Señal a 2.52 parcialmente oscurecida por DMSO); m/z = 456 [M+H]+.

Ejemplo 145

Preparación de 6–[4–[(3–etinilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–etinilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–etinilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.50 – 2.53 (4H, m), 3.55 (2H, s), 3.62 (4H, t), 4.17 (1H, s), 7.37 – 7.41 (3H, m), 7.45 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.52 parcialmente oscurecida por DMSO.); m/z = 387 [M+H]+.

Ejemplo 146

Preparación de tert–butil N–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]carbamato

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con tert–butil N–(4–formilfenil)carbamato fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco

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acuoso) y acetonitrilo como eluentes para dar tert–butil N–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]carbamato.
1H NMR (499.8 MHz, DMSO–d6) δ 1.48 (9H, s), 2.48 (4H, t) 3.46 (2H, s), 3.61 (4H, t), 7.20 (2H, d), 7.42 (2H, d), 7.58 (1H, d), 8.24 (1H, d), 9.29 (1H, s); m/z = 478 [M+H]+.

Ejemplo 147

Preparación de 6–[4–[(6–etoxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–etoxipiridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(6–etoxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.
1H NMR (499.8 MHz, DMSO–d6) δ 1.32 (3H, t), 2.48 – 2.51 (4H, m), 3.49 (2H, s), 3.61 (4H, t), 4.30 (2H, q), 6.78 (1H, d), 7.59 (1H, d), 7.64 – 7.67 (1H, m), 8.06 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 408 [M+H]+.

Ejemplo 148

Preparación de 6–[4–[(6–propan–2–iloxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–propan–2–iloxipiridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(6–propan–2–iloxipiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.
1H NMR (499.8 MHz, DMSO–d6) δ 1.29 (6H, d), 2.49 – 2.52 (4H, m), 3.48 (2H, s), 3.61 (4H, t), 5.21 – 5.26 (1H, m), 6.72 (1H, d), 7.59 (1H, d), 7.62 – 7.65 (1H, m), 8.06 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 422 [M+H]+.

Ejemplo 149

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Preparación de [3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]metanol

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(hidroximetil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar [3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]metanol.

1H NMR (499.8 MHz, DMSO–d6) δ 2.50 – 2.53 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 4.51 (2H, d), 5.15 (1H, t), 7.21 (2H, t), 7.28 – 7.32 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.51 parcialmente oscurecida por DMSO); m/z = 393 [M+H]+.

Ejemplo 150

Preparación de N–[3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]metanosulfonamida

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con N–(3–formilfenil)metanosulfonamida fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N–[3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]metanosulfonamida.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.54 (4H, m), 2.99 (3H, s), 3.53 (2H, s), 3.62 (4H, t), 7.08 (1H, d), 7.13 (1H, d), 7.22 (1H, s), 7.31 (1H, t), 7.59 (1H, d), 8.25 (1H, d), 9.69 (1H, s) (Señal a 2.52 parcialmente oscurecida por DMSO); m/z = 456 [M+H]+.

Ejemplo 151

Preparación de [3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil] metanosulfonato

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con (3–formilfenil) metanosulfonato fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con

mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar [3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil] metanosulfonato.

1H NMR (499.8 MHz, DMSO–d6) δ 2.52 – 2.56 (4H, m), 3.36 (3H, s), 3.61 – 3.64 (6H, m), 7.26 – 7.28 (1H, m), 7.34 (1H, s), 7.37 (1H, d), 7.47 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.54 parcialmente oscurecida por DMSO. Señal de metil distorsionada por agua); m/z = 457 [M+H]+.

Ejemplo 152

Preparación de [4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil] metanosulfonato

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con (4–formilfenil) metanosulfonato fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar [4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil] metanosulfonato.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.55 (4H, m), 3.33 (3H, s), 3.58 (2H, s), 3.63 (4H, t), 7.32 – 7.34 (2H, m), 7.46 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Señal a 2.53 parcialmente oscurecida por DMSO); m/z = 457 [M+H]+.

Ejemplo 153

Preparación de 2–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]acetamida

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–(4–formilfenoxi)acetamida fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 2–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]acetamida.

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1H NMR (499.8 MHz, DMSO–d6) δ 2.48 – 2.51 (4H, m), 3.48 (2H, s), 3.61 (4H, t), 4.42 (2H, s), 6.93 (2H, d), 7.26 (2H, d), 7.36 (1H, s), 7.49 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.50 parcialmente oscurecida por DMSO); m/z = 436 [M+H]+.

Ejemplo 154

Preparación de 2–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]acetonitrilo

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–(4–formilfenoxi)acetonitrilo fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 2–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenoxi]acetonitrilo.

1H NMR (499.8 MHz, DMSO–d6) δ 2.49 – 2.52 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 5.16 (2H, s), 7.05 (2H, d), 7.33 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.51 parcialmente oscurecida por DMSO); m/z = 418 [M+H]+.

Ejemplo 155

Preparación de 6–[4–[[4–(4–metilpiperazin–1–il)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(4–metilpiperazin–1–il)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando a Phenomenex Luna C18 100A, 10µ sílice, diámetro 21mm, longitud 150mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[4–(4–metilpiperazin–1–il)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (300.13 MHz, DMSO–d6) δ 2.23 (3H, s), 2.43 – 2.51 (8H, m), 3.12 (4H, t), 3.43 (2H, s), 3.56 – 3.62 (4H, m), 6.89 (2H, d), 7.15 (2H, d), 7.57 (1H, d), 8.24 (1H, d) (Señal a 2.46 parcialmente oscurecida por DMSO); m/z = 461 [M+H]+.

Ejemplo 156

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Preparación de N,N–dimetil–3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzamida

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–formil–N,N–dimetilbenzamida fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar N,N–dimetil–3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]benzamida.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.55 (4H, m), 2.90 – 3.01 (6H, m), 3.59 (2H, s), 3.63 (4H, t), 7.29 – 7.32 (1H, m), 7.36 (1H, s), 7.39 – 7.43 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.53 parcialmente oscurecida por DMSO); m/z = 434 [M+H]+.

Ejemplo 157

Preparación de 6–[4–[(3–butoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–butoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–butoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 0.94 (3H, t), 1.41 – 1.49 (2H, m), 1.67 – 1.73 (2H, m), 2.50 – 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 3.97 (2H, t), 6.82 – 6.84 (1H, m), 6.90 (2H, t), 7.25 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Señal a 2.52 oscurecida por DMSO); m/z = 435 [M+H]+.

Ejemplo 158

Preparación de 6–[4–[(4–propilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–propilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters

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XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–propilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 0.90 (3H, t), 1.56 – 1.63 (2H, m), 2.48 – 2.51 (4H, m), 2.55 (2H, t), 3.51 (2H, s), 3.61 (4H, t), 7.16 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 405 [M+H]+.

Ejemplo 159

Preparación de 6–[4–[(4–etilfenil)metil]piperazin–1–il]–3–trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–etilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–etilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.19 (3H, t), 2.48 – 2.51 (4H, m), 2.60 (2H, q), 3.50 (2H, s), 3.61 (4H, t), 7.18 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 391 [M+H]+.

Ejemplo 160

Preparación de 6–[4–[(4–morfolin–4–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–morfolin–4–ilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–morfolin–4–ilfenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.48 (4H, t), 3.09 (4H, t), 3.45 (2H, s), 3.60 (4H, t), 3.74 (4H, t), 6.91 (2H, d), 7.18 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 448 [M+H]+.

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Ejemplo 161

Preparación de 6–[4–[[4–(difluorometoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(difluorometoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[4–(difluorometoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.49 – 2.52 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.16 (2H, d), 7.22 (1H, t), 7.39 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 429 [M+H]+.

Ejemplo 162

Preparación de 6–[4–[[3–(difluorometoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(difluorometoxi)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[[3–(difluorometoxi)fenil]metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.51 – 2.55 (4H, m), 3.53 (2H, s), 3.63 (4H, t), 7.07 – 7.11 (1H, m), 7.16 (1H, s), 7.23 (1H, d), 7.24 (1H, t), 7.41 (1H, t), 7.59 (1H, d), 8.26 (1H, d) (Señal a 2.49 parcialmente oscurecida por DMSO); m/z = 429 [M+H]+.

Ejemplo 163

Preparación de etil (E)–3–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]prop–2–enoato

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con etil (*E*)–3–(4–formilfenil)prop–2–enoato fue llevada a cabo de acuerdo al

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Método Sintético General 7. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar etil (*E*)–3–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]prop–2–enoato.

1H NMR (499.8 MHz, DMSO–d6) δ 1.27 (3H, t), 2.51 – 2.54 (4H, m), 3.59 (2H, s), 3.63 (4H, t), 4.21 (2H, q), 6.62 (1H, d), 7.40 (2H, d), 7.59 (1H, d), 7.64 – 7.67 (1H, m), 7.70 (2H, d), 8.25 (1H, d) (Señal a 2.52 parcialmente oscurecida por DMSO); m/z = 461 [M+H]+.

Ejemplo 164

Preparación de 6–[4–[(2–metilsulfonilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–metilsulfonilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–metilsulfonilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.86 – 1.92 (2H, m), 2.67 (2H, t), 2.79 – 2.83 (2H, m), 3.27 (3H, s), 3.74 (2H, t), 3.78 (2H, t), 4.03 (2H, s), 7.51 (1H, d), 7.55 – 7.60 (3H, m), 7.95 (1H, d), 8.23 (1H, d); m/z = 455 [M+H]+.

Ejemplo 165

Preparación de 6–[4–[(3–metilsulfonilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metilsulfonilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–metilsulfonilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.86 – 1.92 (2H, m), 2.64 (2H, t), 2.77 –2.81 (2H, m), 3.18 (3H, s), 3.73 – 3.78 (6H, m), 7.50 (1H, d), 7.53 (1H, d), 7.61 (1H, d), 7.80 (1H, d), 7.84 (1H, s), 8.22 (1H, d); m/z = 455 [M+H]+.

Ejemplo 166

Preparación de 6–[4–[(4–metilsulfonilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–metilsulfonilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metilsulfonilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.86 – 1.92 (2H, m), 2.64 (2H, t), 2.77 (2H, t), 3.19 (4H, s), 3.73 – 3.78 (6H, m), 7.50 (1H, d), 7.53 (2H, d), 7.81 (2H, d), 8.23 (1H, d); m/z = 455 [M+H]+.

Ejemplo 167

Preparación de 6–[4–[(2–metoxifenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–metoxifenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.85 – 1.92 (2H, m), 2.63 (2H, t), 2.76 (2H, t), 3.61 (2H, s), 3.70 – 3.74 (5H, m), 3.76 (2H, t), 6.83 (1H, t), 6.94 (1H, d), 7.19 (1H, t), 7.26 (1H, d), 7.49 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]+.

Ejemplo 168

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Preparación de 3–(trifluorometil)–6–[4–[[4–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[4–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.85 – 1.91 (2H, sm, 2.65 (2H, t), 2.75 (2H, t), 3.73 – 3.77 (6H, m), 7.46 (2H, d), 7.50 (1H, d), 7.58 (2H, d), 8.23 (1H, d); m/z = 445 [M+H]+.

Ejemplo 169

Preparación de 6–[4–[(2–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.85 – 1.91 (2H, m), 2.64 (2H, t), 2.76 (2H, t), 3.68 (2H, s), 3.71 (2H, t), 3.76 (2H, t), 7.06 – 7.11 (2H, m), 7.25 – 7.28 (1H, m), 7.36 (1H, t), 7.48 (1H, d), 8.21 (1H, d); m/z = 395 [M+H]+.

Ejemplo 170

Preparación de 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo

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como eluentes para dar 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo.

1H NMR (499.8 MHz, DMSO–d6) δ 1.84 – 1.91 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.72 (2H, s), 3.73 – 3.79 (4H, m), 7.45 (2H, d), 7.49 (1H, d), 7.69 (2H, d), 8.23 (1H, d); m/z = 402 [M+H]+.

Ejemplo 171

Preparación de 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo.

1H NMR (499.8 MHz, DMSO–d6) δ 1.84 – 1.91 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.69 (2H, s), 3.72 – 3.77 (4H, m), 7.45 (1H, t), 7.50 (1H, d), 7.59 (1H, d), 7.69 (2H, d), 8.22 (1H, d); m/z = 402 [M+H]+.

Ejemplo 172

Preparación de 6–[4–[(3–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.84 – 1.90 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.65 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.01 – 7.04 (2H, m), 7.08 (1H, d), 7.26 – 7.30 (1H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 395 [M+H]+.

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Ejemplo 173

Preparación de 6–[4–[(3–metoxifenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–metoxifenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.84 – 1.90 (2H, m), 2.61 (2H, t), 2.74 (2H, t), 3.60 (2H, s), 3.67 (3H, s), 3.73 – 3.77 (4H, m), 6.77 – 6.82 (3H, m), 7.16 (1H, t), 7.49 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]+.

Ejemplo 174

Preparación de 3–(trifluorometil)–6–[4–[[2–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[2–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.83 – 1.90 (2H, m), 2.65 (2H, t), 2.77 (2H, t), 3.76 (6H, d), 7.42 (1H, t), 7.45 – 7.52 (2H, m), 7.65 (2H, t), 8.22 (1H, d); m/z = 445 [M+H]+.

Ejemplo 175

Preparación de 6–[4–[(3–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–clorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas

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decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.83 – 1.90 (2H, m), 2.64 (2H, t), 2.75 (2H, t), 3.64 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.19 – 7.21 (1H, m), 7.24 – 7.28 (3H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 411 [M+H]+.

Ejemplo 176

Preparación de 6–[4–[(4–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–clorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–clorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.83 – 1.90 (2H, m), 2.61 (2H, t), 2.73 (2H, t), 3.62 (2H, s), 3.71 – 3.76 (4H, m), 7.25 – 7.30 (4H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 411 [M+H]+.

Ejemplo 177

Preparación de 6–[4–[(4–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–fluorofenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.83 – 1.90 (2H, m), 2.61 (2H, t), 2.72 (2H, t), 3.61 (2H, s), 3.71 – 3.75 (4H, m), 7.05 (2H, t), 7.26 – 7.29 (2H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 395 [M+H]+.

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Ejemplo 178

Preparación de 6–[4–[(3–metilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–metilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.83 – 1.90 (2H, m), 2.22 (3H, s), 2.61 (2H, t), 2.73 (2H, t), 3.58 (2H, s), 3.70 – 3.77 (4H, m), 7.03 (3H, d), 7.13 (1H, t), 7.49 (1H, d), 8.22 (1H, d); m/z = 391 [M+H]+.

Ejemplo 179

Preparación de 3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]–1,4–diazepan–1–il]–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.83 – 1.89 (2H, m), 2.65 (2H, t), 2.77 (2H, t), 3.71 – 3.79 (6H, m), 7.45 – 7.51 (2H, m), 7.53 – 7.59 (3H, m), 8.22 (1H, d); m/z = 445 [M+H]+.

Ejemplo 180

Preparación de 2–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas

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decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 2–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,4–diazepan–1–il]metil]benzonitrilo.

1H NMR (499.8 MHz, DMSO–d6) δ 1.82 – 1.89 (2H, m), 2.69 (2H, t), 2.80 (2H, t), 3.71 – 3.78 (6H, m), 7.42 (1H, t), 7.46 – 7.51 (2H, m), 7.57 (1H, t), 7.70 (1H, d), 8.20 (1H, d); m/z = 402 [M+H]+.

Ejemplo 181

Preparación de 6–[4–[(4–metoxifenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metoxifenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.82 – 1.89 (2H, m), 2.59 (2H, t), 2.71 (2H, t), 3.54 (2H, s), 3.70 – 3.74 (7H, m), 6.79 (2H, d), 7.14 (2H, d), 7.48 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]+.

Ejemplo 182

Preparación de 6–[4–[(4–metilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–metilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.82 – 1.89 (2H, m), 2.25 (3H, s), 2.60 (2H, t), 2.71 (2H, t), 3.57 (2H, s), 3.70 – 3.74 (4H, m), 7.03 (2H, d), 7.11 (2H, d), 7.48 (1H, d), 8.21 (1H, d); m/z = 391 [M+H]+.

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Ejemplo 183

Preparación de 6–[4–[(2–metilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–metilbenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 8. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(2–metilfenil)metil]–1,4–diazepan–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 1.78 – 1.85 (2H, m), 2.15 (3H, s), 2.61 (2H, t), 2.71 – 2.77 (2H, m), 3.55 (2H, s), 3.71 (2H, t), 3.75 (2H, t), 7.04 – 7.09 (2H, m), 7.08 – 7.15 (1H, m), 7.16 – 7.18 (1H, m), 7.48 (1H, d), 8.20 (1H, d); m/z = 391 [M+H]+.

Ejemplo 184

Preparación de 3–(trifluorometil)–6–[4–[[6–(trifluorometil)piridin–3–il]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–a]piridina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 6–(trifluorometil)piridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[6–(trifluorometil)piridin–3–il]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–a]piridina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.60 (4H, t), 3.22 (4H, t), 3.73 (2H, s), 7.54 (1H, s), 7.72 – 7.75 (1H, m), 7.90 – 7.94 (2H, m), 8.05 – 8.07 (1H, m), 8.75 (1H, s); m/z = 431 [M+H]+.

Ejemplo 185

Preparación de 3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–a]piridina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 3–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método

Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[3–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3-a]piridina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.58 (4H, t), 3.22 (4H, t), 3.68 (2H, s), 7.54 (1H, s), 7.60 (1H, t), 7.66 (2H, d), 7.70 (1H, s), 7.72 – 7.74 (1H, m), 7.93 (1H, d); m/z = 430 [M+H]+.

Ejemplo 186

Preparación de 3–(trifluorometil)–6–[4–[[4–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3–a]piridina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 4–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[4–[[4–(trifluorometil)fenil]metil]piperazin–1–il]–[1,2,4]triazolo[4,3-a]piridina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.58 (4H, t), 3.22 (4H, t), 3.67 (3H, s), 7.54 (1H, s), 7.58 – 7.60 (2H, m), 7.71 – 7.74 (3H, m), 7.92 – 7.94 (1H, m), m/z = 430 [M+H]+.

Ejemplo 187

Preparación de 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il]piperazin–1–il]metil]benzonitrilo

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 4–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il]piperazin–1–il]metil]benzonitrilo.

1H NMR (499.8 MHz, DMSO–d6) δ 2.58 (4H, t), 3.22 (4H, t), 3.67 (2H, s), 7.54 (1H, s), 7.57 (2H, d), 7.72 – 7.74 (1H, m), 7.83 (2H, d), 7.93 (1H, d); m/z = 387 [M+H]+.

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Ejemplo 188

Preparación de 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il]piperazin–1–il]metil]benzonitrilo

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 3–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridin–6–il]piperazin–1–il]metil]benzonitrilo.

1H NMR (499.8 MHz, DMSO–d6) δ 2.57 (4H, t), 3.22 (4H, t), 3.64 (2H, s), 7.54 (1H, s), 7.58 (1H, t), 7.72 – 7.74 (2H, m), 7.75 – 7.77 (1H, m), 7.80 (1H, s), 7.93 (1H, d); m/z = 387 [M+H]+.

Ejemplo 189

Preparación de 6–[4–[(3–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 3–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(3–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.57 (4H, t), 3.21 (4H, t), 3.60 (2H, s), 7.08 – 7.12 (1H, m), 7.16 – 7.21 (2H, m), 7.38 – 7.42 (1H, m), 7.54 (1H, s), 7.72 – 7.74 (1H, m), 7.93 (1H, d); m/z = 380 [M+H]+.

Ejemplo 190

Preparación de 6–[4–[(4–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 4–clorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters

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XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–clorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.55 (4H, t), 3.20 (4H, t), 3.56 (2H, s), 7.39 (4H, d), 7.53 (1H, s), 7.71 – 7.74 (1H, m), 7.93 (1H, d); m/z = 396 [M–H]+.

Ejemplo 191

Preparación de 6–[4–[(4–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 4–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–fluorofenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.55 (4H, t), 3.20 (4H, t), 3.55 (2H, s), 7.18 (2H, t), 7.37 – 7.40 (2H, m), 7.53 (1H, s), 7.71 – 7.74 (1H, m), 7.93 (1H, d); m/z = 380 [M+H]+.

Ejemplo 192

Preparación de 6–[4–[(4–metoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina

La aminación reductiva de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina con 4–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 9. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[4–[(4–metoxifenil)metil]piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.53 (4H, t), 3.19 (4H, t), 3.49 (2H, s), 3.76 (3H, s), 6.88 – 6.92 (2H, m), 7.25 (2H, d), 7.53 (1H, s), 7.71 – 7.73 (1H, m), 7.92 (1H, d); m/z = 392 [M+H]+.

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Ejemplo 193

Preparación de 6–[2–(piridin–4–ilmetil)–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con piridina–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–(piridin–4–ilmetil)–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina. 1H NMR (499.8 MHz, DMSO–d6) δ 2.98 (2H, s), 3.42 (1H, d), 3.62 (2H, s), 3.75 – 3.78 (2H, m), 7.30 – 7.33 (3H, m), 8.23 (1H, d), 8.48 (2H, q) (Algunos picos oscurecidos por solventes); m/z = 390 [M+H]+.

Ejemplo 194

Preparación de 6–[2–[(3–metoxifenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–[(3–metoxifenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina. 1H NMR (499.8 MHz, DMSO–d6) δ 2.96 (2H, s), 3.55 (2H, s), 3.70 (3H, s), 3.72 – 3.76 (2H, m), 6.79 – 6.81 (1H, m), 6.85 – 6.86 (2H, m), 7.21 (1H, t), 7.31 (1H, d), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 419 [M+H]+.

Ejemplo 195

Preparación de 6–[2–[(4–metoxifenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–metoxibenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una

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columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–[(4–metoxifenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina. 1H NMR (499.8 MHz, DMSO–d6) δ 2.94 – 2.95 (2H, m), 3.40 (2H, s), 3.50 (2H, s), 3.73 (5H, s), 6.85 (2H, d), 7.19 (2H, d), 7.30 (1H, d), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 419 [M+H]+.

Ejemplo 196

Preparación de 3–(trifluorometil)–6–[2–[[3–(trifluorometil)fenil]metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[2–[[3–(trifluorometil)fenil]metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–[1,2,4]triazolo[4,3–b]piridazina. 1H NMR (499.8 MHz, DMSO–d6) δ 2.61 – 2.64 (2H, m), 2.97 – 2.98 (2H, m), 3.34 (1H, s), 3.68 (2H, s), 3.72 – 3.75 (2H, m), 7.31 (1H, d), 7.54 (1H, t), 7.59 – 7.67 (3H, m), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 457 [M+H]+.

Ejemplo 197

Preparación de 3–[[5–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]benzonitrilo

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–[[5–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]benzonitrilo.

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1H NMR (499.8 MHz, DMSO–d6) δ 2.60 – 2.63 (2H, m), 2.97 – 2.98 (2H, m), 3.64 (2H, s), 3.73 – 3.77 (2H, m), 7.31 (1H, d), 7.53 (1H, t), 7.65 (1H, d), 7.71 (2H, d), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 414 [M+H]+.

Ejemplo 198

Preparación de 6–[2–[(3–clorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–clorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–[(3–clorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.59 – 2.62 (2H, m), 2.97 (2H, d), 3.32 – 3.35 (245H, m), 3.59 (2H, s), 3.72 – 3.76 (2H, m), 7.25 – 7.35 (5H, m), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 423 [M+H]+.

Ejemplo 199

Preparación de 3–(trifluorometil)–6–[2–[[4–(trifluorometil)fenil]metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–(trifluorometil)benzaldehído fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[2–[[4–(trifluorometil)fenil]metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.59 – 2.62 (1H, m), 2.97 – 3.01 (2H, m), 3.67 (2H, s), 3.74 – 3.77 (2H, m), 7.31 (1H, d), 7.52 (2H, d), 7.66 (2H, d), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 457 [M+H]+.

Ejemplo 200

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Preparación de 6–[2–[(3–fluorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 3–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–[(3–fluorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.58 – 2.65 (1H, m), 2.97 (2H, d), 3.60 (2H, s), 3.73 – 3.77 (2H, m), 7.03 – 7.07 (1H, m), 7.11 (1H, d), 7.13 (1H, d), 7.30 (1H, t), 7.33 – 7.36 (1H, m), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 407 [M+H]+.

Ejemplo 201

Preparación de 3–(trifluorometil)–6–[2–[[6–(trifluorometil)piridin–3–il]metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 6–(trifluorometil)piridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–(trifluorometil)–6–[2–[[6–(trifluorometil)piridin–3–il]metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.58 – 2.64 (4H, m), 2.93 – 3.02 (2H, m), 3.34 (1H, s), 3.73 – 3.75 (4H, m), 3.77 (1H, s), 7.31 (1H, d), 7.84 (1H, d), 7.99 (1H, d), 8.22 (1H, d), 8.69 (1H, s) (Algunos picos oscurecidos por solventes); m/z = 458 [M+H]+.

Ejemplo 202

Preparación de 4–[[5–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]–1H–piridin–2–ona

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 2–hidroxipiridina–4–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC

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usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 4–[[5-[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]–1H–piridin–2–ona.

1H NMR (499.8 MHz, DMSO–d6) δ 2.58 – 2.59 (2H, m), 2.98 – 2.99 (2H, m), 3.78 (2H, t), 6.11 (1H, d), 6.21 (1H, s), 7.25 (1H, d), 7.32 (1H, d), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 406 [M+H]+.

Ejemplo 203

Preparación de 6–[2–[(4–fluorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–fluorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–[(4–fluorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.56 –2.59) (2H, m), 2.95 (2H, s), 3.56 (2H, s), 3.73 – 3.76 (2H, m), 7.11 (2H, t), 7.31 (1H, d), 7.32 (2H, t), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 407 [M+H]+.

Ejemplo 204

Preparación de 6–[2–[(4–clorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–clorobenzaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–[(4–clorofenil)metil]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

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1H NMR (499.8 MHz, DMSO–d6) δ 2.56 – 2.59 (2H, m), 2.95 (2H, s), 3.57 (2H, s), 3.74 (1H, d), 3.77 (1H, s), 7.29 – 7.36 (5H, m), 8.21 – 8.23 (1H, m) (Algunos picos oscurecidos por solventes); m/z = 423 [M+H]+.

Ejemplo 205

Preparación de 4–[[5–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]benzonitrilo

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con 4–formilbenzonitrilo fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 4–[[5–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il]metil]benzonitrilo.

1H NMR (499.8 MHz, DMSO–d6) δ 2.54 – 2.62 (4H, m), 2.97 – 2.98 (2H, m), 3.67 (2H, s), 3.78 – 3.74 (2H, m), 7.31 (1H, d), 7.50 (2H, d), 8.22 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 414 [M+H]+.

Ejemplo 206

Preparación de 6–[2–(piridin–3–ilmetil)–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

La aminación reductiva de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina con piridina–3–carbaldehido fue llevada a cabo de acuerdo al Método Sintético General 10. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm eluida con mezclas decrecientemente polares de agua (que contienen 0.1% amoniaco acuoso) y acetonitrilo como eluentes para dar 6–[2–(piridin–3–ilmetil)–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (499.8 MHz, DMSO–d6) δ 2.53 – 2.56 (2H, m), 2.59 – 2.62 (2H, m), 2.93 – 3.01 (2H, m), 3.61 (2H, s), 3.72 – 3.76 (2H, m), 7.28 – 7.31 (1H, m), 7.33 (1H, d), 7.68 – 7.70 (1H, m), 8.22 (1H, d), 8.45 – 8.46 (1H, m), 8.49 (1H, d) (Algunos picos oscurecidos por solventes); m/z = 390 [M+H]+.

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Ejemplo 207

Preparación de (3–metoxifenil)–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]metanona

La amina 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina fue acilada con cloruro de 3–metoxibenzoilo mediante el Método Sintético General 11. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar (3–metoxifenil)–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]metanona.

1H NMR (300.132 MHz, DMSO–d6) δ 2.96–3.17 (2H, m), 3.34–3.60 (4H, m), 3.62–3.90 (7H, m), 6.98–7.11 (3H, m), 7.23 (1H, d), 7.34 (1H, t), 8.23 (1H, d); m/z = 433 [M+H]+.

Ejemplo 208

Preparación de 2–metil–1–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]propan–1–ona

La amina 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina fue acilada con cloruro de 2–metilpropanoilo mediante el Método Sintético General 11. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 2–metil–1–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]propan–1–ona.

1H NMR (300.132 MHz, DMSO–d6) δ 0.94–1.05 (6H, m), 2.59–2.70 (1H, m), 2.95–3.19 (2H, m), 3.24–3.29 (1H, m), 3.35–3.54 (3H, m), 3.55–3.64 (1H, m), 3.71–3.83 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Señal a 3.3 parcialmente oscurecida por agua); m/z = 369 [M+H]+.

Ejemplo 209

Preparación de 3–metil–1–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]butan–1–ona

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La amina 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina fue acilada con cloruro de 3–metilbutanoilo mediante el Método Sintético General 11. El producto crudo fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 19 mm, longitud 100 mm) eluida con mezclas decrecientemente polares de agua (que contienen 1% amoniaco acuoso) y acetonitrilo como eluentes para dar 3–metil–1–[2–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–il]butan–1–ona.

1H NMR (300.132 MHz, DMSO–d6) δ 0.84–0.94 (6H, m), 1.92–2.06 (1H, m), 2.09–2.15 (2H, m), 2.92–3.18 (2H, m), 3.24–3.35 (1H, m), 3.35–3.48 (3H, m), 3.54–3.64 (1H, m), 3.67–3.82 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Señal a 3.3 parcialmente oscurecida por agua); m/z = 383 [M+H]+.

Ejemplo 210

Preparación de 6–(5–bencil–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina

Hidrocloruro de 2–bencil–3,3a,4,5,6,6a–hexahidro–1H–pirrolo[3,4–c]pirrol (0.129 g, 0.54 mmol) y luego diisopropiletilamina (0.070 g, 0.54 mmol) fue añadida secuencialmente a una solución de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (0.080 g, 0.36 mmol) en etanol (2mL). La mezcla de reacción fue calentada a 70°C durante 4 horas y luego evaporada para dejar un residuo no volátil. El residuo fue purificado por HPLC preparativa usando una columna Phenomenex Luna C18 100Å (10µ sílice, diámetro 21mm, longitud 150mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% ácido trifluoroacético) y acetonitrilo como eluentes para dar un producto purificado parcialmente que fue además purificado por cromatografía de intercambio iónico usando una columna SCX eluida con amoniaco 7M acuoso en metanol como eluentes para dar 6–(5–bencil–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (0.116 g, 83%) como un sólido blanco.

1H NMR (300.132 MHz, CDCl3) 2.57–2.71 (4H, m), 2.96–3.09 (2H, m), 3.39–3.49 (2H, m), 3.61 (2H, s), 3.74–3.86 (2H, m), 6.87 (1H, d), 7.20–7.34 (5H, m), 7.89 (1H, d); m/z =389 [M+H]+.

630

Ejemplo 211

Preparación de tert–butil 5–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)hexahidropirrolo[3,4–c]pirrol–2(1H)–carboxilato

tert–Butil hexahidropirrolo[3,4–c]pirrol–2(1H)–carboxilato (3.15 g, 14.83 mmol) fue añadido a una mezcla de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (3 g, 13.48 mmol) y diisopropietilamina (4.66 mL, 26.96 mmol) y etanol (50 mL). La mezcla fue calentada hasta 70°C durante un período de 10 minutos, agitada a 70 °C durante 1 hora, y luego se dejó enfriar hasta la temperatura ambiente para dar un precipitado. El precipitado fue recogido por filtración, lavado con etanol (50 mL), y secado al vacío para proporcionar tert–butil 5–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)hexahidropirrolo[3,4–c]pirrol–2(1H)–carboxilato (3.00 g, 55.9 %) como un sólido blanco.

1H NMR (300.132 MHz, DMSO) d 1.39 (s, 9H), 2.96 – 3.09 (m, 2H), 3.16 – 3.26 (m, 2H), 3.35 – 3.47 (m, 2H), 3.48 – 3.60 (m, 2H), 3.67 – 3.80 (m, 2H), 7.23 (d, 1H), 8.22 (d, 1H); m/z 399 ($M+H^+$).

Ejemplo 212

Preparación de 4–((4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)anilina

Una mezcla de ácido trifluoroacético (0.5 mL, 0.15 mmol) y tert–butil 4–((4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)fenilcarbamato (0.072 g, 0.15 mmol) en diclorometano (2 mL) fue agitada a temperatura ambiente durante 2 horas y luego evaporada para dar un residuo no volátil. El residuo fue purificado por HPLC usando una columna Phenomenex Luna C18 100A (10µ sílice, diámetro 21mm, longitud 150mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% TFA) y acetonitrilo como eluentes para dar un producto purificado parcialmente que fue además purificado por cromatografía de intercambio iónico usando una columna SCX eluida con amoniaco 7M acuoso en metanol para dar 4–((4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)anilina (0.032 g, 56.2 %) como un sólido blanco.

1H NMR (300.132 MHz, DMSO–d6) δ 2.24–2.32 (4H, m), 3.38 (2H, s), 3.35–3.49 (4H, m), 4.79 (2H, s), 6.36 (2H, d), 6.79 (2H, d), 7.41 (1H, d), 8.07 (1H, d); m/z = 378 [M+H]+.

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El tert–butil 4–((4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)fenilcarbamato usado como material de partida fue preparado como sigue:

Preparación de tert–butil 4–((4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)fenilcarbamato

Una solución de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.079 g, 0.29 mmol) en una mezcla de ácido acético y diclorometano (1:9; 3 mL) fue añadida a una mezcla de (poliestirilmetil)trimetilamonio cianoborohidruro (4.1 mmol/g, 0.097 g, 0.4 mmol) y ácido N–(4–formilfenil)carbámico tert–butil éster (0.088.4 g, 0.4 mmol). La mezcla de reacción fue agitada durante 4 días y luego filtrada. El filtrado fue evaporado y el residuo no volátil fue purificado por HPLC usando una columna Waters XBridge Prep C18 OBD (5µ sílice, diámetro 21mm, 100mm longitud) eluida con mezclas decrecientemente polares de agua (que contienen 0.05% amoniaco acuoso) y acetonitrilo como eluentes para dar tert–butil 4–((4–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperazin–1–il)metil)fenilcarbamato (0.0722 g, 52 %) como un sólido blanco, el cual fue usado sin purificación adicional.

Ejemplo 213

N–(4–fluorofenil)–2–[3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–carboxamida

1–Fluoro–4–isocianatobenceno (0.026 g, 0.19 mmol) fue añadido a una suspensión de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.05 g, 0.17 mmol) en tolueno (1.5 mL). La mezcla de reacción fue calentada a 70°C durante 1 hora y evaporada para dar un residuo no volátil. El residuo fue purificado por HPLC usando una columna Phenomenex Luna C18 100A (10µ sílice, diámetro 21mm, longitud 150mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% ácido trifluoroacético) y acetonitrilo como eluentes para dar N–(4–fluorofenil)–2–[3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–carboxamida (0.0309 g, 42 %) como un sólido blanco.

Ejemplo 214

N,N–dimetil–2–[3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–sulfonamida

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Cloruro de N,N–dimetilsulfamoilo (0.027 g, 0.19 mmol) y luego diclorometano fue añadido secuencialmente a una mezcla de diisopropiletilamina (0.044 g, 0.34 mmol) y 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.05 g, 0.17 mmol) en tolueno (1.5 mL). La mezcla de reacción fue agitada durante 1 hora y evaporada para dar un residuo no volátil. El residuo fue purificado por HPLC preparativa usando una columna Phenomenex Luna C18 100A (10µ sílice, diámetro 21mm, longitud 150mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% ácido trifluoroacético) y acetonitrilo como eluentes para dar N,N–dimetil–2–[3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazin–6–il]–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–5–sulfonamida (0.0206 g, 30 %) como un sólido blanco.
1H NMR (300.132 MHz, DMSO–d6) δ 2.75 (6H, s), 3.05–3.15 (2H, m), 3.17–3.24 (2H, m), 3.40–3.55 (4H, m), 3.72–3.81 (2H, m), 7.27 (1H, d), 8.23 (1H, d); m/z = 406 [M+H]+.

Ejemplo 215

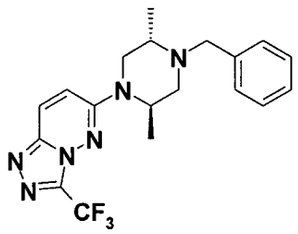
6–(5–etilsulfonil–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina

Cloruro de etanosulfonilo (0.024 g, 0.19 mmol) y luego diclorometano (0.5 mL) fue añadido secuencialmente a una mezcla de diisopropiletilamina (0.044 g, 0.34 mmol) y 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.050 g, 0.17 mmol) en tolueno (1.5 mL). La mezcla de reacción fue agitada durante 1 hora a temperatura ambiente y luego durante 1.5 horas a 50°C y luego evaporada para dar un residuo no volátil. El residuo fue purificado por HPLC preparativa usando una columna Phenomenex Luna C18 100A (10µ sílice, diámetro 21mm, longitud 150mm) eluida con mezclas decrecientemente polares de agua (que contienen 0.1% ácido trifluoroacético) y acetonitrilo como eluentes para dar 6–(5–etilsulfonil–1,3,3a,4,6,6a–hexahidropirrolo[3,4–c]pirrol–2–il)–3–(trifluorometil)–[1,2,4]triazolo[3,4–f]piridazina (0.0143 g, 22 %) como un sólido blanco.
1H NMR (300.132 MHz, DMSO–d6) δ 2.75 (6H, s), 3.05–3.15 (2H, m), 3.17–3.24 (2H, m), 3.40–3.55 (4H, m), 3.72–3.81 (2H, m), 7.27 (1H, d), 8.23 (1H, d); m/z = 406 [M+H]+.

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Ejemplo 216

Preparación de 6–[(2R,5S)–4–bencil–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

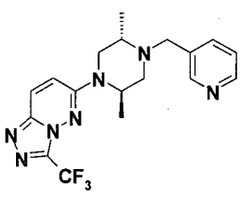


Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (4.45 g, 20 mmol), (2S,5R)–1–bencil–2,5–dimetilpiperazina (4.90 g, 24.00 mmol) y DIPEA (5.14 mL, 30.00 mmol) en DMF (40 mL) fue calentada a 125°C durante 2 horas. La mezcla de reacción fue evaporada hasta secarse, redisuelta en DCM y lavada secuencialmente con K_2CO_3 1M acuoso, agua y salmuera saturada. La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada. El producto crudo fue purificado por cromatografía MPLC en sílice, eluyendo con 75% EtOAc / isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar 6–[(2R,5S)–4–bencil–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (6.16 g, 79%) como una goma color canela.

1H NMR (399.9 MHz, DMSO–d6) δ 1.01 – 1.03 (3H, m), 1.25 (3H, d), 2.34 – 2.37 (1H, m), 2.80 – 2.84 (1H, m), 3.11 (1H, t), 3.44 – 3.48 (1H, m), 3.53 (1H, d), 3.66 (1H, d), 3.93 (1H, d), 4.42 (1H, s), 7.24 – 7.30 (1H, m), 7.31 – 7.41 (4H, m), 7.56 – 7.59 (1H, m), 8.22 – 8.26 (1H, m); m/z = 391 [M+H]+.

Ejemplo 217

Preparación de 6–[(2R,5S)–2,5–dimetil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de piridina–3–carboxaldehido y 6–[(2R,5S)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método

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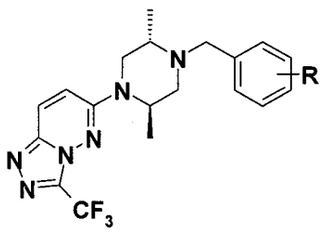
Sintético General 5 para dar 6–[(2R,5S)–2,5–dimetil–4–(3–piridilmetil)piperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina en 84% de rendimiento.
1H NMR (399.9 MHz, CDCl3) δ 1.09 – 1.11 (3H, m), 1.33 (3H, d), 2.36 – 2.40 (1H, m), 2.88 – 2.95 (1H, m), 3.15 – 3.18 (1H, m), 3.53 – 3.59 (2H, m), 3.69 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.03 (1H, d), 7.28 – 7.30 (1H, m), 7.71 – 7.74 (1H, m), 7.91 (1H, d), 8.52 – 8.54 (1H, m), 8.60 (1H, d); m/z = 392 [M+H]+.

La 6–[(2R,5S)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Una solución de 6–[(2R,5S)–4–bencil–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (6.1 g, 15.62 mmol) en etanol (150 mL) y ácido clorhídrico 5M (9.37 mL, 46.87 mmol) fue hidrogenado sobre 10% paladio sobre carbono (1 g, 9.40 mmol) bajo hidrógeno a 1 atmósfera durante 3 días. El catalizador fue filtrado y el filtrado fue evaporado. El residuo fue tomado en DCM y lavado con K_2CO_3 2M acuoso. La fase orgánica fue secada sobre MgSO4 y evaporada. El producto crudo fue purificado por cromatografía MPLC en sílice, gradiente en elución 2 a 5% amoniaco metanólico en DCM. Las fracciones del producto fueron evaporadas hasta casi secarse y cristalizadas a partir de éter para proporcionar 6–[(2R,5S)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (1.430 g, 30.5%) como un sólido cristalino blanco.
1H NMR (400.1 MHz, CDCl3) δ 1.23 – 1.25 (3H, m), 1.33 (3H, d), 2.71 – 2.75 (1H, m), 3.32 – 3.39 (2H, m), 3.47 (1H, d), 3.59 – 3.64 (1H, m), 4.15 – 4.19 (1H, m), 7.04 (1H, d), 7.92 (1H, d) ; m/z = 301 [M+H]+

Ejemplos 218–222

Los siguientes compuestos fueron preparados en 73–82% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(2R,5S)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:

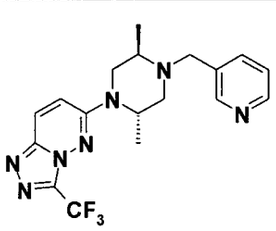


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Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
218	4–CN	δ 1.09 – 1.10 (3H, m), 1.35 (3H, d), 2.33 – 2.36 (1H, m), 2.90 – 2.94 (1H, m), 3.16 (1H, d), 3.58 (2H, d), 3.72 – 3.75 (1H, m), 3.85 (1H, d), 4.32 (1H, s), 7.03 (1H, d), 7.51 (2H, d), 7.63 (2H, d), 7.92 (1H, d)	416
219	3,4–di–F	δ 1.07 (3H, d), 1.33 – 1.35 (3H, m), 2.35 – 2.38 (1H, m), 2.87 – 2.91 (1H, m), 3.13 – 3.16 (1H, m), 3.50 (1H, d), 3.53 – 3.57 (1H, m), 3.62 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.02 – 7.15 (3H, m), 7.21 – 7.30 (1H, m), 7.91 (1H, d)	427
220	3,5–di–F	δ 1.07 – 1.09 (3H, m), 1.36 (3H, d), 2.36 – 2.40 (1H, m), 2.89 – 2.93 (1H, m), 3.14 – 3.17 (1H, m), 3.51 – 3.59 (2H, m), 3.66 (1H, d), 3.85 (1H, d), 4.32 (1H, d), 6.68 – 6.74 (1H, m), 6.91 – 6.95 (2H, m), 7.04 (1H, d), 7.92 (1H, d)	427
221	4–F	δ 1.07 (3H, d), 1.32 (3H, d), 2.35 – 2.39 (1H, m), 2.86 – 2.90 (1H, m), 3.13 – 3.16 (1H, m), 3.50 – 3.56 (2H, m), 3.63 (1H, d), 3.83 (1H, d), 4.30 (1H, t), 7.00 – 7.05 (3H, m), 7.32 – 7.35 (2H, m), 7.89 – 7.91 (1H, m)	409
222	3–CN, 4–F	δ 1.09 (3H, d), 1.34 (3H, d), 2.31 – 2.35 (1H, m), 2.89 – 2.93 (1H, m), 3.12 – 3.16 (1H, m), 3.52 – 3.58 (2H, m), 3.65 – 3.69 (1H, m), 3.84 – 3.87 (1H, m), 4.33 (1H, s), 7.04 (1H, d), 7.20 (1H, t), 7.60 – 7.67 (2H, m), 7.92 (1H, d)	434

Ejemplo 223

Preparación de 6–[(2S,5R)–2,5–dimetil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



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Una mezcla de piridina–3–carboxaldehido y 6–[(2S,5R)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 6–[(2S,5R)–2,5–dimetil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 84% de rendimiento.

1H NMR (399.9 MHz, CDCl3) δ 1.09 – 1.11 (3H, m), 1.33 (3H, d), 2.36 – 2.40 (1H, m), 2.88 – 2.95 (1H, m), 3.15 – 3.18 (1H, m), 3.53 – 3.59 (2H, m), 3.69 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.03 (1H, d), 7.28 – 7.30 (1H, m), 7.71 – 7.74 (1H, m), 7.91 (1H, d), 8.52 – 8.54 (1H, m), 8.60 (1H, d); m/z = 392 [M+H]+.

La 6–[(2S,5R)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de (2R,5S)–tert–butil 2,5–dimetil–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboxilato

Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (4.45 g, 20 mmol), (2R,5S)–tert–butil 2,5–dimetilpiperazina–1–carboxilato (5.14, 24 mmol) y DIPEA (5.14 mL, 30.00 mmol) en DMF (40.0 mL) fue calentada a 125°C durante 2.5 horas. La mezcla de reacción fue evaporada hasta secarse, redisuelta en DCM y lavada secuencialmente con K_2CO_3 1M acuoso, agua y salmuera saturada. La capa orgánica fue secada sobre $MgSO_4$, filtrada y evaporada. El producto crudo fue purificado por cromatografía MPLC en sílice, eluyendo con EtOAc. Las fracciones del producto fueron evaporadas y trituradas con éter. El sólido fue recogido por filtración, lavado con éter y secado al vacío para proporcionar (2R,5S)–tert–butil 2,5–dimetil–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboxilato (6.09 g, 76%) como un sólido cristalino blanco.

1H NMR (399.9 MHz, DMSO–d6) δ 1.14 – 1.21 (6H, m), 1.44 (9H, s), 3.36 – 3.42 (2H, m), 3.71 (1H, d), 3.88 (1H, d), 4.25 – 4.35 (1H, m), 4.47 (1H, s), 7.59 (1H, d), 8.28 (1H, d); m/z = 401 [M+H]+.

Preparación de 6–[(2S,5R)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

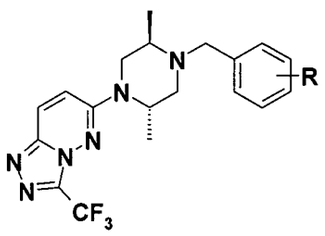
(2R,5S)–tert–Butil 2,5–dimetil–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboxilato (6.01 g, 15 mmol) fue añadido en porciones a TFA agitado (25 mL) durante 5 minutos. Hubo una exoterma moderada y la mezcla de reacción se dejó

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agitar durante unos 15 minutos adicionales. El volumen del TFA fue evaporado y el residuo fue basificado con K_2CO_3 1M acuoso. Este fue extraído rigurosamente con DCM (4 x 200 mL) y la fase orgánica combinada fue secada sobre MgSO4 y evaporada para dar un aceite el cual cristalizó rápidamente. El sólido fue recogido por filtración y secado al vacío para dar 6–[(2S,5R)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (3.52 g, 78%) como un sólido cristalino blanco.
1H NMR (400.1 MHz, CDCl3) δ 1.23 – 1.25 (3H, m), 1.33 (3H, d), 2.71 – 2.75 (1H, m), 3.32 – 3.39 (2H, m), 3.47 (1H, d), 3.59 – 3.64 (1H, m), 4.15 – 4.19 (1H, m), 7.04 (1H, d), 7.92 (1H, d); m/z = 301 [M+H]+.

Ejemplos 224–228

Los siguientes compuestos fueron preparados en 63–84% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(2S,5R)–2,5–dimetilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:



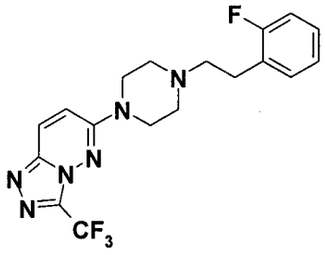
Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
224	3,4–di–F	δ 1.07 (3H, d), 1.33 – 1.35 (3H, m), 2.35 – 2.38 (1H, m), 2.87 – 2.91 (1H, m), 3.13 – 3.16 (1H, m), 3.50 (1H, d), 3.53 – 3.57 (1H, m), 3.62 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.02 – 7.15 (3H, m), 7.21 – 7.30 (1H, m), 7.91 (1H, d)	427
225	3,5–di–F	δ 1.07 – 1.09 (3H, m), 1.36 (3H, d), 2.36 – 2.40 (1H, m), 2.89 – 2.93 (1H, m), 3.14 – 3.17 (1H, m), 3.51 – 3.59 (2H, m), 3.66 (1H, d), 3.85 (1H, d), 4.32 (1H, d), 6.68 – 6.74 (1H, m), 6.91 – 6.95 (2H, m), 7.04 (1H, d), 7.92 (1H, d)	426
226	4–F	δ 1.07 (3H, d), 1.32 (3H, d), 2.35 – 2.39 (1H, m), 2.86 – 2.90 (1H, m), 3.13 – 3.16 (1H, m), 3.50 – 3.56 (2H, m), 3.63 (1H, d), 3.83 (1H, d), 4.30 (1H,	408

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		t), 7.00 – 7.05 (3H, m), 7.32 – 7.35 (2H, m), 7.89 – 7.91 (1H, m)	
227	3–CN, 4–F	δ 1.09 (3H, d), 1.34 (3H, d), 2.31 – 2.35 (1H, m), 2.89 – 2.93 (1H, m), 3.12 – 3.16 (1H, m), 3.52 – 3.58 (2H, m), 3.65 – 3.69 (1H, m), 3.84 – 3.87 (1H, m), 4.33 (1H, s), 7.04 (1H, d), 7.20 (1H, t), 7.60 – 7.67 (2H, m), 7.92 (1H, d)	434
228	4–CN	δ 1.10 (3H, d), 1.35 (3H, d), 2.33 – 2.36 (1H, m), 2.90 – 2.94 (1H, m), 3.14 – 3.17 (1H, m), 3.54 – 3.62 (2H, m), 3.72 – 3.75 (1H, m), 3.85 (1H, s), 4.33 (1H, d), 7.04 (1H, d), 7.50 – 7.52 (2H, m), 7.63 – 7.65 (2H, m), 7.92 (1H, d).	416

Ejemplo 229

Preparación de 6–[4–[2–(2–fluorofenil)etil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



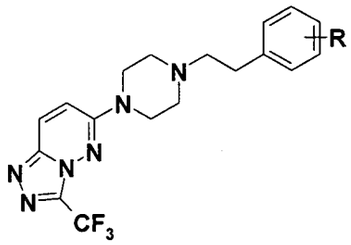
Una solución agitada de dihidrocloruro de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.173 g, 0.5 mmol), DIPEA (0.300 mL, 1.75 mmol) y 2–fluorofenetil bromuro (0.084 mL, 0.60 mmol) en DMF (2 mL) fue calentada a 100°C durante 2.5 horas. La reacción fue incompleta y DIPEA (0.300 mL, 1.75 mmol) y 2–fluorofenetil bromuro (0.084 mL, 0.60 mmol) adicional fueron añadidos. La solución fue agitada a 100°C durante unos 90 minutos adicionales. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–[2–(2–fluorofenil)etil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (0.131 g, 66.4%) como una espuma de color suave.

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1H NMR (399.9 MHz, DMSO–d6) δ 2.53 – 2.61 (6H, m), 2.81 – 2.85 (2H, m), 3.61 (4H, t), 7.12 – 7.17 (2H, m), 7.23 – 7.27 (1H, m), 7.34 – 7.39 (1H, m), 7.61 (1H, d), 8.25 (1H, d); m/z = 395 [M+H]+.

Ejemplos 230–235

Los siguientes compuestos fueron preparados en 24–64% de rendimiento mediante un método análogo al Ejemplo 229, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el fenetil bromuro apropiado:

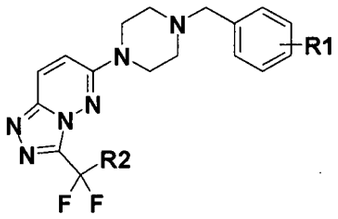


Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
230	4–F	δ 2.63 – 2.67 (6H, m), 2.79 – 2.83 (2H, m), 3.65 (4H, t), 6.96 – 7.01 (2H, m), 7.07 (1H, d), 7.15 – 7.19 (2H, m), 7.93 (1H, d)	395
231	4–Cl	δ 2.63 – 2.67 (6H, m), 2.79 – 2.82 (2H, m), 3.64 (4H, t), 7.06 (1H, d), 7.13 – 7.16 (2H, m), 7.25 – 7.28 (2H, m), 7.93 (1H, d)	411
232	2–Cl	δ 2.66 – 2.71 (6H, m), 2.95 – 2.99 (2H, m), 3.66 (4H, t), 7.07 (1H, d), 7.14 – 7.22 (2H, m), 7.25 (1H, d), 7.34 – 7.36 (1H, m), 7.93 (1H, d)	411
233	3–Cl	δ 2.64 – 2.68 (6H, m), 2.79 – 2.83 (2H, m), 3.65 (4H, t), 7.05 – 7.11 (2H, m), 7.18 – 7.25 (3H, m), 7.93 (1H, s)	411
234	3–F	δ 2.64 – 2.70 (6H, m), 2.82 – 2.86 (2H, m), 3.65 (4H, t), 6.88 – 6.95 (2H, m), 6.99 (1H, s), 7.07 (1H, d), 7.23 – 7.28 (1H, m), 7.93 (1H, d)	395
235	4–CN	δ 2.64 – 2.70 (6H, m), 2.87 – 2.91 (2H, m), 3.64 (4H, t), 7.06 (1H, d), 7.32 – 7.34 (2H, m), 7.58 – 7.61 (2H, m), 7.93 (1H, d)	402

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Ejemplos 236–247

Los siguientes compuestos fueron preparados en 33–89% de rendimiento mediante un método análogo al Ejemplo 216, partiendo de la 6–cloro–[1,2,4]triazolo[4,3–b]piridazina 3–sustituida apropiada (obtenida como se describió en el correspondiente pie de página) y la bencil piperazina apropiada:



Ej.	Nota	R1	R2	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
236	[1]	4–F	H	δ 2.57 (4H, t), 3.54 (2H, s), 3.61 (4H, t), 6.99 – 7.05 (3H, m), 7.12 (1H, t), 7.25 – 7.33 (2H, m), 7.88 – 7.91 (1H, m)	363
237	[1]	4–CN	H	δ 2.59 (4H, t), 3.62 – 3.64 (6H, m), 7.02 (1H, d), 7.12 (1H, t), 7.49 (2H, d), 7.62 – 7.65 (2H, m), 7.91 (1H, d)	370
238	[1]	3–CN	H	δ 2.59 (4H, t), 3.60 (2H, s), 3.63 (4H, t), 7.03 (1H, d), 7.12 (1H, t), 7.45 (1H, t), 7.57 – 7.60 (2H, m), 7.69 (1H, t), 7.91 (1H, d)	370
239	[1]	3–F	H	δ 2.59 (4H, t), 3.57 (2H, s), 3.63 (4H, t), 6.95 – 6.99 (1H, m), 7.02 (1H, d), 7.08 – 7.12 (2H, m), 7.12 (1H, t), 7.25 – 7.32 (1H, m), 7.90 (1H, d)	363
240	[2]	4–F	Me	δ 2.30 (3H, t), 2.57 (4H, t), 3.53 (2H, s), 3.60 (4H, t), 6.98 – 7.01 (1H, m), 7.00 – 7.05 (2H, m), 7.29 – 7.32 (2H, m), 7.88 (1H, d)	377
241	[2]	4–CN	Me	δ 2.30 (3H, t), 2.59 (4H, t), 3.61 – 3.63 (6H, m), 7.00 (1H, d), 7.48 (2H, d), 7.62 – 7.65 (2H, m), 7.90 (1H, d)	384
242	[2]	3–CN	Me	δ 2.30 (3H, t), 2.59 (4H, t), 3.60 (2H, s), 3.63 (4H, t), 7.00 (1H, d), 7.45 (1H, t), 7.56 – 7.60	384

				(2H, m), 7.69 – 7.69 (1H, m), 7.90 (1H, d)	
243	[2]	3–F	Me	δ 2.30 (3H, t), 2.59 (4H, t), 3.56 (2H, s), 3.62 (4H, t), 6.94 – 6.99 (1H, m), 7.00 (1H, d), 7.08 – 7.11 (2H, m), 7.26 – 7.32 (1H, m), 7.89 (1H, d)	377
244	[3]	4–F	Et	δ 1.18 (3H, t), 2.56 – 2.70 (6H, m), 3.53 (2H, s), 3.60 (4H, t), 6.98 – 7.01 (1H, m), 6.99 – 7.05 (2H, m), 7.28 – 7.32 (2H, m), 7.87 – 7.89 (1H, m)	391
245	[3]	4–CN	Et	δ 1.18 (3H, t), 2.60 (4H, q), 2.56 – 2.70 (2H, m), 3.57 – 3.62 (4H, m), 3.60 – 3.63 (2H, m), 7.00 (1H, d), 7.48 (2H, d), 7.62 – 7.65 (2H, m), 7.90 (1H, d)	398
246	[3]	3–CN	Et	δ 1.18 (3H, t), 2.59 – 2.61 (2H, m), 2.56 – 2.70 (4H, m), 3.60 (2H, s), 3.62 (4H, t), 7.00 (1H, d), 7.45 (1H, t), 7.57 – 7.60 (2H, m), 7.68 – 7.69 (1H, m), 7.90 (1H, d)	398
247	[3]	3–F	Et	δ 1.18 (3H, t), 2.56 – 2.70 (6H, m), 3.56 (2H, s), 3.61 (4H, t), 6.94 – 7.00 (1H, m), 7.00 (1H, d), 7.08 – 7.11 (2H, m), 7.27 – 7.32 (1H, m), 7.89 (1H, d)	391

[1] Partiendo de 6–cloro–3–difluorometil–[1,2,4]–triazolo[4,3–b]piridazina, obtenida como se describió en el Método Sintético General 1, preparación de los materiales de partida.

[2] Partiendo de 6–cloro–3–(1,1–difluoroetil)–[1,2,4]–triazolo[4,3–b]piridazina, obtenida en 66% de rendimiento mediante un método análogo al Método Sintético General 1, preparación de los materiales de partida, partiendo de 3–cloropiridazin–6–il hidrazina y ácido 2,2–difluoropropanoico.

1H NMR (399.9 MHz, CDCl3) δ 2.37 (3H, t), 7.25 (1H, d), 8.15 (1H, d); m/z = 219 [M+H]+.

[3] Partiendo de 6–cloro–3–(1,1–difluoropropil)–[1,2,4]–triazolo[4,3–b]piridazina, obtenida en 52% de rendimiento mediante un método análogo al Método Sintético General

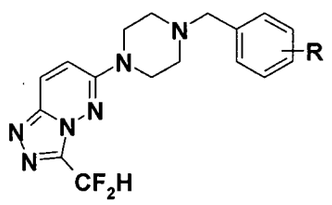
642

1, preparación de los materiales de partida, partiendo de 3–cloropiridazin–6–il hidrazina y ácido 2,2–difluorobutanoico.

1H NMR (399.9 MHz, CDCl3) δ 1.23 (3H, t), 2.60 – 2.74 (2H, m), 7.24 (1H, d), 8.15 (1H, d); m/z = 274 [M+H]+.

Ejemplos 248–263

Los siguientes compuestos fueron preparados en 35–83% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
248	3–Cl	δ 2.60 (4H, d), 3.55 (2H, s), 3.63 (4H, t), 7.02 (1H, d), 6.99 – 7.25 (1H, m), 7.22 – 7.31 (3H, m), 7.37 (1H, s), 7.90 (1H, d)	379
249	2,4–di–F	δ 2.63 (4H, s), 3.62 (3H, s), 3.63 (3H, s), 6.79 – 6.84 (1H, m), 6.85 – 6.90 (1H, m), 7.02 (1H, d), 7.12 (1H, t), 7.38 (1H, q), 7.90 (1H, d)	381
250	3,4–di–F	δ 2.59 (4H, s), 3.53 (2H, s), 3.63 (4H, t), 7.02 (1H, d), 7.06 – 7.13 (2H, m), 6.99 – 7.25 (1H, m), 7.15 – 7.24 (1H, m), 7.90 (1H, d)	381
251	3,5–di–F	δ 2.60 (4H, s), 3.55 (2H, s), 3.64 (4H, s), 6.70 – 6.75 (1H, m), 6.90 – 6.92 (2H, m), 7.03 (1H, d), 7.12 (1H, t), 7.91 (1H, d)	381
252	2,6–di–F	δ 2.66 (4H, s), 3.62 (4H, t), 3.79 (2H, s), 6.89 – 6.94 (2H, m), 6.99 (1H, t), 6.98 – 7.24 (1H, m), 7.23 – 7.31 (1H, m), 7.88 (1H, s)	381
253	2–F, 4–OMe	δ 2.61 – 2.62 (4H, m), 3.60 – 3.63 (6H, m), 3.80 (3H, s), 6.60 – 6.64 (1H, m), 6.68 – 6.70 (1H, m), 7.01 (1H, d), 6.99 – 7.25 (1H, m), 7.24 – 7.28 (1H, m), 7.89 (1H, d)	393

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254	3–Br	δ 2.59 (4H, s), 3.55 (2H, s), 3.63 (4H, s), 7.02 (1H, d), 7.12 (1H, t), 7.19 – 7.23 (1H, m), 7.28 – 7.31 (1H, m), 7.42 (1H, d), 7.52 – 7.53 (1H, m), 7.90 (1H, d)	423
255	3–CF3	δ 2.61 (4H, s), 3.63 (6H, s), 7.02 (1H, d), 7.12 (1H, t), 7.46 (1H, t), 7.55 (2H, d), 7.63 (1H, s), 7.89 – 7.92 (1H, m)	413
256	2,3–di–F	δ 2.64 (4H, t), 3.63 (4H, t), 3.68 (2H, s), 7.02 (1H, d), 7.06 – 7.16 (3H, m), 7.12 (1H, t), 7.90 (1H, d)	381
257	3–OMe, 4–F	δ 2.58 (4H, t), 3.51 (2H, d), 3.62 (4H, t), 3.91 (3H, s), 6.82 – 6.86 (1H, m), 6.99 – 7.05 (3H, m), 7.12 (1H, t), 7.89 – 7.91 (1H, m)	393
258	2–F, 5–OMe	δ 2.64 (4H, t), 3.63 (4H, s), 3.64 (2H, s), 3.80 (3H, s), 6.75 – 6.79 (1H, m), 6.93 – 6.96 (1H, m), 6.97 – 6.99 (1H, m), 7.02 (1H, d), 6.99 – 7.25 (1H, m), 7.89 (1H, d)	393
259	2,5–di–F	δ 2.65 (4H, s), 3.63 (6H, s), 6.92 – 6.99 (1H, m), 7.01 – 7.04 (2H, m), 7.25 (1H, t), 7.12 – 7.18 (1H, m), 7.90 (1H, s)	381
260	3–CN, 4–F	δ 2.59 (4H, t), 3.56 (2H, s), 3.63 (4H, t), 7.03 (1H, d), 7.12 (1H, t), 7.20 (1H, t), 7.58 – 7.62 (1H, m), 7.64 – 7.66 (1H, m), 7.91 (1H, d)	388
261	3–F, 4–OMe	δ 2.57 (4H, t), 3.50 (2H, s), 3.62 (4H, t), 3.89 (3H, s), 6.92 (1H, t), 7.02 (2H, d), 7.10 – 7.13 (1H, m), 7.12 (1H, t), 7.89 (1H, d)	393
262	2–F, 4–CN	δ 2.64 (4H, t), 3.63 (4H, t), 3.69 (2H, s), 7.02 (1H, d), 7.12 (1H, t), 7.35 – 7.38 (1H, m), 7.46 – 7.48 (1H, m), 7.61 (1H, t), 7.91 (1H, d)	388
263	2,6–di–F, 4–CN	δ 2.65 (4H, t), 3.60 – 3.62 (4H, m), 3.78 (2H, t), 7.00 (1H, t), 7.12 (1H, t), 7.24 – 7.25 (2H, m), 7.89 (1H, d)	406

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La 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de tert–butil 4–[3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboxilato

Una solución agitada de 6–cloro–3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazina (3.07 g, 15 mmol), tert–butil piperazina–1–carboxilato (3.35 g, 18.00 mmol) y DIPEA (3.85 mL, 22.50 mmol) en DMF (25 mL) fue calentada a 100°C durante 1 hora. La mezcla de reacción fue evaporada hasta secarse, redisuelta en DCM y lavada secuencialmente con K_2CO_3 1M acuoso, agua y salmuera saturada. La capa orgánica fue secada sobre MgSO4, filtrada y evaporada. El producto crudo fue triturado con éter y el sólido fue recogido por filtración, lavado con éter y secado al vacío para proporcionar tert–butil 4–[3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboxilato (5.05 g, 95%) como un sólido cristalino blanco.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 3.60 (8H, s), 7.04 (1H, d), 7.13 (1H, t), 7.94 (1H, d); m/z = 355 [M+H]+.

Preparación de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina

Ácido clorhídrico 4M en dioxano (10.58 mL, 42.33 mmol) fue añadido a una solución parcial agitada de tert–butil 4–[3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboxilato (5.0 g, 14.11 mmol) en 1,4–dioxano (14.11 mL) a temperatura ambiente y la mezcla fue agitada durante 1 hora. Durante este tiempo dio una solución clara que precipitó una goma, la cual cristalizó con agitación adicional. El precipitado fue recogido por filtración, lavado con éter y secado dando la sal de dihidrocloruro. Esto fue disuelto en MeOH y absorbido en un cartucho SCX, luego eluido con amoniaco 2M en metanol. El producto cristalizó en evaporación y fue triturado con éter. El sólido fue recogido por filtración, lavado con éter y secado al vacío para proporcionar 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina (3.28 g, 91%) como un sólido cristalino blanco.

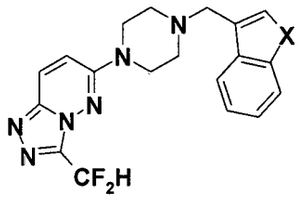
1H NMR (399.9 MHz, CDCl3) δ 3.01 – 3.03 (4H, m), 3.59 (4H, t), 7.02 – 7.05 (1H, m), 7.13 (1H, t), 7.90 (1H, d) ; m/z = 255 [M+H]+.

Ejemplos 264–265

Los siguientes compuestos fueron ambos preparados en 78% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–

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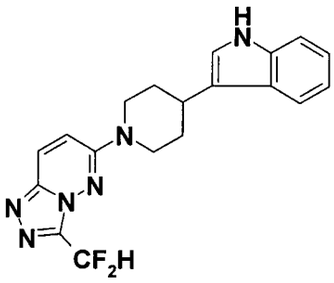
[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 248–263, preparación de los materiales de partida) y el aldehído apropiado:



Ej.	X	11H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
264	S	δ 2.65 (4H, t), 3.62 (4H, t), 3.83 (2H, s), 7.00 – 7.03 (1H, m), 7.25 (1H, t), 7.32 (1H, d), 7.35 – 7.41 (2H, m), 7.85 – 7.91 (2H, m), 7.98 – 8.02 (1H, m)	401
265	NH	δ 2.64 (4H, t), 3.61 (4H, t), 3.79 (2H, d), 7.00 (1H, d), 6.98 – 7.25 (1H, m), 7.12 – 7.16 (2H, m), 7.20 – 7.24 (1H, m), 7.37 – 7.40 (1H, m), 7.75 – 7.78 (1H, m), 7.87 (1H, d), 8.13 (1H, s)	384

Ejemplo 266

Preparación de 3–(difluorometil)–6–[4–(1H–indol–3–il)piperidin–1–il][1,2,4]triazolo[4,3–b]piridazina



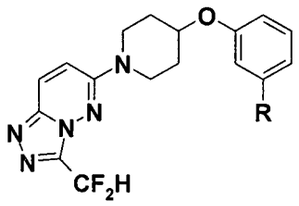
Una mezcla de 3–(piperidin–4–il)–1H–indol y 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 216 para dar 3–(difluorometil)–6–[4–(1H–indol–3–il)piperidin–1–il][1,2,4]triazolo[4,3–b]piridazina en 85% de rendimiento.

1H NMR (399.9 MHz, CDCl3) δ 1.81 – 1.92 (2H, m), 2.23 – 2.26 (2H, m), 3.17 (1H, t), 3.18 – 3.25 (2H, m), 4.36 (2H, s), 6.99 – 6.99 (1H, m), 7.09 – 7.15 (2H, m), 7.15 (1H, t), 7.19 – 7.23 (1H, m), 7.38 – 7.40 (1H, m), 7.65 (1H, s), 7.90 (1H, s), 8.04 (1H, s); m/z = 369 [M+H]+.

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Ejemplos 267–268

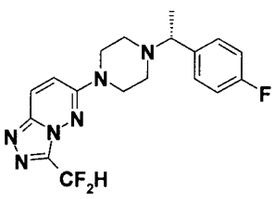
Los siguientes compuestos fueron preparados en 83–89% de rendimiento mediante un método análogo al Ejemplo 216, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina y la 4–ariloxi piperidina apropiada:



Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
267	OMe	δ 1.94 – 2.10 (4H, m), 3.62 – 3.68 (2H, m), 3.80 (3H, s), 3.82 – 3.86 (2H, m), 4.58 – 4.62 (1H, m), 6.49 – 6.56 (3H, m), 7.07 (1H, d), 7.00 – 7.26 (1H, m), 7.20 (1H t), 7.91 (1H, d)	376
268	F	δ 1.94 – 2.11 (4H, m), 3.63 – 3.69 (2H, m), 3.79 – 3.85 (2H, m), 4.58 – 4.62 (1H, m), 6.63 – 6.73 (3H, m), 7.08 (1H, d), 7.13 (1H, t), 7.24 (1H, q), 7.91 (1H, d)	364

Ejemplo 269

Preparación de 3–(difluorometil)–6–[4–[(1R)–1–(4–fluorofenil)etil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



Una solución agitada de 6–cloro–3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazina (103 mg, 0.5 mmol), (R)–1–[1–(4–fluorofenil)etil]piperazina (125 mg, 0. 6mmol) (preparada como se describió en J. Med. Chem. 2007, 50, 3528) y DIPEA (97 mg, 0.75 mmol, 129 µl) en DMF (2 mL) fue calentada a 100°C durante 2 horas. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 3–(difluorometil)–6–[4–[(1R)–

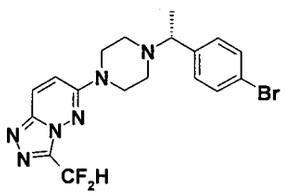
647

1–(4–fluorofenil)etil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina (158 mg, 84%) como una espuma de color suave.

1H NMR (399.9 MHz, CDCl3) δ 1.38 (3H, d), 2.48 – 2.54 (2H, m), 2.59 – 2.64 (2H, m), 3.43 (1H, q), 3.54 – 3.62 (4H, m), 6.99 – 7.05 (3H, m), 7.12 (1H, t), 7.28 – 7.31 (2H, m), 7.88 (1H, d) ; m/z = 377 [M+H]+.

Ejemplo 270

Preparación de 6–[4–[(1R)–1–(4–bromofenil)etil]piperazin–1–il]–3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de (R)–1–[1–(4–bromofenil)etil]piperazina y 6–cloro–3–difluorometil–[1,2,4]–triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 269 para dar 6–[4–[(1R)–1–(4–bromofenil)etil]piperazin–1–il]–3–(difluorometil)–[1,2,4]triazolo[4,3–b]piridazina en 75% de rendimiento.

1H NMR (399.9 MHz, CDCl3) δ 1.37 (3H, d), 2.49 – 2.54 (2H, m), 2.60 – 2.65 (2H, m), 3.41 (1H, q), 3.53 – 3.62 (4H, m), 6.99 (1H, d), 7.12 (1H, t), 7.20 – 7.24 (2H, m), 7.44 – 7.48 (2H, m), 7.88 (1H, d) ; m/z = 437 [M+H]+.

La (R)–1–[1–(4–bromfenil)etil]piperazina usada como material de partida fue preparada como sigue:

Preparación de (R)–1–[1–(4–bromofenil)etil]–4–tosilpiperazina

N,N–Bis(2–cloroetil)–4–metilbencenosulfonamida (4.0 g, 13.50 mmol) y (R)–1–(4–bromofenil)etanamina (2.57 g, 12.83 mmol) en DIPEA (5 mL) fueron agitadas y calentadas a 125°C durante 32 horas. La mezcla oscura resultante fue enfriada hasta 80°C luego una mezcla de EtOH / agua (70/30, 20 mL) fue añadida lentamente para dar un precipitado marrón. El precipitado fue recogido por filtración, lavado con EtOH / agua (70/30) e iso–hexano y secado al aire para proporcionar (R)–1–[1–(4–bromofenil)etil]–4–tosilpiperazina (4.45 g, 78%) como un sólido marrón, el cual fue usado sin purificación adicional.

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1H NMR (399.9 MHz, CDCl3) δ 1.27 (3H, d), 2.40 – 2.45 (5H, m), 2.52 – 2.57 (2H, m), 2.97 (4H, m), 3.32 (1H, q), 7.10 (2H, d), 7.32 (2H, d), 7.40 (2H, d), 7.62 (2H, d); m/z = 423/425 [M+H]+.

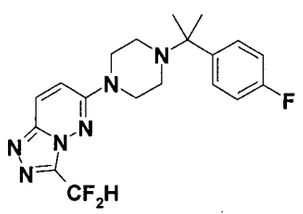
Preparación de (R)–1–[1–(4–bromofenil)etil]piperazina

(R)–1–(1–(4–Bromofenil)etil)–4–tosilpiperazina (4.44 g, 10.49 mmol) y ácido 4–hidroxibenzoico (4.35 g, 31.46 mmol) en ácido bromhídrico (33% en AcOH, 40 mL,) fueron agitados a temperatura ambiente durante 48 horas. Agua (40 mL) fue luego añadida a la mezcla oscura y la agitación se continuó durante unas 2 horas adicionales para dar un sólido beige, el cual fue filtrado y lavado con agua (10 mL). El filtrado combinado y los lavados fueron lavados con tolueno (3 x 50 mL) luego enfriados hasta 5°C y basificados hasta pH >10 con 40% NaOH. La mezcla resultante fue extraída con tert butil metil éter (2 x 50 mL) y los extractos combinados lavados con salmuera saturada, secados sobre $MgSO_4$ y evaporados para dar (R)–1–[1–(4–bromofenil)etil]piperazina (2.69 g, 95%) como un aceite viscoso naranja.

1H NMR (399.9 MHz, CDCl3) δ 1.31 (3H, d), 2.29 – 2.35 (2H, m), 2.37 – 2.48 (2H, m), 2.85 (4H, t), 3.30 (1H, q), 7.19 (2H, d), 7.42 (2H, d); m/z = 269/271 [M+H]+.

Ejemplo 271

Preparación de 3–(difluorometil)–6–[4–[1–(4–fluorofenil)–1–metiletil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



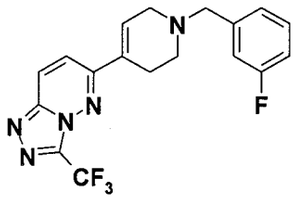
Una mezcla de 1–[1–(4–fluorofenil)–1–metil–etil]piperazina (obtenida como se describió en J. Med. Chem. 2007, 50, 3528) y 6–cloro–3–(difluorometil)–[1,2,4]–triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo a Ejemplo 269 para dar 3–(difluorometil)–6–[4–[1–(4–fluorofenil)–1–metiletil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina en 62% de rendimiento.

1H NMR (399.9 MHz, CDCl3) δ 1.37 (6H, s), 2.61 (4H, t), 3.56 (4H, t), 6.98 – 7.02 (3H, m), 6.98 – 7.24 (1H, m), 7.49 – 7.53 (2H, m), 7.86 – 7.89 (1H, m); m/z = 391 [M+H]+.

649

Ejemplo 272

Preparación de 6–[1–(3–fluorobencil)–1,2,3,6–tetrahidropiridin–4–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de 3–fluorobenzaldehido y 6–(3,6–dihidro–2H–piridin–4–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 6–[1–(3–fluorobencil)–1,2,3,6–tetrahidropiridin–4–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 46% de rendimiento.

1H NMR (399.9 MHz, CDCl3) δ 2.76 (4H, s), 3.29 (2H, d), 3.67 (2H, s), 6.72 (1H, t), 6.95 – 7.00 (1H, m), 7.10 – 7.15 (2H, m), 7.27 – 7.33 (1H, m), 7.54 (1H, d), 8.11 (1H, d); m/z = 376 [M–H]–.

La 6–(3,6–dihidro–2H–piridin–4–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de tert–butil 4–(6–cloropiridazin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato

La solución de $NaHCO_3$ saturada acuosa (10 mL) fue añadida a una solución agitada de 3,6–dicloropiridazina (0.968 g, 6.5 mmol), tert–butil 4–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)–5,6–dihidropiridina–1(2H)–carboxilato (2.010 g, 6.50 mmol) y tetrakis(trifenilfosfina)paladio(0) (0.376 g, 0.33 mmol) en DME (20 mL). El recipiente fue purgado con nitrógeno y la suspensión adicional fue calentada a 80°C durante 9 horas. La mezcla de reacción fue diluida con DCM y lavada con agua. La fase orgánica fue secada sobre MgSO4 y evaporada. El producto crudo fue purificado por cromatografía MPLC en sílice, gradiente en elusión 35 a 45% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar tert–butil 4–(6–cloropiridazin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato (0.929 g, 48.3%) como un sólido cristalino incoloro.

1H NMR (399.9 MHz, CDCl3) δ 1.50 (9H, s), 2.77 – 2.78 (2H, m), 3.67 (2H, t), 4.18 (2H, q), 6.62 (1H, s), 7.45 (1H, d), 7.55 (1H, d); m/z = 240 [M+H–butileno]+.

650

Preparación de tert–butil 4–(6–hidrazinilpiridazin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato

Una mezcla agitada de tert–butil 4–(6–cloropiridazin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato (870 mg, 2.94 mmol) y hidrazina hidrato (4.29 mL, 88.25 mmol) en acetonitrilo (15 mL) fue calentada a 80°C durante 4 horas. La mezcla fue parcialmente evaporada (eliminando MeCN) y diluida con agua (10 mL). La mezcla de reacción fue extraída con DCM (3 x 50 mL). La capa orgánica fue secada sobre Na_2SO_4, filtrada y evaporada para proporcionar el producto crudo como una goma, la cual cristalizó con la trituración con éter. El precipitado fue recogido por filtración, lavado con éter y secado al vacío para proporcionar tert–butil 4–(6–hidrazinilpiridazin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato (503 mg, 58.7%) como un sólido cristalino color crema.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 2.76 – 2.79 (2H, m), 3.65 (2H, t), 4.00 (2H, s), 4.13 (2H, q), 6.07 (1H, s), 6.33 – 6.35 (1H, m), 6.95 (1H, d), 7.43 (1H, d); m/z = 292 [M+H]+.

Preparación de 6–(1,2,3,6–tetrahidropiridin–4–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

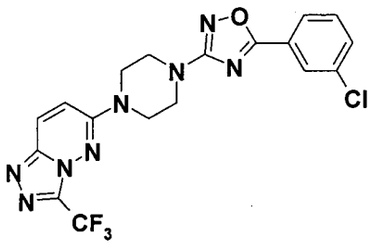
TFA (2 mL) fue añadido en una porción a tert–butil 4–(6–hidrazinilpiridazin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato (480 mg, 1.65 mmol) el cual se disolvió con una efervescencia vigorosa. La solución fue agitada durante 24 horas a 70°C. La solución fue evaporada y el residuo fue disuelto en metanol. Este fue corrido en un cartucho SCX, eluyendo con amoniaco 2M en metanol. Las fracciones que contienen el producto fueron evaporadas hasta secarse y trituradas con éter para proporcionar 6–(1,2,3,6–tetrahidropiridin–4–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (90 mg, 20.29%) como un sólido color crema.

1H NMR (399.9 MHz, DMSO–d6) δ 2.79 (2H, s), 3.37 (2H, t), 3.91 (2H, s), 6.99 (1H, s), 7.96 (1H, d), 8.49 (1H, d), NH no observado; m/z = 270 [M+H]+.

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Ejemplo 273

Preparación de 6–[4–[5–(3–clorofenil)–1,2,4–oxadiazol–3–il]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Cloruro de 3–clorobenzoilo (92 mg, 0.53 mmol) fue añadido a una solución parcial agitada de N–hidroxi–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboximidamida (165 mg, 0.5 mmol) y DIPEA (97 mg, 0.75 mmol) en THF (3 mL). La mezcla de reacción se transformó en una solución clara durante 30 minutos y LCMS después de 1 hora mostró acilación inicial completa. La mezcla de reacción fue calentada a 150°C durante 15 minutos por microondas después de lo cual la LCMS mostró ciclización completa hasta el producto deseado. La mezcla de reacción fue evaporada y el residuo fue hervido brevemente con etanol, enfriado y filtrado para dar 6–[4–[5–(3–clorofenil)–1,2,4–oxadiazol–3–il]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (104 mg, 46%) como un polvo cristalino.

1H NMR (399.9 MHz, DMSO–d6) δ 3.60 – 3.63 (4H, m), 3.78 – 3.81 (4H, m), 7.65 – 7.69 (2H, m), 7.77 – 7.80 (1H, m), 8.01 – 8.06 (2H, m), 8.32 (1H, d); m/z = 451 [M+H]+.

La N–hidroxi–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboximidamida usada como material de partida fue preparada en como sigue:

Preparación de 4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carbonitrilo

Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (3.48 g, 15.65 mmol), piperazina–1–carbonitrilo (2 g, 17.99 mmol) y DIPEA (3.54 mL, 20.34 mmol) en DMF (20 mL) fue calentada a 70°C durante 1 hora. La solución fue evaporada y particionada entre DCM y K_2CO_3 1M acuoso. La fase orgánica fue lavada con salmuera, secada sobre MgSO4, evaporada y triturada con éter. El precipitado fue recogido por filtración, lavado con éter y secado al vacío para proporcionar 4–[3–(trifluorometil)–

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[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carbonitrilo (4.29 g, 92%) como un sólido cristalino color crema.

1H NMR (399.9 MHz, CDCl3) δ 3.41 – 3.43 (4H, m), 3.75 (4H, t), 7.05 (1H, d), 8.02 (1H, d); m/z = 298 [M+H]+.

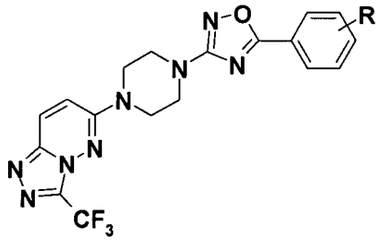
Preparación de N–hidroxi–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboximidamida

Hidroxilamina (50% p/v solución acuosa) (0.667 mL, 10.09 mmol) fue añadida a una suspensión agitada de 4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carbonitrilo (2.5 g, 8.41 mmol) en etanol (16.82 mL) y la suspensión fue agitada a temperatura ambiente. Durante 20 minutos el material de partida fue ampliamente disuelto y el producto comenzó a cristalizar. La mezcla fue agitada durante 2 horas y el precipitado fue recogido por filtración, lavado con EtOH seguido por éter y secado al vacío para proporcionar N–hidroxi–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboximidamida (2.410 g, 87%) como un sólido cristalino incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 3.15 (3H, t), 3.44 – 3.47 (1H, m), 3.58 – 3.63 (4H, m), 5.24 – 5.26 (1H, m), 6.09 & 8.37 (1H, 2S), 7.63 (1H, d), 8.26 – 8.29 (1H, m), 8.38 (1H, s), uno intercambiable no observado); m/z = 331 [M+H]+.

Ejemplos 274–277

Los siguientes compuestos fueron preparados en 43–55% de rendimiento mediante un método análogo al Ejemplo 273, partiendo de N–hidroxi–4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazina–1–carboximidamida y el cloruro de benzoilo apropiado:



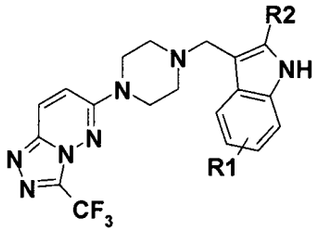
Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
274	4–F	δ 3.59 – 3.62 (4H, m), 3.78 – 3.81 (4H, m), 7.45 – 7.50 (2H, m), 7.66 (1H, d), 8.11 – 8.15 (2H, m), 8.32 (1H, d)	433 [M–H]–

653

275	H	3.60 – 3.63 (4H, m), 3.78 – 3.81 (4H, m), 7.61 – 7.73 (4H, m), 8.05 – 8.08 (2H, m), 8.31 – 8.34 (1H m)	417
276	3–F	δ 3.60 – 3.63 (4H, m), 3.79 – 3.81 (4H, m), 7.58 (1H, d), 7.65 – 7.70 (2H, m), 7.82 – 7.85 (1H, m), 7.91 – 7.93 (1H, m), 8.33 (1H, s)	435
277	4–CN	δ 3.61 – 3.64 (4H, m), 3.79 – 3.81 (4H, m), 7.67 (1H, d), 8.09 – 8.12 (2H, m), 8.21 – 8.24 (2H, m), 8.33 (1H, d)	442

Ejemplos 278–284

Los siguientes compuestos fueron preparados en 9–71% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el indol–3–carboxaldehido apropiado:



Ej.	R1	R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
278	5–CN	H	δ 2.55 (4H, t), 3.61 (4H, t), 3.75 (2H, s), 7.42 – 7.45 (1H, m), 7.50 (1H, s), 7.53 – 7.55 (1H, m), 7.57 (1H, d), 8.20 – 8.20 (1H, m), 8.23 (1H, d), 11.55 (1H, s)	427
279	H	Me	[1] δ 2.44 (3H, s), 2.62 (4H, t), 3.60 (4H t), 3.71 (2H, s), 7.04 (1H, d), 7.08 – 7.16 (2H, m), 7.28 – 7.31 (1H, m), 7.65 (1H, d), 7.89 (2H, m)	416
280	5–Cl	H	δ 2.53 – 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.07 – 7.10 (1H, m), 7.35 – 7.40 (2H, m), 7.57 (1H, d), 7.69 (1H, d), 8.23 (1H, d), 11.16 (1H s)	436
281	5–Br	H	δ 2.53 – 2.57 (4H, m), 3.60 (4H, t), 3.68 (2H, s), 7.18 – 7.21 (1H, m), 7.34 – 7.36 (2H, m), 7.58 (1H, d), 7.83 (1H, d), 8.23 (1H, d), 11.17 (1H s)	480
282	4–Cl	H	δ 2.56 – 2.61 (4H, m), 3.60 (4H, s), 3.86 (2H, s), 7.00 – 7.07 (2H, m), 7.34 – 7.37 (2H, m), 7.59 (1H,	436

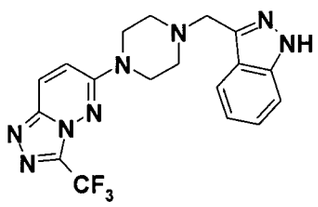
654

			d), 8.24 (1H, d), 11.33 (1H, s)	
283	5–F	H	δ 2.54 – 2.57 (4H, m), 3.60 (4H, t), 3.68 (2H, s), 6.90 – 6.95 (1H, m), 7.34 – 7.41 (3H, m), 7.57 (1H, d), 8.23 (1H, d), 11.05 (1H, s)	420
284	6–F	H	δ 2.54 – 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 6.83 – 6.89 (1H, m), 7.12 – 7.15 (1H, m), 7.27 (1H, d), 7.57 (1H, d), 7.64 – 7.68 (1H, m), 8.23 (1H, d), 11.01 (1H, s)	420

[1] Espectro registrado en CDCl3

Ejemplo 285

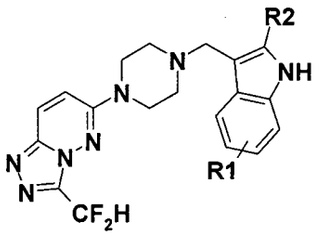
Preparación de 6–[4–(1H–indazol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



1H–Indazol–3–carboxaldehido (75 mg, 0.51 mmol) y (poliestirilmetil)trimetilamonio cianoborohidruro (125 mg, 0.51 mmol) fue añadido a una solución de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (100 mg, 0 37 mmol) en DCM (2 mL) / ácido acético (0.2 mL). La mezcla fue agitada a temperatura ambiente durante 18 horas. La resina fue filtrada y el filtrado fue evaporado. El producto crudo fue purificado por HPLC preparativa (columna Waters XTerra C18, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–(1H–indazol–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (89 mg, 60%) como un sólido blanco. 1H NMR (399.9 MHz, DMSO–d6) δ 2.60 (4H, t), 3.61 (4H, t), 3.92 (2H, s), 7.09 – 7.13 (1H, m), 7.33 – 7.36 (1H, m), 7.50 (1H, d), 7.57 (1H, d), 7.90 (1H, d), 8.23 (1H, d), 12.85 (1H, s); m/z = 403 [M+H]+.

Ejemplos 286–292

Los siguientes compuestos fueron preparados en 57–74% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6-(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina y el indol–3–carboxaldehido apropiado:

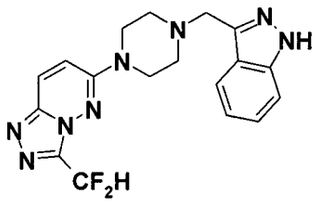


Ej.	R1	R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
286	5–CN	H	δ 2.53 – 2.56 (4H, m), 3.61 (4H, t), 3.75 (2H, s), 7.43 – 7.45 (1H, m), 7.49 – 7.65 (4H, m), 8.15 – 8.21 (2H, m), 11.55 (1H, s)	409
287	5–Cl	H	δ 2.53 – 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.07 – 7.10 (1H, m), 7.37 (2H, t), 7.49 – 7.51 (1H, m), 7.52 (1H, t), 7.70 (1H, d), 8.15 – 8.18 (1H, m), 11.17 (1H, s).	418
288	5–Br	H	δ 2.53 – 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.18 – 7.21 (1H, m), 7.34 (2H, s), 7.52 (1H, t), 7.52 (1H, d), 7.84 (1H, d), 8.15 – 8.18 (1H, m), 11.17 (1H, s).	462
289	4–Cl	H	δ 2.61 (4H, t), 3.60 (4H, t), 3.86 (2H, s), 7.00 – 7.08 (2H, m), 7.34 – 7.37 (2H, m), 7.50 – 7.53 (1H, m), 7.53 (1H, t), 8.17 (1H, d), 11.77 (1H, s).	418
290	5–F	H	δ 2.53 – 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 6.92 (1H, d), 7.34 – 7.42 (3H, m), 7.50 (1H, d), 7.52 (1H, t), 8.15 – 8.18 (1H, m), 11.05 (1H, s)	402
291	H	Cl	δ 2.56 (4H, t), 3.60 (4H, t), 3.69 (2H, s), 7.07 (1H, s), 7.13 – 7.14 (1H, m), 7.29 – 7.31 (1H, m), 7.48 – 7.51 (1H, m), 7.52 (1H, t), 7.66 (1H, s), 8.15 – 8.17 (1H, m), 11.79 (1H, s)	418

292	6–F	H	δ 2.52 (4H, t), 3.59 (4H, s), 3.69 (2H, s), 6.83 – 6.89 (1H, m), 7.12 – 7.15 (1H, m), 7.27 (1H, s), 7.50 (1H, d), 7.39 – 7.64 (1H, m), 7.66 – 7.68 (1H, m), 8.17 (1H, d), 11.01 (1H, s)	402

Ejemplo 293

Preparación de 3–(difluorometil)–6–[4–(1H–indazol–3–ilmetil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina

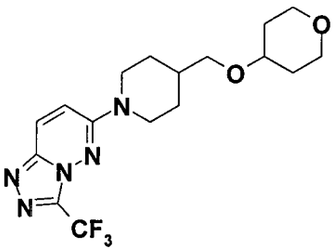


Una mezcla de indazol–3–carboxaldehido y 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 3–(difluorometil)–6–[4–(1H–indazol–3–ilmetil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina en 65% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 2.57 – 2.61 (4H, m), 3.67 (4H, t), 3.92 (2H, s), 7.11 (1H, t), 7.33 – 7.37 (1H, m), 7.48 – 7.52 (2H, m), 7.52 (1H, t), 7.91 (1H, s), 8.17 (1H, d), 12.85 (1H, s); m/z = 385 [M+H]+.

Ejemplo 294

Preparación de 6–[4–[(tetrahidro–2H–piran–4–iloxi)metil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Hidruro de sodio (60% dispersión en aceite, 42 mg, 1.05 mmol) fue añadido a tetrahidro–4H–piran–4–ol (1 g) agitado. 6–[4–(Metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (133 mg, 0.35 mmol) fue añadida y la mezcla fue agitada a 80°C durante 3 horas. La mezcla de reacción fue diluida con MeOH y se corrió un cartucho SCX de 20 g, eluyendo con amoniaco 2M en metanol. La solución

fue evaporada y el producto crudo fue purificado por HPLC preparativa (columna Waters XTerra C18, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 66–[4–[(tetrahidro–2H–piran–4–iloxi)metil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (43 mg, 32%) como un sólido blanco.
1H NMR (399.9 MHz, CDCl3) δ 1.25 – 1.33 (2H, m), 1.46 – 1.55 (2H, m), 1.78 – 1.87 (5H, m), 2.93 – 3.00 (2H, m), 3.27 – 3.28 (2H, m), 3.34 – 3.42 (3H, m), 3.83 – 3.88 (2H, m), 4.16 – 4.20 (2H, m), 7.01 (1H, d), 7.83 (1H, d); m/z = 386 [M+H]+.

La 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metanol

Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (5.56 g, 25 mmol), piperidin–4–ilmetanol (3.17 g, 27.50 mmol) y DIPEA (5.66 mL, 32.50 mmol) en DMF (50 mL) fue calentada a 70°C durante 1 hora. La solución fue evaporada y particionada entre DCM y K_2CO_3 1M acuoso. La fase orgánica fue lavada con salmuera, secada sobre MgSO4, evaporada y triturada con éter. El precipitado fue recogido por filtración, lavado con éter y secado al vacío para proporcionar [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metanol (6.68 g, 89%) como un sólido cristalino color crema.
1H NMR (399.9 MHz, CDCl3) δ 1.31 – 1.41 (2H, m), 1.80 – 1.93 (3H, m), 3.00 – 3.07 (2H, m), 3.57 (2H, t), 4.25 – 4.29 (2H, m), 7.09 (1H, d), 7.90 (1H, d), OH no observado; m/z = 302 [M+H]+.

Preparación de 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

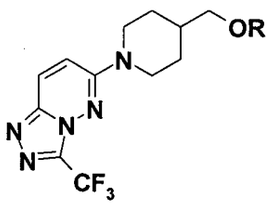
Cloruro de metanosulfonilo (2.83 mL, 36.51 mmol) en DCM (30 mL) fue añadido en forma de gotas a una solución parcial agitada de [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metanol (10 g, 33.19 mmol) y trietilamina (5.09 mL, 36.51 mmol) en DCM (140 mL). La reacción fue agitada durante 20 minutos, apagada con agua (100 mL) y extraída con DCM (2 x 75 mL). La capa orgánica fue secada sobre MgSO4,

filtrada y evaporada para proporcionar un sólido amarillo. El sólido crudo fue triturado con éter para dar un sólido el cual fue recogido por filtración y secado al vacío para dar 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (7.60 g, 60.4%) como un sólido blanco.

1H NMR (400.1 MHz, DMSO) δ 1.32 (2H, ddd), 1.82 (2H, d) 2.09 – 2.02 (1H, m), 3.05 (2H, t), 3.18 (3H, s), 4.11 (2H, d), 4.30 (2H, d), 7.61 (1H, d), 8.22 (1H, d); m/z = 380 [M+H]+.

Ejemplos 295–298

Los siguientes compuestos fueron preparados en 17–71% de rendimiento mediante un método análogo al Ejemplo 294, partiendo de 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el alcohol apropiado:

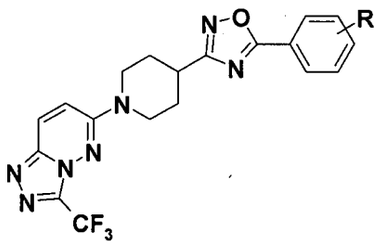


Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
295	ciclopropilmetil	δ 0.12 – 0.15 (2H, m), 0.45 – 0.49 (2H, m), 0.95 – 1.01 (1H, m), 1.22 – 1.32 (2H, m), 1.84 – 1.90 (3H, m), 2.92 – 2.99 (2H, m), 3.20 – 3.21 (2H, m), 3.26 (2H, d), 4.15 – 4.20 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	356
296	2–metoxietil	δ 1.21 – 1.31 (2H, m), 1.83 – 1.93 (3H, m), 2.91 – 2.98 (2H, m), 3.28 – 3.30 (2H, m), 3.32 (3H, s), 3.46 – 3.49 (2H, m), 3.49 – 3.54 (2H, m), 4.14 – 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	360
297	2–morfolinoetil	δ 1.21 – 1.31 (2H, m), 1.80 – 1.89 (3H, m), 2.49 – 2.56 (6H, m), 2.91 – 2.98 (2H, m), 3.25 – 3.27 (2H, m), 3.54 (2H, s), 3.69 (4H, s), 4.15 – 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	415
298	2–propil	δ 1.08 (6H, d), 1.20 – 1.30 (2H, m), 1.78 –	344

		1.86 (3H, m), 2.92 – 2.99 (2H, m), 3.22 (2H, d), 3.44 – 3.50 (1H, m), 4.15 – 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)	

Ejemplos 299–303

Los siguientes compuestos fueron preparados en 1–84% de rendimiento mediante un método análogo al Ejemplo 273, partiendo de N–hidroxi–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidina–4–carboximidamida y el cloruro de benzoilo apropiado.



Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
299	3–Cl	δ 2.01 – 2.10 (2H, m), 2.23 – 2.27 (2H, m), 3.20 – 3.27 (1H, m), 3.28 – 3.35 (2H, m), 4.24 – 4.29 (2H, m), 7.13 (1H, d), 7.47 (1H, t), 7.56 – 7.59 (1H, m), 7.95 (1H, d), 7.99 – 8.02 (1H, m), 8.12 (1H, t)	450
300	4–F	δ 2.00 – 2.10 (2H, m), 2.22 – 2.27 (2H, m), 3.18 – 3.26 (1H, m), 3.28 – 3.35 (2H, m), 4.23 – 4.29 (2H, m), 7.13 (1H, d), 7.19 – 7.25 (2H, m), 7.95 (1H, d), 8.11 – 8.16 (2H, m)	434
301	H	δ 2.00 – 2.12 (2H, m), 2.23 – 2.28 (2H, m), 3.20 – 3.27 (1H, m), 3.28 – 3.35 (2H, m), 4.24 – 4.29 (2H, m), 7.13 (1H, d), 7.51 – 7.55 (2H, m), 7.58 – 7.62 (1H, m), 7.95 (1H, d), 8.11 – 8.14 (2H, m)	416
302	3–F	δ 2.01 – 2.11 (2H, m), 2.23 – 2.28 (2H, m), 3.20 – 3.27 (1H, m), 3.28 – 3.35 (2H, m), 4.24 – 4.29 (2H, m), 7.13 (1H, d), 7.28 – 7.33 (1H, m), 7.49 – 7.54 (1H, m), 7.80 – 7.84 (1H, m), 7.91 – 7.96 (2H, m)	434
303	3–CN	δ 2.00 – 2.10 (2H, m), 2.24 – 2.29 (2H, m), 3.21 – 3.28 (1H, m), 3.28 – 3.35 (2H, m), 4.24 – 4.30 (2H, m), 7.13	441

		(1H, d), 7.67 – 7.71 (1H, m), 7.87 – 7.89 (1H, m), 7.96 (1H, d), 8.34 – 8.36 (1H, m), 8.42 – 8.43 (1H, m)	

La N–hidroxi–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidina–4–carboximidamida usada como material de partida fue preparada como sigue:

Preparación de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidina–4–carbonitrilo

Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (5.56 g, 25 mmol), piperidina–4–carbonitrilo (3.03 g, 27.50 mmol) y DIPEA (5.66 mL, 32.50 mmol) en DMF (50 mL) fue calentada a 70°C durante 1 hora. La solución fue evaporada y particionada entre DCM y K_2CO_3 1M acuoso. La fase orgánica fue lavada con salmuera, secada sobre MgSO4, evaporada y el residuo fue triturado con éter. El sólido fue recogido por filtración, lavado con éter y secado al vacío para proporcionar 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidina–4–carbonitrilo (6.86 g, 93%) como un sólido cristalino color crema.

1H NMR (399.9 MHz, CDCl3) δ 1.97 – 2.12 (4H, m), 2.95 – 3.01 (1H, m), 3.62 – 3.68 (2H, m), 3.80 – 3.86 (2H, m), 7.08 (1H, d), 7.97 (1H, d); m/z = 297 [M+H]+.

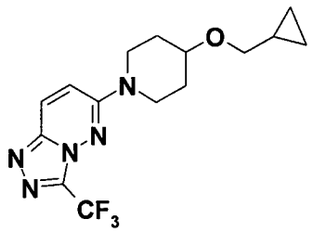
Preparación de N–hidroxi–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidina–4–carboximidamida

Hidroxilamina (50% p/v solución acuosa) (0.669 mL, 10.13 mmol) fue añadida a una suspensión agitada de 1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidina–4–carbonitrilo (2.5 g, 8.44 mmol) en etanol (16.88 mL) y la suspensión fue agitada a temperatura ambiente. Hidroxilamina adicional (50% p/v solución acuosa) (3 mL) fue añadida y la agitación fue continuada durante 18 horas. La mezcla fue luego calentada durante 1 hora. El precipitado fue recogido por filtración, lavado con EtOH y éter y secado al vacío para proporcionar N–hidroxi–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidina–4–carboximidamida (2.380 g, 86%) como un sólido cristalino incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.61 – 1.71 (2H, m), 1.81 – 1.86 (2H, m), 2.32 – 2.38 (1H, m), 3.01 – 3.08 (2H, m), 4.29 (2H, d), 5.32 – 5.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d), 8.81 (1H, s); m/z = 330 [M+H]+.

Ejemplo 304

Preparación de 6–[4–(ciclopropilmetoxi)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

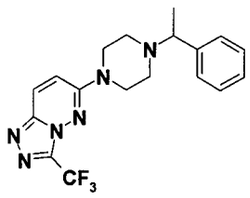


Una mezcla de 4–(ciclopropilmetoxi)piperidina y 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 216 para dar 6–[4–(ciclopropilmetoxi)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 69% de rendimiento.

1H NMR (399.9 MHz, CDCl3) δ 0.20 – 0.24 (2H, m), 0.54 – 0.59 (2H, m), 1.02 – 1.12 (1H, m), 1.70 – 1.79 (2H, m), 1.94 – 2.00 (2H, m), 3.34 (2H, d), 3.40 – 3.44 (2H, m), 3.61 – 3.66 (1H, m), 3.87 – 3.93 (2H, m), 7.10 (1H, d), 7.91 (1H, d); m/z = 342 [M+H]+.

Ejemplo 305

Preparación de 6–[4–(1–feniletil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



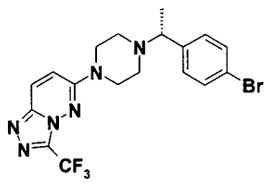
6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (400 mg, 1.80 mmol), 1–(1–feniletil)piperazina (342 mg, 1.80 mmol) y DIPEA (0.34 mL, 1.98 mmol) en DMF (4 mL) fueron agitados y calentados a 80°C durante 30 minutos. La mezcla fue enfriada hasta la temperatura ambiente luego aplicada a una columna SCX y eluida con metanol seguido por amoniaco 2M en metanol. Las fracciones que contienen el producto puro fueron evaporadas para dar un sólido el cual fue recristalizado a partir de MTBE / isohexano para dar 6–[4–(1–feniletil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (516 mg, 76%).

1H NMR (399.9 MHz, CDCl3) δ 1.41 (3H, d), 2.50 – 2.56 (2H, m), 2.60 – 2.66 (2H, m), 3.44 (1H, q), 3.55 – 3.64 (4H, m), 7.03 (1H, d), 7.24 – 7.35 (5H, m), 7.89 (1H, d); m/z = 377 [M+H]+.

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Ejemplo 306

Preparación de 6–[4–[(1R)–1–(4–bromofenil)etil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

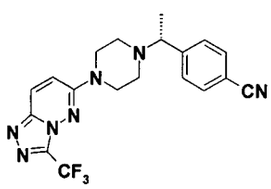


6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (251 mg, 1.13 mmol), (R)–1–[1–(4–bromofenil)etil]piperazina (obtenida como se describió en el Ejemplo 270, preparación de los materiales de partida, 304 mg, 1.13 mmol) y DIPEA (0.20 mL, 1.13 mmol) en DMF (3 mL) fueron agitados y calentados a 80°C durante 1 hora. La solución resultante fue enfriada hasta la temperatura ambiente luego apagada con agua (10 mL) para dar un precipitado marrón pálido. El precipitado fue recogido por filtración, lavado secuencialmente con agua, acetonitrilo y éter y secado al vacío para proporcionar 6–[4–[(1R)–1–(4–bromofenil)etil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (437 mg, 85%) como un sólido marrón pálido.

1H NMR (399.9 MHz, CDCl3) δ 1.37 (3H, d), 2.48 – 2.54 (2H, m), 2.59 – 2.65 (2H, m), 3.40 (1H, q), 3.54 – 3.64 (4H, m), 7.03 (1H, d), 7.21 (2H, d), 7.46 (2H, d), 7.90 (1H, d); m/z = 455/457 [M+H]+.

Ejemplo 307

Preparación de 4–[(1R)–1–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]etil]benzonitrilo



6–[4–[(1R)–1–(4–Bromofenil)etil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 306) (250 mg, 0.55 mmol), cianuro de zinc (38.7 mg, 0.33 mmol), tris(dibencilidenoacetona)dipaladio(0) (5.0 mg, 5.49 µmol), 4,5–bis(difenilfosfino)–9,9–dimetilxanteno (6.3 mg, 10.98 µmol) y N,N,N',N'–tetrametiletilenodiamina (0.017 mL, 0.11 mmol) fueron suspendidos en DMF (2.5 mL) y sellados en un tubo de microondas. La reacción fue calentada hasta 160°C durante 5

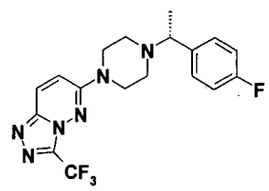
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minutos en un reactor de microondas y enfriada hasta la temperatura ambiente. La mezcla resultante fue aplicada a una columna SCX y eluida con metanol seguido por amoniaco 2M en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas luego purificadas por HPLC preparativa (columna Waters XTerra C18, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 4–[(1R)–1–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]etil]benzonitrilo (168 mg, 76%) como un sólido incoloro.

1H NMR (399.9 MHz, CDCl3) δ 1.39 (3H, d), 2.48 – 2.53 (2H, m), 2.63 – 2.68 (2H, m), 3.49 (1H, q), 3.55 – 3.65 (4H, m), 7.04 (1H, d), 7.48 (2H, d), 7.64 (2H, d), 7.92 (1H, d); m/z = 402 [M+H]+.

Ejemplo 308

Preparación de 6–[4–[(1R)–1–(4–fluorofenil)etil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



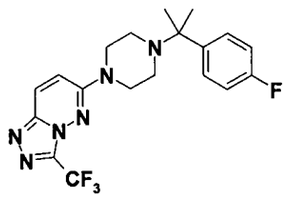
Una mezcla de (R)–1–[1–(4–fluorofenil)etil]piperazina (obtenida como se describió en J. Med. Chem. 2007, 50, 3528) y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método descrito en el Ejemplo 306 para dar 6–[4–[(1R)–1–(4–fluorofenil)etil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 87% de rendimiento.

1H NMR (399.9 MHz, CDCl3) δ 1.38 (3H, d), 2.49 – 2.54 (2H, m), 2.59 – 2.65 (2H, m), 3.43 (1H, q), 3.54 – 3.64 (4H, m), 6.99 – 7.04 (3H, m), 7.29 (2H, dd), 7.90 (1H, d); m/z = 395 [M+H]+.

Ejemplo 309

Preparación de 6–[4–[1–(4–fluorofenil)–1–metiletil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

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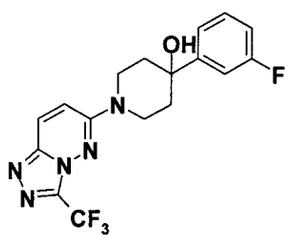


6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (120 mg, 0.54 mmol), DIPEA (0.094 mL, 0.54 mmol) y 1–[2–(4–fluorofenil)propan–2–il]piperazina (obtenida como se describió en J. Med. Chem. 2007, 50, 3528) (120 mg, 0.54 mmol) en DMF (1.5 mL) fueron agitados y calentados a 80°C durante 1 hora. La solución resultante fue enfriada hasta la temperatura ambiente, luego aplicada a una columna SCX y eluida con MeOH seguido por amoniaco 2M en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas, luego purificadas por HPLC preparativa (columna Waters XTerra C18, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–[1–(4–fluorofenil)–1–metiletil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (155 mg, 70%) como un sólido incoloro.

1H NMR (399.9 MHz, CDCl3) δ 1.37 (6H, s), 2.62 (4H, t), 3.57 (4H, t), 6.99 (2H, d), 7.04 (1H, d), 7.51 (2H, dd), 7.90 (1H, d); m/z = 409 [M+H]+.

Ejemplo 310

Preparación de 4–(3–fluorofenil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



Bromuro de 3–fluorofenilmagnesio (1.0M en THF, 1.68 mL, 1.68 mmol) fue añadido en forma de gotas a 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ona (400 mg, 1.40 mmol) en THF (10 mL) enfriados hasta 0°C durante un período de 10 minutos. La mezcla resultante fue agitada a 0°C durante 20 minutos, luego apagada con solución de cloruro de amonio saturada (20 mL) y extraída con acetato de etilo. El extracto fue lavado con salmuera saturada, secado sobre $MgSO_4$ y evaporado hasta un aceite naranja pálido el cual fue triturado con DCM para dar un sólido beige. El sólido fue

605

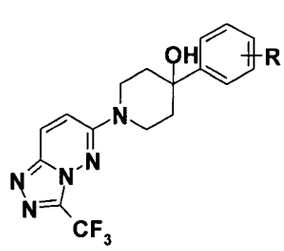
filtrado, lavado con DCM y secado, luego purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 4–(3–fluorofenil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (96 mg, 18%) como un sólido incoloro.
1H NMR (399.9 MHz, DMSO–d6) δ 1.71 – 1.74 (2H, m), 2.00 – 2.08 (2H, m), 3.40 – 3.46 (2H, m), 4.20 – 4.24 (2H, m), 5.37 (1H, s), 7.02 – 7.08 (1H, m), 7.31 – 7.40 (3H, m), 7.66 (1H, d), 8.24 (1H, d).; m/z = 382 [M+H]+.

La 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ona usada como material de partida fue preparada como sigue:

6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (10.0 g, 44.93 mmol), hidrocloruro de 4–piperidona monohidrato (8.48 g, 49.43 mmol) y DIPEA (16.3 mL, 98.85 mmol) en DMF (100 mL) fueron agitados y calentados a 90°C durante 1 hora. El DMF fue luego evaporado al *vacío y* el residuo purificado por cromatografía flash en sílice, eluyendo con 2% MeOH en DCM. Las fracciones puras fueron concentradas para dar un precipitado amarillo pálido. El precipitado fue recogido por filtración, lavado con éter y secado al aire para proporcionar 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ona (10.61 g, 83%) como un sólido amarillo pálido.
1H NMR (399.9 MHz, CDCl3) δ 2.65 (4H, t), 3.98 (4H, t), 7.15 (1H, d), 8.02 (1H, d); m/z = 286 [M+H]+.

Ejemplos 311–314

Los siguientes compuestos fueron preparados en 27–37% de rendimiento mediante un método análogo al Ejemplo 310, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ona y el bromuro de aril magnesio apropiado:

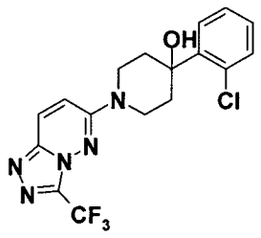


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Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
311	4–OMe	δ 1.71 – 1.74 (2H, m), 1.95 – 2.03 (2H, m), 3.40 – 3.46 (2H, m), 3.74 (3H, s), 4.17 – 4.20 (2H, m), 5.12 (1H, s), 6.88 (2H, d), 7.41 (2H, d), 7.65 (1H, d), 8.23 (1H, d).	394
312	3–OMe	δ 1.71 – 1.74 (2H, m), 1.99 – 2.06 (2H, m), 3.40 – 3.46 (2H, m), 3.76 (3H, s), 4.19 – 4.22 (2H, m), 5.22 (1H, s), 6.80 (1H, dd), 7.05 – 7.09 (2H, m), 7.24 (1H, t), 7.66 (1H, d), 8.24 (1H, d).	394
313	3–Cl	δ 1.70 – 1.73 (2H, m), 2.00 – 2.08 (2H, m), 3.40 – 3.46 (2H, m), 4.21 – 4.24 (2H, m), 5.39 (1H, s), 7.29 (1H, d), 7.36 (1H, t), 7.46 (1H, d), 7.57 (1H, m), 7.66 (1H, d), 8.24 (1H, d).	398
314	2–OMe	δ 1.55 – 1.58 (2H, m), 2.52 – 2.58 (2H, m), 3.40 – 3.48 (2H, m), 3.63 (3H, s), 4.14 – 4.17 (2H, m), 5.10 (1H, s), 6.94 – 6.98 (2H, m), 7.21 – 7.25 (1H, m), 7.61 (1H, m), 7.67 (1H, d), 8.25 (1H, d).	394

Ejemplo 315

Preparación de 4–(2–clorofenil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



Complejo de cloruro de isopropilmagnesio–cloruro de litio (1.0M en THF, 10 mL, 10.00 mmol) fue añadido en forma de gotas a 1–bromo–2–clorobenceno (1.91 g, 9.98 mmol) en THF (2.0 mL) enfriados hasta 0°C durante un período de 10 minutos. La solución resultante fue agitada a 0°C durante 1 hora, luego una alícuota de 20 mL fue añadida en forma de gotas a 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ona (400 mg, 1.40 mmol) en THF (10 mL), enfriada hasta 0°C durante un período de 10 minutos. La solución resultante fue agitada a 0°C durante 10 minutos, luego se dejó calentar lentamente hasta la temperatura ambiente y fue agitada por una hora adicional. La

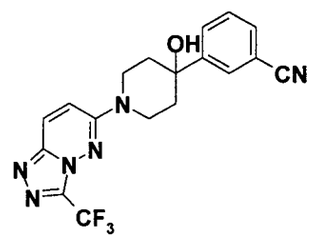
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mezcla de reacción fue luego apagada con cloruro de amonio saturado (30 mL) y extraída con EtOAc. El extracto fue lavado con salmuera saturada, secado sobre $MgSO_4$ y concentrado por evaporación, luego purificado por cromatografía flash en sílice, eluyendo con EtOAc. Las fracciones puras fueron evaporadas hasta secarse para proporcionar 4–(2–clorofenil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (230 mg, 41%) como un sólido incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.68 – 1.71 (2H, m), 2.61 – 2.69 (2H, m), 3.44 – 3.51 (2H, m), 4.20 – 4.24 (2H, m), 5.47 (1H, s), 7.26 – 7.30 (1H, m), 7.36 – 7.40 (2H, m), 7.69 (1H, d), 7.84 – 7.86 (1H, m), 8.26 (1H, d); m/z = 398 [M+H]+.

Ejemplo 316

Preparación de 3–[4–hidroxi–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzonitrilo

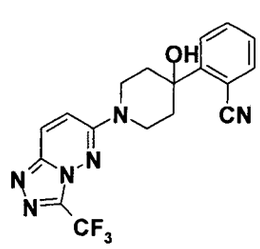


Una mezcla de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ona y 3–bromobenzonitrilo se dejó reaccionar mediante el método del ejemplo 315 para dar 3–[4–hidroxi–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzonitrilo en 26% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.70 – 1.73 (2H, m), 2.04 – 2.11 (2H, m), 3.41 – 3.47 (2H, m), 4.22 – 4.25 (2H, m), 5.49 (1H, s), 7.55 (1H, t), 7.67 (1H, d), 7.71 (1H, m), 7.87 (1H, m), 7.95 (1H, m), 8.25 (1H, d); m/z = 389 [M+H]+.

Ejemplo 317

Preparación de 2–[4–hidroxi–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzonitrilo



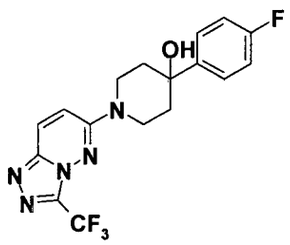
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Una mezcla de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ona y 2–bromobenzonitrilo se dejó reaccionar mediante el método del ejemplo 315 para dar 2–[4–hidroxi–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzonitrilo en 24% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.72 – 1.75 (2H, m), 2.23 – 2.30 (2H, m), 3.39 – 3.45 (2H, m), 4.39 – 4.43 (2H, m), 7.51 – 7.63 (4H, m), 7.72 (1H, d), 8.30 (1H, d), 8.04 (s) & 8.71 (s)(1H); m/z = 389 [M+H]+.

Ejemplo 318

Preparación de 4–(4–fluorofenil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol

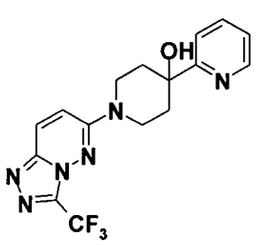


Una mezcla de 4–(4–fluorofenil)piperidin–4–ol y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método del ejemplo 306 para dar 4–(4–fluorofenil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol en 74% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.71 – 1.75 (2H, m), 1.98 – 2.06 (2H, m), 3.40 – 3.46 (2H, m), 4.19 – 4.22 (2H, m), 5.28 (1H, s), 7.14 (2H, t), 7.54 (2H, dd), 7.66 (1H, d), 8.24 (1H, d); m/z = 382 [M+H]+.

Ejemplo 319

Preparación de 4–piridin–2–il–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



Una mezcla de 4–(piridin–2–il)piperidin–4–ol y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método del ejemplo 306

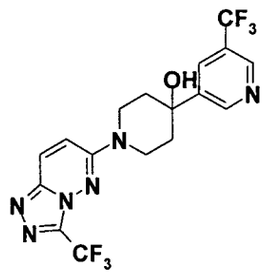
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para dar 4–piridin–2–il–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol en 77% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.66 – 1.69 (2H, m), 2.18 – 2.25 (2H, m), 3.44 – 3.50 (2H, m), 4.20 – 4.23 (2H, m), 5.47 (1H, s), 7.24 – 7.27 (1H, m), 7.67 (1H, d), 7.72 (1H, d), 7.82 (1H, td), 8.25 (1H, d), 8.49 (1H, d); m/z = 365 [M+H]+.

Ejemplo 320

Preparación de 4–[5–(trifluorometil)piridin–3–il]–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



Una mezcla de 4–[5–(trifluorometil)piridin–3–il]piperidin–4–ol y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método del ejemplo 306 para dar 4–[5–(trifluorometil)piridin–3–il]–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol en 75% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.77 – 1.80 (2H, m), 2.12 – 2.20 (2H, m), 3.43 – 3.49 (2H, m), 4.25 – 4.28 (2H, m), 5.69 (1H, s), 7.68 (1H, d), 8.26 (2H, m), 8.87 (1H, d), 9.05 (1H, d); m/z = 433 [M+H]+.

El 4–[5–(trifluorometil)piridin–3–il]piperidin–4–ol usado como material de partida fue preparado como sigue:

Preparación de bencil 4–hidroxi–4–[5–(trifluorometil)piridin–3–il]piperidina–1–carboxilato

Complejo de cloruro de isopropilmagnesio–cloruro de litio (1.0M en THF) (5.31 mL, 5.31 mmol) fue añadido en forma de gotas a 3–bromo–5–(trifluorometil)piridina (1.20 g, 5.31 mmol) en THF (10 mL), enfriados hasta 0 °C durante un período de 10 minutos. La solución resultante fue agitada a 0°C durante 1 hora, luego bencil 4–oxo–1–piperidinacarboxilato (1.24 g, 5.31 mmol) en THF (5 mL) fue añadido en forma de gotas. La mezcla se dejó calentar lentamente hasta la temperatura ambiente y fue agitada durante

1 hora adicional antes de apagar con cloruro de amonio acuoso (25 mL). La mezcla fue luego extraída con tert butil metil éter. El extracto fue lavado con agua seguido por salmuera saturada, secado sobre $MgSO_4$, concentrado por evaporación, luego purificado por cromatografía flash en sílice, gradiente en elusión 20 a 50% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar bencil 4–hidroxi–4–[5–(trifluorometil)piridin–3–il]piperidina–1–carboxilato (1.32 g, 65%) como un aceite amarillo pálido.

1H NMR (399.9 MHz, CDCl3) δ 1.76 – 1.79 (2H, m), 1.94 – 2.08 (2H, m), 3.26 – 3.37 (2H, m), 4.12 – 4.27 (2H, m), 5.16 (2H, s), 5.17 (1H, s), 7.32 – 7.38 (5H, m), 8.05 (1H, m), 8.79 (1H, d), 8.90 (1H, d); m/z = 381 [M+H]+.

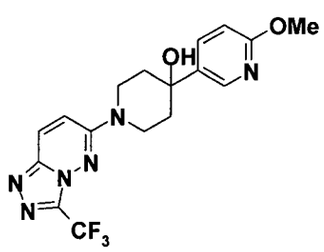
Preparación de 4–[5–(trifluorometil)piridin–3–il]piperidin–4–ol

Bencil 4–hidroxi–4–[5–(trifluorometil)piridin–3–il]piperidina–1–carboxilato (1.30 g, 3.42 mmol), 5% paladio sobre carbono activado (50 mg) y formato de amonio (2.0 g) en etanol (20 mL) fueron agitados y calentados bajo reflujo durante 1 hora, luego enfriados hasta la temperatura ambiente y filtrados a través de tierra diatomácea. El filtrado fue aplicado a una columna SCX y eluido con metanol seguido por amoniaco 2M en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas luego purificadas por cromatografía flash en sílice, gradiente en elusión 10 a 20% amoniaco 2M en metanol en DCM. Las fracciones puras fueron evaporadas hasta secarse para proporcionar 4–[5–(trifluorometil)piridin–3–il]piperidin–4–ol (0.417 g, 50%) como un sólido amarillo pálido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.56 – 1.59 (2H, m), 1.86 – 1.93 (2H, m), 2.77 – 2.80 (2H, m), 2.92 – 2.98 (2H, m), 5.27 (1H, s), 8.17 (1H, s), 8.85 (1H, s), 8.98 (1H, s); m/z = 247 [M+H]+.

Ejemplo 321

Preparación de 4–(6–metoxipiridin–3–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



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Una mezcla de 4–(6–metoxipiridin–3–il)piperidin–4–ol y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método del ejemplo 306 para dar 4–(6–metoxipiridin–3–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol en 58% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.75 – 1.78 (2H, m), 1.99 – 2.04 (2H, m), 3.41 – 3.47 (2H, m), 3.84 (3H, s), 4.18 – 4.21 (2H, m), 5.30 (1H, s), 6.77 (1H, d), 7.66 (1H, d), 7.81 (1H, d), 8.24 (1H, d), 8.28 (1H, s); m/z = 395 [M+H]+.

El 4–(6–metoxipiridin–3–il)piperidin–4–ol usado como material de partida fue preparado como sigue:

Preparación de bencil 4–hidroxi–4–(6–metoxipiridin–3–il)piperidina–1–carboxilato

n–Butillitio (1.6M en hexanos, 6.65 mL, 10.64 mmol) fue añadido en forma de gotas a 5–bromo–2–metoxipiridina (2.0 g, 10.64 mmol) en éter (30 mL) enfriado hasta –78 °C durante un período de 15 minutos. La solución resultante fue agitada a –78°C durante 40 minutos, luego una solución de bencil 4–oxo–1–piperidinacarboxilato (2.48 g, 10.64 mmol) en éter (10 mL) fue añadida en forma de gotas. La reacción se dejó calentar lentamente hasta la temperatura ambiente, luego fue apagada con solución de cloruro de amonio (50 mL) y extraída con EtOAc.

El extracto fue lavado secuencialmente con agua y salmuera saturada, secado sobre $MgSO_4$ y concentrado por evaporación, luego purificado por cromatografía flash en sílice, gradiente en elusión 50 a 80% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar bencil 4–hidroxi–4–(6–metoxipiridin–3–il)piperidina–1–carboxilato (1.90 g, 52%) como un aceite naranja pálido.

1H NMR (399.9 MHz, CDCl3) δ 1.75 – 1.79 (2H, m), 1.88 – 2 02 (2H, m), 3.29 – 3.35 (2H, m), 3.92 (3H, s), 4.03 – 4.16 (2H, m), 5.14 (2H, s), 6.72 (1H, d), 7.36 (5H, m), 7.66 (1H, dd), 8.24 (1H, d); m/z = 343 [M+H]+.

Preparación de 4–(6–metoxipiridin–3–il)piperidin–4–ol

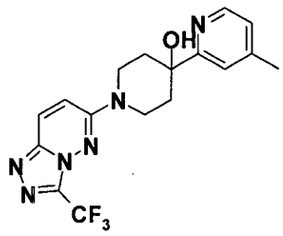
Obtenido en 39% de rendimiento mediante un método análogo al Ejemplo 320, preparación de los materiales de partida, partiendo de bencil 4–hidroxi–4–(6–metoxipiridin–3–il)piperidina–1–carboxilato.

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1H NMR (399.9 MHz, DMSO–d6) δ 1.65 – 1.68 (2H, m), 1.92 – 1.99 (2H, m), 2.92 – 2.95 (2H, m), 3.01 – 3.07 (2H, m), 3.84 (3H, s), 5.13 (1H,br s), 6.79 (1H, d), 7.76 (1H, dd), 8.23 (1H, d); m/z = 209 [M+H]+.

Ejemplo 322

Preparación de 4–(4–metilpiridin–2–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



Una mezcla de 4–(4–metilpiridin–2–il)piperidin–4–ol y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método del ejemplo 306 para dar 4–(4–metilpiridin–2–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol en 81% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.64 – 1.67 (2H, m), 2.20 (2H, td), 2.35 (3H, s), 3.42 – 3.49 (2H, m), 4.19 – 4.22 (2H, m), 5.43 (1H, s), 7.09 (1H, d), 7.55 (1H, s), 7.66 (1H, d), 8.24 (1H, d), 8.34 (1H, d); m/z = 379 [M+H]+.

El 4–(4–metilpiridin–2–il)piperidin–4–ol usado como material de partida fue preparado como sigue:

Preparación de bencil 4–hidroxi–4–(4–metilpiridin–2–il)piperidina–1–carboxilato

Obtenida en 56% de rendimiento mediante un método análogo al Ejemplo 321, preparación de los materiales de partida, partiendo de bencil 4–oxo–1–piperidinacarboxilato y 2–bromo–4–metilpiridina.

1H NMR (399.9 MHz, CDCl3) δ 1.58 – 1.61 (2H, m), 1.87 – 2.00 (2H, m), 3.21 (3H, s), 3.29 – 3.45 (2H, m), 4.09 – 4.29 (2H, m), 5.17 (2H, s), 5.32 (1H, s), 7.03 (1H, d), 7.10 (1H, s), 7.30 – 7.41 (5H, m), 8.37 (1H, d); m/z = 327 [M+H]+.

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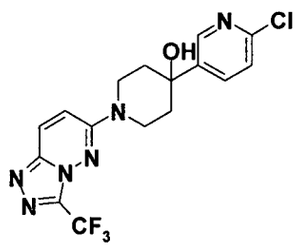
Preparación de 4–(4–metilpiridin–2–il)piperidin–4–ol

Obtenida en 56% de rendimiento mediante un método análogo al Ejemplo 321, preparación de los material de partida, partiendo de bencil 4–hidroxi–4–(4–metilpiridin–2–il)piperidina–1–carboxilato.

1H NMR (399.9 MHz, DMSO–d6) δ 1.39 – 1.42 (2H, m), 2.01 (2H, td), 2.33 (3H, s), 2.73 – 2.76 (2H, m), 2.88 – 2.94 (2H, m), 4.96 (1H, s), 7.06 (1H, d) 7.47 (1H, s), 8.36 (1H, d); m/z = 193 [M+H]+.

Ejemplo 323

Preparación de 4–(6–cloropiridin–3–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



Una mezcla de 4–(6–cloropiridin–3–il)piperidin–4–ol y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método del ejemplo 306 para dar 4–(6–cloropiridin–3–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol en 80% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.74 – 1.78 (2H, m), 2.06 (2H, td), 3.44 (2H, t), 4.21 – 4.25 (2H, m), 5.54 (1H, s), 7.47 (1H, d), 7.67 (1H, d), 7.96 (1H, dd), 8.25 (1H, d), 8.55 (1H, d); m/z = 399 [M+H]+.

El 4–(6–cloropiridin–3–il)piperidin–4–ol usado como material de partida fue preparado como sigue:

Preparación de tert–butil 4–hidroxi–4–(6–cloropiridin–3–il)piperidina–1–carboxilato

n–Butil litio (1.6M en hexanos, 6.50 mL, 10.39 mmol) fue añadido en forma de gotas a 5–bromo–2–cloropiridina (2.0 g, 10.39 mmol) en éter (30 mL), enfriados hasta –78 °C durante un período de 15 minutos. La solución resultante fue agitada a –78°C durante 45 minutos, luego una solución de tert–butil 4–oxo–1–piperidinacarboxilato (1.66 g, 8.31 mmol) en éter (10 mL) fue añadida en forma de gotas. La reacción se dejó calentar

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lentamente hasta la temperatura ambiente, luego fue apagada con solución de cloruro de amonio (50 mL) y extraída con EtOAc. El extracto fue lavado secuencialmente con agua y salmuera saturada, secado sobre $MgSO_4$ y concentrado por evaporación, luego purificado por cromatografía flash en sílice, gradiente en elusión 20 a 50% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar tert–butil 4–(6–cloropiridin–3–il)–4–hidroxipiperidina–1–carboxilato (1.33 g, 41%) como un sólido color crema.

1H NMR (399.9 MHz, CDCl3) δ 1.48 (9H, s), 1.72 – 1.76 (2H, m), 1.90 – 2.01 (2H, m), 3.16 – 3.27 (2H, m), 3.99 – 4.13 (2H, m), 7.31 (1H, d), 7.76 (1H, dd), 8.50 (1H, d); m/z = 313 [M+H]+.

Preparación de 4–(6–cloropiridin–3–il)piperidin–4–ol

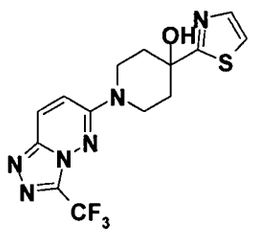
HCl (4M en dioxano, 4.22 mL, 16.88 mmol) fue añadido en una porción a una suspensión agitada de tert–butil 4–(6–cloropiridin–3–il)–4–hidroxipiperidina–1–carboxilato (1.32 g, 4.22 mmol) en acetato de etilo (20 mL) a temperatura ambiente. La mezcla resultante fue agitada a 50°C durante 90 minutos, luego enfriada hasta la temperatura ambiente, diluida con éter (20 mL) y filtrada. El sólido filtrado fue lavado con éter y secado, luego tomado en metanol, aplicado a una columna SCX y eluido con metanol seguido por amoniaco 2M en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas, luego purificadas por cromatografía flash en sílice, gradiente en elusión 10 a 20% amoniaco 2M en metanol en DCM. Las fracciones puras fueron evaporadas hasta secarse para proporcionar 4–(6–cloropiridin–3–il)piperidin–4–ol (0.43 g, 48%) como un sólido naranja pálido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.53 – 1.56 (2H, m), 1.80 (2H, td), 2.72 – 2.75 (2H, m), 2.89 – 2.96 (2H, m), 5.09 (1H, s), 7.46 (1H, d), 7.90 (1H, dd), 8.49 (1H, d); m/z = 213 [M+H]+.

Ejemplo 324

Preparación de 4–(1,3–tiazol–2–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol

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Una mezcla de 4–(1,3–tiazol–2–il)piperidin–4–ol y 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el método del Ejemplo 306 para dar 4–(1,3–tiazol–2–il)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol en 65% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.86 – 1.89 (2H, m), 2.15 (2H, td), 3.44 – 3.51 (2H, m), 4.16 – 4.19 (2H, m), 6.28 (1H, s), 7.62 (1H, d), 7.66 (1H, d), 7.72 (1H, d), 8.26 (1H, d); m/z = 371 [M+H]+.

El 4–(1,3–tiazol–2–il)piperidin–4–ol usado como material de partida fue preparado como sigue:

Preparación de tert–butil 4–hidroxi–4–(1,3–tiazol–2–il)piperidina–1–carboxilato

Obtenida en 80% de rendimiento mediante un método análogo al Ejemplo 323, preparación de los materiales de partida, partiendo de tert–butil 4–oxo–1–piperidinacarboxilato y 2–bromotiazol.

1H NMR (399.9 MHz, CDCl3) δ 1.47 (9H, s), 1.85 – 1.88 (2H, m), 2.11 (2H, td), 3.24 – 3.35 (2H, m), 3.92 – 4.08 (2H, m), 7.30 (1H, d), 7.71 (1H, d); m/z = 285 [M+H]+.

Preparación de 4–(1,3–tiazol–2–il)piperidin–4–ol

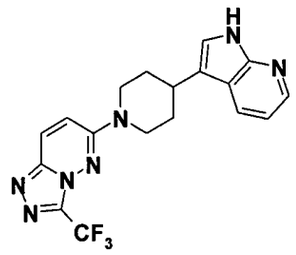
Obtenida en 82% de rendimiento mediante un método análogo al Ejemplo 323, preparación de los materiales de partida, partiendo de tert–butil 4–hidroxi–4–(2–tiazolil)piperidina–1–carboxilato.

1H NMR (399.9 MHz, DMSO–d6) δ 1.77 – 1.80 (2H, m), 2.14 (2H, td), 3.02 – 3.04 (4H, m), 6.17 (1H, br s), 7.61 (1H, d), 7.74 (1H, d); m/z = 185 [M+H]+.

Ejemplo 325

Preparación de 6–[4–(1H–pirrolo[2,3–b]piridin–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

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6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (150 mg, 0.72 mmol), 3–(piperidin–4–il)–1H–pirrolo[2,3–b]piridina (145 mg, 0.72 mmol) y DIPEA (0.14 mL, 0.79 mmol) en DMF (2.0 mL) fueron agitados y calentados a 80°C durante 1 hora. La mezcla resultante fue luego enfriada hasta la temperatura ambiente y apagada en agua (10 mL) para dar un sólido beige. El sólido fue recogido por filtración, lavado secuencialmente con agua, acetonitrilo y éter, y secado al aire para dar 6–[4–(1H–pirrolo[2,3–b]piridin–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (217 mg, 78%) como un sólido incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.70 – 1.81 (2H, m), 2.09 – 2.12 (2H, m), 3.12 – 3.26 (3H, m), 4.40 – 4.43 (2H, m), 7.03 (1H, dd), 7.25 (1H, d), 7.67 (1H, d), 8.04 (1H, d), 8.19 (1H, dd), 8.24 (1H, d), 11.34 (1H, s); m/z = 388 [M+H]+.

La 4–(1H–pirrolo[5,4–b]piridin–3–il)piperidina usada como material de partida fue preparada como sigue:

Preparación de tert–butil 4–(1H–pirrolo[2,3–b]piridin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato

Hidróxido de potasio (1.90 g, 33.86 mmol) fue añadido a 1H–pirrolo[2,3–b]piridina (1.0 g, 8.46 mmol) y tert–butil 4–oxopiperidina–1–carboxilato (3.37 g, 16.93 mmol) en metanol (25 mL) a temperatura ambiente, luego la solución resultante fue agitada a 65°C durante 18 horas. La mezcla fue enfriada hasta la temperatura ambiente, apagada en cloruro de amonio acuoso diluido (80 mL) y extraída con acetato de etilo. El extracto fue lavado secuencialmente con agua y salmuera saturada, secado sobre $MgSO_4$, concentrado por evaporación y purificado por cromatografía flash en sílice, usando 5% MeOH en eluente DCM. Las fracciones puras fueron combinadas y concentradas por evaporación, luego trituradas con éter para dar un precipitado incoloro. El precipitado fue recogido por filtración, lavado con éter y secado al aire para proporcionar tert–butil 4–(1H–pirrolo[2,3–b]piridin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato (1.37 g, 54%) como un sólido incoloro.

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1H NMR (399.9 MHz, CDCl3) δ 1.51 (9H, s), 2.57 (2H, m), 3.68 (2H, m), 4.14 (2H, m), 6.15 (1H, m), 7.13 (1H, dd), 7.33 (1H, s), 8.20 (1H, d), 8.34 (1H, d), 10.29 (1H, s); m/z = 300 [M+H]+.

Preparación de tert–butil 4–(1H–pirrolo[2,3–b]piridin–3–il)piperidina–1–carboxilato

tert–Butil 4–(1H–pirrolo[2,3–b]piridin–3–il)–5,6–dihidropiridina–1(2H)–carboxilato (1.35 g, 4.51 mmol), formato de amonio (1.42 g, 22.55 mmol) y 5% paladio sobre carbono activado (50 mg) en etanol (25 mL) fueron agitados y refluidos durante 1 hora. La mezcla resultante fue enfriada hasta la temperatura ambiente y filtrada a través de tierra diatomácea. El filtrado fue concentrado por evaporación, luego tratado con cloruro de amonio acuoso diluido (50 mL) y extraído con DCM. El extracto fue lavado con agua, secado sobre MgSO4 y evaporado hasta un sólido incoloro. El sólido fue triturado con éter, luego recogido por filtración y secado al vacío para dar tert–butil 4–(1H–pirrolo[2,3–b]piridin–3–il)piperidina–1–carboxilato (1.088 g, 80%) como un sólido incoloro.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 1.64 – 1.74 (2H, m), 2.00 – 2.03 (2H, m), 2.86 – 3.00 (3H, m), 4.16 – 4.34 (2H, m), 7.06 – 7.10 (2H, m), 7.96 (1H, d), 8.31 (1H, s), 9.73 (1H, s); m/z = 302 [M+H]+.

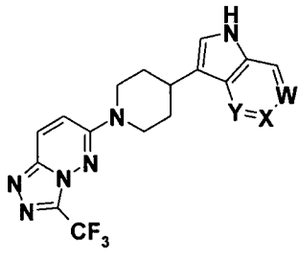
Preparación de 4–(1H–pirrolo[5,4–b]piridin–3–il)piperidina

TFA (5.0 mL, 3.58 mmol) fue añadido en una porción a temperatura ambiente a una suspensión agitada de tert–butil 4–(1H–pirrolo[2,3–b]piridin–3–il)piperidina–1–carboxilato (1.08 g, 3.58 mmol) en DCM (8 mL). La solución resultante fue agitada durante 30 minutos, luego aplicada a una columna SCX y eluida con MeOH seguido por amoniaco 2M en metanol. Las fracciones puras fueron combinadas y concentradas por evaporación, luego trituradas con éter para dar un sólido el cual fue recogido por filtración y secado con aire para dar 3–(piperidin–4–il)–1H–pirrolo[2,3–b]piridina (0.64 g, 88%) como un sólido incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.54 – 1.63 (2H, m), 1.85 – 1.89 (2H, m), 2.62 – 2.68 (2H, m), 2.81 – 2.87 (1H, m), 3.02 – 3.05 (2H, m), 7.01 (1H, dd), 7.18 (1H, s), 7.98 (1H, d), 8.17 (1H, d), 11.28 (1H, s); m/z = 202 [M+H]+.

Ejemplos 326–328

Los siguientes compuestos fueron preparados en 40–60% de rendimiento mediante un método análogo al Ejemplo 325, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la 4–(1H–pirrolopiridin–3–il)piperidina apropiada:

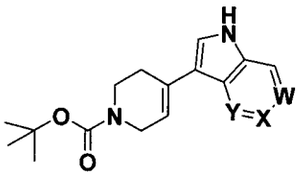


Ej.	W	X	Y	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
326	CH	N	CH	δ 1.72 – 1.82 (2H, m), 2.13 – 2.16 (2H, m), 3.18 – 3.27 (3H, m), 4.40 – 4.43 (2H, m), 7.22 (1H, dd), 7.32 (1H, d), 7.68 (1H, d) 8.14 (1H, d), 8.24 (1H, d), 8.93 (1H, s), 11.23 (1H, s).	388
327	N	CH	CH	δ 1.71 – 1.81 (2H, m), 2.09 – 2.12 (2H, m), 3.12 – 3.27 (3H, m), 4.40 – 4.43 (2H, m), 7.40 (1H, d), 7.60 (1H, d), 7.68 (1H, d), 8.07 (1H, d), 8.25 (1H, d), 8.70 (1H, d), 11.33 (1H, s).	388
328	CH	CH	N	δ 1.81 – 1.92 (2H, m), 2.17 – 2.20 (2H, m), 3.18 – 3.30 (3H, m), 4.40 (2H, d), 7.08 (1H, dd), 7.42 (1H, d), 7.67 (1H, d), 7.71 (1H, dd), 8.24 (1H, d), 8.29 (1H, dd), 11.02 (1H, s).	388

Las 4–(1H–pirrolopiridin–3–il)piperidinas isoméricas usadas como material de partida en los Ejemplos 326–328 fueron preparadas en 3 pasos como sigue:

Preparación de tert–butil 4–(1H–pirrolopiridin–3–il)–3,6–dihidro–2H–piridina–1–carboxilatos

Obtenida en 49–54% de rendimiento mediante un procedimiento análogo al Ejemplo 325, preparación de los materiales de partida, partiendo de tert–butil 4–oxopiperidina–1–carboxilato y la 1H–pirrolopiridina apropiada.

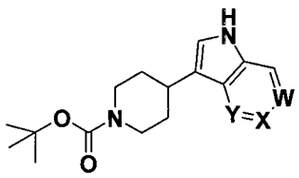


674

Precursor para el Ej.	W	X	Y	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
326	CH	N	CH	δ 1.51 (9H, s), 2.55 – 2.61 (2H, m), 3.69 (2H, t), 4.16 (2H, m), 6.23 (1H, m), 7.22 (1H, s), 7.31 (1H, d), 8.33 (1H, d), 9.20 (2H, m).	300
327	N	CH	CH	δ 1.51 (9H, s), 2.54 – 2.62 (2H, m), 3.68 – 3.71 (2H, m), 4.12 – 4.19 (2H, m), 6.16 (1H, m), 7.38 (1H, s), 7.77 (1H, d), 8.29 (1H, d), 8.83 (1H, s), 9.63 (1H, br s).	300
328	CH	CH	N	δ 1.49 (9H, s), 2.57 – 2.60 (2H, m), 3.68 – 3.71 (2H, m), 4.17 – 4.19 (2H, m), 7.13 (1H, dd), 7.20 (1H, m), 7.36 (1H, d), 7.65 (1H, dd), 8.36 (1H, s), 8.53 (1H, dd).	300

Preparación de tert–butil 4–(1H–pirrolopiridin–3–il)piperidina–1–carboxilatos

Obtenida en 75–81% de rendimiento mediante un procedimiento análogo al Ejemplo 325, preparación de los materiales de partida, partiendo del tert–butil 4–(1H–pirrolopiridin–3–il)–3,6–dihidro–2H–piridina–1–carboxilato apropiado.

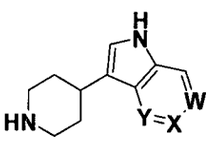


Precursor para el Ej.	W	X	Y	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
326	CH	N	CH	δ 1.49 (9H, s), 1.63 – 1.74 (2H, m), 2.04 – 2.07 (2H, m), 2.88 – 2.95 (2H, m), 3.00 – 3.08 (1H, m), 4.16 – 4.34 (2H, m), 7.03 (1H, s), 7.31 (1H,	302

				dd), 8.29 (1H, d), 8.96 (1H, d), 9.04 (1H, br s).	
327	N	CH	CH	δ 1.49 (9H, s), 1.64 – 1.74 (2H, m), 1.98 – 2.02 (2H, m), 2.86 – 2.92 (2H, m), 2.97 – 3.05 (1H, m), 4.16 – 4.37 (2H, m), 6.25 (1H, br s), 7.58 (1H, s), 7.76 (1H, d), 8.11 (1H, d), 9.26 (1H, s).	302
328	CH	CH	N	δ 1.48 (9H, s), 1.60 – 1.70 (2H, m), 2.14 – 2.17 (2H, m), 2.90 – 2.96 (2H, m), 3.22 – 3.30 (1H, m), 4.21 (2H, m), 7.11 (1H, dd), 7.18 (1H, d), 7.64 (1H, dd), 8.31 (1H, s), 8.47 (1H, dd).	302

Preparación de 4–(1H–pirrolopiridin–3–il)piperidinas

Obtenida en 72–100% de rendimiento mediante un procedimiento análogo al Ejemplo 325, preparación de los materiales de partida, partiendo de los tert–butil 4–(1H–pirrolopiridin–3–il)piperidina–1–carboxilatos apropiado.

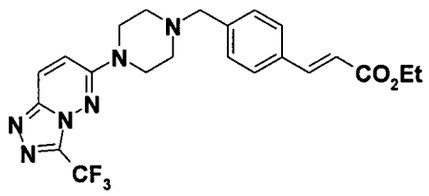


Precursor para el Ej.	W	X	Y	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
326	CH	N	CH	δ 1.60 – 1.70 (2H, m), 1.92 – 1.95 (2H, m), 2.69 – 2.75 (2H, m), 2.91 – 2.99 (1H, m), 3.07 – 3.10 (2H, m), 7.17 (1H, s), 7.32 (1H, d), 8.13 (1H, d), 8.89 (1H, s), 11.20 (1H, s).	202
327	N	CH	CH	δ 1.53 – 1.64 (2H, m), 1.85 –	202

				1.88 (2H, m), 2.63 – 2.68 (2H, m), 2.82 – 2.88 (1H, m), 3.02 – 3.05 (2H, m), 7.33 (1H, s), 7.55 (1H, d), 8.05 (1H, d), 8.69 (1H, s), 11.27 (1H, s).	
328	CH	CH	N	δ 1.59 – 1.69 (2H, m), 1.96 – 2.00 (2H, m), 2.63 – 2.70 (2H, m), 2.96 – 3.06 (3H, m), 7.06 (1H, dd), 7.35 (1H, d), 7.69 (1H, dd), 8.28 (1H, dd), 10.96 (1H, s).	202

Ejemplo 329

Preparación de etil (2E)–3–[4–([4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil)fenil]prop–2–enoato

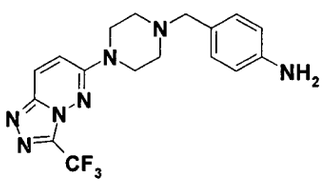


Una mezcla de etil (E)–3–(4–formilfenil)prop–2–enoato y 6–(piperazin–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 7 para dar etil (2E)–3–[4–([4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil)fenil]prop–2–enoato en 59% de rendimiento.

1H NMR (300.1 MHz, DMSO–d6) δ 1.27 (3H, t), 2.49 – 2.51 (4H, m), 3.58 (2H, s), 3.62 (4H, t), 4.20 (2H, q), 6.61 (1H, d), 7.39 (2H, d), 7.54 – 7.73 (4H, m), 8.24 (1H, d); m/z = 461 [M+H]+.

Ejemplo 330

Preparación de 4–[[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]anilina

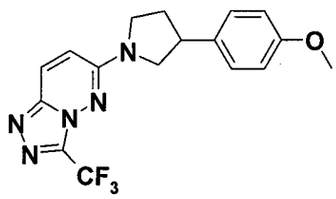


TFA (0.5 mL, 0.15 mmol) fue añadido a tert–butil N–[4–[[4–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]fenil]carbamato (obtenida como se describió en el Ejemplo 146, 72 mg, 0.15 mmol) en DCM (2 mL). La solución resultante fue agitada a temperatura ambiente durante 2 horas y luego evaporada hasta secarse. El producto crudo fue purificado por HPLC preparativa usando mezclas decrecientemente polares de agua (que contienen 0.1% TFA) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas y además purificadas por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 7M en metanol y las fracciones puras fueron evaporadas hasta secarse para proporcionar 4–[[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]anilina (32 mg, 56%).

1H NMR (300.1 MHz, DMSO–d6) δ 2.29 (4H, t), 3.18 (2H, s), 3.42 (4H, t), 4.79 (2H, s), 6.36 (2H, d), 6.79 (2H, d), 7.41 (1H, d), 8.07 (1H, d); m/z = 378 [M+H]+.

Ejemplo 331

Preparación de 6–[3–(4–metoxifenil)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

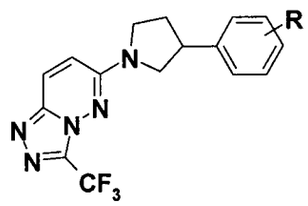


Una solución de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (50 mg, 0.22 mmol) en etanol (1 mL) fue añadida a hidrocloruro de 3–(4–metoxifenil)pirrolidina (71 mg, 0.33 mmol). La mezcla de reacción fue tratada con DIPEA (86 mg, 0.66 mmol) y la mezcla fue calentada a 70°C durante 16 horas. La mezcla de reacción fue evaporada para dejar un residuo no volátil que fue purificado por cromatografía en fase inversa preparativa para dar 6–[3–(4–metoxifenil)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (45 mg, 55%).

1H NMR (300.1 MHz, DMSO–d6) δ 2.00 – 2.18 (1H, m), 2.30 – 2.42 (1H, m), 3.33 – 3.66 (3H, m), 3.68 – 3.83 (4H, m), 3.89 – 4.06 (1H, m), 6.88 – 6.96 (2H, m), 7.24 – 7.34 (3H, m), 8.23 (1H, d); m/z = 364 [M+H]+.

Ejemplos 332–334

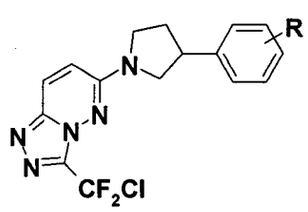
Los siguientes compuestos fueron preparados en 64–77% de rendimiento mediante un método análogo al Ejemplo 331, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el hidrocloruro de arilpirrolidina apropiado :



Ej.	R	1H NMR (300.1 MHz, DMSO–d6)	m/z [M+H]+
332	3–CN	6–cδ 2.08 – 2.25 (1H, m), 2.37 – 2.48 (1H, m), 3.41 – 3.71 (3H, m), 3.72 – 3.86 (1H, m), 3.98 – 4.11 (1H, m), 7.31 (1H, d), 7.58 (1H, t), 7.72 – 7.77 (2H, m), 7.88 (1H, t), 8.26 (1H, d)	359
333	2–CO2Me	6–cδ 2.14 – 2.30 (1H, m), 2.31 – 2.44 (1H, m), 3.41 – 3.68 (2H, m), 3.71 – 3.83 (1H, m), 3.86 (3H, s), 3.97 (1H, t), 4.10 – 4.23 (1H, m), 7.31 (1H, d), 7.36 – 7.43 (1H, m), 7.55 – 7.61 (2H, m), 7.77 (1H, d), 8.24 (1H, d)	392
334	3–CO2Me	6–cδ 2.15 – 2.33 (1H, m), 2.47 – 2.58 (1H, m), 3.47 – 3.81 (3H, m), 3.82 – 3.92 (1H, m), 3.94 (3H, s), 4.06 – 4.21 (1H, m), 7.41 (1H, d), 7.60 (1H, t), 7.73 – 7.79 (1H, m), 7.92 – 7.98 (1H, m), 8.03 (1H, t), 8.32 (1H, d)	392

Ejemplos 335–338

Los siguientes compuestos fueron preparados en 52–74% de rendimiento mediante un método análogo al Ejemplo 331, partiendo de 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina y el hidrocloruro de arilpirrolidina apropiado :–



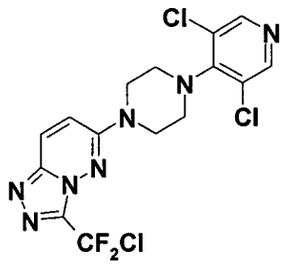
Ej.	R	1H NMR (300.1 MHz, CDCl3)	m/z [M+H]+
335	4–CF3	δ 2.17 – 2.32 (1H, m), 2.49 – 2.61 (1H, m), 3.54 – 3.75 (3H, m), 3.81 – 3.91 (1H, m), 4.03 – 4.11 (1H, m), 6.89 (1H, d), 7.42 (2H, d), 7.64 (2H, d), 7.95 (1H, d)	418
336	3–CF3	δ 2.18 – 2.34 (1H, m), 2.49 – 2.61 (1H, m), 3.52 – 3.75 (3H, m), 3.83 – 3.93 (1H, m), 4.04 – 4.13 (1H, m), 6.89 (1H, d), 7.47 – 7.53 (2H, m), 7.53 – 7.60 (2H, m), 7.95 (1H, d)	418
337	H (S–enantiómero)	δ 2.16 – 2.32 (1H, m), 2.45 – 2.56 (1H, m), 3.52 – 3.72 (3H, m), 3.80 – 3.91 (1H, m), 3.98 – 4.11 (1H, m), 6.89 (1H, d), 7.27 – 7.33 (3H, m), 7.34 – 7.42 (2H, m), 7.93 (1H, d)	350
338	H (R–enantiómero)	δ 2.16 – 2.31 (1H, m), 2.45 – 2.56 (1H, m), 3.51 – 3.72 (3H, m), 3.79 – 3.90 (1H, m), 3.98 – 4.10 (1H, m), 6.89 (1H, d), 7.27 – 7.33 (3H, m), 7.34 – 7.42 (2H, m), 7.92 (1H, d)	350

La 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue obtenida en 70% de rendimiento mediante un método análogo al Método Sintético General 1, preparación de los material de partida, partiendo de 3–cloropiridazin–6–il hidrazina y ácido clorodifluoroacético.

1H NMR (300.1 MHz, DMSO) d 7.77 (d, 1H), 8.68 (d, 1H); m/z = 239 [M+H]+.

Ejemplo 339

Preparación de 3–[cloro(difluoro)metil]–6–[4–(3,5–dicloropiridin–4–il)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina

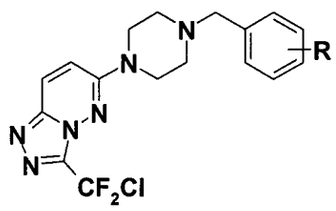


Una solución de 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 335–338, preparación de los materiales de partida) (53 mg, 0.22 mmol) en etanol (1 mL) fue añadida a 1-(3,5–dicloropiridin–4–il)piperazina (77 mg, 0.33 mmol). La mezcla de reacción fue tratada con DIPEA (43 mg, 0.33 mmol) y la mezcla fue calentada a 70°C durante 4 horas. La mezcla de reacción fue evaporada para dejar un residuo no volátil que fue purificado por cromatografía en fase inversa preparativa para dar 3–[cloro(difluoro)metil]–6–[4–(3,5–dicloropiridin–4–il)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina (28 mg, 29%).

1H NMR (300.1 MHz, CDCl3) δ 3.48 – 3.54 (4H, m), 3.78 – 3.84 (4H, m), 7.13 (1H, d), 7.99 (1H, d), 8.41 (2H, s); m/z = 434 [M+H]+.

Ejemplos 340–343

Los siguientes compuestos fueron preparados en 50–73% de rendimiento mediante un método análogo al Ejemplo 339, partiendo de 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina y el bencil piperazina apropiado:



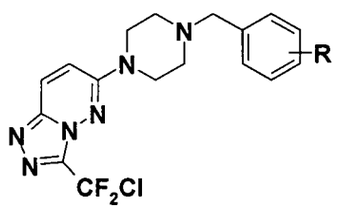
Ej.	R	1H NMR (300.1 MHz, CDCl3)	m/z [M+H]+
340	H	δ 2.60 (4H, t), 3.58 (2H, s), 3.64 (4H, t), 7.06 (1H, d), 7.27 – 7.37 (5H, m), 7.92 (1H, d)	379
341	4–F	δ 2.58 (4H, t), 3.54 (2H, s), 3.63 (4H, t), 6.98 – 7.09 (3H, m), 7.27 – 7.35 (2H, m), 7.92 (1H, d)	397
342	4–CN	δ 2.60 (4H, t), 3.60 – 3.69 (6H, m), 7.07 (1H, d), 7.49 (2H, d), 7.64 (2H, d), 7.94 (1H, d)	404
343	3–CN	δ 2.60 (4H, t), 3.60 (2H, s), 3.66 (4H, t), 7.07 (1H, d), 7.46 (1H, t), 7.56 – 7.62 (2H, m), 7.70 (1H, s) 7.94 (1H,	404

686

		d)	

Ejemplos 344–348

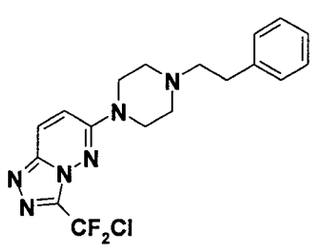
Los siguientes compuestos fueron preparados en 24–76% de rendimiento mediante un método análogo al Ejemplo 339, partiendo de 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina y el bencil piperazina apropiado:



Ej.	R	1H NMR (300.1 MHz, DMSO–d6)	m/z [M+H]+
344	3–Br	δ 2.49 – 2.52 (4H, m), 3.56 (2H, s), 3.63 (4H, t), 7.28 – 7.38 (2H, m), 7.45 – 7.50 (1H, m), 7.53 – 7.55 (1H, m), 7.58 (1H, d), 8.24 (1H, d)	459
345	3–F	δ 2.50 – 2.55 (4H, m), 3.57 (2H, s), 3.64 (4H, t), 7.05 – 7.21 (3H, m), 7.34 – 7.44 (1H, m), 7.58 (1H, d), 8.24 (1H, d)	397
346	4–CF3	δ 2.50 – 2.57 (4H, m), 3.60 – 3.69 (6H, m), 7.55 – 7.62 (3H, m), 7.68 – 7.75 (2H, m), 8.25 (1H, d)	447
347	3–CF3	δ 2.50 – 2.53 (4H, m), 3.60 – 3.68 (6H, m), 7.55 – 7.70 (5H, m), 8.24 (1H, d)	447
348	4–Br	δ 2.49 – 2.52 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 7.31 (2H, d), 7.50 – 7.61 (3H, m), 8.24 (1H, d)	459

Ejemplo 349

Preparación de 3–[cloro(difluoro)metil]–6–[4–(2–feniletil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina

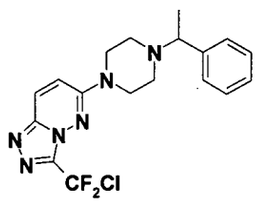


Una mezcla de 1–fenetilpiperazina y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 339 para dar 3–[cloro(difluoro)metil]–6–[4–(2–feniletil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina en 71% de rendimiento.

1H NMR (300.1 MHz, CDCl3) δ 2.64 – 2.73 (6H, m), 2.81 – 2.89 (2H, m), 3.67 (4H, t), 7.08 (1H, d), 7.19 – 7.34 (5H, m), 7.93 (1H, d); m/z = 393 [M+H]+.

Ejemplo 350

Preparación de 3–[cloro(difluoro)metil]–6–[4–(1–feniletil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina

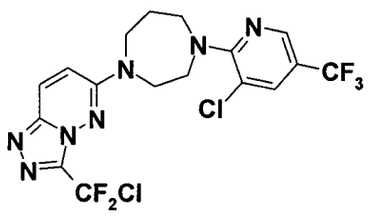


Una mezcla de 1–(1–feniletil)piperazina y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 339 para dar 3–[cloro(difluoro)metil]–6–[4–(1–feniletil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina en 64% de rendimiento.

1H NMR (499.8 MHz, DMSO–d6) δ 1.32 (3H, d), 2.39 – 2.57 (4H, m), 3.47 (1H, q), 3.58 (4H, t), 7.22 – 7.27 (1H, m), 7.30 – 7.35 (4H, m), 7.53 (1H, d), 8.20 (1H, d); m/z = 393 [M+H]+.

Ejemplo 351

Preparación de 3–[cloro(difluoro)metil]–6–[4–[3–cloro–5–(trifluorometil)piridin–2–il]–1,4–diazepan–1–il][1,2,4]triazolo[4,3–b]piridazina



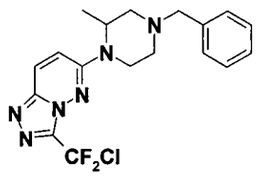
Una mezcla de 1–(3–cloro–5–trifluorometil–2–piridil)–1,4–diazepan y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 339 para dar 3–[cloro(difluoro)metil]–6–[4–[3–cloro–5–

(trifluorometil)piridin–2–il]–1,4–diazepan–1–il][1,2,4]triazolo[4,3–b]piridazina en 62% de rendimiento.

1H NMR (300.1 MHz, CDCl3) δ 2.09 – 2.19 (2H, m), 3.75 (2H, t), 3.81 (2H, t), 4.01 (4H, s), 7.04 (1H, d), 7.70 – 7.72 (1H, m), 7.94 (1H, d), 8.29 – 8.31 (1H, m); m/z = 482 [M+H]+.

Ejemplo 352

Preparación de 6–(4–bencil–2–metilpiperazin–1–il)–3–[cloro(difluoro)metil][1,2,4]triazolo[4,3–b]piridazina

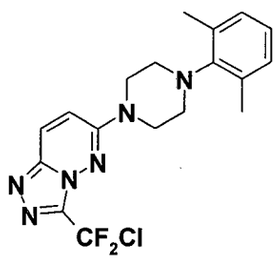


Una mezcla de 1–bencil–3–metil–piperazina y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 339 para dar 6–(4–bencil–2–metilpiperazin–1–il)–3–[cloro(difluoro)metil][1,2,4]triazolo[4,3–b]piridazina en 41% de rendimiento.

1H NMR (300.1 MHz, DMSO–d6) δ 1.26 (3H, d), 2.06 – 2.19 (1H, m), 2.22 – 2.30 (1H, m), 2.75 (1H, d), 2.94 (1H, d), 3.14 – 3.27 (1H, m), 3.53 (2H, q), 4.04 (1H, d), 4.41 – 4.53 (1H, m), 7.23 – 7.39 (5H, m), 7.56 (1H, d), 8.24 (1H, d); m/z = 393 [M+H]+.

Ejemplo 353

Preparación de 3–[cloro(difluoro)metil]–6–[4–(2,6–dimetilfenil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



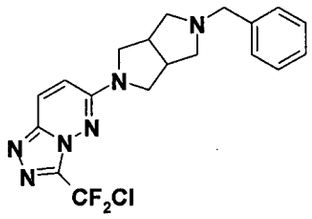
Una mezcla de 1–(2,6–dimetilfenil)piperazina y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 339 para dar 3–[cloro(difluoro)metil]–6–[4–(2,6–dimetilfenil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina en 64% de rendimiento.

1H NMR (300.1 MHz, CDCl3) δ 2.35 (6H, s), 3.26 (4H, t), 3.74 (4H, t), 7.00 – 7.05 (3H, m), 7.14 (1H, d), 7.95 (1H, d); m/z = 393 [M+H]+.

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Ejemplo 354

Preparación de 6–(5–bencilhexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–[cloro(difluoro)metil][1,2,4]triazolo[4,3–b]piridazina



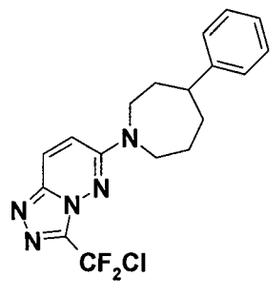
Una mezcla de hidrocloruro de 2–bencilhexahidropirrolo[3,4–c]pirrol y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 331 para dar 6–(5–bencilhexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–[cloro(difluoro)metil][1,2,4]triazolo[4,3–b]piridazina en 66% de rendimiento.

1H NMR (300.1 MHz, CDCl3) δ 2.58 – 2.75 (4H, m), 3.04 (2H, s), 3.41 – 3.50 (2H, m), 3.63 (2H, s), 3.76 – 3.85 (2H, m), 6.88 (1H, d), 7.22 – 7.33 (5H, m), 7.90 (1H, d); m/z = 405 [M+H]+.

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Ejemplo 355

Preparación de 3–[cloro(difluoro)metil]–6–(4–fenilazepan–1–il)[1,2,4]triazolo[4,3–b]piridazina

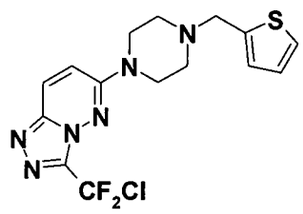


Una mezcla de hidrocloruro de 4–fenilazepan y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 331 para dar 3–[cloro(difluoro)metil]–6–(4–fenilazepan–1–il)[1,2,4]triazolo[4,3–b]piridazina en 69% de rendimiento.

1H NMR (499.8 MHz, DMSO–d6) δ 1.64 – 1.90 (4H, m), 1.98 – 2.09 (2H, m), 2.68 (1H, t), 3.59 – 3.75 (2H, m), 3.76 – 3.86 (1H, m), 3.87 – 3.96 (1H, m), 7.10 – 7.20 (3H, m), 7.24 (2H, t), 7.49 (1H, d), 8.20 (1H, d); m/z = 378 [M+H]+.

Ejemplo 356

Preparación de 3–[cloro(difluoro)metil]–6–[4–(tiofen–2–ilmetil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



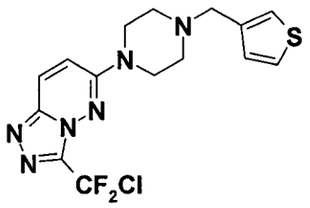
Una mezcla de 1–(tiofen–2–ilmetil)piperazina y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 339 para dar 3–[cloro(difluoro)metil]–6–[4–(tiofen–2–ilmetil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina en 74% de rendimiento.

1H NMR (300.1 MHz, DMSO–d6) δ 2.52 – 2.59 (4H, m), 3.63 (4H, t), 3.77 (2H, s), 6.97 – 7.01 (2H, m), 7.44 – 7.48 (1H, m), 7.58 (1H, d), 8.24 (1H, d); m/z = 385 [M+H]+.

Ejemplo 357

Preparación de 3–[cloro(difluoro)metil]–6–[4–(tiofen–3–ilmetil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina

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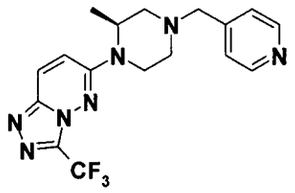


Una mezcla de 1–(tiofen–3–ilmetil)piperazina y 6–cloro–3–[cloro(difluoro)metil]–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante un método análogo al Ejemplo 339 para dar 3–[cloro(difluoro)metil]–6–[4–(tiofen–3–ilmetil)piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina en 70% de rendimiento.

1H NMR (300.1 MHz, DMSO–d6) δ 2.49 – 2.52 (4H, m), 3.56 (2H, s), 3.62 (4H, t), 7.06 – 7.10 (1H, m), 7.33 – 7.37 (1H, m), 7.49 – 7.52 (1H, m), 7.58 (1H, d), 8.24 (1H, d); m/z = 385 [M+H]+.

Ejemplo 358

Preparación de 6–[(2S)–2–metil–4–(piridin–4–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de piridina–4–carboxaldehido y 6–[(2S)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 6–[(2S)–2–metil–4–(piridin–4–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 53% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.29 (3H, d), 2.15 – 2.21 (1H, m), 2.30 – 2.34 (1H, m), 2.74 (1H, d), 2.94 (1H, d), 3.22 – 3.28 (1H, m), 3.52 (1H, d), 3.63 (1H, d), 4.04 (1H, d), 4.48 (1H, s), 7.39 (2H, d), 7.39 (1H, s), 7.58 (1H, d), 8.26 (1H, d), 8.54 – 8.55 (2H, m); m/z = 378 [M+H]+.

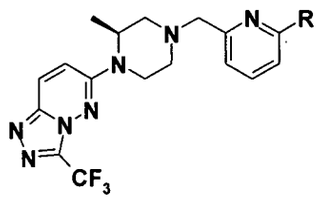
La 6–[(2S)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada en 2 pasos en 64% de rendimiento total mediante un método análogo al Ejemplo 223, preparación de los materiales de partida, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]–triazolo[4,3–b]piridazina y (3S)–tert–butil 3–metilpiperazina–1–carboxilato.

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1H NMR (399.9 MHz, DMSO–d6) δ 1.23 (3H, d), 2.42 (1H, m), 2.65 (1H, m), 2.85 (2H, m), 3.04 (2H, m), 3.91 (1H, m), 4.35 (1H, m), 7.56 (1H, d), 8.23 (1H, d); m/z = 387 [M+H]+.

Ejemplos 359–360

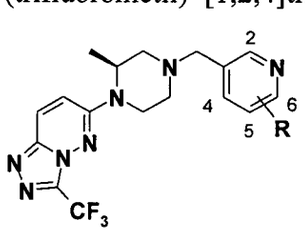
Los siguientes compuestos fueron preparados en 31 – 84% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(2S)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 358, preparación de los materiales de partida) y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
359	H	δ 1.27 – 1.29 (3H, m), 2.18 – 2.25 (1H, m), 2.35 - 2.39 (1H, m), 2.79 (1H, d), 2.96 – 2.99 (1H, m), 3.21 – 3.27 (1H, m), 3.62 (1H, d), 3.70 (1H, d), 4.03 (1H, d), 4.48 (1H, s), 7.27 – 7.31 (1H, m), 7.52 (1H, s), 7.54 (1H, s), 7.58 (1H, d), 7.79 – 7.83 (1H, m), 8.26 (1H, d), 8.51 – 8.53 (1H, m)	378
360	Br	δ 1.28 – 1.30 (3H, m), 2.20 – 2.27 (1H, m), 2.37 - 2.41 (1H, m), 2.79 (1H, d), 2.97 (1H, d), 3.22 – 3.27 (1H, m), 3.61 (1H, d), 3.69 (1H, d), 4.04 (1H, d), 4.49 (1H, s), 7.56 (2H, t), 7.58 (1H, d), 7.79 (1H, t), 8.26 (1H, d)	456

Ejemplos 361–366

Los siguientes compuestos fueron preparados en 32 – 84% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(2S)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:

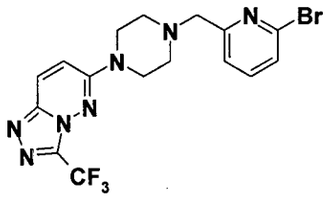


Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+

361	6–CF3	δ 1.27 – 1.28 (3H, m), 2.16 – 2.23 (1H, m), 2.33 – 2.37 (1H, m), 2.77 (1H, d), 2.95 (1H, d), 3.20 – 3.27 (1H, m), 3.66 (1H, d), 3.74 (1H, d), 4.03 (1H, d), 4.49 (1H, d), 7.58 (1H, d), 7.91 (1H, d), 8.06 – 8.08 (1H, m), 8.26 (1H, d), 8.76 (1H, d)	446
362	2–Cl	δ 1.28 – 1.29 (3H, m), 2.22 – 2.29 (1H, m), 2.42 – 2.46 (1H, m), 2.80 (1H, d), 2.95 (1H, d), 3.20 – 3.27 (1H, m), 3.62 (2H, s), 4.04 (1H, d), 4.50 (1H, t), 7.46 – 7.49 (1H, m), 7.59 (1H, d), 7.99 – 8.01 (1H, m), 8.26 (1H, d), 8.34 – 8.36 (1H, m)	421
363	2–Cl, 5–F	δ 1.29 – 1.31 (3H, m), 2.24 – 2.31 (1H, m), 2.46 – 2.49 (1H, m), 2.82 (1H, d), 2.97 (1H, d), 3.24 – 3.28 (1H, m), 3.63 (2H, s), 4.03 (1H, d), 4.50 (1H, t), 7.60 (1H, d), 7.91 – 7.94 (1H, m), 8.27 (1H, d), 8.41 (1H, d)	430
364	6–OMe	δ 1.23 (3H, d), 2.24 – 2.27 (1H, m), 2.74 (1H, d), 3.43 (1H, d), 3.53 (1H, d), 3.86 (2H, s), 4.02 (1H, d), 4.47 (1H, d), 6.81 – 6.83 (1H, m), 7.57 (1H, d), 7.67 – 7.70 (1H, m), 8.10 (1H, d), 8.25 (1H, d)	409
365	5–Br, 2–F	δ 1.25 – 1.27 (3H, m), 2.18 – 2.24 (1H, m), 2.36 – 2.40 (1H, m), 2.79 (1H, d), 2.96 (1H, d), 3.22 – 3.27 (1H, m), 3.56 – 3.64 (2H, m), 4.01 – 4.05 (1H, m), 4.49 (1H, d), 7.58 (1H, d), 8.20 (1H, d), 8.26 (1H, d), 8.32 – 8.33 (1H, m)	476
366	5–F	δ 1.26 – 1.27 (3H, m), 2.14 – 2.21 (1H, m), 2.31 – 2.35 (1H, m), 2.76 (1H, d), 2.95 (1H, d), 3.20 – 3.27 (1H, m), 3.59 (1H, d), 3.67 (1H, d), 4.03 (1H, d), 4.48 (1H, s), 7.58 (1H, d), 7.67 – 7.71 (1H, m), 8.26 (1H, d), 8.45 (1H, t), 8.50 (1H, d)	396

Ejemplo 367

Preparación de 6–[4–[(6–bromopiridin–2–il)metil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

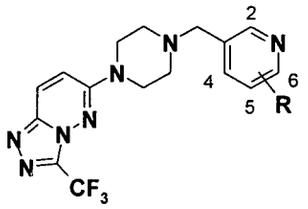


Una mezcla de 6–bromopiridina–2–carboxaldehido y 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 6–[4–[(6–bromopiridin–2–il)metil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 66% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 2.56 – 2.61 (4H, m), 3.64 (4H, t), 3.66 (2H, s), 7.53 – 7.54 (1H, m), 7.55 – 7.56 (1H, m), 7.60 (1H, d), 7.77 (1H, t), 8.26 (1H, d); m/z = 444 [M+H]+.

Ejemplos 368–377

Los siguientes compuestos fueron preparados en 20 – 79% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
368	6–CF3	δ 2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.50 (1H, d), 7.90 (1H, d), 8.04 – 8.07 (1H, m), 8.26 (1H, d), 8.74 (1H, d)	474 [1]
369	2–Cl	δ 2.61 (4H, t), 3.66 (6H, s), 7.45 – 7.48 (1H, m), 7.61 (1H, d), 7.97 – 7.99 (1H, m), 8.27 (1H, d), 8.34 – 8.35 (1H, m)	398
370	2–Cl, 5–F	δ 2.64 (4H, t), 3.66 – 3.67 (6H, m), 7.62 (1H, d), 7.90 – 7.93 (1H, m), 8.27 (1H, d), 8.40 (1H, d)	416

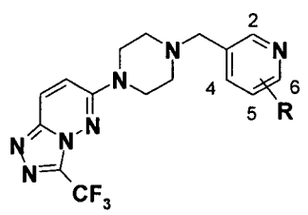
695

371	5–F	δ 2.55 (4H, t), 3.63 (6H, t), 7.60 (1H, d), 7.67 – 7.71 (1H, m), 8.26 (1H, d), 8.44 (1H, t), 8.50 (1H, d)	424 [1]
372	5–Br, 2–F	δ 2.58 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.59 (1H, d), 8.20 (1H, d), 8.26 (1H, d), 8.32 – 8.33 (1H, m)	462
373	4–OMe	δ 2.56 (4H, t), 3.53 (2H, s), 3.63 (4H, t), 3.88 (3H, s), 6.99 – 7.02 (1H, m), 7.59 (1H, d), 7.72 – 7.75 (1H, m), 8.08 – 8.10 (1H, m), 8.25 (1H, d)	394
374	6–Br	δ 2.54 (4H, s), 3.57 – 3.61 (2H, m), 3.62 – 3.63 (4H, m), 7.59 (1H, d), 7.64 (1H, d), 7.72 – 7.74 (1H, m), 8.26 (1H, d), 8.36 (1H, d)	444
375	5–OMe	δ 2.53 – 2.56 (4H, m), 3.59 – 3.62 (2H, m), 3.63 (4H, d), 3.84 (3H, s), 7.33 (1H, q), 7.58 (1H, d), 8.14 (1H, d), 8.21 – 8.22 (1H, m), 8.23 – 8.25 (1H, m)	394
376	2–Br	δ 2.53 – 2.57 (4H, m), 3.60 – 3.64 (6H, m), 7.59 (1H, d), 8.02 (1H, t), 8.26 (1H, d), 8.54 (1H, d), 8.63 (1H, d)	444
377	4–Br	δ 2.59 – 2.63 (4H, m), 3.62 – 3.66 (4H, m), 3.68 (2H, s), 7.61 (1H, d), 7.72 (1H, d), 8.27 (1H, d), 8.36 (1H, d), 8.62 (1H, s)	444

[1] Detectado como un aducto con acetonitrilo usado como solvente para la determinación de la masa espectral.

Ejemplos 378–379

Los siguientes compuestos fueron preparados en 33 – 54% de rendimiento mediante un método análogo al Ejemplo 307, partiendo de la bromopiridina apropiada (obtenida como se describió en el correspondiente pie de página):



Ej.	R	Nota	H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
378	2–CN	[1]	δ 2.61 (4H, t), 3.63 (4H, t), 3.78 (2H, s), 7.61	389

696

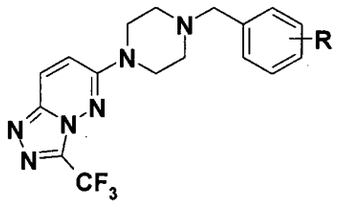
			(1H, d), 7.74 – 7.77 (1H, m), 8.08 – 8.10 (1H, m), 8.27 (1H, d), 8.68 – 8.70 (1H, m)	
379	4–CN	[2]	δ 2.61 (4H, s), 3.63 (4H, s), 3.76 (2H, s), 7.60 (1H, d), 7.88 (1H, s), 8.26 (1H, d), 8.75 (1H, s), 8.85 (1H, s)	389

[1] Partiendo de 6–[4–[(2–bromopiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina, obtenida como se describió en el Ejemplo 376.

[2] Partiendo de 6–[4–[(4–bromopiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina, obtenida como se describió en el Ejemplo 377.

Ejemplos 380–393

Los siguientes compuestos fueron preparados en 23 – 93% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
380	2,6–di–F, 4–CN	δ 2.65 (4H, m), 3.62 (4H, m), 3.78 (2H, s), 7.03 (1H, d), 7.25 (2H, m), 7.92 (1H, d)	424
381	2,3–di–F	δ 2.64 (4H, m), 3.63 (4H, m), 3.69 (2H, s), 7.13 (4H, m), 7.92 (1H, d)	399
382	2,4–di–F	1H NMR (399.9 MHz, DMSO–d6) δ 2.52 (4H, m), 3.30 (2H, s), 3.61 (4H, m), 7.09 (1H, m), 7.22 (1H, m), 7.50 (1H, m), 7.58 (1H, d), 8.25 (1H, d)	399
383	3,4–di–F	1H NMR (399.9 MHz, DMSO–d6) δ 3.29 (4H, m), 3.55 (2H, s), 3.62 (4H, m), 7.19 (1H, m), 7.40 (2H, m), 7.59 (1H, d), 8.26 (1H, d)	399

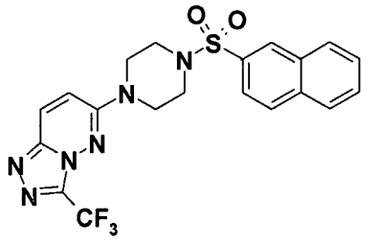
697

384	2,6–di–F	δ 2.76 (4H, m), 3.67 (4H, m), 3.85 (2H, s), 7.08 (2H, m), 7.44 (2H, m), 8.15 (1H, d)	399
385	2–F, 4–OMe	δ 2.91 (4H, s), 3.74 (4H, s), 3.81 (3H, s), 3.91 (2H, s), 6.82 (2H, m), 7.40 (1H, m), 7.49 (1H, d), 8.18 (1H, d)	411
386	2,5–di–F	δ 2.78 (4H, m), 3.70 (4H, m), 3.80 (2H, s), 7.16 (1H, m), 7.22 (1H, m), 7.31 (1H, m), 7.49 (1H, d), 8.16 (1H, d)	399
387	3–CN, 4–F	1H NMR (399.9 MHz, DMSO–d6) δ 3.29 (4H, m), 3.60 (2H, s), 3.63 (4H, m), 7.52 (1H, m), 7.60 (1H, d), 7.77 (1H, m), 7.87 (1H, m), 8.26 (1H, d)	406
388	3–F, 4–OMe	1H NMR (399.9 MHz, DMSO–d6) δ 3.30 (4H, m), 3.49 (2H, s), 3.62 (4H, m), 3.84 (3H, s), 7.14 (3H, m), 7.59 (1H, d), 8.25 (1H, d)	411
389	2–F, 4–CN	1H NMR (399.9 MHz, DMSO–d6) δ 2.57 (4H, m), 3.30 (2H, s), 3.63 (4H, m), 7.60 (1H, d), 7.70 (2H, m), 7.85 (1H, m), 8.26 (1H, d)	406
390	2–F, 5–OMe	1H NMR (399.9 MHz, DMSO–d6) δ 2.55 (4H, m), 3.30 (3H, s), 3.62 (4H, m), 3.76 (2H, s), 6.88 (1H, m), 6.98 (1H, m), 7.12 (1H, m), 7.59 (1H, d), 8.25 (1H, d)	411
391	3,5–di–F	1H NMR (399.9 MHz, DMSO–d6) δ 3.30 (4H, m), 3.59 (2H, s), 3.64 (4H, m), 7.11 (3H, m), 7.60 (1H, d), 8.26 (1H, d)	399
392	3–OMe, 4–F	1H NMR (399.9 MHz, DMSO–d6) δ 2.52 (4H, m), 3.52 (2H, s), 3.63 (4H, m), 3.85 (3H, s), 6.90 (1H, m), 7.15 (2H, m), 7.59 (1H, d), 8.26 (1H, d)	411
393	3–F, 4–CN	δ 2.55 (4H, m), 3.65 (4H, m), 3.67 (2H, s), 7.42 (1H, m), 7.51 (1H, m), 7.60 (1H, d), 7.91 (1H, m), 8.26 (1H, d)	406

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Ejemplo 394

Preparación de 6–[4–(naftalen–2–ilsulfonil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

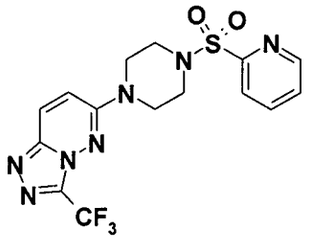


Cloruro de naftaleno–2–sulfonilo (175 mg, 0.77 mmol) fue añadido a 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (150 mg, 0.55 mmol) en piridina (2 mL). La solución resultante fue agitada a temperatura ambiente durante 18 horas. La mezcla de reacción fue evaporada para eliminar la piridina. El producto crudo fue purificado por HPLC preparativa (columna Phenomenex Gemini C18 110A (axia), 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–(naftalen–2–ilsulfonil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (168 mg, 66%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 3.15 (4H, m), 3.72 (4H, m), 7.49 (1H, d), 7.74 (3H, m), 8.07 (1H, d), 8.19 (3H, m), 8.49 (1H, s); m/z = 463 [M+H]+.

Ejemplo 395

Preparación de 6–[4–(piridin–2–ilsulfonil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

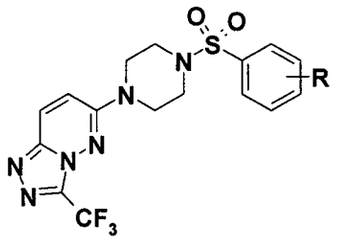


Obtenida en 32% de rendimiento mediante un método análogo al Ejemplo 394, partiendo de cloruro de piridina–2–sulfonilo y 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (399.9 MHz, DMSO–d6) δ 3.28 (4H, m), 3.63 (4H, m), 7.47 (1H, d), 7.64 (1H, m), 7.90 (1H, m), 8.06 (1H, m), 8.20 (1H, d), 8.68 (1H, m); m/z = 414 [M+H]+.

Ejemplos 396–405

Los siguientes compuestos fueron preparados en 7 – 90% de rendimiento mediante un método análogo al Ejemplo 394, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el cloruro de sulfonilo apropiado:

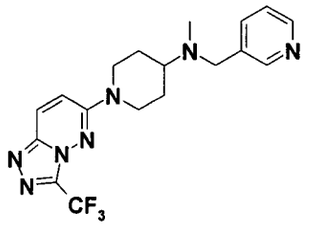


Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
396	3–OMe	δ 3.09 (4H, m), 3.71 (4H, m), 3.85 (3H, s), 7.23 (1H, m), 7.32 (2H, m), 7.56 (2H, m), 8.28 (1H, d)	443
397	2–OMe	δ 3.27 (4H, m), 3.67 (4H, m), 3.89 (3H, s), 7.12 (1H, m), 7.26 (1H, m), 7.56 (1H, d), 7.65 (1H, m), 7.78 (1H, m), 8.28 (1H, d)	443
398	4–OMe	δ 2.96 (4H, m), 3.63 (4H, m), 3.76 (3H, s), 7.09 (2H, m), 7.44 (1H, d), 7.63 (2H, m), 8.17 (1H, d)	443
399	2,5–di–OMe	δ 3.20 (4H, m), 3.59 (4H, m), 3.70 (3H, s), 3.76 (3H, s), 7.16 (3H, m), 7.48 (1H, d), 8.20 (1H, d)	473
400	2–F	δ 3.16 (4H, m), 3.64 (4H, m), 7.42 (3H, m), 7.72 (2H, m), 8.19 (1H, d)	431
401	3–F	δ 3.14 (4H, m), 3.72 (4H, m), 7.63 (5H, m), 8.26 (1H, d)	431
402	3,4–di–OMe	δ 3.06 (4H, m), 3.71 (4H, m), 3.85 (6H, m), 7.18 (2H, m), 7.36 (1H, m), 7.53 (1H, d), 8.26 (1H, d)	473
403	2–CN	δ 3.29 (4H, m), 3.74 (4H, m), 7.57 (1H, d), 7.94 (2H, m), 8.07 (1H, m), 8.18 (1H, m), 8.23 (1H, d)	438
404	2,4–di–OMe	δ 3.21 (4H, m), 3.67 (4H, m), 3.85 (3H, s), 3.87 (3H, s), 6.68 (1H, m), 6.73 (1H, m), 7.56 (1H, d), 7.69 (1H, d), 8.27 (1H, d)	473

405	4–F	δ 3.09 (4H, m), 3.72 (4H, m), 7.51 (3H, m), 7.86 (2H, m), 8.26 (1H, d)	431

Ejemplo 406

Preparación de N–metil–N–(piridin–3–ilmetil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–amina



DIPEA (0.174 mL, 1.00 mmol) fue añadido a N–metil–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–amina (100 mg, 0.34 mmol) y 3–(bromometil)piridina hidrobromuro (127 mg, 0.50 mmol) en DMA (2 mL) y la mezcla fue sellada en un tubo de microondas. La reacción fue calentada hasta 150°C durante 15 minutos en el reactor de microondas y enfriada hasta la temperatura ambiente. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 30 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar N–metil–N–(piridin–3–ilmetil)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–amina (113 mg, 78%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.59 (2H, m), 1.91 (2H, m), 2.12 (2H, s), 2.75 (1H, m), 3.03 (2H, m), 3.61 (3H, s), 4.34 (2H, m), 7.35 (1H, m), 7.63 (1H, d), 7.70 (1H, m), 8.23 (1H, d), 8.48 (2H, m); m/z = 392 [M+H]+.

La N–metil–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–amina usada como material de partida fue preparada como sigue:

Preparación de tert–butil metil[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]carbamato

DIPEA (1.355 mL, 7.78 mmol) fue añadido a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.865 g, 3.89 mmol) y tert–butil metil(piperidin–4–il)carbamato (1 g, 4.67 mmol) en DMA (15 mL). La solución resultante fue agitada a 50°C

401

durante 2 horas. La mezcla de reacción fue evaporada y diluida con DCM (100 mL), y lavada secuencialmente con agua (100 mL) y salmuera saturada (100 mL). La capa orgánica fue secada sobre MgSO4, filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente en elusión 0 a 10% MeOH en DCM. Las fracciones puras fueron evaporadas hasta secarse para proporcionar tert–butil metil[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]carbamato (1.500 g, 96%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.40 (9H, s), 1.71 (4H, m), 2.67 (3H, s), 3.05 (2H, m), 4.06 (1H, s), 4.38 (2H, m), 7.63 (1H, d), 8.24 (1H, d); m/z = 401 [M+H]+.

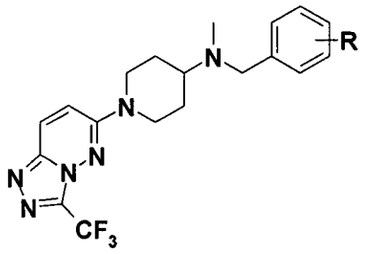
Preparación de N–metil–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–amina

tert–Butil metil[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]carbamato (1.5 g, 3.75 mmol) fue disuelto en TFA (5 mL) y DCM (5 mL). La solución resultante fue agitada a temperatura ambiente durante 2 horas. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 2M en metanol y fracciones puras fueron evaporadas hasta secarse para proporcionar N–metil–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–amina (1.090 g, 97%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.30 (2H, m), 1.91 (2H, m), 2.59 (1H, m), 3.16 (2H, m), 3.30 (3H, s), 4.11 (2H, m), 7.61 (1H, d), 8.22 (1H, d); m/z = 301 [M+H]+.

Ejemplos 407–411

Los siguientes compuestos fueron preparados en 39 – 78% de rendimiento mediante un método análogo al Ejemplo 406, partiendo de N–metil–1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–amina y el bencil bromuro apropiado:

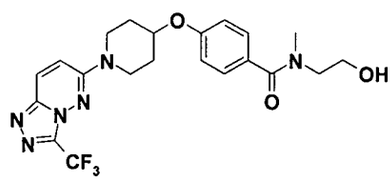


Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
407	4–F	δ 1.58 (2H, m), 1.90 (2H, m), 2.11 (2H, s), 2.73 (1H,	409

		m), 3.02 (2H, m), 3.56 (3H, s), 4.32 (2H, m), 7.13 (2H, m), 7.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d)	
408	3,4–di–F	δ 1.57 (2H, m), 1.89 (2H, m), 2.13 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.56 (3H, s), 4.33 (2H, m), 7.16 (1H, m), 7.35 (2H, m), 7.63 (1H, d), 8.23 (1H, d)	427
409	4–CN	δ 1.59 (2H, m), 1.90 (2H, m), 2.13 (2H, s), 2.65 (1H, m), 3.05 (2H, m), 3.66 (3H, s), 4.34 (2H, m), 7.65 (4H, m), 7.98 (1H, m), 8.27 (1H, m)	416
410	3,5–di–F	δ 1.57 (2H, m), 1.89 (2H, m), 2.15 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.61 (3H, s), 4.33 (2H, m), 7.06 (3H, m), 7.63 (1H, d), 8.23 (1H, d)	427
411	3–CN, 4–F	δ 1.58 (2H, m), 1.89 (2H, m), 2.13 (2H, s), 2.74 (1H, m), 3.04 (2H, m), 3.60 (3H, s), 4.33 (2H, m), 7.48 (1H, m), 7.63 (1H, d), 7.73 (1H, m), 7.82 (1H, m), 8.23 (1H, d)	434

Ejemplo 412

Preparación de N–(2–hidroxietil)–N–metil–4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzamida



DIPEA (0.087 mL, 0.5 mmol) fue añadido a ácido 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoico (100 mg, 0.25 mmol), 2–(metilamino)etanol (20.28 mg, 0.27 mmol) y HATU (114 mg, 0.3 mmol) en DMF (2 mL). La solución resultante fue agitada a temperatura ambiente durante 24 horas. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, 21 mm diámetro, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar N–(2–hidroxietil)–N–metil–4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzamida (64 mg, 55%).

1H NMR (399.9 MHz, DMSO–d6) δ 1.75 (2H, m), 2.10 (2H, m), 2.98 (3H, s), 3.56 (6H, m), 3.99 (2H, m), 4.76 (1H, m), 7.04 (2H, d), 7.39 (2H, d), 7.65 (1H, d), 8.27 (1H, d); m/z = 465 [M+H]+.

El ácido 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoico usado como material de partida fue preparado como sigue:

Preparación de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol

4–Hidroxipiperidina (10.91 g, 107.84 mmol) fue añadida a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (20 g, 89.87 mmol) y DIPEA (23.48 mL, 134.80 mmol) en DMF (200 mL). La solución resultante fue agitada a 125°C durante 2 horas. La mezcla de reacción fue evaporada hasta secarse, redisuelta en DCM y purificada por cromatografía flash en sílice, gradiente en elusión 0 a 5% MeOH en DCM. Las fracciones puras fueron evaporadas hasta secarse para dar un sólido beige el cual fue agitado con éter, luego filtrado para proporcionar 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (22.64 g, 88%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.46 (2H, m), 1.85 (2H, m), 3.32 (2H, m), 3.78 (1H, m), 3.96 (2H, m), 4.78 (1H, d), 7.61 (1H, d), 8.22 (1H, d); m/z = 288 [M+H]+.

Preparación de 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoato de etilo

DIAD (2.262 mL, 11.49 mmol) fue añadida a 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (3 g, 10.44 mmol), 4–hidroxibenzoato de etilo (1.909 g, 11.49 mmol) y trifenilfosfina (3.01 g, 11.49 mmol) en THF (50 mL) bajo nitrógeno. La solución resultante fue agitada a temperatura ambiente durante 4 horas. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 2M en metanol. El sólido crudo fue triturado con MeOH para dar un sólido el cual fue recogido por filtración y secado al vacío para dar 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoato de etilo (2.220 g, 49%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.33 (3H, t), 1.76 (2H, m), 2.11 (2H, m), 3.55 (2H, m), 3.98 (2H, m), 4.29 (2H, q), 4.83 (1H, m), 7.13 (2H, m), 7.56 (1H, d), 7.92 (2H, m), 8.27 (1H, d); m/z = 436 [M+H]+.

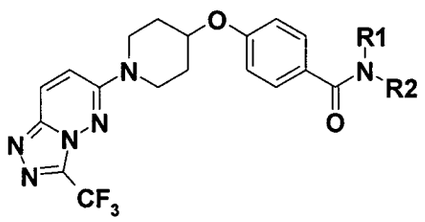
Preparación de ácido 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoico

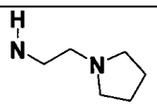
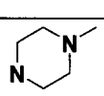
Hidróxido de litio monohidrato (0.488 g, 20.40 mmol) fue añadido a 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoato de etilo (2.22 g, 5.10 mmol) en MeOH (80 mL) y agua (40.0 mL). La suspensión resultante fue agitada a 50°C durante 2 días. La reacción fue enfriada hasta la temperatura ambiente, el metanol fue evaporado y el residuo acuoso tratado con ácido cítrico hasta que la precipitación cesó. El precipitado fue recogido por filtración, lavado con agua y secado para proporcionar ácido 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoico (2.020 g, 97%) como un sólido.

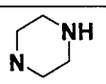
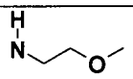
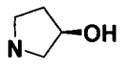
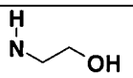
1H NMR (399.9 MHz, DMSO–d6) δ 1.76 (2H, m), 2.12 (2H, m), 3.54 (2H, m), 3.99 (2H, m), 4.82 (1H, m), 7.10 (2H, m), 7.66 (1H, d), 7.90 (2H, m), 8.26 (1H, d), 12.60 (1H, s); m/z = 408 [M+H]+.

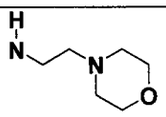
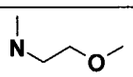
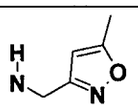
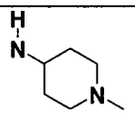
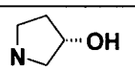
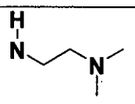
Ejemplos 413–429

Los siguientes compuestos fueron preparados en 9 – 62% de rendimiento mediante un método análogo al Ejemplo 412, partiendo de ácido 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoico y la amina apropiada:



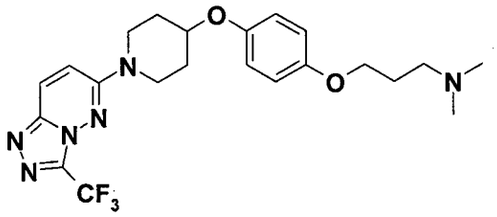
Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
413		δ 1.72 (6H, m), 2.10 (2H, m), 2.49 (4H, m), 2.57 (2H, m), 3.37 (2H, m), 3.55 (2H, m), 3.99 (2H, m), 4.79 (1H, m), 7.07 (2H, d), 7.65 (1H, d), 7.82 (2H, d), 8.26 (2H, m)	504
414		δ 1.75 (2H, m), 2.10 (2H, m), 2.20 (3H, s), 2.32 (4H, m), 3.50 (6H, m), 3.98 (2H, m), 4.76 (1H, m), 7.06 (2H, d), 7.35 (2H, d), 7.65 (1H, d), 8.26	490

		(1H, d)	
415		δ 1.75 (2H, m), 2.10 (2H, m), 2.68 (4H, m), 3.41 (4H, m), 3.54 (2H, m), 3.98 (2H, m), 4.75 (1H, m), 7.05 (2H, m), 7.34 (2H, m), 7.65 (1H, d), 8.26 (1H, d)	476
416		1H NMR (499.803 MHz, DMSO–d6) δ 1.72 (2H, m), 2.08 (2H, m), 3.26 (3H, s), 3.41 (4H, m), 3.51 (2H, m), 3.96 (2H, m), 4.77 (1H, m), 7.05 (2H, d), 7.63 (1H, d), 7.82 (2H, d), 8.24 (1H, d), 8.33 (1H, m)	465
417	NMe2	δ 1.76 (2H, m), 2.11 (2H, m), 2.97 (6H, s), 3.53 (2H, m), 3.99 (2H, m), 4.76 (1H, m), 7.05 (2H, d), 7.38 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	435
418		δ 1.76 (3H, m), 1.94 (1H, m), 2.10 (2H, m), 3.53 (5H, m), 3.98 (2H, m), 4.28 (1H, m), 4.77 (1H, m), 4.94 (1H, m), 7.05 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.26 (1H, d)	477
419		δ 1.80 (6H, m), 2.10 (2H, m), 3.50 (6H, m), 3.98 (2H, m), 4.76 (1H, m), 7.04 (2H, d), 7.51 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	461
420		δ 1.75 (2H, m), 2.10 (2H, m), 3.56 (10H, m), 3.98 (2H, m), 4.77 (1H, m), 7.07 (2H, m), 7.39 (2H, m), 7.65 (1H, d), 8.26 (1H, d)	477
421	NHMe	δ 1.75 (2H, m), 2.10 (2H, m), 2.77 (3H, m), 3.53 (2H, m), 3.98 (2H, m), 4.79 (1H, m), 7.06 (2H, d), 7.65 (1H, m), 7.81 (2H, d), 8.27 (2H, m)	421
422	NHEt	δ 1.12 (3H, t), 1.75 (2H, m), 2.10 (2H, m), 3.30 (2H, m), 3.54 (2H, m), 3.98 (2H, m), 4.79 (1H, m), 7.06 (2H, d), 7.66 (1H, d), 7.82 (2H, d), 8.27 (2H, m)	435
423		δ 1.75 (2H, m), 2.11 (2H, m), 3.34 (2H, m), 3.53 (4H, m), 3.98 (2H, m), 4.69 (1H, t), 4.79 (1H, m), 7.07 (2H, d), 7.66 (1H, d), 7.84 (2H, d), 8.27 (2H,	451

		m)	
424		δ 1.75 (2H, m), 2.10 (2H, m), 2.42 (4H, m), 2.57 (2H, m), 3.38 (2H, m), 3.55 (6H, m), 3.93 (2H, m), 4.79 (1H, m), 7.07 (2H, d), 7.65 (1H, d), 7.81 (2H, d), 8.25 (2H, m)	520
425		δ 1.74 (2H, m), 2.11 (2H, m), 2.98 (3H, s), 3.25 (3H, m), 3.52 (6H, m), 3.99 (2H, m), 4.75 (1H, m), 7.05 (2H, d), 7.36 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	479
426		δ 1.75 (2H, m), 2.11 (2H, m), 2.37 (3H, s), 3.54 (2H, m), 3.99 (2H, m), 4.45 (2H, d), 4.80 (1H, m), 6.14 (1H, s), 7.09 (2H, d), 7.66 (1H, d), 7.87 (2H, d), 8.26 (1H, d), 8.90 (1H, m)	502
427		δ 1.63 (2H, m), 1.80 (4H, m), 1.99 (2H, m), 2.14 (2H, m), 2.22 (3H, s), 2.82 (2H, m), 3.60 (2H, m), 3.77 (1H, m), 4.02 (2H, m), 4.84 (1H, m), 7.11 (2H, d), 7.70 (1H, d), 7.88 (2H, d), 8.10 (1H, d), 8.31 (1H, d)	504
428		δ 1.76 (3H, m), 1.93 (1H, m), 2.10 (2H, m), 3.55 (5H, m), 3.98 (2H, m), 4.29 (1H, m), 4.77 (1H, m), 4.94 (1H, m), 7.05 (2H, d), 7.50 (2H, d), 7.65 (1H, d), 8.26 (1H, d)	477
429		1H NMR (500.13 MHz, DMSO–d6) δ 1.72 (2H, m), 2.08 (2H, m), 2.16 (6H, s), 2.37 (2H, m), 3.32 (2H, m), 3.51 (2H, m), 3.95 (2H, m), 4.77 (1H, m), 7.04 (2H, d), 7.63 (1H, d), 7.80 (2H, d), 8.19 (1H, m), 8.24 (1H, m)	478

Ejemplo 430

Preparación de N,N–dimetil–3–[4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]fenoxi]propan–1–amina



DIAD (0.05 mL, 0.29 mmol) fue añadida a 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]fenol, 3–dimetilamino–1–propanol (100 mg, 0.26 mmol (33 mg, 0.32 mmol) y trifenilfosfina (76 mg, 0.29 mmol) en THF (2 mL). La solución resultante fue agitada a temperatura ambiente durante 4 horas. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar el producto (19.1 mg, 16%) como una goma.

1H NMR (399.9 MHz, DMSO–d6) δ 1.74 (2H, m), 1.86 (2H, m), 2.08 (2H, m), 2.19 (6H, s), 2.39 (2H, m), 3.57 (2H, m), 3.99 (4H, m), 4.58 (1H, m), 6.94 (4H, m), 7.69 (1H, d), 8.30 (1H, d); m/z = 465 [M+H]+.

El 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]fenol usado como material de partida fue preparado como sigue:

Preparación de 6–[4–[4–(benciloxi)fenoxi]piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

DIAD (2.262 mL, 11.49 mmol) fue añadida a 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (3 g, 10.44 mmol), 4–(benciloxi)fenol (2.300 g, 11.49 mmol) y trifenilfosfina (3.01 g, 11.49 mmol) en THF (50 mL) bajo nitrógeno. La solución resultante fue agitada a temperatura ambiente durante 4 horas. El aceite crudo fue triturado con MeOH para dar un sólido el cual fue recogido por filtración y secado al vacío para dar 6–[4–[4–(benciloxi)fenoxi]piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (2.53 g, 52%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.75 (2H, m), 2.08 (2H, m), 3.56 (2H, m), 3.99 (2H, m), 4.60 (1H, m), 5.10 (2H, s), 7.00 (4H, m), 7.44 (5H, m), 7.69 (1H, d), 8.30 (1H, d); m/z = 470 [M+H]+.

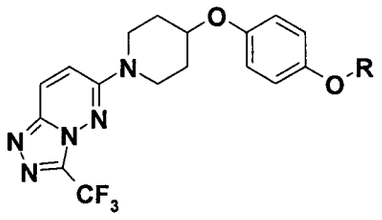
Preparación de 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4il]oxi]fenol

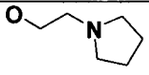
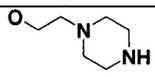
10% Paladio sobre carbono (0.574 g, 0.54 mmol) fue añadido a 6–[4–[4–(benciloxi)fenoxi]piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (2.53 g, 5.39 mmol) en MeOH (30 mL) bajo una atmósfera de hidrógeno. La suspensión resultante fue agitada a temperatura ambiente durante 24 horas. La mezcla de reacción fue evaporada. El producto crudo fue purificado por cromatografía flash en sílice, gradiente en elusión 0 a 3% MeOH en DCM. Las fracciones puras fueron evaporadas hasta secarse para proporcionar 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4il]oxi]fenol (1.760 g, 86%) como una goma la cual cristalizó con agitación.

1H NMR (399.9 MHz, DMSO–d6) δ 1.69 (2H, m), 2.01 (2H, m), 3.51 (2H, m), 3.94 (2H, m), 4.46 (1H, m), 6.69 (2H, m), 6.83 (2H, m), 7.64 (1H, d), 8.25 (1H, d), 8.94 (1H, s); m/z = 380 [M+H]+.

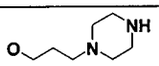
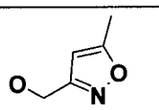
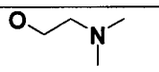
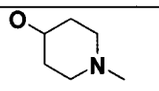
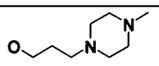
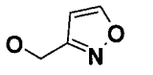
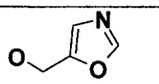
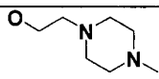
Ejemplos 431–442

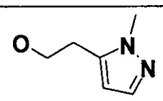
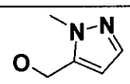
Los siguientes compuestos fueron preparados en 8 – 43% de rendimiento mediante un método análogo al Ejemplo 430, partiendo de 4–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]fenol y el alcohol apropiado:



Ej.	OR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
431		δ 1.70 (6H, m), 2.03 (2H, m), 2.52 (4H, m), 2.76 (2H, m), 3.52 (2H, m), 3.97 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)	477
432		δ 1.74 (2H, m), 2.08 (2H, m), 2.44 (2H, m), 2.67 (4H, m), 2.74 (4H, m), 3.23 (2H, m), 3.55	492

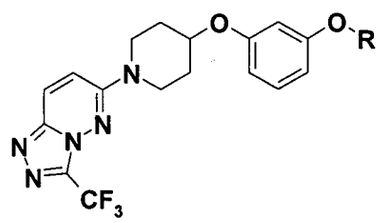
709

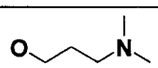
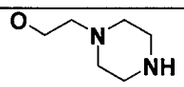
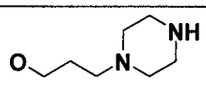
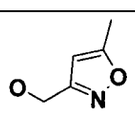
		(2H, m), 4.05 (2H, m), 4.59 (1H, m), 6.74 (1H, m), 6.94 (4H, m), 7.69 (1H, d), 8.30 (1H, d)	
433		δ 1.68 (2H, m), 1.81 (2H, m), 2.01 (2H, m), 2.27 (4H, m), 2.35 (2H, m), 2.66 (4H, m), 3.49 (2H, m), 3.92 (4H, m), 4.52 (1H, m), 6.84 (2H, m), 6.91 (2H, m), 7.62 (1H, d), 8.23 (1H, d)	506
434		δ 1.75 (2H, m), 2.08 (2H, m), 2.47 (3H, s), 3.57 (2H, m), 4.00 (2H, m), 4.61 (1H, m), 5.13 (2H, m), 6.37 (1H, m), 7.01 (4H, m), 7.69 (1H, d), 8.30 (1H, d)	475
435		δ 1.70 (2H, m), 2.03 (2H, m), 2.22 (6H, s), 2.61 (2H, m), 3.52 (2H, m), 3.96 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)	451
436		δ 1.68 (4H, m), 1.94 (2H, m), 2.08 (2H, m), 2.19 (3H, m), 2.64 (4H, m), 3.56 (2H, m), 3.99 (2H, m), 4.26 (1H, m), 4.59 (1H, m), 6.95 (4H, m), 7.69 (1H, d), 8.30 (1H, d)	477
437		δ 1.70 (2H, m), 1.84 (2H, m), 2.03 (2H, m), 2.15 (3H, s), 2.34 (10H, m), 3.52 (2H, m), 3.94 (4H, m), 4.53 (1H, m), 6.86 (2H, m), 6.94 (2H, m), 7.64 (1H, d), 8.25 (1H, d)	520
438		δ 1.68 (2H, m), 2.01 (2H, m), 3.49 (2H, m), 3.93 (2H, m), 4.54 (1H, m), 5.15 (2H, s), 6.67 (1H, d), 6.95 (4H, m), 7.62 (1H, d), 8.23 (1H, d), 8.92 (1H, d)	461
439		δ 1.70 (2H, m), 2.04 (2H, m), 3.52 (2H, m), 3.95 (2H, m), 4.56 (1H, m), 5.12 (2H, s), 6.97 (4H, m), 7.31 (1H, s), 7.64 (1H, d), 8.25 (1H, d), 8.41 (1H, s)	461
440		δ 1.70 (2H, m), 2.03 (2H, m), 2.15 (3H, s), 2.39 (8H, m), 2.66 (2H, m), 3.51 (2H, m), 3.97 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)	506

441		δ 1.70 (2H, m), 2.03 (2H, m), 2.82 (2H, t), 3.52 (2H, m), 3.79 (3H, s), 3.95 (2H, m), 4.03 (2H, t), 4.54 (1H, m), 6.91 (4H, m), 7.56 (1H, s), 7.56 (1H, s), 7.64 (1H, d), 8.25 (1H, d)	488
442		δ 1.71 (2H, m), 2.04 (2H, m), 3.53 (2H, m), 3.84 (3H, s), 3.95 (2H, m), 4.58 (1H, m), 5.11 (2H, s), 6.35 (1H, m), 6.98 (4H, m), 7.33 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	474

Ejemplos 443–446

Los siguientes compuestos fueron preparados en 7 – 33% de rendimiento mediante un método análogo al Ejemplo 430, partiendo de 3–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]fenol y el alcohol apropiado:



Ej.	OR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
443		δ 1.72 (2H, m), 1.84 (2H, m), 2.06 (2H, m), 2.15 (6H, s), 2.35 (2H, m), 3.54 (2H, m), 3.97 (4H, m), 4.69 (1H, m), 6.55 (3H, m), 7.18 (1H, m), 7.64 (1H, d), 8.26 (1H, d)	465
444		δ 1.73 (2H, m), 2.06 (2H, m), 2.40 (4H, m), 2.66 (6H, m), 3.53 (2H, m), 3.96 (2H, m), 4.06 (2H, m), 4.69 (1H, m), 6.56 (3H, m), 7.18 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	492
445		δ 1.69 (2H, m), 1.83 (2H, m), 2.04 (2H, m), 2.29 (4H, m), 2.36 (2H, m), 2.70 (4H, m), 3.51 (2H, m), 3.94 (4H, m), 4.66 (1H, m), 6.53 (3H, m), 7.16 (1H, m), 7.63 (1H, d), 8.24 (1H, d)	506
446		δ 1.72 (2H, m), 2.07 (2H, m), 2.42 (3H, s), 3.52 (2H, m), 3.97 (2H, m), 4.69 (1H, m), 5.13 (2H, s), 6.33 (1H, s), 6.64 (3H, m), 7.21 (1H,	475

		m), 7.65 (1H, d), 8.26 (1H, d)	

El 3–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]fenol usado como material de partida fue preparado como sigue:

Preparación de 6–[4–[3–(benciloxi)fenoxi]piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Obtenida en 40% de rendimiento mediante un procedimiento análogo al Ejemplo 430, preparación de los materiales de partida, partiendo de 3–(benciloxi)fenol y 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol.

1H NMR (399.9 MHz, DMSO–d6) δ 1.71 (2H, m), 2.05 (2H, m), 3.51 (2H, m), 3.96 (2H, m), 4.67 (1H, m), 5.10 (2H, s), 6.63 (3H, m), 7.19 (1H, m), 7.40 (5H, m), 7.64 (1H, d), 8.26 (1H, d); m/z = 470 [M+H]+.

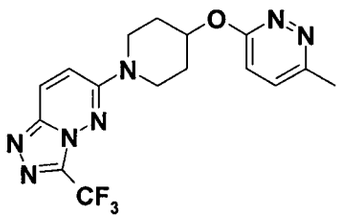
Preparación de 3–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]fenol

Obtenida en 80% de rendimiento mediante un procedimiento análogo al Ejemplo 430, preparación de los materiales de partida, partiendo de 6–[4–[3–(benciloxi)fenoxi]piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina.

1H NMR (399.9 MHz, DMSO–d6) δ 1.71 (2H, m), 2.06 (2H, m), 3.53 (2H, m), 3.95 (2H, m), 4.60 (1H, m), 6.40 (3H, m), 7.07 (1H, m), 7.64 (1H, d), 8.25 (1H, d), 9.36 (1H, s); m/z = 380 [M+H]+.

Ejemplo 447

Preparación de 6–[4–[(6–metilpiridazin–3–il)oxi]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

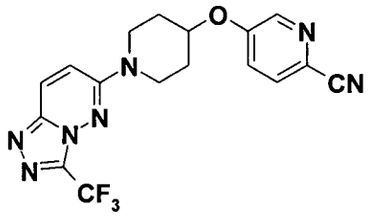


DIAD (0.102 mL, 0.52 mmol) fue añadida a 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (obtenido como se describió en el Ejemplo 310, preparación de los materiales de partida) (135 mg, 0.47 mmol), 6–metilpiridazin–3(2H)–

ona (56.9 mg, 0.52 mmol) y trifenilfosfina (136 mg, 0.52 mmol) en THF (5 mL). La solución resultante fue agitada a temperatura ambiente durante 3 días. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 2M en metanol y evaporado para dar el producto crudo. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–[(6–metilpiridazin–3–il)oxi]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (22.00 mg, 12%) como un sólido. 1H NMR (399.9 MHz, DMSO–d6) δ 1.91 (4H, m), 2.25 (3H, s), 3.22 (2H, m), 4.42 (2H, m), 5.10 (1H, m), 6.89 (1H, d), 7.32 (1H, d), 7.66 (1H, d), 8.27 (1H, d); m/z = 380 [M+H]+.

Ejemplo 448

Preparación de 5–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]piridina–2–carbonitrilo

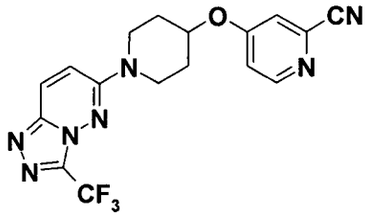


Una solución de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (150 mg, 0.52 mmol) e hidruro de sodio (60% dispersión en aceite, 22.98 mg, 0.57 mmol) en DMF (5 mL) fue agitada durante 30 minutos a temperatura ambiente bajo nitrógeno. 5–Cloropicolinonitrilo (80 mg, 0.57 mmol) fue añadido a la mezcla de reacción. La solución resultante fue agitada a 50°C durante 18 horas. La mezcla de reacción fue diluida con unas pocas gotas de MeOH. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 5–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]piridina–2–carbonitrilo (55.0 mg, 27%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.78 (2H, m), 2.13 (2H, m), 3.53 (2H, m), 3.99 (2H, m), 4.95 (1H, m), 7.69 (2H, m), 8.02 (1H, d), 8.27 (1H, d), 8.50 (1H, m); m/z = 390 [M+H]+.

Ejemplo 449

Preparación de 4–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]piridina–2–carbonitrilo

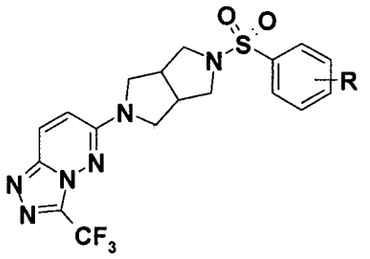


Obtenida en 62% de rendimiento mediante un procedimiento análogo al Ejemplo 448, partiendo de 4–cloro–2–cianopiridina y 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol.

1H NMR (399.9 MHz, DMSO–d6) δ 1.76 (2H, m), 2.14 (2H, m), 3.51 (2H, m), 4.01 (2H, m), 4.95 (1H, m), 7.37 (1H, m), 7.66 (1H, d), 7.81 (1H, m), 8.27 (1H, d), 8.55 (1H, m); m/z = 390 [M+H]+.

Ejemplos 450–455

Los siguientes compuestos fueron preparados en 16 – 83% de rendimiento mediante un método análogo al Ejemplo 394, partiendo de 6–(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Método Sintético General 10, preparación de los materiales de partida) y el cloruro de sulfonilo apropiado:

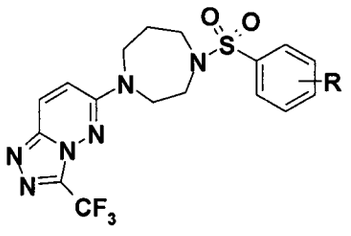


Ej.	R	1H NMR (399.9 MHz, $CDCl_3$)	m/z [M+H]+
450	3–F	δ 3.04 – 3.10 (2H, m), 3.28 – 3.32 (2H, m), 3.35 – 3.39 (2H, m), 3.46 – 3.50 (2H, m), 3.75 – 3.79 (2H, m), 6.79 (1H, d), 7.29 – 7.35 (1H, m), 7.51 – 7.57	457

		(2H, m), 7.62 – 7.64 (1H, m), 7.93 (1H, d)	
451	2–OMe	δ 3.06 – 3.11 (2H, m), 3.38 – 3.44 (4H, m), 3.67 – 3.72 (2H, m), 3.76 – 3.80 (2H, m), 3.90 (3H, s), 6.81 (1H, d), 6.99 – 7.07 (2H, m), 7.50 – 7.54 (1H, m), 7.90 – 7.94 (2H, m)	469
452	2–F	δ 3.09 – 3.13 (2H, m), 3.38 – 3.46 (4H, m), 3.66 (2H, q), 3.79 (2H, q), 6.81 (1H, d), 7.18 – 7.31 (2H, m), 7.55 – 7.61 (1H, m), 7.89 – 7.95 (2H, m)	457
453	4–F	δ 3.03 – 3.10 (2H, m), 3.27 – 3.30 (2H, m), 3.36 – 3.46 (4H, m), 3.78 (2H, q), 6.78 (1H, d), 7.2 – 7.25 (2H, m), 7.83 – 7.87 (2H, m), 7.93 (1H, d)	457
454	3–OMe	δ 3.01 – 3.06 (2H, m), 3.27 – 3.30 (2H, m), 3.34 – 3.38 (2H, m), 3.45 – 3.49 (2H, m), 3.73 – 3.77 (2H, m), 3.84 (3H, s), 6.77 (1H, d), 7.11 – 7.14 (1H, m), 7.33 (1H, t), 7.38 – 7.47 (2H, m), 7.92 (1H, d)	469
455	4–OMe	δ 3.00 – 3.05 (2H, m), 3.23 – 3.27 (2H, m), 3.35 – 3.44 (4H, m), 3.73 – 3.77 (2H, m), 3.86 (3H, s), 6.77 (1H, d), 6.98 – 7.01 (2H, m), 7.75 – 7.79 (2H, m), 7.92 (1H, d)	469

Ejemplos 456–461

Los siguientes compuestos fueron preparados en 54 – 96% de rendimiento mediante un método análogo al Ejemplo 394, partiendo de 6–(1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Método Sintético General 8, preparación de los materiales de partida) y el cloruro de sulfonilo apropiado:

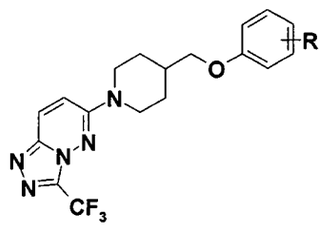


Ej.	R	1H NMR (399.9 MHz, $CDCl_3$)	m/z [M+H]+
456	3–F	δ 2.05 – 2.11 (2H, m), 3.36 (2H, t), 3.54 (2H, t), 3.82 (2H, t), 3.90 (2H, t), 6.94 (1H, d), 7.14 – 7.19 (1H, m),	445

		7.36 – 7.41 (1H, m), 7.43 – 7.46 (1H, m), 7.52 – 7.55 (1H, m), 7.93 (1H, d)	
457	4–F	δ 2.06 – 2.12 (2H, m), 3.29 (2H, t), 3.51 (2H, t), 3.83 (2H, t), 3.90 (2H, t), 6.95 (1H, d), 7.09 – 7.15 (2H, m), 7.75 – 7.80 (2H, m), 7.94 (1H, d)	445
458	3–OMe	δ 2.03 – 2.09 (2H, m), 3.37 (2H, t), 3.54 (2H, t), 3.78 – 3.81 (5H, m), 3.88 (2H, t), 6.90 – 6.95 (2H, m), 7.22 – 7.23 (1H, m), 7.28 – 7.31 (2H, m), 7.90 (1H, d)	457
459	2–OMe	δ 2.07 – 2.13 (2H, m), 3.31 (2H, t), 3.56 – 3.58 (2H, m), 3.87 – 3.91 (7H, m), 6.94 – 7.04 (3H, m), 7.46 – 7.50 (1H, m), 7.90 – 7.94 (2H, m)	457
460	2–F	δ 2.06 – 2.12 (2H, m), 3.41 (2H, t), 3.60 (2H, t), 3.85 (2H, t), 3.90(2H, t), 6.98 (1H, d), 7.03 – 7.08 (1H, m), 7.19 – 7.23 (1H, m), 7.44 – 7.50 (1H, m), 7.85 – 7.89 (1H, m), 7.94 (1H, d)	445
461	4–OMe	δ 2.02 – 2.08 (2H, m), 3.34 (2H, t), 3.50 (2H, t), 3.78 – 3.81 (5H, m), 3.87 (2H, t), 6.81 – 6.84 (2H, m), 6.91 (1H, d), 7.64 – 7.67 (2H, m), 7.90 (1H, d)	457

Ejemplos 462–476

Los siguientes compuestos fueron preparados en 15 – 70% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de [1–[3–(trifluoro metil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metanol (obtenido como se describió en el Ejemplo 294, preparación de los materiales de partida) y el fenol apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d_6)	m/z [M+H]+
462	2–OMe	δ 1.32 – 1.43 (2H, m), 1.90 – 1.94 (2H, m), 2.09 – 2.15 (1H, m), 3.05 – 3.12 (2H, m), 3.76 (3H, s), 3.85 (2H, d), 4.30 – 4.34 (2H, m), 6.85 – 6.92 (2H, m),	408

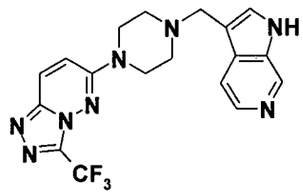
716

		6.95 – 6.98 (2H, m), 7.63 (1H, d), 8.23 (1H, d)	
463	4–F	δ 1.33 – 1.42 (2H, m), 1.89 – 1.92 (2H, m), 2.07 – 2.13 (1H, m), 3.03 – 3.11 (2H, m), 3.85 (2H, d), 4.30 – 4.34 (2H, m), 6.94 – 6.97 (2H, m), 7.09 – 7.13 (2H, m), 7.63 (1H, d), 8.23 (1H, d)	396
464	3–F	δ 1.33 – 1.43 (2H, m), 1.88 – 1.92 (2H, m), 2.07 – 2.14 (1H, m), 3.04 – 3.11 (2H, m), 3.90 (2H, d), 4.30 – 4.34 (2H, m), 6.73 – 6.84 (3H, m), 7.28 – 7.34 (1H, m), 7.63 (1H, d), 8.23 (1H, d)	396
465	4–OMe	δ 1.31 – 1.41 (2H, m), 1.88 – 1.92 (2H, m), 2.05 – 2.11 (1H, m), 3.03 – 3.10 (2H, m), 3.70 (3H, s), 3.81 (2H, d), 4.30 – 4.34 (2H, m), 6.84 – 6.89 (4H, m), 7.63 (1H, d), 8.23 (1H, d)	408
466	3–OMe	δ 1.32 – 1.42 (2H, m), 1.89 – 1.93 (2H, m), 2.05 – 2.14 (1H, m), 3.04 – 3.11 (2H, m), 3.73 (3H, s), 3.86 (2H, d), 4.30 – 4.34 (2H, m), 6.49 – 6.54 (3H, m), 7.17 (1H, t), 7.63 (1H, d), 8.23 (1H, d)	408
467	2–F	δ 1.34 – 1.44 (2H, m), 1.89 – 1.93 (2H, m), 2.11 – 2.18 (1H, m), 3.05 – 3.12 (2H, m), 3.96 (2H, d), 4.30 – 4.34 (2H, m), 6.91 – 6.97 (1H, m), 7.10 – 7.23 (3H, m), 7.63 (1H, d), 8.23 (1H, d)	396
468	4–CF3	δ 1.34 – 1.44 (2H, m), 1.89 – 1.94 (2H, m), 2.10 – 2.19 (1H, m), 3.05 – 3.12 (2H, m), 3.97 (2H, d), 4.31 – 4.34 (2H, m), 7.13 (2H, d), 7.62 – 7.66 (3H, m), 8.24 (1H, d)	446
469	2–CN	δ 1.39 – 1.49 (2H, m), 1.91 – 1.94 (2H, m), 2.15 – 2.22 (1H, m), 3.07 – 3.14 (2H, m), 4.06 (2H, d), 4.32 – 4.36 (2H, m), 7.08 – 7.12 (1H, m), 7.26 (1H, d), 7.63 – 7.68 (2H, m), 7.71 – 7.73 (1H, m), 8.24 (1H, d)	403
470	4–Cl	δ 1.32 – 1.42 (2H, m), 1.88 – 1.92 (2H, m), 2.05 – 2.14 (1H, m), 3.03 – 3.10 (2H, m), 3.87 (2H, d), 4.29 – 4.33 (2H, m), 6.95 – 6.99 (2H, m), 7.29 – 7.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d)	412

471	2–CF3	δ 1.39 – 1.49 (2H, m), 1.88 – 1.91 (2H, m), 2.12 – 2.19 (1H, m), 3.06 – 3.13 (2H, m), 4.02 (2H, d), 4.31 – 4.35 (2H, m), 7.09 (1H, t), 7.25 (1H, d), 7.60 – 7.65 (3H, m), 8.24 (1H, d)	446
472	3–CF3	δ 1.35 – 1.45 (2H, m), 1.91 – 1.94 (2H, m), 2.09 – 2.18 (1H, m), 3.05 – 3.12 (2H, m), 3.97 (2H, d), 4.31 – 4.34 (2H, m), 7.24 – 7.30 (3H, m), 7.53 (1H, t), 7.64 (1H, d), 8.24 (1H, d)	446
473	3–Cl	δ 1.32 – 1.42 (2H, m), 1.87 – 1.92 (2H, m), 2.07 – 2.15 (1H, m), 3.04 – 3.11 (2H, m), 3.91 (2H, d), 4.30 – 4.33 (2H, m), 6.92 – 6.94 (1H, m), 6.98 – 7.00 (1H, m), 7.03 (1H, t), 7.31 (1H, t), 7.63 (1H, d), 8.23 (1H, d)	412
474	4–CN	δ 1.33 – 1.44 (2H, m), 1.87 – 1.92 (2H, m), 2.08 – 2.17 (1H, m), 3.05 – 3.11 (2H, m), 3.99 (2H, d), 4.30 – 4.34 (2H, m), 7.11 – 7.14 (2H, m), 7.63 (1H, d), 7.75 – 7.78 (2H, m), 8.23 (1H, d)	403
475	2–Cl	δ 1.37 – 1.48 (2H, m), 1.92 – 1.96 (2H, m), 2.12 – 2.19 (1H, m), 3.06 – 3.13 (2H, m), 3.98 (2H, d), 4.31 – 4.35 (2H, m), 6.93 – 6.97 (1H, m), 7.14 – 7.16 (1H, d), 7.28 – 7.32 (1H, m), 7.41 – 7.43 (1H, m), 7.64 (1H, d), 8.24 (1H, d)	412
476	3–CN	δ 1.34 – 1.43 (2H, m), 1.88 – 1.92 (2H, m), 2.10 – 2.16 (1H, m), 3.05 – 3.12 (2H, m), 3.96 (2H, d), 4.30 – 4.34 (2H, d), 7.29 – 7.32 (1H, m), 7.39 – 7.41 (1H, m), 7.43 – 7.44 (1H, m), 7.47 – 7.51 (1H, m), 7.63 (1H, d), 8.24 (1H, d)	403

Ejemplo 477

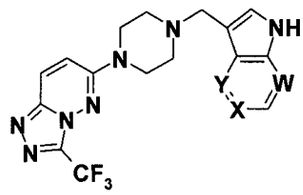
Preparación de 6–[4–(1H–pirrolo[2,3–c]piridin–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 68% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 1H–pirrolo[2,3–c]piridina–3–carboxaldehido (obtenido como se describió en J Chem. Soc. (C) 1970, 498). 1H NMR (399.9 MHz, DMSO–d6) δ 2.25 (4H, t), 3.60 (4H, t) 3.73 (2H, s), 7.53 (1H, s), 7.57 (1H, d), 7.63 – 7.65 (1H, m), 8.10 (1H, d), 8.23 (1H, d), 8.72 (1H, d), 11.47 (1H, s); m/z = 403 [M+H]+.

Ejemplos 478–480

Los siguientes compuestos fueron preparados en 61–82% de rendimiento mediante el Método Sintético General 5, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el 1H–pirrolopiridina–3–carboxaldehido apropiado (obtenido como se describió en el correspondiente pie de página):



Ej.	W	X	Y	Nota	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
478	N	CH	CH	[1]	δ 2.55 (4H, s), 3.60 (4H, s), 3.71 (2H, s), 7.04 – 7.07 (1H, m), 7.39 (1H, s), 7.57 (1H, d), 8.07 (1H, d), 8.20 – 8.24 (2H, m), 11.48 (1H, s)	403
479	CH	CH	N	[2]	δ 2.59 (4H, t), 3.60 (4H, t), 3.81 (2H, s), 7.08 – 7.11 (1H, m), 7.55 – 7.58 (2H, m), 7.73 – 7.75 (1H, m), 8.22 (1H, d), 8.32 – 8.34 (1H, m), 11.21 (1H, s)	403
480	CH	N	CH	[3]	δ 2.56 (4H, t), 3.62 (4H, t), 3.77 (2H, s), 7.34 – 7.35 (1H, m), 7.36 (1H, d), 7.58 (1H, d), 8.16 (1H, d), 8.23 (1H,	403

719

					d), 8.97 (1H, d), 11.34 (1H, s)	

[1] Obtenido de 1H–pirrolo[2,3–b]piridina–3–carboxaldehido, preparado como se describió en Bioorg. Med. Chem. 2004, 12 , 5505.

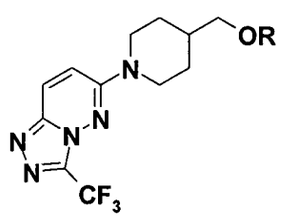
[2] Obtenido de 1H–pirrolo[3,2–b]piridina–3–carboxaldehido, preparado como se describió en la Sol. De Pat. US 2007/0123535, página 35.

[3] Obtenido de 1H–pirrolo[3,2–c]piridina–3–carboxaldehido, preparado como sigue: Una solución de 1H–pirrolo[3,2–c]piridina (2.95 g, 25 mmol) y hexametilenotetramina (5.26 g, 37.50 mmol) en ácido acético(25 mL) y agua (50 mL) fue calentada bajo reflujo durante 4 horas. La mezcla de reacción fue evaporada y el residuo fue purificado por cromatografía MPLC en sílice, gradiente en elusión 5 a 10% amoniaco–metanol en DCM. Las fracciones que contienen el producto fueron evaporadas hasta secarse y trituradas con MeCN para proporcionar 1H–pirrolo[3,2–c]piridina–3–carbaldehido (0.170 g, 4.65%) como un sólido cristalino blanco.

1H NMR (399.9 MHz, DMSO–d6) δ 7.52 – 7.54 (1H, m), 8.36 (1H, d), 8.42 (1H, s), 9.30 (1H, d), 10.01 (1H, s), 12.41 (1H, s); m/z = 188 [M+H]+ (detectado como un aducto con acetonitrilo usado en la determinación de la masa espectral).

Ejemplos 481–482

Los siguientes compuestos fueron preparados en 10–48% de rendimiento mediante un método análogo al Ejemplo 294, partiendo de 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el alcohol apropiado:

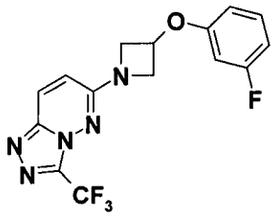


Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
481	oxetan–3–il	δ 1.31 – 1.42 (2H, m), 1.86 – 1.97 (3H, m), 3.00 – 3.07 (2H, m), 3.24 (2H, d) 4.23 – 4.28 (2H, m), 4.50 – 4.55 (1H, m), 4.57 – 4.60 (2H, m), 4.75 – 4.78 (2H, m), 7.09 (1H, d), 7.90 (1H, d)	358
482	2,2,2–trifluoroetil	δ 1.35 – 1.39 (2H, m), 1.90 – 1.99 (3H, m), 2.99 – 3.06 (2H, m), 3.50 – 3.52 (2H, m),	384

		3.83 (2H, q), 4.24 – 4.28 (2H, m), 7.09 (1H, d), 7.91 (1H, d)	

Ejemplo 483

Preparación de 6–[3–(3–fluorofenoxi)azetidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una solución parcialmente agitada de 6–[3–(metanosulfoniloxi)azetidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (169 mg, 0.5 mmol), 3–fluorofenol (112 mg, 1.5 mmol) y carbonato de potasio (207 mg, 1.5 mmol) en DMF (3 mL) fue calentada a 100°C durante 24 horas. La mezcla de reacción fue filtrada y el producto fue aislado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para dar 6–[3–(3–fluorofenoxi)azetidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (58 mg, 33%) como un sólido.

1H NMR (399.9 MHz, CDCl3) δ 4.17 – 4.21 (2H, m), 4.50 – 4.54 (2H, m), 5.05 – 5.10 (1H, m), 6.44 – 6.47 (1H, m), 6.50 – 6.52 (1H, m), 6.60 (1H, d), 6.66 – 6.71 (1H, m), 7.18 – 7.24 (1H, m), 7.88 (1H, d); m/z = 354 [M+H]+.

La 6–[3–(metanosulfoniloxi)azetidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina de partida fue preparada como sigue:

Preparación de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]azetidin–3–ol

Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (5.56 g, 25 mmol), hidrocloruro de azetidin–3–ol (3.01 g, 27.50 mmol) y DIPEA (10.89 mL, 62.50 mmol) en DMF (50 mL) fue calentada a 70°C durante 1 hora. La solución fue lentamente diluida con agua y el producto cristalizó. El precipitado fue recogido por filtración, lavado con agua, secado bien y lavado con éter. Este fue secado al vacío para

proporcionar 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]azetidin–3–ol (5.30 g, 82%) como un sólido cristalino blanco.

1H NMR (399.9 MHz, DMSO–d6) δ 3.88 (2H, q), 4.32 – 4.36 (2H, m), 4.61 – 4.65 (1H, m), 5.82 – 5.83 (1H, m), 7.04 (1H, d), 8.22 (1H, d); m/z = 260 [M+H]+.

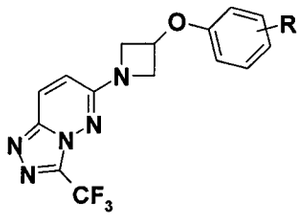
Preparación de 6–[3–(metanosulfoniloxi)azetidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

Cloruro de metanosulfonilo (0.929 mL, 12 mmol) fue añadido en forma de gotas a una solución parcialmente agitada de 1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)azetidin–3–ol (2.59 g, 10 mmol) y trietilamina (1.951 mL, 14 mmol) en DCM (17 mL) a 0°C. La solución se dejó calentar hasta la temperatura ambiente y fue agitada durante 30 minutos. El precipitado fue recogido por filtración, lavado con un poco de DCM, un poco de etanol y éter. Este fue secado al vacío para proporcionar 6–[3–(metanosulfoniloxi)azetidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (2.400 g, 71.2%) como un sólido cristalino blanco.

1H NMR (399.9 MHz, DMSO–d6) δ 3.32 (3H, s), 4.25 – 4.29 (2H, m), 4.54 – 4.59 (2H, m), 5.45 – 5.50 (1H, m), 7.11 (1H, d), 8.29 (1H, d); m/z = 338 [M+H]+.

Ejemplos 484–486

Los siguientes compuestos fueron preparados en 49–56% de rendimiento mediante un método análogo al Ejemplo 483, partiendo de 6–[3–(metanosulfoniloxi)azetidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el fenol apropiado:



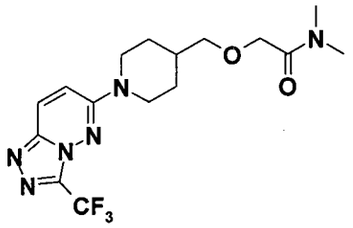
Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
484	4–F	δ 4.16 – 4.20 (2H, m), 4.48 – 4.52 (2H, m), 5.02 – 5.07 (1H, m), 6.60 (1H, d), 6.66 – 6.70 (2H, m), 6.92 – 6.98 (2H, m), 7.88 (1H, d)	354
485	3–OMe	δ 3.74 (3H, s), 4.16 – 4.20 (2H, m), 4.48 – 4.53 (2H, m), 5.05 – 5.10 (1H, m), 6.29 – 6.32 (2H, m), 6.51 – 6.54 (1H, m), 6.60 (1H, d), 7.13 – 7.18 (1H, m), 7.88	366

722

		(1H, d)	
486	4–OMe	δ 3.72 (3H, s), 4.15 – 4.19 (2H, m), 4.46 – 4.50 (2H, m), 5.00 – 5.05 (1H, m), 6.60 (1H, d), 6.65 – 6.69 (2H, m), 6.77 – 6.82 (2H, m), 7.88 (1H, d)	366

Ejemplo 487

Preparación de N,N–dimetil–2–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metoxi]acetamida



Una solución agitada de metil 2–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metoxi]acetato (95 mg, 0.25 mmol) en 2M dimetilamina en metanol (2.0 mL, 4.00 mmol) fue calentada a 120°C en un reactor de microondas durante 1 hora. La mezcla de reacción fue evaporada y el producto crudo fue purificado por LCMS preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar N,N–dimetil–2–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metoxi]acetamida (48.0 mg, 48.8%) como un sólido blanco.

1H NMR (399.9 MHz, CDCl3) δ 1.32 – 1.43 (2H, m), 1.93 (2H, d), 1.98 – 2.02 (1H, m), 2.96 (3H, s), 3.00 (3H, s), 3.03 – 3.07 (2H, m), 3.41 – 3.43 (2H, m), 4.15 (2H, s), 4.25 (2H, d), 7.09 (1H, d), 7.90 (1H, d); m/z = 387 [M+H]+.

El metil 2–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metoxi]acetato usado como material de partida fue preparado como sigue:

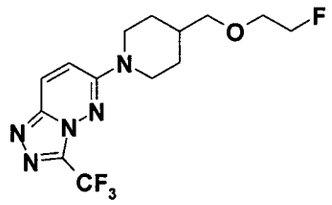
Hidruro de sodio (60% dispersión en aceite, 0.120 g, 3.0 mmol) fue añadido a metil glicolato puro (1.544 mL, 20.0 mmol). Cuando la efervescencia había disminuido 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.759 g, 2.0 mmol) fue añadida y la mezcla fue calentada a 100°C durante 40 minutos. La mezcla de reacción fue particionada entre DCM y agua. La fase orgánica fue

lavada con agua y salmuera, secada sobre $MgSO_4$ y evaporada El producto fue aislado por cromatografía MPLC en sílice, eluyendo con acetato de etilo. Las fracciones que contienen el producto fueron evaporadas hasta un aceite el cual cristalizó a partir de éter, dando metil 2–[[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metoxi]acetato (0.130 g, 17%).

1H NMR (399.9 MHz, CDCl3) δ 1.33 – 1.43 (2H, m), 1.92 – 2.02 (3H, m), 3.00 – 3.07 (2H, m), 3.42 – 3.44 (2H, m), 3.76 (3H, s), 4.09 (2H, s), 4.23 - 4.26 (2H, m), 7.08 (1H, d), 7.90 (1H, d); m/z = 374 [M+H]+.

Ejemplo 488

Preparación de 6–[4–[(2–fluoroetoxi)metil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Trifloruro de (dietilamino)azufre (0.059 mL, 0.45 mmol) fue añadido en forma de gotas a una solución agitada de 2–[[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il)metoxi]etanol (104 mg, 0.3 mmol) en DCM (3 mL) a –70°C. La solución se dejó calentar hasta la temperatura ambiente y agitar durante 18 horas. La solución fue diluida con DCM y lavada con K_2CO_3 2M acuoso. La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–[(2–fluoroetoxi)metil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (22.0 mg, 21%) como un sólido blanco.

1H NMR (399.9 MHz, CDCl3) δ 1.30 – 1.40 (2H, m), 1.90 – 2.01 (3H, m), 2.99 – 3.06 (2H, m), 3.40 (2H, d), 3.65 – 3.74 (2H, m), 4.23 – 4.27 (2H, m), 4.49 – 4.63 (2H, m), 7.09 (1H, d), 7.90 (1H, d); m/z = 348 [M+H]+.

El 2–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metoxi]etanol de partida fue preparado como sigue:

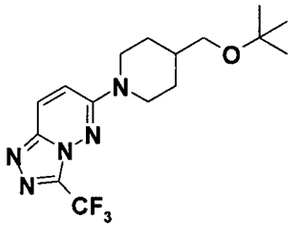
724

Hidruro de sodio (60% dispersión en aceite, 0.180 g, 4.5 mmol) fue añadido a tetrahidropiraniletilenoglicol puro (3 g, 20.5 mmol). Cuando la efervescencia había disminuido 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 294, preparación de los materiales de partida) (1.138 g, 3 mmol) fue añadida y la mezcla fue calentada a 100°C durante 40 minutos. La mezcla de reacción fue particionada entre DCM y agua. La fase orgánica fue lavada con agua y salmuera, secada sobre $MgSO_4$ y evaporada. El producto intermedio crudo fue disuelto en metanol (20 mL) y ácido p–toluenosulfónico monohidrato (0.855 g, 4.5 mmol) fue añadido. La solución fue agitada durante 1 hora y luego evaporada. La mezcla de reacción fue particionada entre DCM y agua y la fase orgánica fue lavada con agua y salmuera, secada sobre $MgSO_4$ y evaporada. El producto fue aislado por cromatografía MPLC en sílice, eluyendo con 5% metanol / DCM. Las fracciones que contienen el producto fueron evaporadas dando un sólido cristalino el cual fue triturado con éter, dando 2–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metoxi]etanol (0.563 g, 54%)

1H NMR (399.9 MHz, CDCl3) δ 1.31 – 1.41 (2H, m), 1.89 – 2.00 (3H, m), 2.99 – 3.06 (2H, m), 3.38 – 3.39 (2H, m), 3.55 – 3.57 (2H, m), 3.74 – 3.76 (2H, m), 4.23 – 4.27 (2H, m), 7.08 (1H, d), 7.90 (1H, d), OH no observado; m/z = 346 [M+H]+.

Ejemplo 489

Preparación de 6–[4–(tert–butoximetil)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



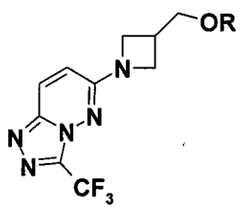
Una solución agitada de [1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]metanol (obtenida como se describió en el Ejemplo 294, preparación de los materiales de partida) (151 mg, 0.5 mmol) y ácido p–toluenosulfónico monohidrato (190 mg, 1.0 mmol) en DCM (2 mL) fue enfriada hasta –70°C y 2–metilpropeno (1 mL, 10.48 mmol) fue condensado en un cilindro. La mezcla fue agitada durante 2 días a temperatura ambiente en un tubo sellado. El tubo fue reenfriado para abrirse, luego se dejó

calentar hasta la temperatura ambiente con agitación. La solución fue diluida con DCM y lavada con K_2CO_3 2M acuoso. La fase orgánica fue secada sobre $MgSO_4$ y evaporada. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–(4–(tert–butoximetil)piperidin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (98 mg, 54%) como un sólido blanco.

1H NMR (399.9 MHz, CDCl3) δ 1.18 (9H, s), 1.24 – 1.35 (2H, m), 1.79 – 1.84 (1H, m), 1.92 (2H, d), 2.98 – 3.05 (2H, m), 3.23 (2H, d), 4.25 (2H, d), 7.09 (1H, d), 7.89 (1H, d); m/z = 358 [M+H]+.

Ejemplos 490–493

Los siguientes compuestos fueron preparados en 43–63% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]azetidin–3–il]metanol y el fenol apropiado:



Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
490	3–fluorofenil	δ 3.26 – 3.33 (1H, m), 4.08 – 4.11 (2H, m), 4.18 (2H, d), 4.34 (2H, t), 6.61 – 6.66 (2H, m), 6.68 – 6.73 (2H, m), 7.21 – 7.27 (1H, m), 7.92 (1H, s)	368
491	3–fluorofenil	δ 3.25 – 3.32 (1H, m), 4.08 – 4.11 (2H, m), 4.15 (2H, d), 4.34 (2H, t), 6.64 (1H, d), 6.84 – 6.87 (2H, m), 6.96 – 7.02 (2H, m) 7.91 (1H, d)	368
492	piridin–3–il	δ 3.30 – 3.37 (1H, m), 4.10 – 4.13 (2H, m), 4.26 (2H, d), 4.37 (2H, t), 6.65 (1H, d), 7.20 – 7.26 (2H, m), 7.93 (1H, d), 8.27 – 8.28	351

726

		(1H, m), 8.34 (1H, q)	
493	pirimidin–2–il	δ 3.32 – 3.40 (1H, m), 4.10 – 4.13 (2H, m), 4.34 (2H, t), 4.61 – 4.63 (2H, m), 6.64 (1H, d), 7.00 (1H, t), 7.90 (1H, d), 8.54 (2H, d)	352

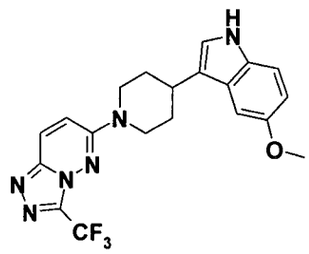
El [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]azetidin–3–il]metanol de partida fue preparado como sigue:

Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (4.44 g, 20.0 mmol), azetidin–3–ilmetanol (2.25 g, 22.0 mmol) y DIPEA (5.21 mL, 30.0 mmol) en DMF (40 mL) fue calentada a 70°C durante 1 hora. La solución fue evaporada y particionada entre agua y K_2CO_3 2M acuoso. La fase orgánica fue lavada con agua y salmuera y secada sobre $MgSO_4$. El producto crudo fue purificado por cromatografía MPLC en sílice, eluyendo con 5% MeOH en DCM. Las fracciones puras fueron evaporadas hasta secarse y triturada con éter, dando [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]azetidin–3–il]metanol (1.65 g, 30%) como un sólido cristalino color crema.

1H NMR (399.9 MHz, DMSO–d6) δ 2.87 (1H, t), 3.59 (2H, t), 3.86 – 3.89 (2H, m), 4.14 (2H, t), 4.88 (1H, t), 7.03 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]+.

Ejemplo 494

Preparación de 6–[4–(5–metoxi–1H–indol–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



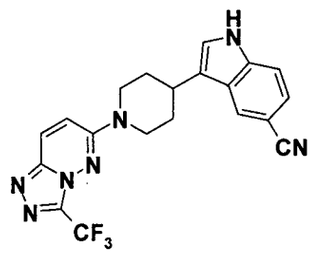
6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (150 mg, 0.72 mmol), 5–metoxi–3–(piperidin–4–il)–1H–indol (obtenido como se describió en la Sol Int. PCT WO 2004006922, Producto intermedio 37) (166 mg, 0.72 mmol) y DIPEA (0.138 mL, 0.79 mmol) en DMF (2 mL) fueron agitados y calentadas a 80°C durante 1 hora. La mezcla resultante fue enfriada hasta la temperatura ambiente y apagada en agua (10 mL) para dar

un precipitado. El sólido fue recogido por filtración, lavado secuencialmente con agua, acetonitrilo y éter, y secado al aire para dar 6–[4–(5–metoxi–1H–indol–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (189 mg, 53%) como un sólido incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.67 – 1.75 (2H, m), 2.10 – 2.13 (2H, m), 3.08 – 3.14 (1H, m), 3.18 – 3.25 (2H, m), 3.76 (3H, s), 4.39 – 4.42 (2H, m), 6.73 (1H, d), 7.07 (2H, s), 7.23 (1H, d), 7.67 (1H, d), 8.24 (1H, d), 10.63 (1H, s); m/z 417 [M+H]+.

Ejemplo 495

Preparación de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carbonitrilo

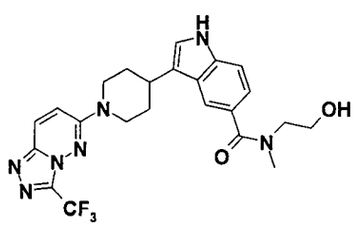


Obtenido en 88% de rendimiento mediante un procedimiento análogo al Ejemplo 494, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 3–(piperidin–4–il)–1H–indol–5–carbonitrilo (obtenido como se describió en la Sol. Int. PCT Int. WO 2001043740, Ejemplo 3).

1H NMR (399.9 MHz, DMSO–d6) δ 1.68 – 1.78 (2H, m), 2.11 – 2.13 (2H, m), 3.18 – 3.24 (3H, m), 4.40 – 4.43 (2H, m), 7.36 (1H, s), 7.42 (1H, d), 7.51 (1H, d), 7.68 (1H, d), 8.24 (2H, m), 11.43 (1H, s); m/z 410 [M–H]–.

Ejemplo 496

Preparación de N–(2–hidroxietil)–N–metil–3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxamida



HATU (139 mg, 0.37 mmol) fue añadido en forma de porciones a temperatura ambiente a una mezcla agitada de ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxílico (150 mg, 0.35 mmol), 2–(metilamino)etanol (0.034 mL, 0.42 mmol) y DIPEA (0.073 mL, 0.42 mmol) en DMF (2.0 mL). La solución resultante fue agitada durante 2 horas, luego purificada por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar N–(2–hidroxietil)–N–metil–3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxamida (155 mg, 91%) como un sólido incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.68 – 1.78 (2H, m), 2.09 – 2.13 (2H, m), 3.01 (3H, s), 3.13 – 3.24 (3H, m), 3.29 – 3.70 (4H, m), 4.40 – 4.43 (2H, m), 4.78 (1H, t), 7.14 (1H, dd), 7.21 (1H, d), 7.36 (1H, d), 7.68 (1H, d), 7.71 (1H, s), 8.25 (1H, d), 11.03 (1H, s); m/z = 488 [M+H]+.

El ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxílico usado como material de partida fue preparado como sigue:

Preparación de ácido 3–[1–(tert–butoxicarbonil)–1,2,3,6–tetrahidropiridin–4–il]–1H–indol–5–carboxílico

Hidróxido de potasio (5.17 g, 92.08 mmol) fue añadido a ácido 1H–indol–5–carboxílico (3.71 g, 23.02 mmol) y tert–butil 4–oxopiperidina–1–carboxilato (9.17 g, 46.04 mmol) en metanol (80 mL) a temperatura ambiente y la solución resultante fue agitada a 65°C durante 18 horas. La mezcla fue luego enfriada hasta la temperatura ambiente, apagada en agua (100 mL) y extraída con acetato de etilo (2 x 100 mL). Los extractos fueron desechados y la fase acuosa acidificada hasta pH 2–3 con ácido clorhídrico 2M para dar un sólido amarillo pálido. El sólido fue recogido por filtración, lavado secuencialmente con agua y éter y secado al aire para dar ácido 3–[1–(tert–butoxicarbonil)–1,2,3,6–tetrahidropiridin–4–il]–1H–indol–5–carboxílico (5.62 g, 71.3%) como un sólido incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.45 (9H, s), 2.50 – 2.55 (2H, m), 3.59 (2H, t), 4.06 – 4.11 (2H, m), 6.16 (1H, m), 7.46 (1H, d), 7.55 (1H, d), 7.76 (1H, dd), 8.48 (1H, s), 11.51 (1H, s), 12.45 (1H, br s); m/z = 341 [M–H]–.

729

Preparación de metil 3–[1–(tert–butoxicarbonil)–1,2,3,6–tetrahidropiridin–4–il]–1H–indol–5–carboxilato

Yodometano (1.22 mL, 19.63 mmol) fue añadido en una porción a ácido 3–[1–(tert–butoxicarbonil)–1,2,3,6–tetrahidropiridin–4–il]–1H–indol–5–carboxílico (6.72 g, 19.63 mmol) y carbonato de potasio (3.26 g, 23.55 mmol) en DMF (60 mL) a temperatura ambiente. La mezcla resultante fue agitada a temperatura ambiente durante 3 horas luego apagada en agua (200 mL) y extraída con MTBE (2 x 100 mL) El extracto fue lavado secuencialmente con agua (3 x 100 mL) y salmuera saturada, secado sobre $MgSO_4$ y concentrado por evaporación, luego purificado por cromatografía flash en sílice, gradiente en elusión 20 a 35% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar metil 3–[1–(tert–butoxicarbonil)–1,2,3,6–tetrahidropiridin–4–il]–1H–indol–5–carboxilato (5.09 g, 73%) como un sólido incoloro.

1H NMR (399.9 MHz, CDCl3) δ 1.51 (9H, s), 2.55 – 2.58 (2H, m), 3.67 – 3.70 (2H, m), 3.95 (3H, s), 4.14 – 4.18 (2H, m), 6.23 (1H, m), 7.22 (1H, d), 7.38 (1H, d), 7.93 (1H, dd), 8.42 (1H, s), 8.63 (1H, s); m/z = 355 [M–H]–.

Preparación de metil 3–[1–(tert–butoxicarbonil)piperidin–4–il]–1H–indol–5–carboxilato

Metil 3–[1–(tert–butoxicarbonil)–1,2,3,6–tetrahidropiridin–4–il]–1H–indol–5–carboxilato (5.0 g, 14.03 mmol), formato de amonio (4.42 g, 70.14 mmol) y paladio (5% en carbón activado, 200 mg) en etanol (80 mL) fueron agitados y refluidos durante 1 hora. La mezcla resultante fue enfriada hasta la temperatura ambiente y filtrada a través de tierra diatomácea. El filtrado fue concentrado por evaporación luego tratado con cloruro de amonio acuoso diluido (100 mL) y extraído con acetato de etilo. El extracto fue lavado secuencialmente con agua y salmuera saturada, secado sobre $MgSO_4$ y evaporado hasta un sólido incoloro. El sólido fue triturado con éter, luego recogido por filtración y secado al aire para dar metil 3–[1–(tert–butoxicarbonil)piperidin–4–il]–1H–indol–5–carboxilato (4.59 g, 91%) como un sólido incoloro.

1H NMR (399.9 MHz, CDCl3) δ 1.49 (9H, s), 1.60 – 1.70 (2H, m), 2.03 – 2.06 (2H, m), 2.88 – 2.95 (2H, m), 3.03 (1H, tt), 3.94 (3H, s), 4.17 – 4.32 (2H, m), 7.01 (1H, d), 7.37 (1H, d), 7.90 (1H, dd), 8.26 (1H, s), 8.39 (1H, s); m/z = 357 [M–H]–.

Preparación de metil 3–(piperidin–4–il)–1H–indol–5–carboxilato

TFA (10 mL) fue añadido en una porción a temperatura ambiente a una solución agitada de metil 3–[1–(tert–butoxicarbonil)piperidin–4–il]–1H–indol–5–carboxilato (4.58 g, 12.78 mmol) en DCM (30 mL). La solución resultante fue agitada durante 30 minutos luego aplicada a una columna SCX y eluida con metanol seguido por amoniaco 2M en metanol. Las fracciones puras fueron combinadas y concentradas por evaporación, luego trituradas con éter para dar un sólido el cual fue recogido por filtración y secado al aire para dar metil 3–(piperidin–4–il)–1H–indol–5–carboxilato (2.69 g, 81%) como un sólido amarillo pálido.
1H NMR (399.9 MHz, DMSO–d6) δ 1.53 – 1.63 (2H, m), 1.86 – 1.89 (2H, m), 2.64 – 2.70 (2H, m), 2.86 – 2.92 (1H, m), 3.02 – 3.05 (2H, m), 3.85 (3H, s), 7.21 (1H, d), 7.42 (1H, d), 7.71 (1H, dd), 8.26 (1H, s), 11.20 (1H, s); m/z = 257 [M–H]–.

Preparación de metil 3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxilato

6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (1.8 g, 8.09 mmol), metil 3–(piperidin–4–il)–1H–indol–5–carboxilato (2.09 g, 8.09 mmol) y DIPEA (1.55 mL, 8.90 mmol) en DMF (25 mL) fueron agitados y calentados a 80°C durante 1 hora. La mezcla resultante fue luego enfriada hasta la temperatura ambiente y apagada en agua (60 mL) para dar un precipitado el cual fue recogido por filtración, lavado secuencialmente con agua, acetonitrilo y éter y secado al vacío para dar metil 3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxilato (3.29 g, 92%) como un sólido color crema.
1H NMR (399.9 MHz, DMSO–d6) δ 1.70 – 1.80 (2H, m), 2.09 – 2.12 (2H, m), 3.21 – 3.28 (3H, m), 3.85 (3H, s), 4.40 – 4.43 (2H, m), 7.28 (1H, d), 7.44 (1H, d), 7.68 (1H, d), 7.73 (1H, dd), 8.25 (1H, d), 8.31 (1H, d), 11.26 (1H, s); m/z = 445 [M+H]+.

Preparación de ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxílico

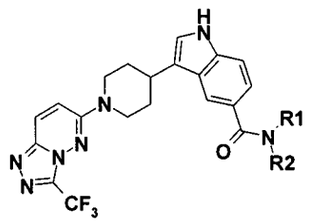
Metil 3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxilato (3.28 g, 7.38 mmol) y NaOH 2M (10 mL, 7.38 mmol) en metanol (80 mL) fueron calentados bajo reflujo durante 40 horas. La solución resultante fue concentrada por evaporación, luego acidificada hasta pH 2–3 con ácido clorhídrico 2M para dar un precipitado incoloro. El precipitado fue recogido por filtración, lavado secuencialmente con agua, acetonitrilo y éter y secado al vacío para proporcionar ácido 3–

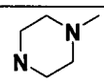
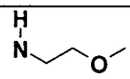
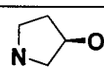
[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxílico (2.83 g, 89%) como un sólido incoloro.

1H NMR (399.9 MHz, DMSO–d6) δ 1.69 – 1.79 (2H, m), 2.09 – 2.13 (2H, m), 3.18 – 3.26 (3H, m), 4.40 – 4.43 (2H, m), 7.23 (1H, d), 7.37 (1H, d), 7.68 (1H, d), 7.72 (1H, dd), 8.25 (1H, d), 8.29 (1H, s), 11.19 (1H, s); m/z = 431 [M+H]+.

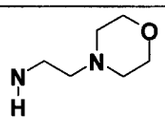
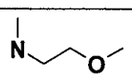
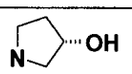
Ejemplos 497–505

Los siguientes compuestos fueron preparados en 75–98% de rendimiento mediante un método análogo al Ejemplo 496, partiendo de ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxílico y la amina apropiada:



Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
497		δ 1.68 – 1.78 (2H, m), 2.08 – 2.12 (2H, m), 2.18 (3H, s), 2.25 – 2.35 (4H, m), 3.15 – 3.24 (3H, m), 3.42 – 3.61 (4H, m), 4.40 – 4.43 (2H, m), 7.11 (1H, dd), 7.23 (1H, d), 7.38 (1H, d), 7.68 (1H, s), 7.69 (1H, d), 8.26 (1H, d), 11.07 (1H, s)	513
498		δ 1.70 – 1.81 (2H, m), 2.14 – 2.17 (2H, m), 3.15 – 3.25 (3H, m), 3.29 (3H, s), 3.44 – 3.50 (4H, m), 4.43 – 4.46 (2H, m), 7.22 (1H, d), 7.36 (1H, d), 7.64 (1H, dd), 7.70 (1H, d), 8.20 (1H, s), 8.27 (1H, d), 8.41 (1H, t), 11.09 (1H, s)	488
499	NMe2	δ 1.68 – 1.78 (2H, m), 2.09 – 2.12 (2H, m), 2.99 (6H, s), 3.13 – 3.24 (3H, m), 4.40 – 4.43 (2H, m), 7.14 (1H, dd), 7.21 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.70 (1H, s), 8.25 (1H, d), 11.05 (1H, s).	458
500		δ 1.66 – 2.01 (4H, m), 2.09 – 2.12 (2H, m), 3.16 – 3.29 (3H, m), 3.46 – 3.70 (4H, m), 4.22 (m) & 4.34 (m, 1H), 4.40 – 4.43 (2H, m), 4.91 (d) &	500

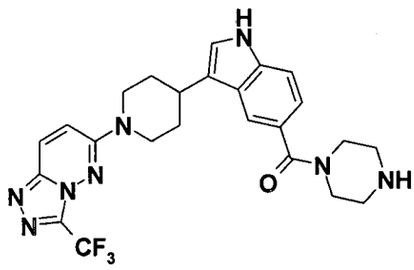
732

		5.02 (d, 1H), 7.22 (1H, d), 7.27 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.25 (1H, d), 11.06 (1H, s)	
501		δ 1.68 – 1.93 (6H, m), 2.08 – 2.12 (2H, m), 3.15 – 3.24 (3H, m), 3.43 – 3.51 (4H, m), 4.40 – 4.43 (2H, m), 7.21 (1H, d), 7.27 (1H, dd), 7.36 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.26 (1H, d), 11.05 (1H, s)	484
502		δ 1.68 – 1.78 (2H, m), 2.09 – 2.12 (2H, m), 3.15 – 3.24 (3H, m), 3.47 – 3.65 (8H, m), 4.40 – 4.43 (2H, m), 7.14 (1H, dd), 7.23 (1H, d), 7.39 (1H, d), 7.69 (1H, d), 7.71 (1H, s), 8.26 (1H, d), 11.08 (1H, s)	500
503		δ 1.71 – 1.81 (2H, m), 2.14 – 2.16 (2H, m), 2.44 (4H, m), 2.47 – 2.50 (2H, m), 3.14 – 3.25 (3H, m), 3.42 (2H, q), 3.58 (4H, t), 4.43 – 4.46 (2H, m), 7.22 (1H, d), 7.37 (1H, d), 7.62 (1H, dd), 7.70 (1H, d), 8.16 (1H, s), 8.27 (1H, d), 8.28 (1H, t), 11.08 (1H, s)	543
504		δ 1.69 – 1.79 (2H, m), 2.09 – 2.12 (2H, m), 2.99 (3H, s), 3.14 – 3.29 (6H, m), 3.40 – 3.64 (4H, m), 4.40 – 4.44 (2H, m), 7.12 (1H, dd), 7.21 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.70 (1H, s), 8.25 (1H, d), 11.04 (1H, s)	502
505		δ 1.67 – 2.00 (4H, m), 2.09 – 2.12 (2H, m), 3.16 – 3.29 (3H, m), 3.45 – 3.70 (4H, m), 4.22 (m) & 4.34 (m, 1H), 4.40 – 4.43 (2H, m), 4.91 (d) & 5.02 (d, 1H), 7.22 (1H, d), 7.27 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.25 (1H, d), 11.06 (1H, s)	500

Ejemplo 506

733

Preparación de 6–[4–[5–(piperazin–1–ilcarbonil)–1H–indol–3–il]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



TFA (1 mL) fue añadido en una porción a temperatura ambiente a una solución agitada de tert–butil [4–[3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carbonil]piperazina–1–carboxilato (190 mg, 0.32 mmol) en DCM (2 mL). La solución resultante fue agitada durante 1 hora luego aplicada a una columna SCX y eluida con MeOH seguido por amoniaco 2M en MeOH. Las fracciones puras fueron combinadas y concentradas por evaporación luego trituradas con éter para dar un sólido el cual fue recogido por filtración y secado al aire para dar 6–[4–[5–(piperazin–1–ilcarbonil)–1H–indol–3–il]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (156 mg, 99%) como un sólido incoloro.

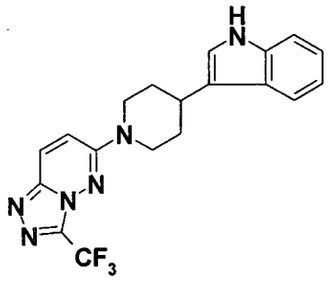
1H NMR (399.9 MHz, DMSO–d6) δ 1.68 – 1.78 (2H, m), 2.09 – 2.12 (2H, m), 2.83 – 2.93 (4H, m), 3.15 – 3.24 (3H, m), 3.50 – 3.64 (4H, m), 4.40 – 4.44 (2H, m), 7.14 (1H, dd), 7.23 (1H, d), 7.39 (1H, d), 7.69 (1H, d), 7.71 (1H, s), 8.26 (1H, d), 11.09 (1H, s); m/z = 499 [M+H]+.

El tert–butil [4–[3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carbonil]piperazina–1–carboxilato usado como material de partida fue preparado en 91% de rendimiento mediante un método análogo al Ejemplo 496, partiendo de ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]–1H–indol–5–carboxílico y tert–butil 1–piperazinacarboxilato.

m/z = 599 [M+H]+.

Ejemplo 507

Preparación de 6–[4–(1H–indol–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

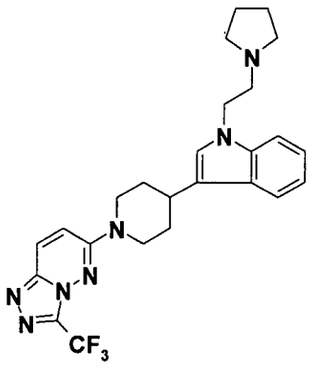


Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.223 g, 1.0 mmol), 3–(piperidin–4–il)–1H–indol (0.240 g, 1.20 mmol) y DIPEA (0.257 mL, 1.50 mmol) en DMF (3 mL) fue calentada a 70°C durante 1 hora. La mezcla de reacción fue corrida en un cartucho SCX, el cual fue lavado con MeOH y eluido con amoniaco 2M en metanol. El producto crudo fue purificado por cromatografía MPLC en sílice, eluyendo con acetato de etilo. Las fracciones puras fueron evaporadas hasta una goma la cual cristalizó con trituración con éter para proporcionar 6–[4–(1H–indol–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (0.119 g, 31%) como un sólido cristalino incoloro.

1H NMR (399.9 MHz, CDCl3) δ 1.81 – 1.92 (2H, m), 2.25 (2H, d), 3.15 – 3.27 (3H, m), 4.37 (2H, d), 6.99 – 6.99 (1H, m), 7.11 – 7.15 (2H, m), 7.19 – 7.24 (1H, m), 7.38 – 7.40 (1H, m), 7.64 (1H, d), 7.92 (1H, d), 8.02 (1H, s); m/z = 387 [M+H]+.

Ejemplo 508

Preparación de 6–[4–[1–(2–pirrolidin–1–iletil)–1H–indol–3–il]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



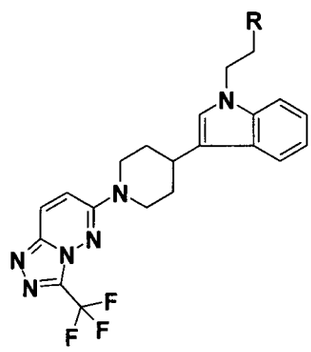
Hidruro de sodio (60% dispersión en aceite, 31 mg, 0.75 mmol) fue añadido a 6–[4–(1H–indol–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (obtenida

como se describió en el Ejemplo 507) (150 mg, 0.39 mmol) suspendida en DMF (2 mL) a 0°C bajo nitrógeno. La mezcla resultante fue agitada a 0°C durante 30 minutos, luego hidrocloruro de 1–(2–cloroetil)pirrolidina (72.6 mg, 0.43 mmol) en DMF (1 mL) fue añadido. La mezcla resultante fue agitada a temperatura ambiente durante 18 horas. La mezcla de reacción fue evaporada para proporcionar el producto crudo. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para dar 6–[4–[1–(2–pirrolidin–1–iletil)–1H–indol–3–il]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (52.0 mg, 27.7%) como un sólido blanco.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.63 – 1.67 (4H, m), 1.71 – 1.76 (2H, m), 2.09 (1H, d), 2.11 (1H, s), 2.45 – 2.48 (4H, m), 2.76 (2H, t), 3.15 (1H, t), 3.19 – 3.25 (2H, m), 3.38 (1H, s), 4.20 (2H, t), 4.40 (2H, d), 6.99 – 7.03 (1H, m), 7.10 – 7.14 (1H, m), 7.18 (1H, s), 7.42 (1H, d), 7.61 (1H, s), 7.67 (1H, d), 8.24 (1H, d); m/z 485 [M+H]+.

Ejemplos 509–510

Los siguientes compuestos fueron preparados en 26–32% de rendimiento mediante un procedimiento análogo al Ejemplo 508, partiendo de 6–[4–(1H–indol–3–il)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el cloruro de alquilo apropiado:



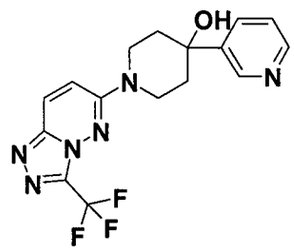
Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
509	Me2N	δ 1.70 – 1.74 (1H, m), 2.11 (2H, d), 2.18 (6H, s), 2.58 (2H, t), 3.15 (1H, t), 3.21 (1H, d), 3.25 – 3.26 (1H, m), 3.35 (1H, d), 4.18 (2H, t), 4.41 (2H, d), 7.00 (1H, t), 7.10 – 7.13 (1H, m), 7.18 (1H, s), 7.42 (1H, d), 7.63 (1H, s), 7.67 (1H, d), 8.24 (1H, d)	459

736

510	MeO	δ 1.70 – 1.74 (2H, m), 2.10 (1H, d), 2.12 (1H, s), 3.15 – 3.19 (1H, m), 3.22 (4H, s), 3.64 (2H, t), 4.26 (2H, t), 4.39 – 4.43 (2H, m), 6.99 – 7.03 (1H, m), 7.10 – 7.14 (1H, m), 7.15 (1H, s), 7.44 (1H, d), 7.61 (1H, s), 7.67 (1H, d), 8.25 (1H, d)	446

Ejemplo 511

Preparación de 4–piridin–3–il–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol



Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.445 g, 2.0 mmol), 4–(piridin–3–il)piperidin–4–ol (obtenida como se describió en la Solicitud Canadiense de Patente CA2076191, Ejemplo 87) (ver también el Ejemplo 87 en EP0533344B1) (0.392 g, 2.20 mmol) y DIPEA (0.453 mL, 2.60 mmol) en DMF (4 mL) fue calentada a 70°C durante 1 hora. La solución fue evaporada y particionada entre DCM (20 mL) y carbonato de potasio 1M acuoso (20 mL). La fase orgánica fue lavada con cloruro de sodio acuoso saturado, secado sobre $MgSO_4$ y evaporada hasta secarse, y el residuo fue triturado con éter. El sólido precipitado fue recogido por filtración, lavado con éter y secado al vacío para proporcionar 4–piridin–3–il–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (0.270 g, 37%) como un sólido cristalino blanco.

1H NMR (399.9 MHz, DMSO–d6) δ 1.76 – 1.79 (2H, m), 2.03 – 2.11 (2H, m), 3.43 – 3.49 (2H, m), 4.23 (2H, d), 5.43 (1H, s), 7.33 – 7.37 (1H, m), 7.67 (1H, d), 7.87 – 7.90 (1H, m), 8.25 (1H, d), 8.45 – 8.46 (1H, m), 8.74 (1H, d); m/z = 363 [M–H]–.

Ejemplo 511.1

Preparación a gran escala de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol

Una solución agitada de 6-cloro-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (24.29

g, 109.15 mmol), 4-(piridin-3-il)piperidin-4-ol (21.40 g, 120.07 mmol) y DIPEA (24.72 ml, 141.90 mmol) en DMF (95 ml) se calentó a 80°C durante 1 hora. La solución se enfrió hasta temperatura ambiente y se diluyó lentamente con agua, y se sembró para obtener un precipitado cristalino. El precipitado se recogió por filtración, se lavó con agua, acetonitrilo y éter, y se secó al vacío para obtener 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol (36.1 g, 91%) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 1.76 (2H, d), 2.03 - 2.09 (2H, m), 3.41 - 3.47 (2H, m), 4.23 (2H, d), 5.47 (1H, s), 7.33 - 7.37 (1H, m), 7.68 (1H, d), 7.87 - 7.90 (1H, m), 8.26 (1H, d), 8.44 - 8.46 (1H, m), 8.74 (1H, d); m/z = 365 [M+H]+.

El 4-(piridin-3-il)piperidin-4-ol empleado como material de partida se preparó como se indica a continuación:-

Preparación de 4-hidroxi-4-(piridin-3-il)piperidin-1-carboxilato de bencilo

Se agregó una solución de 3-bromopiridina (9.09 mL, 94.31 mmol) en éter dietílilco (50 mL) gota a gota a una solución agitada de n-butillitio 1.6M en hexano (58.9 mL, 94.31 mmol) en éter dietílico (500 mL) enfriada hasta -78°C, en el transcurso de un periodo de 15 minutos en atmósfera de nitrógeno. La suspensión resultante se agitó a -78°C durante 1 hora. Se agregó una solución de 4-oxopiperidin-1-carboxilato de bencilo (20 g, 85.74 mmol) en éter dietílico (50 mL) y THF (50 mL) gota a gota durante 15 minutos. La mezcla de reacción se agitó a -78°C durante 1 hora, se calentó hasta 0°C durante 2.5 horas y se neutralizó con solución saturada de cloruro de amino (500 ml). La mezcla se extrajo con acetato de etilo (2 x 500 mL) y los extractos combinados se lavaron con solución acuosa saturada de cloruro sódico (200 mL), posteriormente se secaron con $MgSO_4$ y se filtraron a través de un lecho corto de sílice. El lecho de sílice se lavó con acetato de etilo (4 x 250 mL) y el filtrado se concentró al vacío. El residuo se purificó por cromatografía flash en gel de sílice eluyendo con acetato de etilo. Las fracciones puras se evaporaron a sequedad para obtener 4-hidroxi-4-(piridin-3-il)piperidin-1-carboxilato de bencilo (12.8 g, 48%) como un aceite.

1H NMR (400.1 MHz, CDCl3) δ 1.71 - 1.82 (2H, m), 1.84 - 2.02 (2H, m), 3.25 - 3.43 (2H, m), 3.48 - 3.66 (1H, m), 4.03 - 4.19 (2H, m), 5.15 (2H, s), 7.27 - 7.39 (6H, m), 7.79 - 7.82 (1H, m), 8.37 - 8.40 (1H, m), 8.69 (1H, d); m/z = 313 [M+H]+.

Preparación de 4-(piridin-3-il)piperidin-4-ol

Se disolvió 4-hidroxi-4-(piridin-3-il)piperidin-1-carboxilato de bencilo (32.7 g, 104.69 mmol) en etanol (350 mL) y se hidrogenó con paladio al 10% sobre carbón (3.2 g) con una presión de 2 bar a 30°C. Una vez finalizada la capturación de hidrógeno, la mezcla se filtró a través de un lecho de tierra de diatomeas para eliminar el catalizador y el lecho se lavó con etanol. El filtrado se concentró a sequedad al vacío para obtener un aceite el cual cristalizó en reposo durante la noche. El sólido se recristalizó con MTBE (100 mL), se recogió por filtración, se lavó con MTBE (2 x 50 ml) y se secó en una estufa al vacío a 40°C para obtener 4-(piridin-3-il)piperidin-4-ol (14.9 g, 80%) como un sólido.
1H NMR (400.1 MHz, DMSO-d6) δ 1.53 - 1.61 (2H, m), 1.86 (2H, m), 2.74 - 2.83 (2H, m), 2.96 (2H, m), 7.34 (1H, m), 7.83 (1H, m), 8.43 (1H, m), 8.59 (1H, d).

Ejemplo 511.2

Preparación de la Forma A anhidra de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol cristalino

Una solución agitada de 6-cloro-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (16.69 g, 75 mmol), 4-(piridin-3-il)piperidin-4-ol (14.70 g, 82.50 mmol) y N-etildiisopropilamina (16.98 mL, 97.50 mmol) en DMF (75 mL) fue calentada a 80 °C durante1h. La solución fue enfriada a temperatura ambiente y lentamente diluida con agua, con sembrado, dando un precipitado cristalino. El precipitado fue recogido mediante filtración, lavado con agua, acetonitrilo y éter, y secado al vacío a 50°C para dar la Forma Anhidra A de 4-(piridin-3-il)-1-(3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il)piperidin-4-ol (25.2 g, 92 %) como un sólido crema cristalino, el cual se utilizó sin purificar o más. Aproximadamente 30 mg de material fueron suspendidos en aproximadamente 1 ml de acetato de etilo y agitados utilizando un agitador magnético durante 3 días a temperatura ambiente. El material resultante fue secado al aire y analizado.

La Forma Anhidra A de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol fue caracterizada proporcionando un patrón de difracción de rayos X en polvo sustancialmente como se muestra en la Figura 1. La intendidad de los picos para los valores correspondientes de 2θ se muestra en la Tabla A a continuación.

La Forma Anhidra A de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol puede, por lo tanto, también ser caracterizada proporcionando al menos uno de los siguientes valores de 2θ cuando se mide utilizando radiación CuKa: 9.18°, 15.51°, 16.01°, 18.94° y 24.59°.

Tabla A

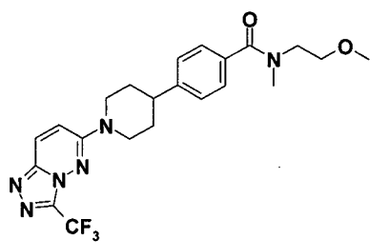
Ángulo 2-Theta ° (2θ)	Intensidad %
8.296	42
9.176	87.2
9.961	16.7
10.411	11.7
14.352	49
15.022	25.7
15.513	68.9
16.007	100
17.026	33.5
18.458	9.3
18.939	69.6
19.181	28
19.823	27.6
20.353	36.2

Ángulo 2-Theta ° (2θ)	Intensidad %
20.609	17.9
21.804	51.4
22.653	17.5
23.377	38.5
24.151	10.5
24.585	71.2
25.43	55.6
26.12	18.3
26.349	40.1
26.592	14.4
27.431	15.6
29.375	25.7
31.83	22.6
37.332	12.1

El análisis DSC mostró que la Forma Anhidra A de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol comienza a fundirse a aproximadamente 230°C y alcanza un máximo a aproximadamente 232°C.

Ejemplo 512

Preparación de N–(2–metoxietil)–N–metil–4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzamida



Una mezcla de ácido 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico (79 mg, 0.20 mmol), N–(2–metoxietil)metilamina (21 mg, 0.24 mmol), DIPEA (0.105 mL, 0.61 mmol) y HATU (92 mg, 0.24 mmol) en DMA (3 mL) fue agitada a temperatura ambiente durante 16 horas. La mezcla de reacción fue purificada por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm,

longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para dar N–(2–metoxietil)–N–metil–4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzamida (77 mg, 82%) como un sólido.

1H NMR (399.9 MHz, CDCl3) δ 1.81 (2H, m), 2.02 (2H, m), 2.86 (1H, m), 3.04 – 3.17 (5H, m), 3.29 – 3.48 (5H, m), 3.69 (2H, m), 4.39 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.38 (2H, d), 7.94 (1H, d); m/z = 463 [M+H]+.

El ácido 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico usado como material de partida fue preparado como sigue:

Preparación de 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoato de metilo

6–Cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (2 g, 8.99 mmol), 4–(piperidin–4–il)benzoato de metilo (CAS 281235–04–9, 2.168 g, 9.89 mmol) y DIPEA (3.91 mL, 22.47 mmol) fueron disueltos en DMA (10 mL) y sellados en un tubo de microondas. La mezcla fue calentada hasta 110°C durante 5 minutos en el reactor de microondas y enfriada hasta la temperatura ambiente. La mezcla de reacción fue añadida en forma de gotas a agua agitada (30 mL), agitada durante 10 minutos, luego el precipitado fue recogido por filtración, lavado con éter (2 x 2 mL) y secado para dar 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoato de metilo (3.32 g, 91%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.73 (2H, m), 1.92 (2H, m), 2.98 (1H, m), 3.13 (2H, m), 3.84 (3H, s), 4.44 (2H, m), 7.44 (2H, d), 7.68 (1H, d), 7.91 (2H, d), 8.27 (1H, d); m/z = 406 [M+H]+.

Preparación de ácido 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico

Hidróxido de litio monohidrato (0.154 g, 3.66 mmol) fue añadido a 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoato de metilo (1.35 g, 3.33 mmol) en una mezcla de metanol (30 mL) y agua (15 mL). La suspensión resultante fue agitada a 50°C durante 16 horas. La mezcla fue enfriada hasta la temperatura ambiente, el metanol evaporado y el residuo acuoso tratado con ácido cítrico 1M hasta que

la precipitación cesó. El precipitado fue recogido por filtración, lavado con agua y secado para dar ácido 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico (1.26 g, 97%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.69 – 1.79 (2H, m), 1.93 (2H, m), 2.94 – 3.02 (1H, m), 3.11 – 3.17 (2H, m), 4.44 (2H, m), 7.41 (2H, d), 7.67 (1H, d), 7.89 (2H, d), 8.25 (1H, d), 12.79 (1H, s); m/z = 392 [M+H]+.

Ejemplo 512.1

Método alternativo para la preparación de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida

Se agregó 4-metilmorfolina (17.56 mL, 159.70 mmol) gota a gota al ácido 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzoico (25 g, 63.88 mmol) y 2-cloro-4,6-dimetoxi-1,3,5-triazina (13.46 g, 76.66 mmol) suspendidos en DMF (250 mL) a 0°C. La suspensión resultante se agitó durante 10 minutos, posteriormente se agregó 2-metoxi-N-metiletanamina (5.69 g, 63.88 mmol) y la mezcla se calentó hasta temperatura ambiente y se agitó durante 16 horas. La mezcla de reacción se concentró y se diluyó con DCM (1000 mL), y se lavó con agua (500 mL). La fase acuosa se volvió a extraer con DCM (500 mL), posteriormente las fases orgánicas combinadas se lavaron con NaHCO3 saturado (500 mL) y salmuera saturada (250 mL), y se secaron con $MgSO_4$, se filtraron y evaporaron para obtener el producto crudo. El producto crudo se recristalizó con éter y el sólido resultante se recogió por filtración y se secó al vacío, luego se purificó por cromatografía flash en sílice con un gradiente de elución de 0 a 5% de MeOH en DCM. Las fracciones puras se evaporaron a sequedad para obtener N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida (23.45 g, 79%) como un sólido.

1H NMR (399.9 MHz, CDCl3) δ 1.81 (2H, m), 2.02 (2H, m), 2.86 (1H, m), 3.04 - 3.17 (5H, m), 3.30 - 3.49 (5H, m), 3.69 (2H, m), 4.39 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.39 (2H, d), 7.93 (1H, d); m/z = 463 [M+H]+.

El ácido 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzoico empleado como material de partida se preparó como se indica a continuación:-

Preparación de 4-(piridin-4-il)benzoato de sodio

Una solución de carbonato de sodio (830 g, 7834.20 mmol) en agua (6800 mL) se agregó gota a gota en 30 minutos a una suspensión agitada del ácido 4-boronobenzoico (520 g, 3133.68 mmol), clorhidrato de 4-bromopiridina (622 g, 3196.35 mmol) y acetato de

paladio (II) (1.407 g, 6.27 mmol) en etanol (2600 mL) y agua (3600 mL) a 20°C. La reacción se agitó durante 10 minutos, posteriormente se agregó una sal trisódica del ácido 3,3',3"-fosfinidinetris(bencenosulfónico) (solución al 30% p/w en agua) (36.8 g, 18.80 mmol) y la mezcla se calentó a 85°C durante 4 horas. La mezcla de reacción se enfrió hasta 55°C y se agitó durante 2 horas, posteriormente la suspensión resultante se agitó a 20°C durante 16 horas. El sólido se recogió por filtración, se lavó con acetona (3 x 1250 mL), y se secó en una estufa al vacío a 60°C para obtener 4-(piridin-4-il)benzoato sódico (690 g, 99%) como un sólido.

1H NMR (400.1MHz, DMSO-d6) δ 7.72 (4H, m), 7.97 (2H, d), 8.62 (2H, d); m/z = 200 [M+H]+.

Preparación de 4-(piridin-4-il)benzoato de metilo

Se agregó cloruro de tionilo (683 mL, 9358.59 mmol) gota a gota durante 20 minutos a una suspensión de 4-(piridin-4-il)benzoato de sodio (690 g, 3119.53 mmol) en metanol (15 L) a -10°C, manteniendo la temperatura inferior a 15°C. La mezcla se agitó durante 10 minutos, luego se calentó hasta 65°C durante 15 horas. La mezcla de reacción se enfrió hasta 20°C y el solvente se evaporó. El residuo sólido se dividió entre acetato de etilo (14 L) y solución acuosa saturada de bicarbonato de sodio (14 L). La capa orgánica se separó y la capa acuosa se extrajo con acetato de etilo (7 L). Las capas orgánicas combinadas se lavaron con agua (14 L) y salmuera saturada (7 L), se secaron con sulfato de magnesio, se filtraron y evaporaron a sequedad para obtener 4-(piridin-4-il)benzoato de meitlo (570 g, 86%) como un sólido.

1H NMR (400.1MHz, DMSO-d6) δ 3.89 (3H, s), 7.78 (2H, d) 7.97 (2H, d), 8.09 (2H, d), 8.69 (2H, d); m/z = 214 [M+H]+.

Preparación de 4-(piperidin-4-il)benzoato de metilo

Se agitaron 4-(piridin-4-il)benzoato de metilo (285 g, 1336.57 mmol) y paladio (al 5% sobre carbono, 50% de humedad, JM Type 87L) (57 g, 13.39 mmol) en metanol (2850 mL) en un atmósfera de hidrógeno a 5 bar y 70°C durante 15 horas. El catalizador se eliminó por filtración y se lavó con metanol (2850 mL). El solvente se evaporó a sequedad para obtener 4-(piperidin-4-il)benzoato de metilo (291 g, 99%) como un sólido.

1H NMR (400.1 MHz, DMSO-d6) δ 1.51 (2H, m), 1.68 (2H, m), 2.54 - 2.69 (3H, m), 3.02 (2H, m), 3.84 (3H, s), 7.37 (2H, d), 7.89 (2H, d); m/z = 220 [M+H]+.

Preparación de 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzoato de metilo

Se agregó DIPEA (88 mL, 505.27 mmol) a 6-cloro-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (45.0 g, 202.11 mmol) y 4-(piperidin-4-il)benzoato de metilo (48.75 g, 222.32 mmol) en DMA (250 mL). La suspensión resultante se agitó a 100°C durante 1 hora posteriormente se enfrió hasta temperatura ambiente. La mezcla de reacción se agregó gota a gota a agua (1500 mL) con agitación. Se continuó agitando durante 10 minutos, posteriormente el precipitado se recogió por filtración, se lavó con agua (300 mL) y éter (250 mL x 2), y se secó para obtener 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzoato de metilo (76 g, 93%) como un sólido.

1H NMR (400.1 MHz, DMSO-d6) d 1.63 - 1.83 (2H, m), 1.85 - 2.01 (2H, m), 2.94 - 3.03 (1H, m), 3.08 - 3.18 (2H, m), 3.84 (3H, s), 4.36 - 4.52 (2H, m), 7.44 (2H, d), 7.68 (1H, d), 7.91 (2H, d), 8.27 (1H, d); m/z = 406 [M+H]+.

Preparación del ácido 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzoico

Se agregó hidróxido de litio monohidrato (9.06 g, 215.94 mmol) a 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzoato de metilo (79.58 g, 196.31 mmol) en una mezcla de MeOH (800 mL) y agua (400 mL). La suspensión resultante se agitó a 65°C durante 16 horas. La mezcla se enfrió hasta temperatura ambiente, el metanol se evaporó y los residuos acuosos se diluyeron con agua (600 mL), se filtraron y se trataron posteriormente con ácido cítrico 1M hasta que la precipitación cesó. El precipitado se recogió por filtración, se lavó con agua y se secó para obtener el ácido 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzoico (77 g, 101%) como un sólido.

1H NMR (400.1 MHz, DMSO-d6) d 1.67 - 1.79 (2H, m), 1.88 - 1.96 (2H, m), 2.91 - 3.02 (1H, m), 3.07 - 3.18 (2H, m), 4.39 - 4.48 (2H, m), 7.41 (2H, d), 7.68 (1H, d), 7.88 (2H, d), 8.26 (1H, d); m/z = 392 [M+H]+.

Ejemplo 512.2

Preparación de la Forma A anhidra de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida cristalina

4-Metilmorfolina (17.56 mL, 159.70 mmol) fue añadida gota a gota a ácido 4-(1-(3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il)piperidin-4-il)benzoico (25 g, 63.88 mmol) y 2-cloro-4,6-dimetoxi-1,3,5-triazina (13.46 g, 76.66 mmol) fue suspendida en DMF (250 mL) enfriado a 0 °C. La suspensión resultante fue agitada durante 10 minutos, después 2-metoxi-N-metiletanamina (5.69 g, 63.88 mmol) fue añadida y la mezcla se calentó a temperatura ambiente y se agitó durante 16 horas. La mezcla de reacción fue

concentrada y diluida con DCM (1 L), y lavada con agua (500 mL). La fase acuosa fue reextraída con DCM (500 mL), después los extractos orgánicos combinados fueron lavados con $NaHCO_3$ saturado (500 mL) seguido por solución acuosa de cloruro sódico saturada (25 mL), despúes secados sobre $MgSO_4$, filtrados y evaporados para dar el producto crudo. Éste fue entonces triturado en éter, el sólido fue filtrado y secado al vacío. LCMS muestra que contiene una impureza de 2.5%. El product crudo fue purificado por cromatografía sobre gel de sílice ultrarápida (flash), gradiente de elución de 0 a 5% de MeOH en DCM. Las fracciones puras fueron evaporadas a sequedad para dar la Forma Anhidra A de N-(2-metoxietil)-N-metil-4-(1-(3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il)piperidin-4-il)benzamida (23.45 g, 79%) como un sólido de color hueso.

La Forma Anhidra A de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida se caracteriza proporcionando un patrón de difracción de rayos X en polvo sustancialmente como se muestra en la Figura 2. La intensidad de los picos para los valores correspondientes de 2θ se muestra en la Tabla B a continuación.

La Forma Anhidra A de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida puede, por lo tanto, también ser caracterizada proporcionando al menos uno de los siguientes valores de 2θ cuando se mide utilizando radiación CuKa: 12.34°, 15.78°, 20.42°, 23.75° y 24.73°.

Tabla B

Ángulo 2-Theta ° (2θ)	**Intensidad %**
6.283	8.3
7.922	1.3
9.65	1.5
12.341	12.3
12.689	7.1
14.92	4.6
15.78	100
16.893	1.5
18.783	4
19.283	7.9
20.424	17.7

Ángulo 2-Theta ° (2θ)	**Intensidad %**
24.339	3.7
24.728	9.5
25.375	3.4
26.93	4.9
28.138	2.7
29.08	1.6
31.16	1.3
31.855	1.6
32.496	1.2
33.141	3.3
34.793	1.3

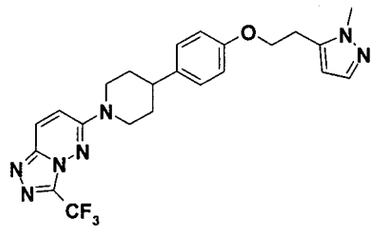
20.986	3.3
21.574	2.7
22.494	3.9
23.311	2.6
23.746	18.8

36.343	1.5
36.782	1.4
38.01	1.3
38.637	1.6

El análisis DSC mostró que la Forma Anhidra A de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida comienza a fundirse a aproximadamente 167°C y alcanza un máximo a aproximadamente 169°C.

Ejemplo 513

Preparación de 6–[4–[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



DIAD (78 µl, 0.386 mmol) fue añadida en forma de gotas a 4-[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol (117 mg, 0.322 mmol), trifenilfosfina (101 mg, 0.386 mmol) y 2–(1–metil–1H–pirazol–5–il)etanol (obtenida como se describió en la Sol. Int. PCT WO 2007017222, Producto intermedio1) (49 mg, 0.386 mmol) en THF (2 mL). La mezcla resultante fue agitada a temperatura ambiente durante 16 horas y luego añadida a una columna SCX. El producto crudo fue eluido usando amoniaco 2M en metanol y las fracciones que contienen el producto fueron evaporadas. El producto fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para dar 6–[4–[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (79 mg, 52%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.67 (2H, m), 1.88 (2H, m), 2.77 – 2.84 (3H, m), 3.10 (2H, m), 3.78 (3H, s), 4.05 (2H, t), 4.41 (2H, m), 6.88 (2H, d), 7.18 (2H, d), 7.33 (1H, s), 7.55 (1H, s), 7.66 (1H, d), 8.24 (1H, d); m/z = 472 [M+H]+.

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El 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol usado como material de partida fue preparado como sigue:

DIPEA (5.84 mL, 33.54 mmol) fue añadido a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (2.99 g, 13.41 mmol) y hidrocloruro de 4–(piperidin–4–il)fenol (CAS 263139–27–1, 3.01 g, 14.08 mmol) en DMF (30 mL). La solución resultante fue agitada a 80°C durante 1 hora. La mezcla fue enfriada hasta la temperatura ambiente, evaporada hasta secarse y redisuelta en DCM (200 mL). La solución fue lavada con agua (200 mL) y salmuera saturada (200 mL), secada sobre $MgSO_4$ y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente en elusión 50 a 70% acetato de etilo en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol (4.47 g, 92%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.63 (2H, m), 1.86 (2H, m), 2.74 (1H, m), 3.08 (2H, m), 4.40 (2H, m), 6.69 (2H, d), 7.05 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.19 (1H, s); m/z = 364 [M+H]+.

Ejemplo 513.1

Preparación a gran escala de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

Se agregó DIAD (19.73 mL, 100.18 mmol) gota a gota a 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenol (28 g, 77.06 mmol), 2-(1-metil-1H-pirazol-5-il)etanol (14.53 g, 100.18 mmol) y trifenilfosfina (26.3 g, 100.18 mmol) en THF (250 mL). La solución resultante se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se evaporó a sequedad y se redisolvió en DCM (1 L), y la solución se lavó secuencialmente con NaOH 2M (300 mL x 2) y salmuera saturada (250 mL). La capa orgánica se secó con MgSO4, se filtró y evaporó para obtener el producto crudo. El producto crudo se purificó por cromatografía flash en sílice, eluyendo con 75% de EtOAc en isohexano seguido de un gradiente de 0 a 3% de MeOH en DCM. Las fracciones que contenían el producto deseado se evaporaron a sequedad, posteriormente se redisolvieron en DCM (500 mL) y la solución se lavó con NaOH 2M (300 mL x 2) seguido de salmuera (250 mL), y luego se secaron con $MgSO_4$, se filtraron y evaporaron.

El residuo se purificó además por cromatografía flash en sílice con un gradiente de elución de 80 a 100% de EtOAc en isohexano. Las fracciones puras se evaporaron a sequedad para obtener 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (18.21 g, 50.1%) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 1.67 (2H, m), 1.88 (2H, m), 2.81 (1H, m), 3.07 - 3.14 (4H, m), 3.79 (3H, s), 4.18 (2H, t), 4.41 (2H, m), 6.14 (1H, d), 6.89 (2H, d), 7.19 (2H, d), 7.30 (1H, d), 7.66 (1H, d), 8.24 (1H, d); m/z = 472 [M+H]+.

El 2-(1-metil-1H-pirazol-5-il)etanol empleado como material de partida se preparó como se indica a continuación:-

Se agregó n-butillitio (1.6M en hexanos) (1226 mL, 1961.78 mmol) gota a gota a 1-metil-1H-pirazol (153.4 g, 1868.37 mmol) en THF (3000 mL) enfriado a –78 °C en el transcurso de un periodo de una hora en atmósfera de nitrógeno. La solución resultante se agitó a –60°C durante 30 minutos, posteriormente se calentó hasta –10 °C y se agitó durante 40 minutos más. Una solución de oxirano (210 mL, 4203.82 mmol) en THF (600 mL) se agregó lentamente a -10°C seguida de más THF (1000 mL) y la suspensión resultante se agitó a -10°C durante 30 minutos, posteriormente a 0°C durante 30 minutos. Posteriormente, la mezcla se dejó calentar gradualmente hasta temperatura ambiente en atmósfera de nitrógeno y se agitó durante 16 horas. La mezcla de reacción se neutralizó con solución saturada de NH_4Cl (2000 ml), las capas se separaron y la fase acuosa se extrajo con n-butanol (3 x 1000 ml). Las capas orgánicas combinadas se lavaron con salmuera saturada (1500 ml), se secaron con $MgSO_4$, se filtraron y evaporaron para obtener un aceite, el cual se azeotropó con tolueno (1000 ml) para obtener un aceite con algo de sólido. El aceite se disolvió en DCM y el sólido insoluble se filtró y se lavó con DCM. El filtrado se purificó por cromatografía empleando una columna de sílice Novasep para HPLC prep, eluyendo con un gradiente de 5-10% de metanol en DCM. Las fracciones puras se evaporaron a sequedad para obtener 2-(1-metil-1H-pirazol-5-il)etanol (195 g, 83%) como un aceite.

1H NMR (400.1 MHz, DMSO-d6) δ 2.77 (2H, t), 3.63 (2H, m), 3.74 (3H, s), 4.74 (1H, t), 6.04 (1H, m), 7.26 (1H, d).

El 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenol empleado como material de partida se preparó como se indica a continuación:-

Preparación de 4-(trifluorometilsulfoniloxi)-5,6-dihidropiridin-1(2H)-carboxilato de bencilo

Una solución de 4-oxopiperidin-1-carboxilato de bencilo (88.57 g, 379.70 mmol) en THF (300 mL) se agregó gota a gota a bis(trimetilsilil)amida de litio (1M en THF) (418 mL, 417.67 mmol) a -78 °C en el transcurso de un periodo de 1 hora en atmósfera de nitrógeno. La mezcla resultante se agitó a -78°C durante 90 minutos, posteriormente se agregó una solución de 1,1,1-trifluoro-N-fenil-N-(trifluorometilsulfonil)metanosulfonamida (142 g, 398.68 mmol) en THF (600 mL) gota a gota durante un periodo de 1 hora. La mezcla resultante se agitó a -78°C durante 30 minutos, luego se dejó calentar hasta temperatura ambiente y se agitó durante 16 horas. La mezcla de reacción se neutralizó con NaOH 2M (450 mL). Las capas se separaron y la capa orgánica se lavó con NaOH 2M (360 mL). El solvente se evaporó, posteriormente el residuo se redisolvió en éter dietílico (1500 mL) y la solución se lavó con agua (500 mL). La capa orgánica se secó con $MgSO_4$, se filtró y evaporó para obtener 4-(trifluorometilsulfoniloxi)-5,6-dihidropiridin-1(2H)-carboxilato de bencilo (124 g, 81%) como un aceite.

1H NMR (399.9 MHz, DMSO-d6) δ 2.43 (2H, m), 3.62 (2H, m), 4.06 (2H, m), 5.10 (2H, s), 6.02 (1H, m), 7.34 (5H, m).

Preparación de 4-(4-hidroxifenil)-5,6-dihydropiridine-1(2H)-carboxilato de bencilo

Se agregó carbonato de sodio (96 g, 909.79 mmol) a 4-(trifluorometilsulfoniloxi)-5,6-dihidropiridin-1(2H)-carboxilato de bencilo (123.1 g, 303.26 mmol) y el ácido 4-hidroxifenilborónico (46.0 g, 333.59 mmol) en una mezcla de dioxano (1000 mL) y agua (250 mL). La mezcla resultante se burbujeó con nitrógeno durante 10 minutos, posteriormente se agregó 1,1'-bis(difenilfosfino)ferrocenodicloropaladio (II) (5.49 g, 7.58 mmol) y la mezcla de reacción se calentó a 80°C durante 1 hora, posteriormente se enfrió hasta temperatura ambiente. La mezcla de reacción se diluyó con DCM (2 L) y se lavó con agua (2 L). El extracto del lavado acuoso se reextrajo con DCM (1 L), posteriormente las capas orgánicas combinadas se lavaron con salmuera saturada (500 mL), se secaron con MgSO4, se filtraron y evaporaron para obtener el producto crudo. El producto crudo se purificó por cromatografía flash en sílice con un gradiente de elución de 10 a 30% de EtOAc en isohexano. Las fracciones que contenían el producto deseado se evaporaron a sequedad, luego se trituraron con isohexano, se filtraron y se secaron para obtener 4-(4-hidroxifenil)-5,6-dihidropiridin-1(2H)-carboxilato de bencilo (62.3 g, 66.4%) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 2.44 (2H, m), 3.61 (2H, m), 4.05 (2H, m), 5.12 (2H, s), 5.99 (1H, m), 6.73 (2H, d), 7.26 (2H, d), 7.32 - 7.40 (5H, m), 9.45 (1H, s); m/z = 310 [M+H]+.

Preparación de 4-(piperidin-4-il)fenol

Se agitaron 4-(4-Hidroxifenil)-5,6-dihidropiridin-1(2H)-carboxilato de bencilo (37.7 g, 121.86 mmol) y paladio al 5% sobre carbón (7.6 g, 3.57 mmol) en metanol (380 mL) en atmósfera de hidrógeno a 5 bar y 25°C durante 2 horas. El catalizador se eliminó por filtración, se lavó con MeOH y se evaporaron los solventes. El material crudo se recristalizó con éter dietílico, posteriormente el producto deseado se recogió por filtración y se secó al vacío para obtener 4-(piperidin-4-il)fenol (20.36 g, 94%) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 1.46 (2H, m), 1.65 (2H, m), 2.45 (1H, m), 2.58 (2H, m), 3.02 (2H, m), 6.68 (2H, d), 7.00 (2H, d), 9.15 (1H, s); m/z = 178 [M+H]+.

Preparación de 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenol

Se agregó DIPEA (48.2 mL, 276.86 mmol) a 6-cloro-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (24.65 g, 110.74 mmol) y 4-(piperidin-4-il)fenol (20.61 g, 116.28 mmol) en DMF (200 mL). La solución resultante se agitó a 80°C durante 1 hora. La mezcla de reacción se enfrió hasta temperatura ambiente, luego se evaporó a sequedad y se redisolvió en DCM (1 L) y se lavó con agua (2 x 1 L). La capa orgánica se lavó con salmuera saturada (500 mL), posteriormente se secó con MgSO4, se filtró y evaporó para obtener el producto crudo. El producto crudo se recristalizó con éter para obtener 4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenol (36.6 g, 91%) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 1.64 (2H, m), 1.87 (2H, m), 2.75 (1H, m), 3.09 (2H, m), 4.40 (2H, m), 6.69 (2H, d), 7.05 (2H, d), 7.65 (1H, d), 8.24 (1H, d), 9.15 (1H, s); m/z = 364 [M+H]+.

Ejemplo 513.2

Preparación de la Forma A anhidra de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina cristalina

DIAD (3.70 mL, 18.77 mmol) fue añadido a 4-(1-(3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il)piperidin-4-il)fenol (6.2 g, 17.06 mmol), 2-(1-metil-1H-pirazol-5-il)etanol (2.368 g, 18.77 mmol) y trifenilfosfina (4.92 g, 18.77 mmol) en THF (150 mL) en atmósfera de nitrógeno. La solución resultante fue agitada a temperatura ambiente durante 1 día. El producto crudo fue purificado por cromatografía de intercambio iónico, utilizando una columan SCX. El producto deseado fue eluido de la columna utilizando NH_3/MeOH 2M y las fracciones puras fueron evaporadas a sequedad para dar el producto crudo. El producto crudo fue purificado por cromatografía sobre gel de sílica ultrarápida (flash), con

un gradiente de elución de 0 a 5% de MeOH en DCM. Las fracciones puras fueron evaporadas a sequedad para dar el producto crudo. El producto fue disuelto en DCM (100 mL) y lavado con NaOH 2M (100 mL) dos veces. La fase organic fue evaporada para dar la Forma Anhidra A 6-(4-(4-(2-(1-metil-1H-pirazol-5-il)etoxi)fenil)piperidin-1-il)-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (4.95 g, 61.5 %) como un sólido blanco.

La Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina se caracteriza proporcionando un patrón de difracción de rayos X en polvo sustancialmente como se muestra en la Figura 3. La intensidad de los picos para los valores correspondientes de 2θ se muestra en la Tabla C a continuación.

La Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina puede, por lo tanto, también ser caracterizada proporcionando al menos uno de los siguientes valores 2θ cuando se mide utilizando radiación CuKa: 4.90°, 13.47°, 15.93°, 16.64° y 22.83°.

Tabla C

Ángulo 2-Theta ° (2θ)	**Intensidad %**
4.898	100
9.784	8
11.503	17.1
11.942	2.7
12.966	4
13.473	24
14.719	13.8
15.934	26.6
16.642	33.4
17.359	6.5
18.322	1.8
18.669	6.5
19.195	22.1
19.666	4.9
20.257	2.8
20.581	11

Ángulo 2-Theta ° (2θ)	**Intensidad %**
24	13.5
24.396	14.8
25.985	6.4
26.752	6.5
27.146	6.5
28.104	1.8
28.545	2.7
29.016	2
29.461	8.7
29.737	5.8
30.121	4.7
30.654	3
31.371	1.3
31.853	1.8
33.656	3.4
34.28	1.4

20.866	2.2
21.334	3.4
21.641	2.4
22.834	24
23.7	3.1

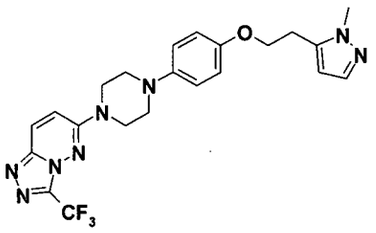
35.851	2.2
36.424	2.3
37.617	1.8
38.531	1.3

Al análisis DSC mostró que la Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina comienza a fundirse a a aproximadamente 159°C y alcanza un máximo a aproximadamente 162°C.

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Ejemplo 514

Preparación de 6–[4–[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



DIAD (0.162 mL, 0.82 mmol) fue añadido a 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]fenol (250 mg, 0.69 mmol), 2-(1–metil–1H–pirazol–5–il)etanol (obtenido como se describió en la Sol. Int. PCT WO 2007017222, Producto intermedio1) (130 mg, 1.03 mmol) y trifenilfosfina (270 mg, 1.03 mmol) en THF (5 mL). La solución resultante fue agitada a temperatura ambiente durante 18 horas, luego añadida a una columna SCX. El producto crudo fue eluido usando amoniaco 2M en metanol y las fracciones que contienen el producto fueron evaporadas. El producto fue purificado por cromatografía flash en sílice, gradiente en elusión 0 a 3% metanol en DCM. Las fracciones puras fueron evaporadas hasta secarse para proporcionar 6–[4-[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (111 mg, 34%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 2.81 (2H, t), 3.17 (4H, m), 3.75 (4H, m), 3.78 (3H, s), 4.02 (2H, t), 6.87 (2H, d), 6.96 (2H, d), 7.33 (1H, s), 7.56 (1H s), 7.69 (1H, d), 8.30 (1H, d); m/z = 473 [M+H]+.

El 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]fenol usado como material de partida fue preparado como sigue:

DIPEA (12.15 mL, 69.78 mmol) fue añadido a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (10.35 g, 46.52 mmol) y 1–(4-hidroxifenil)piperazina (CAS 56621–48–8, 9.12 g, 51.17 mmol) en DMF (80 mL). La solución resultante fue agitada a 80°C durante 1 hora. La mezcla de reacción fue enfriada hasta la temperatura ambiente, evaporada hasta secarse y el residuo redisuelto en DCM (250 mL). La solución fue lavada con agua (200 mL), secada sobre MgSO4 y evaporada para proporcionar el producto crudo, el cual fue triturado con dietil éter. El sólido resultante fue recogido por

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filtración y secado al vacío para dar 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]fenol (14.27 g, 84%) como un sólido.
1H NMR (399.9 MHz, DMSO–d6) δ 3.12 (4H, m), 3.75 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.67 (1H, d), 8.28 (1H, d), 8.87 (1H, s); m/z = 365 [M+H]+.

Ejemplo 514.1

Preparación a gran escala de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

Se agregó DIAD (20.73 mL, 105.27 mmol) gota a gota a 4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenol (32.0 g, 87.72 mmol), 2-(1-metil-1H-pirazol-5-il)etanol (preparado como se describe en el Ejemplo 513, preparación de materiales de partida) (16.6 g, 131.58 mmol) y trifenilfosfina (34.5 g, 131.58 mmol) en THF (320 mL) a 0°C en atmósfera de nitrógeno. La solución resultante se agitó a temperatura ambiente durante 3 días. La mezcla de reacción se evaporó a sequedad y se redisolvió DCM (700 mL), y la solución se lavó secuencialmente con NaOH 2M (200 mL x 2) y salmuera saturada (200 mL). La capa orgánica se secó con $MgSO_4$, se filtró y evaporó para obtener el producto crudo. El producto crudo se purificó por cromatografía flash en sílice, eluyendo con un gradiente de 80 a 100% de EtOAc en isohexano seguido de EtOAc, posteriormente un gradiente de 0 a 3% de MeOH en DCM. Las fracciones puras se evaporaron a sequedad para obtener 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (28.7 g, 69.3%) como un sólido.
1H NMR (399.9 MHz, DMSO-d6) δ 3.07 (2H, t), 3.18 (4H, m), 3.76 (4H, m), 3.79 (3H, s), 4.15 (2H, t), 6.14 (1H, d), 6.88 (2H, d), 6.97 (2H, d), 7.30 (1H, d), 7.67 (1H, d), 8.28 (1H, d); m/z = 473 [M+H]+.

El 4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenol empleado como material de partida se preparó como se indica a continuación:-
DIPEA (52.4 mL, 300.84 mmol) se agregó a 6-cloro-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (44.6 g, 200.56 mmol) y 1-(4-hidroxifenil)piperazina (39.32 g, 220.61 mmol) en DMF (450 mL). La solución resultante se agitó a 80°C durante 2 horas. La mezcla de reacción se enfrió hasta temperatura ambiente, luego se evaporó a sequedad y se dividió entre DCM (2 L) y agua (1 L) que contenía metanol (250 mL) para facilitar la solubilidad. El material insoluble se recogió por filtración, se lavó con metanol y se secó para obtener el producto deseado. El filtrado orgánico se separó de la capa acuosa, luego se lavó con salmuera saturada (500 mL), se secó con $MgSO_4$ y se evaporó para obtener una goma

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marrón. Esta se rescristalizó con éter y el sólido resultante se recogió por filtración, se lavó con DCM seguido de metanol, se combinó con el precipitado anterior y se secó para obtener 4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenol (63.8 g, 87%) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 3.12 (4H, m), 3.75 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.67 (1H, d), 8.28 (1H, d), 8.87 (1H, s); m/z = 365 $[M+H]^+$.

Ejemplo 514.2

Preparación de la Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina cristalina

DIAD (7.78 mL, 39.53 mmol) fue añadido gota a gota a 4-(4-(3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il)piperazin-1-il)fenol (12 g, 32.94 mmol), 2-(1-metil-1H-pirazol-5-il)etanol (6.23 g, 49.41 mmol) y trifenilfosfina(12.96 g, 49.41 mmol) en THF (250 mL). La solución resultante fue agitada a temperatura ambiente durante 18 horas, después fue dividida y añadida a una serie de columnas SCX (6). El producto crudo fue eluido de las columnas utilizando NH_3/MeOH 2M y los solventes fueron evaporados. EL producto crudo fue diluido con DCM (200 mL) y lavado con NaOH 2M (200 mL x 2). La fase organic fue secada sobre $MgSO_4$, filtrada y evaporada, y luego fue purificada por cromatografía sobre gel de sílica ultrarápida (flash), con un gradiente de elución de 0 a 3% de MeOH en DCM. Las fracciones puras fueron evaporadas a sequedad dando un sólido amarillo, que fue triturado en éter para dar la Forma Anhidra A de 6-(4-(4-(2-(1-metil-1H-pirazol-5-il)etoxi)fenil)piperazin-1-il)-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (9.18g, 59.0 %) como un sólido crema.

La Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina se caracteriza proporcionando un patrón de difracción de rayos X en polvo sustancialmente como se muestra en Figura 4. La intensidad de los picos para los valores correspondientes de 2θ se muestra en la Tabla D a continuación.

La Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina puede, por lo tanto, también ser caracterizada proporcionando al menos unos de los siguientes valores de 2θ cuando se miden utilizando radiación CuKa: 6.90°, 15.38°, 21.55°, 24.48° y 27.56°.

Tabla D

Ángulo 2-Theta ° (2θ)	Intensidad %
6.903	23.4
9.6	8.6
10.776	11.2
12.818	13.3
13.162	3.3
13.845	10
14.436	3.1
15.376	19.2
16.436	11
17.457	4.1
18.247	3.6
18.916	14.9
19.266	3.4
20.182	3
21.03	4.3
21.545	100
22.36	12.4
22.625	3.3
23.552	5.6
23.76	4.7

Ángulo 2-Theta ° (2θ)	Intensidad %
24.479	40.9
25.2	2.2
25.755	7.2
26.465	2.7
27.561	17.1
27.833	11.8
28.206	6.2
29.098	2.1
29.928	2.1
30.587	1.6
31.201	4.8
32.489	1.8
33.326	1.8
34.042	2.3
34.618	3
36.18	1.7
36.538	1.7
37.448	1.3
38.17	1.5
39.324	2.4

El análisis DSC mostró que la Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina comienza a fundirse a aproximadamente 178°C y alacanza un máximo a aproximadamente 179°C.

Ejemplo 514.3

Preparación de fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

Se agregaron 3ml de acetona a 50mg de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina y se calentó para obtener una solución. Se disolvieron 12.3mg de ácido fumárico en 3ml de acetona. La solución del compuesto se agregó a la solución del contraión y la mezcla resultante se agitó con calentamiento. La solución se dejó secar al aire y, una vez se redujo el volumen considerablemente, el fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina precipitó.

El fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina se caracteriza por tener un patrón de difracción de rayos X en polvo sustancialmente como el que se muestra en la Figura 5. La intensidad de los picos para los valores 2θ correspondientes se muestran a continuación en la Tabla E.

Así pues, el fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina se puede caracterizar también ya que tiene al menos uno de los siguientes valores 2θ cuando se mide con radiación CuKa: 11.72°, 16.46°, 17.58° y 21.89°.

Tabla E

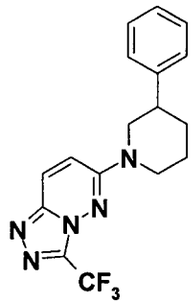
Ángulo 2-Theta ° (2θ)	Intensidad %
4.514	20.3
5.897	14.2
11.724	56.6
12.215	12.3
13.225	6.9
16.464	73.5
17.582	61.3
19.738	17.4
20.261	15

Ángulo 2-Theta ° (2θ)	Intensidad %
21.18	21.1
21.894	100
23.863	13
24.174	12.7
25.826	8.6
26.752	8.8
28.776	7.8
30.541	18.9
31.509	8.1

El análisis DSC mostró que el fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina tiene una endoterma de fusión con inicio a aproximadamente 153°C y un pico a aproximadamente 155°C (esta va seguida de un suceso de recristalización y subsecuente fusión).

Ejemplo 515

Preparación de 6–(3–fenilpiperidin–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

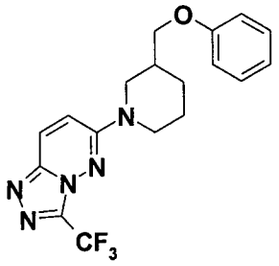


Una solución de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (49 mg, 0.22 mmol) en EtOH (1.0 mL) fue añadida a una mezcla de 3–fenilpiperidina (53 mg, 0.33 mmol) y DIPEA (57 µL, 0.33 mmol) en EtOH (1.0 mL). La mezcla de reacción fue calentada hasta 70°C toda la noche y el producto crudo fue purificado por LCMS preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 5% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para dar 6–(3–fenilpiperidin–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (46 mg, 61%).

1H NMR (700.03 MHz, DMSO–d_6) δ 1.62 – 1.68 (1H, m), 1.82 – 1.88 (2H, m), 1.96 – 1.98 (1H, m), 2.83 – 2.87 (1H, m), 3.10 – 3.15 (1H, m), 4.30 – 4.36 (3H, m), 7.25 – 7.28 (1H, m), 7.33 – 7.38 (4H, m), 7.68 (1H, d), 8.23 (1H, d); m/z = 348 [M+H]+.

Ejemplo 516

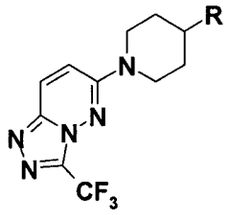
Preparación de 6–[3–(fenoximetil)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 60% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 3–(fenoximetil)piperidina. 1H NMR (700.03 MHz, DMSO–d_6) δ 1.45 – 1.50 (1H, m), 1.56 – 1.61 (1H, m), 1.79 – 1.82 (1H, m), 1.90 – 1.92 (1H, m), 2.08 – 2.11 (1H, m), 3.07 (1H, dd), 3.16 – 3.20 (1H, m), 3.91 (1H, dd), 3.96 (1H, dd), 4.10 – 4.13 (1H, m), 4.31 (1H, dd), 6.93 – 6.97 (3H, m), 7.28 – 7.31 (2H, m), 7.60 (1H, d), 8.21 (1H, d); m/z = 378 [M+H]+

Ejemplos 517–518

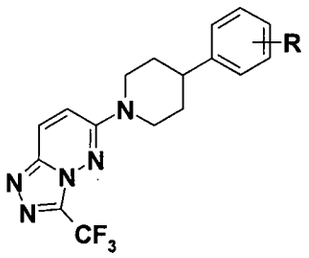
Los siguientes compuestos fueron preparados en 45–46% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la piperidina 4–sustituida apropiada:



Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
517	etoximetil	δ 1.11 (3H, t), 1.21 – 1.27 (2H, m), 1.79 (2H, d), 1.85 – 1.88 (1H, m), 3.00 – 3.04 (2H, m), 3.42 (2H, q), 4.27 (2H, d), 7.60 (1H, d), 8.21 (1H, d), (2H oscurecida por agua)	330
518	propoxi	δ 0.89 (3H, t), 1.50 – 1.56 (4H, m), 1.91 – 1.95 (2H, m), 3.36 – 3.40 (1H, m), 3.41 (2H, t), 3.55 – 3.59 (1H, m), 3.89 – 3.92 (2H, m), 7.62 (1H, d), 8.22 (1H, d), (1H oscurecida por agua)	330

Ejemplos 519–526

Los siguientes compuestos fueron preparados en 23–63% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la 4–aril piperidina apropiada:



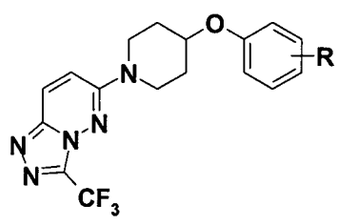
Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
519	H	δ 1.69 – 1.75 (2H, m), 1.92 (2H, d), 2.85 – 2.90 (1H, m), 3.10 – 3.14 (2H, m), 4.42 – 4.44 (2H, m), 7.20 – 7.22 (1H, m), 7.27 – 7.28 (2H, m), 7.30 – 7.32 (2H, m), 7.66 (1H, d), 8.24 (1H, d)	348
520	2–OMe	δ 1.67 – 1.73 (2H, m), 1.85 (2H, d), 3.10 – 3.14 (2H, m), 3.81 (3H, s), 4.42 (2H, d), 6.89 – 6.91 (1H, m), 6.99 (1H, d), 7.17 – 7.21 (2H, m), 7.65 (1H, d), 8.24 (1H, d), (2H oscurecida por agua)	378
521	4–SO2Me	δ 1.73 – 1.79 (2H, m), 1.94 (2H, d), 3.01 – 3.06 (1H, m), 4.45 (2H, d), 7.57 (2H, d), 7.67 (1H, d), 7.86 – 7.87 (2H, m), 8.26 (1H, d), (5H oscurecida por agua)	426
522	4–CONHMe	δ 1.70 – 1.76 (2H, m), 1.92 (2H, d), 2.78 (3H, d), 2.92 – 2.96 (1H, m), 3.11 – 3.15 (2H, m), 4.43 (2H, d), 7.36 (2H, d), 7.66 (1H, d), 7.76 – 7.78 (2H, m), 8.25 (1H, d), 8.32 (1H, q)	405
523	4–OMe	δ 1.64 – 1.70 (2H, m), 1.87 – 1.89 (2H, m), 2.79 – 2.84 (1H, m), 3.08 – 3.12 (2H, m), 3.73 (3H, s), 4.41 (2H, d), 6.86 – 6.88 (2H, m), 7.18 – 7.20 (2H, m), 7.66 (1H, d), 8.24 (1H, d)	378
524	4–CF3	δ 1.72 – 1.78 (2H, m), 1.94 (2H, d), 2.99 – 3.03 (1H, m), 3.12 – 3.16 (2H, m), 4.44 (2H, d), 7.53 (2H, d),	416

		7.66 – 7.68 (3H, m), 8.25 (1H, s)	
525	3–F	δ 1.69 – 1.75 (2H, m), 1.92 (2H, d), 2.90 – 2.94 (1H, m), 3.09 – 3.14 (2H, m), 4.42 (2H, d), 7.01 – 7.04 (1H, m), 7.13 (2H, t), 7.34 – 7.37 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	366
526	3–OMe	δ 1.69 – 1.75 (2H, m), 1.90 – 1.92 (2H, m), 2.83 – 2.87 (1H, m), 3.09 – 3.13 (2H, m), 3.74 (3H, s), 4.42 (2H, d), 6.77 – 6.79 (1H, m), 6.83 (1H, d), 6.84 (1H, t), 7.22 (1H, t), 7.66 (1H, d), 8.24 (1H, d)	378

760

Ejemplos 527–532

Los siguientes compuestos fueron preparados en 56–65% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la 4–ariloxi piperidina apropiada:



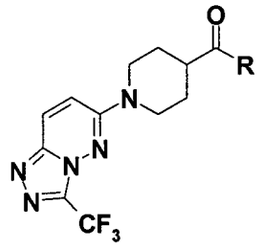
Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
527	3–OMe	δ 1.70 – 1.75 (2H, m), 2.05 – 2.08 (2H, m), 3.52 – 3.55 (2H, m), 3.74 (3H, s), 3.94 – 3.97 (2H, m), 4.67 – 4.70 (1H, m), 6.53 (1H, dd), 6.56 (1H, t), 6.60 (1H, dd), 7.20 (1H, t), 7.64 (1H, d), 8.25 (1H, d)	394
528	4–OMe	δ 1.68 – 1.73 (2H, m), 2.01 – 2.05 (2H, m), 3.50 – 3.54 (2H, m), 3.72 (3H, s), 3.92 – 3.96 (2H, m), 4.52 – 4.56 (1H, m), 6.86 – 6.88 (2H, m), 6.94 – 6.97 (2H, m), 7.64 (1H, d), 8.25 (1H, d)	394
529	2–F	δ 1.74 – 1.79 (2H, m), 2.07 – 2.10 (2H, m), 3.52 – 3.56 (2H, m), 3.94 – 3.98 (2H, m), 4.68 – 4.71 (1H, m), 6.98 – 7.01 (1H, m), 7.15 (1H, t), 7.22 – 7.25 (1H, m), 7.28 – 7.31 (1H, m), 7.64 (1H, d), 8.26 (1H, d)	382
530	2–Cl	δ 1.78 – 1.83 (2H, m), 2.05 – 2.09 (2H, m), 3.62 – 3.66 (2H, m), 3.87 – 3.91 (2H, m), 4.79 – 4.82 (1H,	398

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		m), 6.98 – 7.01 (1H, m), 7.29 – 7.30 (1H, m), 7.31 – 7.33 (1H, m), 7.44 – 7.46 (1H, m), 7.64 (1H d), 8.26 (1H, d)	
531	2–OMe	δ 1.71 – 1.76 (2H, m), 2.01 – 2.04 (2H, m), 3.51 – 3.55 (2H, m), 3.77 (3H, s), 3.94 – 3.98 (2H, m), 4.55 – 4.58 (1H, m), 6.88 – 6.91 (1H, m), 6.95 – 6.97 (1H, m), 7.01 (1H, m), 7.08 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	394
532	3–F	δ 1.71 – 1.75 (2H, m), 2.06 – 2.10 (2H, m), 3.51 – 3.54 (2H, m), 3.95 – 3.99 (2H, m), 4.71 – 4.74 (1H, m), 6.76 – 6.79 (1H, m), 6.86 (1H, dd), 6.90 – 6.93 (1H, m), 7.31 – 7.34 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	382

Ejemplos 533–534

Los siguientes compuestos fueron preparados en 43–62% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la piperidina 4–sustituida apropiada:



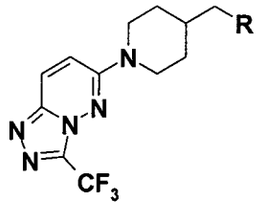
Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
533	fenil	δ 1.62 – 1.68 (2H, m), 1.93 – 1.96 (2H, m), 3.79 – 3.84 (1H, m), 4.30 – 4.31 (2H, m), 7.56 – 7.58 (2H, m), 7.63 (1H, d), 7.66 – 7.69 (1H, m), 8.03 – 8.04 (2H, m), 8.24 (1H, d). (2H oscurecida por agua)	376
534	4–fluorofenil	δ 1.61 – 1.67 (2H, m), 1.92 – 1.95 (2H, m), 3.78 – 3.82 (1H, m), 4.30 (2H, d), 7.37 – 7.40 (2H, m), 7.63 (1H, d), 8.11 – 8.14 (2H, m),	394

		8.24 (1H, d), (2H oscurecida por agua)	

762

Ejemplos 535–539

Los siguientes compuestos fueron preparados en 53–63% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la piperidina 4–sustituida apropiada:

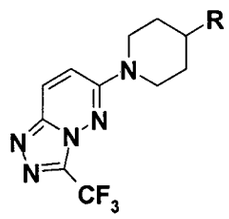


Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
535	fenil	δ 1.21 – 1.27 (2H, m), 1.68 – 1.71 (2H, m), 1.83 – 1.89 (1H, m), 2.55 (2H, d), 2.95 – 2.99 (2H, m), 4.25 (2H, d), 7.19 – 7.21 (3H, m), 7.29 – 7.31 (2H, m), 7.58 (1H, d), 8.21 (1H, d)	362
536	4–fluorofenil	δ 1.20 – 1.26 (2H, m), 1.67 – 1.69 (2H, m), 1.81 – 1.86 (1H, m), 2.55 (2H, d), 2.95 – 2.99 (2H, m), 4.25 (2H, d), 7.09 – 7.13 (2H, m), 7.21 – 7.24 (2H, m), 7.58 (1H, d), 8.21 (1H, d)	380
537	piridin–2–il	δ 1.26 – 1.32 (2H, m), 1.68 – 1.70 (2H, m), 2.08 – 2.13 (1H, m), 2.70 (2H, d), 2.98 – 3.02 (2H, m), 4.24 (2H, d), 7.20 – 7.22 (1H, m), 7.25 (1H, d), 7.59 (1H, d), 7.69 – 7.72 (1H, m), 8.21 (1H, d), 8.50 – 8.51 (1H, m)	363
538	piridin–4–il	δ 1.23 – 1.29 (2H, m), 1.67 – 1.69 (2H, m), 1.90 – 1.95 (1H, m), 2.58 (2H, d), 2.97 – 3.01 (2H, m), 4.25 (2H, d), 7.23 – 7.24 (2H, m), 7.59 (1H, d), 8.21 (1H, d), 8.47 – 8.48 (2H, m)	363
539	piridin–3–il	δ 1.23 – 1.29 (2H, m), 1.68 – 1.70 (2H, m), 1.86 – 1.91 (1H, m), 2.58 (2H, d), 2.96 – 3.00 (2H, m), 4.26 (2H, d), 7.33 (1H, dd), 7.59 (1H, d), 7.62 – 7.64 (1H, m), 8.21 (1H, d), 8.42 – 8.43 (2H, m)	363

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Ejemplos 540–543

Los siguientes compuestos fueron preparados en 40–63% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la piperidina 4–sustituida apropiada:



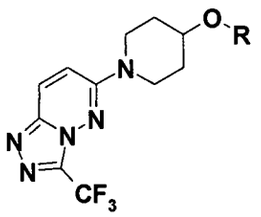
Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
540	piridin–4–il	δ 1.69 – 1.75 (2H, m), 1.94 (2H, d), 2.90 – 2.94 (1H, m), 3.11 – 3.15 (2H, m), 4.43 (2H, d), 7.31 – 7.32 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 8.48 – 8.49 (2H, m)	349
541	benzotriazol–1–il	δ 2.27 – 2.32 (4H, m), 4.48 (2H, s), 5.27 – 5.32 (1H, m), 7.42 – 7.44 (1H, m), 7.57 – 7.59 (1H, m), 7.72 (1H, d), 7.98 (1H, d), 8.06 (1H, d), 8.30 (1H, d), (2H oscurecida por agua)	389
542	indol–1–il	δ 2.03 – 2.10 (4H, m), 4.49 (2H, d), 4.75 – 4.80 (1H, m), 6.45 (1H, d), 7.02 – 7.05 (1H, m), 7.14 – 7.17 (1H, m), 7.49 (1H, d), 7.55 (1H, d), 7.61 (1H, d), 7.70 (1H, d), 8.28 (1H, d), (2H oscurecida por agua)	387
543	(3,5–dimetoxi)pirimidin–2–il	δ 1.81 – 1.87 (2H, m), 2.09 – 2.11 (2H, m), 3.00 – 3.04 (1H, m), 3.88 (6H, s), 4.31 – 4.33 (2H, m), 6.08 (1H, s), 7.65 (1H, d), 8.24	410

		(1H, d), (2H oscurecida por agua)	

764

Ejemplos 544–546

Los siguientes compuestos fueron preparados en 33–57% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la piperidina 4–sustituida apropiada:



Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
544	pirazinil	δ 1.79 – 1.84 (2H, m), 2.12 – 2.16 (2H, m), 3.54 – 3.57 (2H, m), 3.98 – 4.02 (2H, m), 5.30 – 5.34 (1H, m), 7.66 (1H, d), 8.22 – 8.23 (2H, m), 8.26 (1H, d), 8.31 (1H, d)	366
545	piridin–4–il	δ 1.73 – 1.78 (2H, m), 2.10 – 2.14 (2H, m), 3.51 – 3.55 (2H, m), 3.97 – 4.00 (2H, m), 4.84 - 4.87 (1H, m), 7.03 – 7.04 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.39 – 8.40 (2H, m)	365
546	piridin–2–il	δ 1.74 – 1.79 (2H, m), 2.10 – 2.14 (2H, m), 3.51 – 3.54 (2H, m), 3.99 – 4.02 (2H, m), 5.30 – 5.33 (1H, m), 6.81 (1H, d), 6.97 – 6.99 (1H, m), 7.65 (1H, d), 7.70 – 7.73 (1H, m), 8.17 – 8.19 (1H, m), 8.25 (1H, d)	365

Ejemplos 547–550

Los siguientes compuestos fueron preparados en 25–65% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el piperidin–4–ol 4–sustituido apropiado:

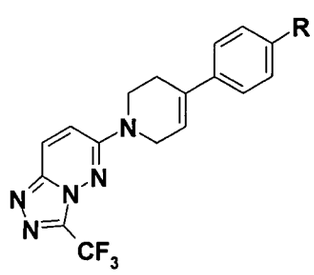


765

Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+
547	fenil	δ 1.74 (2H, d), 2.01 – 2.05 (2H, m), 3.43 – 3.47 (2H, m), 4.20 – 4.22 (2H, m), 5.20 (1H, s), 7.22 – 7.24 (1H, m), 7.32 – 7.34 (2H, m), 7.50 – 7.52 (2H, m), 7.66 (1H, d), 8.24 (1H, d)	364
548	bencil	δ 1.50 (2H, d), 1.56 – 1.60 (2H, m), 2.73 (2H, s), 4.01 (2H, d), 4.51 (1H, s), 7.19 – 7.21 (1H, m), 7.23 – 7.24 (2H, m), 7.27 (2H, t), 7.58 (1H, d), 8.19 (1H, d), (2H oscurecida por agua)	378
549	2–fluorofenil	δ 1.76 (2H, d), 2.23 – 2.27 (2H, m), 3.45 (2H, t), 4.19 – 4.21 (2H, m), 5.47 (1H, s), 7.09 – 7.12 (1H, m), 7.21 – 7.23 (1H, m), 7.30 – 7.33 (1H, m), 7.66 – 7.70 (2H, m), 8.25 (1H, d)	382
550	piridin–4–il	δ 1.71 (2H, d), 2.01 – 2.06 (2H, m), 3.42 – 3.46 (2H, m), 4.22 – 4.24 (2H, m), 7.49 – 7.50 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 8.51 – 8.52 (2H, m)	365

Ejemplos 551–552

Los siguientes compuestos fueron preparados en 50–56% de rendimiento mediante un método análogo al Ejemplo 515, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y la 4–aril tetrahidropiridina apropiada:



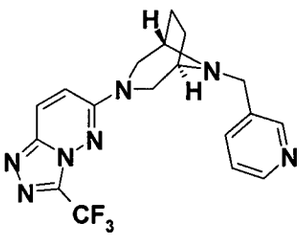
Ej.	R	1H NMR (700.03 MHz, DMSO–d_6)	m/z [M+H]+

551	H	δ 2.67 – 2.69 (2H, m), 3.90 (2H, t), 4.27 (2H, q), 6.31 – 6.32 (1H, m), 7.29 (1H, t), 7.37 – 7.39 (2H, m), 7 49 – 7.51 (2H, m), 7.68 (1H, d), 8.29 (1H, d)	346
552	F	δ 2.66 – 2.67 (2H, m), 3.89 (2H, t), 4.26 (2H, q), 6.29 – 6.30 (1H, m), 7.19 – 7.22 (2H, m), 7.52 – 7.55 (2H, m), 7.68 (1H, d), 8.29 (1H, d)	364

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Ejemplo 553

Preparación de 6–[(1R,5S)–8–(piridin–3–ilmetil)–3,8–diazabiciclo[3.2.1]oct–3–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de piridina–3–carboxaldehido y 6–[(1R,5S)–3,8–diazabiciclo[3.2.1]oct–3–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 6–[(1R,5S)–8–(piridin–3–ilmetil)–3,8–diazabiciclo[3.2.1]oct–3–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 68% de rendimiento.

1H NMR (399.9 MHz, DMSO–d6) δ 1.64 – 1.68 (2H, m), 2.03 – 2.06 (2H, m), 3.19 (2H, d), 3.31 – 3.34 (2H, m, parcialmente oscurecida por pico del solvente), 3.64 (2H, s), 3.82 – 3.85 (2H, m), 7.36 – 7.40 (1H, m), 7.51 (1H, d), 7.81 – 7.84 (1H, m), 8.24 (1H, d), 8.48 – 8.49 (1H, m), 8.59 (1H, d); m/z = 390 [M+H]+.

La 6–[(1R,5S)–3,8–diazabiciclo[3.2.1]oct–3–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de (1R,5S)–tert–butil 3–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–3,8–diazabiciclo[3.2.1]octano–8–carboxilato

Una solución agitada de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (312 mg, 1.40 mmol), (1R,5S)–tert–butil 3,8–diazabiciclo[3.2.1]octano–8–carboxilato (312 mg, 1.47 mmol) y DIPEA (0.36 ml, 2.10 mmol) en etanol (7.00 ml) fue calentada a 70°C durante 18 horas. Al enfriar se formó un precipitado blanco el cual fue recogido por filtración, lavado con etanol (10 mL) y secado al vacío para proporcionar (1R,5S)–tert–

767

butil 3–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)–3,8–diazabiciclo[3.2.1]octano–8–carboxilato (384 mg, 69%) como un sólido cristalino blanco. 1H NMR (399.9 MHz, DMSO–d6) δ 1.44 (9H, s), 1.71 – 1.72 (2H, m), 1.88 – 1.90 (2H, m), 3.13 (2H, d), 3.97 (2H, d), 4.29 (2H, s), 7.54 (1H, d), 8.28 (1H, d); m/z = 399 [M+H]+.

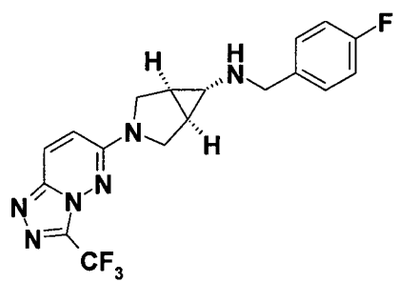
Preparación de 6–((1R,5S)–3,8–diazabiciclo[3.2.1]octan–3–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina

TFA (2.42 ml, 31.4 mmol) fue añadido a una solución agitada de (1R,5S)–tert–butil 3–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)–3,8–diazabiciclo[3.2.1]octano–8–carboxilato (443 mg, 1.11 mmol) en DCM (4.50 ml) a 25°C. La solución resultante fue agitada a temperatura ambiente durante 18 horas. La mezcla de reacción fue diluida con metanol y el producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido usando amoniaco 7M en metanol y evaporada hasta secarse para proporcionar 6–[(1R,5S)–3,8–diazabiciclo[3.2.1]oct–3–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (336 mg, 100%) como un sólido blanco.

1H NMR (399.9 MHz, DMSO–d6) δ 1.61 – 1.71 (4H, m), 3.05 – 3.08 (2H, m), 3.55 (2H, s), 3.81 – 3.84 (2H, m), 7.50 (1H, d), 8.22 (1H, d), NH no observado; m/z = 299 [M+H]+.

Ejemplo 554

Preparación de (1α,5α,6α) N–(4–fluorobencil)–3–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–3–azabiciclo[3.1.0]hexan–6–amina



(1α,5α,6α) 3–[3–(Trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–3–azabiciclo[3.1.0]hexan–6–amina (150 mg, 0.53 mmol), sulfato de magnesio monohidrato (361 mg, 2.64 mmol) y 4–fluorobenzaldehido (98 mg, 0.79 mmol) fueron añadidos a DCM (10 mL) y la mezcla fue agitada toda la noche a 25°C. La mezcla cruda fue purificada por cromatografía flash en sílice, gradiente en elusión 0 a 10% MeOH en DCM. Las fracciones

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apropiadas fueron evaporadas hasta secarse, y el producto intermedio imina y ácido acético (0.2 mL, 3.49 mmol) fueron añadidos a MeOH (15 mL). Cianoborohidruro sodio (0.040 mL, 0.70 mmol) fue añadido y la mezcla fue agitada durante 20 minutos. El producto crudo fue purificado por cromatografía de intercambio iónico usando una columna SCX, eluyendo con amoniaco 3.5M en metanol. Las fracciones apropiadas fueron evaporadas hasta secarse para proporcionar una goma clara, la cual fue purificada por cromatografía flash en sílice, gradiente en elusión 0 a 10% MeOH en DCM. Las fracciones que contienen el producto fueron evaporadas hasta secarse y el residuo fue cristalizado a partir de una mezcla de éter y isohexano para dar (1α,5α,6α) N–(4–fluorobencil)–3–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–3–azabiciclo[3.1.0]hexan–6–amina (125 mg, 60%).

1H NMR (400.1 MHz, CDCl3) δ 1.81 (2H, s), 1.84 (1H, s), 2.02 (1H, t), 3.59 (2H, d), 3.68 (2H, d), 3.81 (2H, s), 6.76 (1H, d), 7.01 (2H, t), 7.27 (2H, t), 7 87 (1H, d); m/z = 393 [M+H]+.

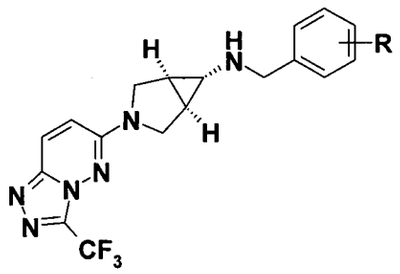
La (1α,5α,6α) 3–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–3–azabiciclo[3.1.0]hexan–6–amina usada como material de partida fue preparada en 2 pasos en 78% de rendimiento total mediante un método análogo al Ejemplo 223, preparación de los materiales de partida, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]–triazolo[4,3–b]piridazina y (1α,5α,6α) tert–butil 3–azabiciclo[3.1.0]hex–6–ilcarbamato (obtenida como se describió en Synlett. 1996, 1097).

1H NMR (400.1 MHz, CDCl3) δ 1.60 (2H, s), 1.77 (2H, s), 2.21 (1H, s), 3.61 (2H, d), 3.72 (2H, d), 6.78 (1H, d), 7.87 (1H, d); m/z = 285 [M+H]+.

Ejemplos 555–557

Los siguientes compuestos fueron preparados en 50–85% de rendimiento mediante un método análogo al Ejemplo 554, partiendo de (1α,5α,6α) 3–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–3–azabiciclo[3.1.0]hexan–6–amina y el aldehído apropiado:

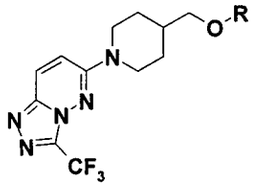
769



Ej.	R	1H NMR (400.1 MHz, CDCl3)	m/z [M+H]+
555	3–Cl	δ 1.82 (2H, s), 1.89 (1H, s), 2.02 (1H, t), 3.60 (2H, d), 3.68 (2H, d), 3.82 (2H, s), 6.76 (1H, d), 7.17 (1H, d), 7.28 – 7.24 (2H, m), 7.31 (1H, s), 7.87 (1H, d)	409
556	3–F	δ 1.83 (2H, s), 1.89 (1H, s), 2.04 (1H, t), 3.59 (2H, d), 3.68 (2H, d), 3.84 (2H, s), 6.76 (1H, d), 6.95 (1H, t), 7.02 (1H, d), 7.07 (1H, d), 7.31 – 7.26 (1H, m), 7.87 (1H, d)	393
557	4–CN	δ 1.82 (2H, s), 1.89 (1H, s), 2.05 (1H, t), 3.60 (2H, d), 3.68 (2H, d), 3.91 (2H, s), 6.76 (1H, d), 7.43 (2H, d), 7.62 (2H, d), 7.87 (1H, d)	399

Ejemplos 558–559

Los siguientes compuestos fueron preparados en 5–36% de rendimiento mediante un método análogo al Ejemplo 448, partiendo de [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metanol (obtenida como se describió en el Ejemplo 294, preparación de los materiales de partida) y el cloro heterociclo apropiado:



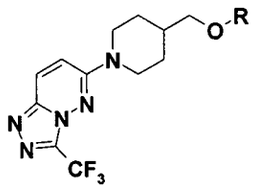
Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
558	pirimidin–2–il	δ 1.39 (2H, ddd), 1.91 – 1.87 (2H, m), 2.21 – 2.08 (1H, m), 3.07 (2H, t), 4.21 (2H, d), 4.34 – 4.31 (2H, m), 7.14 (1H, t), 7.63 (1H, d), 8.23 (1H, d), 8.60 (2H, d)	380
559	3–bromopiridin–2–il	δ 1.46 – 1.36 (2H, m), 1.91 – 1.87 (2H, m), 2.18 – 2.05 (1H, m), 3.11 – 3.04 (2H, m),	458

		4.24 (2H, d), 4.34 – 4.31 (2H, m), 6.95 (1H, dd), 7.63 (1H, d), 8.03 (1H, d), 8.15 (1H, d), 8.23 (1H, d)	

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Ejemplos 560–561

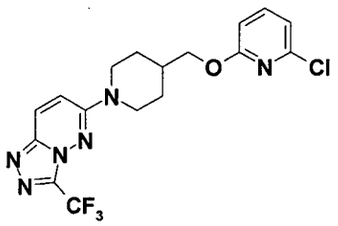
Los siguientes compuestos fueron preparados en 30–37% de rendimiento mediante un método análogo al Ejemplo 294, partiendo de 6–[4–(metanosulfoniloximetil)piperidin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el piridinol apropiado:



Ej.	R	1H NMR (400.1 MHz, DMSO–d6)	m/z [M+H]+
560	piridin–3–il	1.38 (2H, ddd), 1.93 – 1.90 (2H, m), 2.16 – 2.10 (1H, m), 3.11 – 3.04 (2H, m), 3.96 (2H, d), 4.33 – 4.30 (2H, m), 7.32 (1H, dd), 7.39 (1H, dd), 7.63 (1H, d), 8.16 (1H, dd), 8.23 (1H, d), 8.30 (1H, d)	379
561	piridin–4–il	δ 1.38 (2H, ddd), 1.91 – 1.88 (2H, m), 2.21 – 2.11 (1H, m), 3.11 – 3.04 (2H, m), 3.97 (2H, d), 4.33 – 4.30 (2H, m), 6.97 – 6.96 (2H, m), 7.62 (1H, d), 8.23 (1H, d), 8.38 – 8.37 (2H, m)	379

Ejemplo 562

Preparación de 6–[4–[[(6–cloropiridin–2–il)oxi]metil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

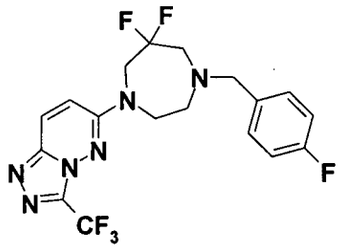


Obtenida en 75% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de [1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]metanol (obtenida como se describió en el Ejemplo 294, preparación de los materiales de partida) y 6–cloropiridin–2–ol.

1H NMR (400.1 MHz, DMSO–d6) δ 1.37 (2H, ddd), 1.89 – 1 87 (2H, m), 2.14 – 2.08 (1H, m), 3.06 (2H, t), 4.14 (2H, d), 4.33 – 4.30 (2H, m), 6.84 (1H, d), 7.08 (1H, d), 7.62 (1H, d), 7.76 (1H, t), 8.22 (1H, d); m/z = 413 [M+H]+.

Ejemplo 563

Preparación de 6–[6,6–difluoro–4–(4–fluorobencil)–1,4–diazepan–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Cianotrihidroborato de sodio (58.5 mg, 0.93 mmol) fue añadido a una mezcla agitada de 6–(6,6–difluoro–1,4–diazepan–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (200 mg, 0.62 mmol), 4–fluorobenzaldehido (93 mg, 0.75 mmol) y ácido acético(71.1 µl, 1.24 mmol) en metanol (10 mL) a temperatura ambiente. La mezcla resultante fue agitada a 21°C durante 20 horas. La mezcla de reacción fue concentrada hasta secarse, diluida con metanol y unas pocas gotas de amoniaco 7M en metanol fueron añadidas. La mezcla fue concentrada hasta secarse, el residuo fue diluido con DCM y las sales fueron filtradas. El filtrado fue concentrado y purificado por cromatografía flash en gel de sílice eluyendo con 0 a 20% acetonitrilo en DCM. Las fracciones que contienen el producto fueron concentradas para dar para dar 6–[6,6–difluoro–4–(4–fluorobencil)–1,4–diazepan–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (154 mg, 55%).

1H NMR (500 MHz, DMSO–d6) δ 2.82–2.88 (m, 2H), 3.02–3.11 (m, 2H), 3.73 (s, 2H), 3.79–3.84 (m, 2H), 4.28–4.36 (m, 2H), 6.95 (dd, 2H), 7.23 (dd, 2H), 7.61 (d, 1H), 8.32 (d, 1H); m/z = 431[M+H]+.

La 6–(6,6–difluoro–1,4–diazepan–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada como sigue:

Preparación de tert–butil 6,6–difluoro–1,4–diazepan–1–carboxilato

Di–tert–butil dicarbonato (5.29 ml, 23.0 mmol) en DCM (50 mL) fue añadido en forma de gotas a una mezcla enfriada con hielo de 6,6–difluoro–1,4–diazepan (3.6 g, 26.4 mmol, obtenida como se describió en Synthesis, 2003, 223) y DIPEA (2.30 mL, 13.2 mmol) en

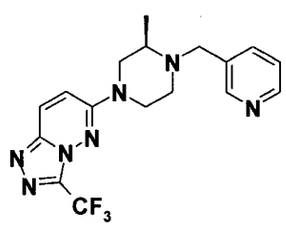
DCM (100 mL). La mezcla resultante fue agitada a temperatura ambiente durante 15 horas. La mezcla fue concentrada hasta secarse y diluida con agua y acetato de etilo. El material insoluble fue eliminado por filtración y la fase orgánica fue separada, lavada con salmuera, secada sobre sulfato de magnesio y concentrada. El residuo fue purificado por cromatografía flash en gel de sílice eluyendo con 0 a 4% metanol en DCM. Las fracciones que contienen el producto fueron concentradas para proporcionar tert–butil 6,6–difluoro–1,4–diazepan–1–carboxilato (3.45 g, 55.2%) como un sólido blanco. 1H NMR (500 MHz, CDCl3) δ 1.47 (s, 9H), 2.90–3.00 (m, 2H), 3.05–3.15 (m, 2H), 3.41–3.54 (m, 2H), 3.78–3.94 (m, 2H).

Preparación de 6–(6,6–difluoro–1,4–diazepan–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

Una mezcla de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (1 g, 4.49 mmol), tert–butil 6,6–difluoro–1,4–diazepan–1–carboxilato (1.06 g, 4.49 mmol) y DIPEA (1.56 ml, 8.99 mmol) en DMA (15 mL) fue agitada a 135°C durante 6 horas. La mezcla de reacción fue concentrada hasta secarse y DCM (30 mL) fue añadido. La solución fue enfriada en un baño de hielo y TFA (15 mL) fue añadido. La mezcla resultante fue agitada a temperatura ambiente durante 4 horas. La mezcla de reacción fue concentrada hasta secarse, diluida con agua, basificada con hidróxido de sodio 6M acuoso y extraída con DCM. La fase orgánica fue lavada con agua y salmuera, secada sobre sulfato de magnesio y concentrada. El residuo fue purificado por cromatografía flash en gel de sílice eluyendo con 0 a 4% metanol en DCM para dar 6–(6,6–difluoro–1,4–diazepan–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (0.820 g, 56.6%) como un sólido beige. 1H NMR (500 MHz, DMSO–d6) δ 2.80 (bs, 1H), 2.94–3.07 (m, 4H), 3.74–3.81 (m, 2H), 4.24–4.31 (m, 2H), 7.58 (d, 1H), 8.30 (d, 1H); m/z = 323 [M+H]+.

Ejemplo 564

Preparación de 6–[(3R)–3–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de piridina–3–carboxaldehido y 6–[(3R)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5, para dar 6–[(3R)–3–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 58% de rendimiento.

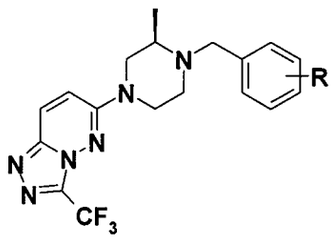
1H NMR (399.9 MHz, DMSO–d_6) δ 1.16 (3H, d), 2.24 – 2.30 (1H, m), 2.53 – 2.63 (1H, m), 2.72 – 2.76 (1H, m), 3.09 – 3.14 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.35 (1H, d), 3.84 – 3.89 (1H, m), 3.92 – 4.00 (2H, m), 7.36 – 7.39 (1H, m), 7.61 (1H, d), 7.74 – 7.77 (1H, m), 8.25 (1H, d), 8.47 – 8.49 (1H, m), 8.54 (1H, d); m/z = 378 $[M+H]^+$.

La 6–[(3R)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada en 2 pasos en 75% de rendimiento total mediante un método análogo al Ejemplo 223, preparación de los materiales de partida, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y (3R)–tert–butil 2–metilpiperazina–1–carboxilato.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.04 (3H, d), 2.37 (1H, s), 2.54 – 2.60 (1H, m), 2.68 – 2.75 (2H, m), 2.87 – 3.00 (2H, m), 4.07 – 4.11 (2H, m), 7.61 (1H, d), 8.23 (1H, d).

Ejemplos 565–569

Los siguientes compuestos fueron preparados en 29–45% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(3R)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 564, preparación de los materiales de partida) y el aldehído apropiado:



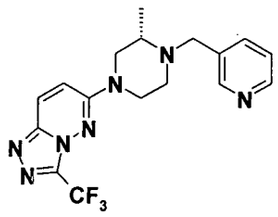
Ej.	R	1H NMR (399.9 MHz, DMSO–d_6)	m/z $[M+H]^+$
565	4–CN	δ 1.13 (3H, d), 2.26 – 2.32 (1H, m), 2.61 – 2.65 (1H, m), 2.70 – 2.75 (1H, m), 3.10 – 3.15 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.41 (1H, d), 3.85 – 3.89 (1H, m), 3.93 – 3.97 (1H, m), 4.03 (1H, d), 7.58 (2H, d), 7.60 – 7.63 (1H, m), 7.80 – 7.83 (2H, m), 8.26 (1H, d)	402

774

566	3,4–di–F	δ 1.13 (3H, d), 2.24 – 2.29 (1H, m), 2.59 – 2.63 (1H, m), 2.71 – 2.76 (1H, m), 3.10 – 3.15 (1H, m), 3.28 – 3.32 (2H + H_2O, m), 3.84 – 3.89 (2H, m), 3.93 (1H, d), 7.18 – 7.21 (1H, m), 7.36 – 7.42 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	413
567	3,5–di–F	δ 1.12 (3H, d), 2.27 – 2.32 (1H, m), 2.59 – 2.62 (1H, m), 2.74 – 2.78 (1H, m), 3.11 – 3.16 (1H, m), 3.33 – 3.38 (2H, m), 3.86 – 3.97 (3H, m), 7.08 – 7.13 (3H, m), 7.62 (1H, d), 8.26 (1H, d)	413
568	4–F	δ 1.14 (3H, d), 2.20 – 2.26 (1H, m), 2.56 – 2.61 (1H, m), 2.70 – 2.75 (1H, m), 3.08 – 3.14 (1H, m), 3.26 – 3.33 (2H, m), 3.84 – 3.96 (3H, m), 7.14 – 7.18 (2H, m), 7.36 – 7.40 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	395
569	3–CN, 4–F	δ 1.13 (3H, d), 2.24 – 2.30 (1H, m), 2.60 – 2.65 (1H, m), 2.71 – 2.76 (1H, m), 3.10 – 3.16 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.36 (1H, d), 3.85 – 3.98 (3H, m), 7.49 – 7.53 (1H, m), 7.61 (1H, d), 7.75 – 7.79 (1H, m), 7.86 – 7.88 (1H, m), 8.26 (1H, d)	420

Ejemplo 570

Preparación de 6–[(3S)–3–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de piridina–3–carboxaldehido y 6–[(3S)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 6–[(3S)–3–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 62% de rendimiento.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.16 (3H, d), 2.24 – 2.30 (1H, m), 2.53 – 2.63 (1H, m), 2.72 – 2.76 (1H, m), 3.09 – 3.14 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.35 (1H, d),

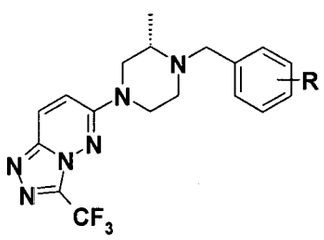
3.84 – 3.89 (1H, m), 3.92 – 4.00 (2H, m), 7.36 – 7.39 (1H, m), 7.61 (1H, d), 7.74 – 7.77 (1H, m), 8.25 (1H, d), 8.47 – 8.49 (1H, m), 8.54 (1H, d); m/z = 378 $[M+H]^+$.

La 6–[(3S)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada en 2 pasos en 71.5% de rendimiento total mediante un método análogo al Ejemplo 223, preparación de los materiales de partida, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y (3S)–tert–butil 2–metilpiperazina–1–carboxilato.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.04 (3H, d), 2.37 (1H, s), 2.54 – 2.60 (1H, m), 2.68 – 2.75 (2H, m), 2.87 – 3.00 (2H, m), 4.07 – 4.11 (2H, m), 7.61 (1H, d), 8.23 (1H, d).

Ejemplos 571–575

Los siguientes compuestos fueron preparados en 36–55% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(3S)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 570, preparación de los materiales de partida) y el aldehído apropiado:

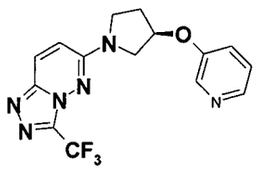


Ej.	R	1H NMR (399.9 MHz, DMSO–d_6)	m/z $[M+H]^+$
571	4–CN	δ 1.13 (3H, d), 2.26 – 2.32 (1H, m), 2.61 – 2.65 (1H, m), 2.70 – 2.75 (1H, m), 3.10 – 3.15 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.41 (1H, d), 3.85 – 3.89 (1H, m), 3.93 – 3.97 (1H, m), 4.03 (1H, d), 7.58 (2H, d), 7.60 – 7.63 (1H, m), 7.80 – 7.83 (2H, m), 8.26 (1H, d)	402
572	3,4–di–F	δ 1.13 (3H, d), 2.24 – 2.29 (1H, m), 2.59 – 2.63 (1H, m), 2.71 – 2.76 (1H, m), 3.10 – 3.15 (1H, m), 3.28 – 3.32 (2H + H_2O, m), 3.84 – 3.89 (2H, m), 3.93 (1H, d), 7.18 – 7.21 (1H, m), 7.36 – 7.42 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	413
573	3,5–di–F	δ 1.12 (3H, d), 2.27 – 2.32 (1H, m), 2.59 – 2.62 (1H,	413

		m), 2.74 – 2.78 (1H, m), 3.11 – 3.16 (1H, m), 3.33 – 3.38 (2H, m), 3.86 – 3.97 (3H, m), 7.08 – 7.13 (3H, m), 7.62 (1H, d), 8.26 (1H, d)	
574	4–F	δ 1.14 (3H, d), 2.20 – 2.26 (1H, m), 2.56 – 2.61 (1H, m), 2.70 – 2.75 (1H, m), 3.08 – 3.14 (1H, m), 3.26 – 3.33 (2H, m), 3.84 – 3.96 (3H, m), 7.14 – 7.18 (2H, m), 7.36 – 7.40 (2H, m), 7.61 (1H, d), 8.25 (1H, d)	395
575	3–CN, 4–F	δ 1.13 (3H, d), 2.24 – 2.30 (1H, m), 2.60 – 2.65 (1H, m), 2.71 – 2.76 (1H, m), 3.10 – 3.16 (1H, m), 3.28 – 3.32 (1H + H_2O, m), 3.36 (1H, d), 3.85 – 3.98 (3H, m), 7.49 – 7.53 (1H, m), 7.61 (1H, d), 7.75 – 7.79 (1H, m), 7.86 – 7.88 (1H, m), 8.26 (1H, d)	420

Ejemplo 576

Preparación de 6–[(3R)–3–(piridin–3–iloxi)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 68% de rendimiento mediante un procedimiento análogo al Ejemplo 216, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y (3R)–3–(piridin–3–iloxi)pirrolidina.

1H NMR (399.9 MHz, DMSO–d_6) δ 2.27 – 2.38 (2H, m), 3.63 – 3.88 (4H, m), 5.30 – 5.34 (1H, m), 7.32 (1H, d), 7.35 – 7.39 (1H, m), 7.47 – 7.50 (1H, m), 8.21 – 8.23 (1H, m), 8.25 (1H, d), 8.34 (1H, d); m/z = 351 [M+H]+.

La (3R)–3–(piridin–3–iloxi)pirrolidina usada como material de partida fue preparada como sigue:

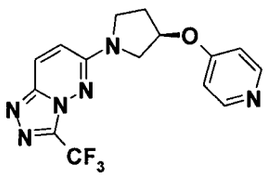
DIAD (0.631 mL, 3.20 mmol) en DCM (5 ml) fue añadido en forma de gotas a una mezcla de (S)–tert–butil 3–hidroxipirrolidina–1–carboxilato (500 mg, 2.67 mmol), piridin–3–ol (305 mg, 3.20 mmol) y trifenilfosfina (840 mg, 3.20 mmol) en DCM (20 ml), enfriada en un baño de hielo. La mezcla se dejó calentar hasta la temperatura ambiente, agitada durante 1 hora y luego concentrada. El residuo fue disuelto en dioxano (15 mL) y HCl 4M en

dioxano (15 mL) fue añadido. La mezcla fue agitada durante 1 hora y concentrada. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 7M en metanol y las fracciones puras fueron evaporadas hasta secarse para proporcionar (3R)–3–(piridin–3–iloxi)pirrolidina (405 mg, 92%) como un aceite incoloro.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.72 – 1.79 (1H, m), 1.99 – 2.08 (1H, m), 2.75 – 2.81 (1H, m), 2.84 – 2.95 (2H, m), 3.05 – 3.09 (1H, m), 4.90 – 4.95 (1H, m), 7.30 – 7.37 (2H, m), 8.15 – 8.16 (1H, m), 8.25 (1H, d); m/z = 165 [M+H]+.

Ejemplo 577

Preparación de 6–[(3R)–3–(piridin–4–iloxi)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 60% de rendimiento mediante un procedimiento análogo al Ejemplo 216, partiendo de 3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina y (3R)–3–(piridin–4–iloxi)pirrolidina.

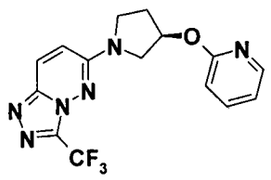
1H NMR (399.9 MHz, DMSO–d_6) δ 2.25 – 2.30 (1H, m), 2.34 – 2.41 (1H, m), 3.61 – 3.90 (4H, m), 5.34 – 5.38 (1H, t), 7.03 – 7.04 (2H, m), 7.32 (1H, d), 8.25 (1H, d), 8.41 – 8.43 (2H, m); m/z = 351 [M+H]+.

La (3R)–3–(piridin–4–iloxi)pirrolidina usada como material de partida fue preparada en 61% de rendimiento mediante un método análogo al Ejemplo 576, preparación de los materiales de partida, partiendo de (3S)–tert–butil 3–hidroxipirrolidina–1–carboxilato y piridin–4–ol.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.71 – 1.79 (1H, m), 2.01 – 2.10 (1H, m), 2.75 – 2.81 (1H, m), 2.86 – 2.93 (2H, m), 3.05 – 3.14 (1H, m), 4.93 – 4.97 (1H, m), 6.91 – 6.93 (2H, m), 8.36 – 8.38 (2H, m); m/z = 165 [M+H]+.

Ejemplo 578

Preparación de 6–[(3R)–3–(piridin–2–iloxi)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 63% de rendimiento mediante un procedimiento análogo al Ejemplo 216, partiendo de 3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina y (3R)–3–(piridin–2–iloxi)pirrolidina.

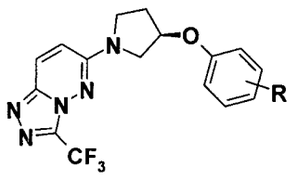
1H NMR (399.9 MHz, DMSO–d_6) δ 2.25 – 2.30 (1H, m), 2.33 – 2.42 (1H, m), 3.65 – 3.76 (3H, m), 3.89 (1H, d), 5.69 – 5.72 (1H, m), 6.82 – 6.84 (1H, m), 7.00 – 7.04 (1H, m), 7.29 – 7.32 (1H, m), 7.71 – 7.75 (1H, m), 8.21 – 8.24 (2H, m); m/z = 351 [M+H]+.

La (3R)–3–(piridin–2–iloxi)pirrolidina usada como material de partida fue preparada en 65% de rendimiento mediante un método análogo al Ejemplo 576, preparación de los materiales de partida, partiendo de tert–butil (3S)–3–hidroxipirrolidina–1–carboxilato y piridin–2–ol.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.72 – 1.80 (1H, m), 1.97 – 2.06 (1H, m), 2.75 – 2.84 (2H, m), 2.87 – 2.94 (1H, m), 3.05 – 3.10 (1H, m), 5.34 – 5.38 (1H, m), 6.75 – 6.77 (1H, m), 6.93 – 6.96 (1H, m), 7.66 – 7.70 (1H, m), 8.15 – 8.17 (1H, m); m/z = 165 [M+H]+.

Ejemplos 579–586

Los siguientes compuestos fueron preparados en 29–45% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de (3S)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]pirrolidin–3–ol y el fenol apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d_6)	m/z [M+H]+
579	4–CF3	δ 2.26 – 2.42 (2H, m), 3.63 – 3.90 (4H, m), 5.33 – 5.37 (1H, m), 7.20 (2H, d), 7.32 (1H, d), 7.69 (2H, d), 8.25 (1H, d)	418

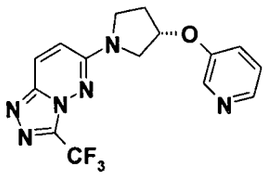
580	4–CN	δ 2.25 – 2.29 (1H, m), 2.33 – 2.41 (1H, m), 3.62 – 3.90 (4H, m), 5.35 – 5.38 (1H, s), 7.17 – 7.21 (2H, m), 7.31 (1H, d), 7.79 – 7.82 (2H, m), 8.25 (1H, d)	375
581	4–F	δ 2.22 – 2.34 (2H, m), 3.61 – 3.84 (4H, m), 5.17 – 5.20 (1H, m), 7.00 – 7.05 (2H, m), 7.12 – 7.18 (2H, m), 7.31 (1H, d), 8.24 (1H, d)	368
582	4–OMe	δ 2.20 – 2.34 (2H, m), 3.54 – 3.89 (7H, m), 5.10 – 5.13 (1H, m), 6.87 – 6.90 (2H, m), 6.93 – 6.95 (2H, m), 7.31 (1H, d), 8.24 (1H, d)	380
583	3–CF3	δ 2.28 – 2.37 (2H, m), 3.63 – 3.86 (4H, m), 5.35 – 5.39 (1H, m), 7.31 – 7.34 (4H, m), 7.55 – 7.59 (1H, m), 8.25 (1H, d)	418
584	3–CN	δ 2.23 – 2.29 (1H, m), 2.31 – 2.38 (1H, m), 3.62 – 3.89 (4H, m), 5.31 – 5.35 (1H, m), 7.32 (1H, d), 7.34 – 7.37 (1H, m), 7.45 (1H, d), 7.51 – 7.55 (2H, m), 8.25 (1H, d)	375
585	3–F	δ 2.23 – 2.36 (2H, m), 3.61 – 3.87 (4H, m), 5.24 – 5.28 (1H, m), 6.78 – 6.86 (2H, m), 6.89 – 6.93 (1H, m), 7.30 – 7.38 (2H, m), 8.25 (1H, d)	368
586	3–OMe	δ 2.23 – 2.37 (2H, m), 3.56 – 3.92 (7H, m), 5.20 – 5.24 (1H, m), 6.54 – 6.60 (3H, m), 7.22 (1H, t), 7.32 (1H, d), 8.24 (1H, d)	380

El (3S)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]pirrolidin–3–ol usado como material de partida fue preparado en 77% de rendimiento mediante un método análogo al Ejemplo 216, preparación de los materiales de partida, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]–triazolo[4,3–b]piridazina y (S)–pirrolidin–3–ol.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.93 – 1.98 (1H, m), 2.03 – 2.08 (1H, m), 3.42 (1H, d), 3.55 – 3.62 (3H, m), 4.43 – 4.45 (1H, m), 5.07 (1H, d), 7.26 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]+.

Ejemplo 587

Preparación de 6–[(3S)–3–(piridin–3–iloxi)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 74% de rendimiento mediante un procedimiento análogo al Ejemplo 447, partiendo de (3R)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]pirrolidin–3–ol y piridin–3–ol.

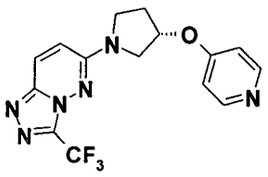
1H NMR (399.9 MHz, DMSO–d_6) δ 2.27 – 2.38 (2H, m), 3.63 – 3.88 (4H, m), 5.31 – 5.34 (1H, m), 7.32 (1H, d), 7.35 – 7.39 (1H, m), 7.47 – 7.50 (1H, m), 8.21 – 8.23 (1H, m), 8.25 (1H, d), 8.34 (1H, d); m/z = 351 [M+H]+.

El (3R)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]pirrolidin–3–ol usado como material de partida fue preparado en 81% de rendimiento mediante un método análogo al Ejemplo 216, preparación de los materiales de partida, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]–triazolo[4,3–b]piridazina y (R)–pirrolidin–3–ol.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.93 – 1.98 (1H, m), 2.03 – 2.08 (1H, m), 3.42 (1H, d), 3.55 – 3.62 (3H, m), 4.43 – 4.45 (1H, m), 5.07 (1H, d), 7.26 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]+.

Ejemplo 588

Preparación de 6–[(3S)–3–(piridin–4–iloxi)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 75% de rendimiento mediante un procedimiento análogo al Ejemplo 216, partiendo de 3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina y (3S)–3–(piridin–4–iloxi)pirrolidina.

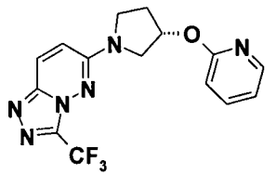
1H NMR (399.9 MHz, DMSO–d_6) δ 2.25 – 2.30 (1H, m), 2.34 - 2.43 (1H, m), 3.61 – 3.90 (4H, m), 5.34 – 5.37 (1H, m), 7.03 – 7.04 (2H, m), 7.32 (1H, d), 8.25 (1H, d), 8.41 – 8.43 (2H, m); m/z = 351 [M+H]+.

La (3S)–3–(piridin–4–iloxi)pirrolidina usada como material de partida fue preparada en 61% de rendimiento mediante un método análogo al Ejemplo 576, preparación de los materiales de partida, partiendo de tert–butil (3R)–3–hidroxipirrolidina–1–carboxilato y piridin–4–ol.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.71 – 1.79 (1H, m), 2.01 – 2.10 (1H, m), 2.75 – 2.81 (1H, m), 2.86 – 2.93 (2H, m), 3.05 – 3.14 (1H, m), 4.93 – 4.97 (1H, m), 6.91 – 6.93 (2H, m), 8.36 – 8.38 (2H, m); m/z = 165 [M+H]+.

Ejemplo 589

Preparación de 6–[(3S)–3–(piridin–2–iloxi)pirrolidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 62% de rendimiento mediante un procedimiento análogo al Ejemplo 216, partiendo de 3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina y (3S)–3–(piridin–2–iloxi)pirrolidina.

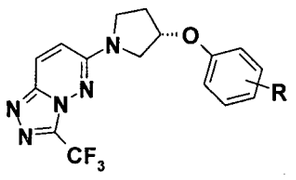
1H NMR (399.9 MHz, DMSO–d_6) δ 2.25 – 2.30 (1H, m), 2.33 – 2.42 (1H, m), 3.65 – 3.76 (3H, m), 3.89 (1H, d), 5.70 – 5.72 (1H, m), 6.82 – 6.84 (1H, m), 7.01 – 7.04 (1H, m), 7.31 (1H, d), 7.71 – 7.75 (1H, m), 8.21 – 8.25 (2H, m); m/z = 351 [M+H]+.

La (3S)–3–(piridin–2–iloxi)pirrolidina usado como material de partida fue preparado en 62% de rendimiento mediante un método análogo al Ejemplo 576, preparación de los materiales de partida, partiendo de tert–butil (3R)–3–hidroxipirrolidina–1–carboxilato y piridin–2–ol.

1H NMR (399.9 MHz, DMSO–d_6) δ 1.72 – 1.80 (1H, m), 1.97 – 2.06 (1H, m), 2.75 – 2.84 (2H, m), 2.87 – 2.94 (1H, m), 3.05 – 3.10 (1H, m), 5.34 – 5.38 (1H, m), 6.75 – 6.77 (1H, m), 6.93 – 6.96 (1H, m), 7.66 – 7.70 (1H, m), 8.15 – 8.17 (1H, m); m/z = 165 [M+H]+.

Ejemplos 590–592

Los siguientes compuestos fueron preparados en 22–51% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de (3R)–1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]pirrolidin–3–ol (obtenido como se describió en el Ejemplo 587, preparación de los materiales de partida) y el fenol apropiado:

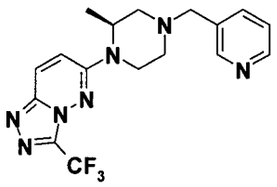


Ej.	R	1H NMR (399.9 MHz, DMSO–d_6)	m/z [M+H]+
590	3–CN	δ 2.24 – 2.29 (1H, m), 2.31 – 2.39 (1H, m), 3.62 – 3.89	375

		(4H, m), 5.33 (1H, s), 7.32 (1H, d), 7.34 – 7.37 (1H, m), 7.43 – 7.46 (1H, m), 7.51 – 7.55 (2H, m), 8.24 - 8.26 (1H, m)	
591	4–CN	δ 2.27 – 2.30 (1H, m), 2.33 – 2.39 (1H, m), 3.62 – 3.90 (4H, m), 5.37 (1H, s), 7.17 – 7.21 (2H, m), 7.31 (1H, d), 7.79 – 7.83 (2H, m), 8.25 (1H, d)	375
592	4–CF3	δ 2.26 – 2.31 (1H, m), 2.33 – 2.40 (1H, m), 3.63 – 3.90 (4H, m), 5.35 (1H, s), 7.20 (2H, d), 7.32 (1H, d), 7.69 (2H, d), 8.25 (1H, d)	418

Ejemplo 593

Preparación de 6–[(2S)–2–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

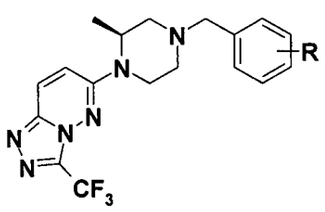


Una mezcla de piridina–3–carboxaldehido y 6–[(2S)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 358, preparación de los materiales de partida) se dejó reaccionar mediante el Método Sintético General 5, para dar 6–[(2S)–2–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en 76% de rendimiento.

1H NMR (500.1MHz, DMSO–d6, 373K) δ 1.31 (3H, d), 2.42 (1H, m), 2.56 (1H, m), 2.88 (1H, m), 3.04 (1H, m), 3.33 (1H, m), 3.77 (2H, m), 4.05 (1H, m), 4.51 (1H, m), 7.47 (2H, m), 7.91 (1H, m), 8.15 (1H, d), 8.56 (1H, m), 8.63 (1H, m); m/z = 378 [M+H]+.

Ejemplos 594–598

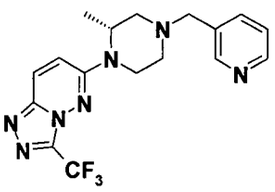
Los siguientes compuestos fueron preparados en 43–89% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(2S)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:



Ej.	R	1H NMR (400.1 MHz, CDCl3)	m/z [M+H]+
594	4–CN	δ 1.47 (3H, d), 2.70 (1H, m), 2.86 (1H, m), 3.20 (1H, m), 3.50 (1H, m), 3.63 (1H, m), 4.01 (1H, d), 4.15 (2H, m), 4.55 (1H, m), 7.05 (1H, d), 7.60 (2H, d), 7.73 (2H, d), 8.05 (1H, d)	402
595	3,4–di–F	δ 1.35 (3H, d), 2.22 (1H, m), 2.36 (1H, m), 2.76 (1H, m), 2.95 (1H, m), 3.33 (1H, m), 3.44 (1H, d), 3.55 (1H, d), 3.98 (1H, m), 4.33 (1H, m), 7.04 – 7.16 (3H, m), 7.23 (1H, m), 7.93 (1H, d)	413
596	3,5–di–F	δ 1.48 (3H, d), 2.73 (1H, m), 2.90 (1H, m), 3.28 (1H, m), 3.57 (1H, m), 3.67 (1H, m), 4.00 (1H, d), 4.15 (2H, m), 4.58 (1H, m), 6.89 (1H, m), 7.01 (2H, m), 7.05 (1H, d), 8.06 (1H, d)	413
597	4–F	δ 1.51 (3H, d), 2.83 (1H, m), 3.02 (1H, m), 3.41 (1H, m), 3.77 (2H, m), 4.18 (2H, m), 4.35 (1H, d), 4.64 (1H, m), 7.03 (1H, d), 7.15 (2H, m), 7.45 (2H, m), 8.05 (1H, d)	395
598	3–CN, 4–F	δ 1.36 (3H, d), 2.25 (1H, m), 2.41 (1H, m), 2.74 (1H, m), 2.92 (1H, m), 3.33 (1H, m), 3.49 (1H, d), 3.58 (1H, d), 3.99 (1H, m), 4.34 (1H, m), 7.06 (1H, d), 7.21 (1H, m), 7.63 (2H, m), 7.94 (1H, d)	420

Ejemplo 599

Preparación de 6–[(2R)–2–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Una mezcla de piridina–3–carboxaldehido y 6–[(2R)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina se dejó reaccionar mediante el Método Sintético General 5 para dar 6–[(2R)–2–metil–4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina en rendimiento cuantitativo.

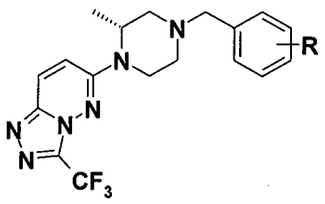
1H NMR (500.1MHz, DMSO–d6, 373K) δ 1.30 (3H, d), 2.37 (1H, m), 2.55 (1H, m), 2.85 (1H, m), 3.02 (1H, m), 3.32 (1H, m), 3.73 (2H, m), 4.04 (1H, m), 4.50 (1H, m), 7.45 (2H, m), 7.87 (1H, m), 8.15 (1H, d), 8.54 (1H, m), 8.61 (1H, m); m/z = 378 [M+H]+.

La 6–[(2R)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina usada como material de partida fue preparada en 2 pasos en 74% de rendimiento total mediante un método análogo al Ejemplo 223, preparación de los materiales de partida, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y (3R)–tert–butil 3–metilpiperazina–1–carboxilato.

1H NMR (399.1 MHz, DMSO–d6) δ 1.23 (3H, d), 2.43 (1H, m), 2.65 (1H, m), 2.85 (2H, m), 3.04 (2H, m), 3.91 (1H, m), 4.35 (1H, m), 7.56 (1H, d), 8.23 (1H, d); m/z = 287 [M+H]+.

Ejemplos 600–604

Los siguientes compuestos fueron preparados en 56–93% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(2R)–2–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:

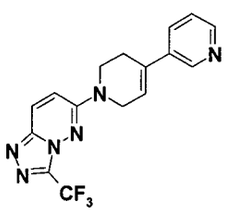


Ej.	R	1H NMR (400.1 MHz, CDCl3)	m/z [M+H]+
600	4–CN	δ 1.46 (3H, d), 2.68 (1H, m), 2.84 (1H, m), 3.18 (1H, m), 3.48 (1H, m), 3.62 (1H, m), 3.99 (1H, d), 4.14 (2H, m), 4.54 (1H, m), 7.05 (1H, d), 7.59 (2H, d), 7.72 (2H, d), 8.04 (1H, d)	402
601	3,4–di–F	δ 1.47 (3H, d), 2.70 (1H, m), 2.87 (1H, m) 3.25 (1H, m), 3.56 (1H, m), 3.66 (1H, m), 3.97 (1H, d), 4.14 (2H, m), 4.57 (1H, m), 7.02 – 7.33 (4H, m), 8.04 (1H,	413

		d)	
602	3,5–di–F	δ 1.47 (3H, d), 2.68 (1H, m), 2.85 (1H, m), 3.23 (1H, m), 3.52 (1H, m), 3.64 (1H, m), 3.95 (1H, d), 4.12 (2H, m), 4.56 (1H, m), 6.88 (1H, m), 7.00 (2H, m), 7.05 (1H, d), 8.05 (1H, d)	413
603	4–F	δ 1.50 (3H, d), 2.82 (1H, m), 3.00 (1H, m), 3.39 (1H, m), 3.75 (2H, m), 4.17 (2H, m), 4.33 (1H, c), 4.63 (1H, m), 7.02 (1H, d), 7.15 (2H, m), 7.45 (2H, m), 8.05 (1H, d)	395
604	3–CN, 4–F	δ 1.35 (3H, d), 2.25 (1H, m), 2.41 (1H, m), 2.74 (1H, m), 2.93 (1H, m), 3.33 (1H, m), 3.49 (1H, c), 3.58 (1H, d), 3.99 (1H, m), 4.35 (1H, m), 7.06 (1H, d), 7.21 (1H, m), 7.63 (2H, m), 7.94 (1H, d)	420

Ejemplo 605

Preparación de 1'–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–1',2',3',6'–tetrahidro–3,4'–bipiridina



Carbonato de sodio (114 mg, 1.08 mmol) fue añadido a 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,2,3,6–tetrahidropiridin–4–il trifluorometanosulfonato (150 mg, 0.36 mmol) y 3–(4,4,5,5–tetrametil–1,3,2–dioxaborolan–2–il)piridina (81 mg, 0.40 mmol) en una mezcla de DME (2 mL) y agua (0.5 mL). La mezcla fue burbujeada con nitrógeno durante 10 minutos luego tetrakis(trifenilfosfina)paladio(0) (20.77 mg, 0.02 mmol) fue añadido y la mezcla fue agitada a 80°C durante 3 horas. La mezcla de reacción fue enfriada hasta la temperatura ambiente y diluida con EtOAc (3 mL) y agua (2 mL). La capa orgánica fue separada y secada, y el solvente fue evaporado para dar el producto crudo. La purificación por cromatografía flash en sílice, gradiente en elusión 0 a 3% MeOH en DCM, dio 1'–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–1',2',3',6'–tetrahidro–3,4'–bipiridina (100 mg, 80%).

1H NMR (399.1 MHz, DMSO–d6) δ 2.70 (2H, m), 3.91 (2H, m), 4.29 (2H, m), 6.44 (1H, m), 7.41 (1H, m), 7.69 (1H, d), 7.89 (1H, m), 8.30 (1H, d), 8.5((1H, m), 8.74 (1H, m); m/z = 347 [M+H]+.

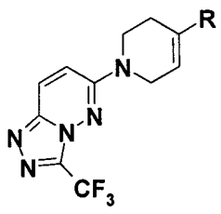
El 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,2,3,6–tetrahidropiridin–4–il trifluorometanosulfonato usado como material de partida fue preparado como sigue:

Una solución de 1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–ona (obtenida como se describió en el Ejemplo 310, preparación de los materiales de partida) (11.08 g, 38.85 mmol) en THF (200 mL) fue añadida en forma de gotas a litio bis(trimetilsilil)amida 1M en THF (42.7 mL, 42.73 mmol) a –78 °C, durante un período de 30 minutos bajo nitrógeno. La suspensión resultante fue agitada a –78°C durante 20 minutos, luego una solución de N–feniltrifluorometanosulfonimida (15.27 g, 42.73 mmol) en THF (150 ml) fue añadida en forma de gotas durante un período de 10 minutos. La mezcla fue agitada a –78°C durante 30 minutos luego se dejó calentar hasta la temperatura ambiente toda la noche. La mezcla de reacción fue apagada con cloruro de amonio acuoso saturado (5 mL), luego concentrada y diluida con DCM (500 mL), lavada con agua (300 mL) luego salmuera (300 mL) y evaporada para proporcionar el producto crudo. DCM (100 mL) fue añadido al producto crudo, el precipitado fue recogido por filtración y el filtrado fue purificado por cromatografía flash en sílice, gradiente en elusión 50 a 80% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse y combinadas con el precipitado previamente recogido para proporcionar 1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)–1,2,3,6–tetrahidropiridin–4–il trifluorometanosulfonato (12.91 g, 80%).

1H NMR (399.9 MHz, DMSO–d6) δ 2.63 (2H, m), 3.90 (2H, m), 4.25 (2H, m), 6.19 (1H, m), 7.67 (1H, d), 8.33 (1H, d); m/z = 418 [M+H]+.

Ejemplos 606–609

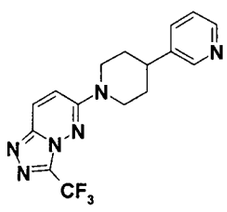
Los siguientes compuestos fueron preparados en 54–77% de rendimiento mediante un método análogo al Ejemplo 605, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,2,3,6–tetrahidropiridin–4–il trifluorometanosulfonato y el ácido heteroaril borónico o el ácido borónico pinacol éster apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
606	3–fluoropiridin–4–il	δ 2.68 (2H, m), 3.90 (2H, m), 4.31 (2H, m), 6.47 (1H, m), 7.49 (1H, m), 7.68 (1H, d), 8.31 (1H, d), 8.44 (1H, m), 8.57 (1H, d)	365
607	5–fluoropiridin–3–il	δ 2.71 (2H, m), 3.91 (2H, m), 4.30 (2H, m), 6.55 – 6.57 (1H, m), 7.70 (1H, d), 7.84 – 7.88 (1H, m), 8.30 (1H, d), 8.50 (1H, m), 8.63 (1H, m)	365
608	5–(etoxicarbonil)piridin–3–il	δ 1.36 (3H, t), 2.75 (2H, m), 3.92 (2H, m), 4.31 (2H, m), 4.38 (2H, q), 6.56 (1H, m), 7.69 (1H, d), 8.29 – 8.32 (2H, m), 8.98 – 9.00 (2H, m)	419
609	5–fluoro–6–metoxipiridin–3–il	δ 2.66 (2H, m), 3.89 (2H, m), 3.97 (3H, s), 4.26 – 4.27 (2H, m), 6.38 (1H, m), 7.69 (1H, d), 7.87 – 7.91 (1H, m), 8.11 (1H, d), 8.29 (1H, d)	395

Ejemplo 610

Preparación de 6–(4–piridin–3–ilpiperidin–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



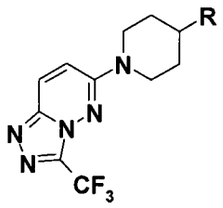
789

Una mezcla de 1'–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]–1',2',3',6'–tetrahidro–3,4'–bipiridina (obtenida como se describió en el Ejemplo 605) (82 mg, 0.24 mmol) y 10% paladio sobre carbono (25.2 mg, 0.02 mmol) en MeOH (10 mL) fue agitada bajo una atmósfera de hidrógeno a presión atmosférica durante 3 días. El catalizador fue eliminado por filtración y el solvente evaporado para dar el producto crudo, el cual fue purificado por cromatografía flash en sílice, gradiente en elusión 0 a 3% MeOH en DCM. La fracciones que contienen el producto deseado fueron evaporadas hasta secarse para dar 6–(4–piridin–3–ilpiperidin–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (24 mg, 29%).

1H NMR (399.1 MHz, DMSO–d6) δ 1.75 (2H, m), 1.93 (2H, m), 2.94 (1H, m), 3.14 (2H, m), 4.44 (2H, m), 7.33 (1H, m), 7.69 (2H, m), 8.26 (1H, d), 8.43 (1H, m), 8.53 (1H, d); m/z = 349 [M+H]+.

Ejemplos 611–614

Los siguientes compuestos fueron preparados en 13–57% de rendimiento mediante un método análogo al Ejemplo 610, partiendo de la tetrahidro bipiridina apropiada (obtenida como se describió en los Ejemplos 606–609):



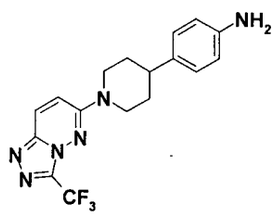
Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
611	3–fluoropiridin–4–il	δ 1.79 (2H, m), 1.91 (2H, m), 3.21 (3H, m), 4.44 (2H, m), 7.44 (1H, m), 7.67 (1H, d), 8.26 (1H, d), 8.38 (1H, d), 8.51 (1H, d)	367
612	5–fluoropiridin–3–il	δ 1.75 – 1.79 (2H, m), 1.94 (2H, m), 2.98 – 3.17 (3H, m), 4.43 – 4.46 (2H, m), 7.66 – 7.72 (2H, m), 8.26 (1H, d), 8.43 (2H, m)	367
613	5–(etoxicarbonil)piridin–3–il	δ 1.34 (3H, t), 1.78 - 1.82 (2H, m), 1.96 (2H, m), 3.08 – 3.17	462 [1]

		(3H, m), 4.36 (2H, q), 4.46 (2H, m), 7.67 (1H, d), 8.16 (1H, m), 8.26 (1H, d), 8.79 (1H, m), 8.96 (1H, m)	
614	5–fluoro–6–metoxipiridin–3–il	δ 1.70 – 1.74 (2H, m), 1.90 (2H, m), 2.92 (1H, m), 3.08 – 3.14 (2H, m), 3.92 (3H, s), 4.43 (2H, m), 7.65 – 7.69 (2H, m), 7.91 (1H, m), 8.25 (1H, d)	397

[1] Detectado como un aducto con acetonitrilo usado como solvente en la determinación de la masa espectral

Ejemplo 615

Preparación de 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina



DIPEA (1.631 mL, 9.36 mmol) fue añadido a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (1.389 g, 6.24 mmol) y 4–(piperidin–4–il)anilina (1.21 g, 6.86 mmol) en DMF (30 mL). La solución resultante fue agitada a 80°C durante 2 horas. La mezcla de reacción fue evaporada hasta secarse, redisuelta en DCM y purificada por cromatografía flash en gel de sílice, gradiente en elusión 0 a 3% MeOH en DCM. Las fracciones puras fueron evaporadas hasta secarse para dar 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina (1.910 g, 84%) como un sólido.

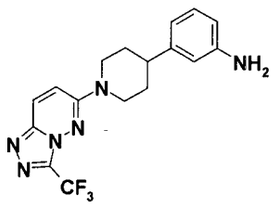
1H NMR (399.9 MHz, CDCl3) δ 1.72 – 1.79 (2H, m), 1.96 – 2.00 (2H, m), 2.70 – 2.73 (1H, m), 3.06 – 3.14 (2H, m), 3.60 (2H, s), 4.33 – 4.38 (2H, m), 6.65 (2H, d), 7.01 (2H, d), 7.12 (1H, d), 7.91 (1H, d); m/z = 363 [M+H]+.

La 4–(piperidin–4–il)anilina usada como material de partida fue preparada como sigue:

TFA (5 mL) fue añadido a tert–butil 4–(4–aminofenil)piperidina–1–carboxilato (1.9 g, 6.87 mmol, CAS 170011–57–1) en DCM (5 mL). La solución resultante fue agitada a temperatura ambiente durante 2 horas luego añadida a una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 2M en metanol y el solvente evaporado hasta secarse para dar 4–(piperidin–4–il)anilina (1.210 g, 100%) como un sólido.
m/z = 177 [M+H]+.

Ejemplo 616

Preparación de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina

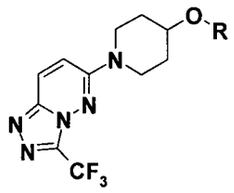


Obtenida en 78% de rendimiento mediante un procedimiento análogo al Ejemplo 615, partiendo de 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 3–(piperidin–4–il)anilina.
1H NMR (399.9 MHz, CDCl3) δ 1.76 – 1.80 (2H, m), 2.00 (2H, m), 2.74 (1H, m), 3.07 – 3.14 (2H, m), 3.64 (2H, s), 4.34 – 4.39 (2H, m), 6.54 – 6.63 (3H, m), 7.11 (2H, m), 7.92 (1H, d); m/z = 363 [M+H]+.

La 3–(piperidin–4–il)anilina usada como material de partida fue preparada en 97% de rendimiento mediante un procedimiento análogo al Ejemplo 615, preparación de los materiales de partida, partiendo de tert–butil 4–(3–aminofenil)piperidina–1–carboxilato (CAS 387827–19–2).
m/z = 177 [M+H]+.

Ejemplos 617–622

Los siguientes compuestos fueron preparados en 9–67% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (obtenido como se describió en el Ejemplo 412, preparación de los materiales de partida) y el hidroxi heterociclo apropiado:

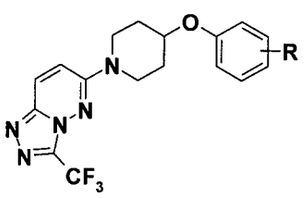


Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
617	5–cloropiridin–3–il	δ 1.75 (2H, m), 2.10 (2H, m), 3.52 (2H, m), 3.99 (2H, m), 4.85 (1H, m), 7.65 (1H, d), 7.74 (1H, m), 8.25 (2H, m), 8.33 (1H, d)	399
618	5–cloropiridin–2–il	δ 1.73 – 1.81 (2H, m), 2.08 – 2.14 (2H, m), 3.49 – 3.56 (2H, m), 3.96 – 4.02 (2H, m), 5.25 – 5.28 (1H, m), 6.88 (1H, d), 7.65 (1H, d), 7.80 – 7.83 (1H, m), 8.22 – 8.27 (2H, m)	399
619	pirimidin–4–il	δ 1.78 – 1.83 (2H, m), 2.12 – 2.17 (2H, m), 3.51 – 3.58 (2H, m), 3.97 – 4.03 (2H, m), 5.41 (1H, m), 6.95 – 6.97 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.53 – 8.55 (1H, m), 8.80 (1H, m)	366
620	5–bromopirimidin–2–il	δ 1.80 – 1.86 (2H, m), 2.12 – 2.16 (2H, m), 3.51 – 3.58 (2H, m), 3.96 – 4.02 (2H, m), 5.22 – 5.25 (1H, m), 7.66 (1H, d), 8.26 (1H, d), 8.78 (2H, s)	444
621	4–trifluorometilpiridin–2–il	δ 1.76 – 1.85 (2H, m), 2.11 – 2.16 (2H, m), 3.53 – 3.60 (2H, m), 3.97 – 4.03 (2H, m), 5.37 – 5.41 (1H, m), 7.20 (1H, d), 7.33 – 7.34 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.46 (1H, d)	433
622	4–metilpirimidin–2–il	δ 1.78 – 1.82 (2H, m), 2.10 – 2.15 (2H, m), 2.41 (3H, s), 3.53 – 3.59	380

		(2H, m), 3.95 – 4.01 (2H, m), 5.26 (1H, m), 7.02 (1H, d), 7.66 (1H, d), 8.26 (1H, d), 8.45 (1H, d)	

Ejemplos 623–627

Los siguientes compuestos fueron preparados en 12–29% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (obtenido como se describió en el Ejemplo 412, preparación de los materiales de partida) y el fenol apropiado:

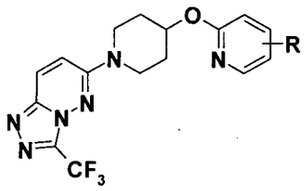


Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
623	3–CN	δ 1.72 – 1.75 (2H, m), 2.08 – 2.13 (2H, m), 3.48 – 3.55 (2H, m), 3.96 – 4.01 (2H, m), 4.80 (1H, m), 7.35 – 7.38 (1H, m), 7.40 – 7.43 (1H, m), 7.49 – 7.56 (2H, m), 7.65 (1H, d), 8.26 (1H, d)	389
624	4–CF3	δ 1.75 – 1.78 (2H, m), 2.09 – 2.11 (2H, m), 3.52 – 3.58 (2H, m), 3.96 – 4.00 (2H, m), 4.84 (1H, m), 7.21 (2H, d), 7.64 – 7.68 (3H, m), 8.27 (1H, d)	432
625	4–F	δ 1.69 – 1.76 (2H, m), 2.03 – 2.09 (2H, m), 3.49 – 3.55 (2H, m), 3.93 – 3.99 (2H, m), 4.62 – 4.65 (1H, m), 7.02 – 7.06 (2H, m), 7.11 – 7.15 (2H, m), 7.64 (1H, d), 8.25 (1H, d)	382
626	3–CF3	δ 1.73 – 1.78 (2H, m), 2.07 – 2.12 (2H, m), 3.52 – 3.59 (2H, m), 3.95 – 4.00 (2H, m), 4.84 (1H, m), 7.30 – 7.35 (3H, m), 7.53 – 7.57 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	432
627	4–CN	δ 1.74 – 1.77 (2H, m), 2.09 (2H, m), 3.51 – 3.56 (2H, m), 3.96 – 4.00 (2H, m), 4.86 (1H, m), 7.20 (2H, d), 7.65 (1H, d), 7.79 (2H, d), 8.26 (1H, d)	389

794

Ejemplos 628–629

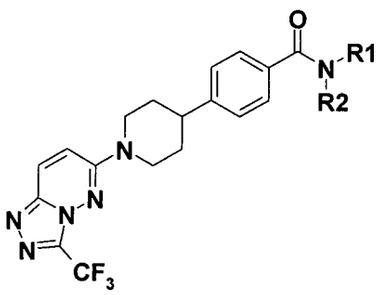
Los siguientes compuestos fueron preparados en 23–48% de rendimiento mediante un método análogo al Ejemplo 448, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (obtenido como se describió en el Ejemplo 412, preparación de los materiales de partida) y la cloropiridina apropiada:



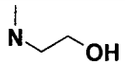
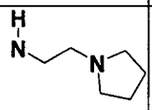
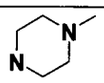
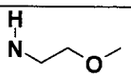
Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
628	5–CN	δ 1.78 – 1.84 (2H, m), 2.13 – 2.16 (2H, m), 3.51 – 3.57 (2H, m), 3.97 – 4.03 (2H, m), 5.39 – 5.42 (1H, m), 7.01 (1H, d), 7.66 (1H, d), 8.16 – 8.18 (1H, m), 8.27 (1H, d), 8.71 (1H, d)	390
629	4–CN	δ 1.78 – 1.81 (2H, m), 2.11 (2H, m), 3.51 – 3.57 (2H, m), 3.98 – 4.02 (2H, m), 5.35 (1H, m), 7.38 (1H, m), 7.41 – 7.43 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.42 – 8.43 (1H, m)	390

Ejemplos 630–635

Los siguientes compuestos fueron preparados en 10–90% de rendimiento mediante un método análogo al Ejemplo 512, partiendo de ácido 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico y la amina apropiada:

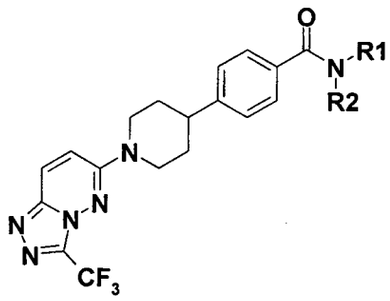


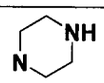
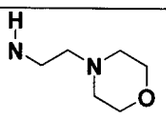
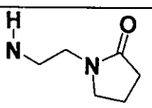
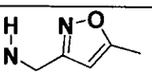
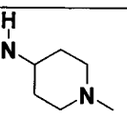
Ej.	NR1R2	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+

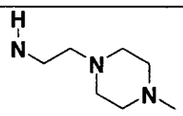
630		δ 1.76 – 1.86 (2H, m), 2.03 (2H, m), 2.84 – 2.90 (1H, m), 3.08 – 3.17 (5H, m), 3.72 – 3.90 (4H, m), 4.37 – 4.41 (2H, m), 7.13 (1H, d), 7.26 (2H, d), 7.42 (2H, d), 7.94 (1H, d)	449
631		δ 1.77 – 1.84 (6H, m), 2.02 – 2.05 (2H, m), 2.54 – 2.57 (4H, m), 2.70 (2H, m), 2.89 (1H, m), 3.10 – 3.18 (2H, m), 3.52 – 3.57 (2H, m), 4.38 – 4.41 (2H, m), 6.79 (1H, t), 7.13 (1H, d), 7.29 (2H, d), 7.75 (2H, d), 7.94 (1H, d)	488
632		δ 1.81 (2H, m), 2.02 (2H, m), 2.33 (3H, s), 2.43 (4H, m), 2.87 (1H, m), 3.13 (2H, m), 3.48 – 3.78 (4H, m), 4.39 (2H, m), 7.13 (1H, d), 7.26 (2H, d), 7.37 (2H, d), 7.94 (1H, d)	474
633		δ 1.76 – 1.87 (2H, m), 2.01 – 2.05 (2H, m), 2.87 – 2.93 (1H, m), 3.10 – 3.18 (2H, m), 3.38 (3H, s), 3.56 (2H, m), 3.63 – 3.67 (2H, m), 4.38 – 4.41 (2H, m), 6.48 (1H, t), 7.14 (1H, d), 7.29 (2H, d), 7.75 (2H, d), 7.95 (1H, d)	449
634	NMe2	δ 1.79 – 1.86 (2H, m), 2.00 – 2.04 (2H, m), 2.85 (1H, s), 2.98 – 3.17 (8H, m), 4.37 – 4.41 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.38 (2H, d), 7.94 (1H, d)	419
635		δ 1.79 – 1.83 (2H, m), 2.00 – 2.04 (2H, m), 2.87 (1H, m), 3.10 – 3.17 (2H, m), 3.69 (8H, m), 4.37 – 4.41 (2H, m), 7.13 (1H, d), 7.27 (2H, d), 7.38 (2H, d), 7.95 (1H, d)	461

Ejemplos 636–642

Los siguientes compuestos fueron preparados en 5–85% de rendimiento mediante un método análogo al Ejemplo 512, partiendo de ácido 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico y la amina apropiada:

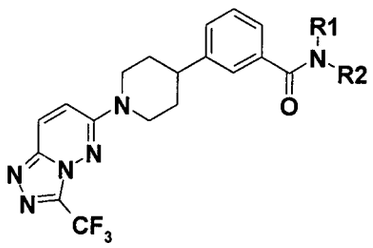


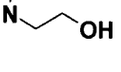
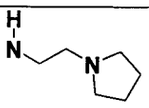
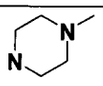
Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
636		δ 1.68 – 1.78 (2H, m), 1.92 – 1.97 (2H, m), 2.65 (4H, m), 2.89 – 2.97 (1H, m), 3.09 – 3.16 (2H, m), 3.44 – 3.52 (4H, m), 4.47 (2H, m), 7.38 (2H, d), 7.67 (1H, d), 7.81 (2H, d), 8.26 (1H, d)	460
637	NHEt	δ 1.14 (3H, t), 1.68 – 1.79 (2H, m), 1.92 (2H, m), 2.91 – 2.97 (1H, m), 3.10 – 3.16 (2H, m), 4.44 (2H, d), 7.36 (2H, d), 7.67 (1H, d), 7.78 (2H, d), 8.25 (1H, d), 8.36 (1H, t), (2H oscurecida por agua)	419
638		δ 1.74 (2H, m), 1.92 (2H, m), 2.94 (1H, m), 3.14 (2H, m), 3.40 (2H, m), 3.60 (4H, m), 4.44 (2H, m), 7.37 (2H, d), 7.67 (1H, d), 7.78 (2H, d), 8.26 (1H, d), 8.33 (1H, t), (2H oscurecida por agua, 4H oscurecida por DMSO)	504
639		δ 1.72 – 1.79 (2H, m), 1.87 – 1.94 (4H, m), 2.16 – 2.20 (2H, m), 2.91 – 2.97 (1H, m), 3.10 – 3.16 (2H, m), 3.33 – 3.43 (6H, m), 4.44 (2H, d), 7.37 (2H, d), 7.67 (1H, d), 7.75 (2H, d), 8.25 (1H, d), 8.43 (1H, t)	502
640		δ 1.72 – 1.78 (2H, m), 1.92 (2H, m), 2.37 (3H, s), 2.96 (1H, m), 3.11 – 3.17 (2H, m), 4.42 – 4.46 (4H, m), 6.14 (1H, s), 7.39 (2H, d), 7.67 (1H, d), 7.83 (2H, d), 8.26 (1H, d), 8.97 (1H, t)	486
641		δ 1.54 – 1.78 (6H, m), 1.92 (2H, m), 2.00 – 2.10 (2H, m), 2.21 (3H, s), 2.81 (2H, m), 2.91 – 2.98	488

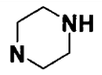
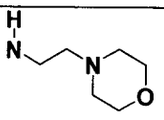
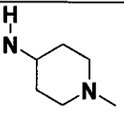
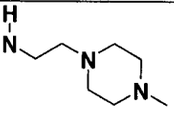
		(1H, m), 3.10 – 3.16 (2H, m), 3.72 – 3.76 (1H, m), 4.44 (2H, m), 7.36 (2H, d), 7.67 (1H, d), 7.79 (2H, d), 8.14 (1H, d), 8.25 (1H, d)	
642		δ 1.74 (2H, m), 1.92 (2H, m), 2.17 (3H, s), 2.32 – 2.48 (10H, m), 2.94 (1H, m), 3.13 (2H, m), 3.36 (2H, m), 4.44 (2H, m), 7.36 (2H, d), 7.67 (1H, d), 7.77 (2H, d), 8.27 (2H, m)	517

Ejemplos 643–652

Los siguientes compuestos fueron preparados en 16–73% de rendimiento mediante un método análogo al Ejemplo 512, partiendo de ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico y la amina apropiada:



Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
643		δ 1.69 – 1.77 (2H, m), 1.93 (2H, m), 2.89 – 2.97 (4H, m), 3.10 – 3.16 (2H, m), 3.49 – 3.61 (4H, m), 4.43 (2H, m), 4.75 (1H, t), 7.23 – 7.24 (1H, m), 7.30 – 7.35 (3H, m), 7.67 (1H, d), 8.25 (1H, d)	449
644		δ 1.64 – 1.71 (4H, m), 1.73 – 1.80 (2H, m), 1.94 (2H, m), 2.46 – 2.49 (4H, m), 2.56 (2H, m), 2.91 – 2.97 (1H, m), 3.11 – 3.17 (2H, m), 3.35 – 3.39 (2H, m), 4.45 (2H, m), 7.37 – 7.44 (2H, m), 7.67 – 7.69 (2H, m), 7.74 (1H, s), 8.26 (1H, d), 8.38 (1H, t)	488
645		δ 1.73 (2H, m), 1.93 (2H, m), 2.19 (3H, s), 2.30 (4H, m), 2.94 (1H, m), 3.13 (2H, m), 3.33 – 3.66 (4H, m), 4.43 (2H, m), 7.21 (1H, m), 7.27 (1H, s),	474

		7.38 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	
646		δ 1.68 – 1.78 (2H, m), 1.92 – 1.97 (2H, m), 2.69 (4H, m), 2.89 – 2.97 (1H, m), 3.09 – 3.16 (2H, m), 3.44 – 3.52 (4H, m), 4.43 (2H, m), 7.19 – 7.22 (1H, m), 7.26 (1H, s), 7.31 – 7.40 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	460
647	NMe2	δ 1.68 – 1.79 (2H, m), 1.93 (2H, m), 2.88 – 2.97 (7H, m), 3.09 – 3.16 (2H, m), 4.42 – 4.45 (2H, m), 7.22 – 7.25 (1H, m), 7.29 (1H, s), 7.34 – 7.39 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	419
648		δ 1.69 – 1.78 (2H, m), 1.93 (2H, m), 2.90 – 2.96 (1H, m), 3.10 – 3.16 (2H, m), 3.60 (8H, m), 4.43 (2H, m), 7.23 – 7.26 (1H, m), 7.31 (1H, s), 7.36 – 7.41 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	461
649	NHMe	δ 1.75 (2H, m), 1.94 (2H, m), 2.78 (3H, d), 2.94 (1H, m), 3.14 (2H, m), 4.45 (2H, m), 7.40 (2H, m), 7.68 (2H, m), 7.74 (1H, s), 8.26 (1H, d), 8.38 (1H, m)	405
650		δ 1.75 (2H, m), 1.94 (2H, m), 2.44 (6H, m), 2.95 (1H, m), 3.14 (2H, m), 3.38 (2H, m), 3.57 (4H, m), 4.46 (2H, m), 7.41 (2H, m), 7.68 (2H, m), 7.73 (1H, s), 8.26 (1H, d), 8.36 (1H, t)	504
651		δ 1.58 (2H, m), 1.76 (4H, m), 1.94 (4H, m), 2.16 (3H, s), 2.77 (2H, m), 2.94 (1H, m), 3.13 (2H, m), 3.73 (1H, m), 4.46 (2H, m), 7.40 (2H, m), 7.68 (2H, m), 7.74 (1H, s), 8.18 (1H, d), 8.26 (1H, d)	488
652		δ 1.75 (2H, m), 1.94 (2H, m), 2.14 (3H, s), 2.30 (4H, m), 2.43 (4H, m), 2.56 (2H, m), 2.95 (1H, m), 3.14 (2H, m), 3.36 (2H, m), 4.45 (2H, m), 7.41 (2H, m), 7.68 (2H, m), 7.73 (1H, s), 8.26 (1H, d), 8.33 (1H, t)	517

El ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico usado como material de partida fue preparado como sigue:

Preparación de 3–(piridin–4–il)benzoato de etilo

Obtenido en 92% de rendimiento mediante un procedimiento análogo al Ejemplo 605, partiendo de hidrocloruro de 4–bromopiridina y ácido 3–(etoxicarbonil)fenilboronico.
1H NMR (399.9 MHz, DMSO–d6) δ 1.37 (3H, t), 4.38 (2H, q), 7.71 (1H, m), 7.76 (2H, d), 8.08 (2H, m), 8.30 (1H, s), 8.69 (2H, d); m/z = 228 [M+H]+.

Preparación de 3–(piperidin–4–il)benzoato de etilo

3–(Piridin–4–il)benzoato de etilo (1.46 g, 6.42 mmol), 5% paladio sobre carbono (50% húmedo) (0.301 g, 0.07 mmol) y ácido cítrico monohidrato (0.601 g, 2.86 mmol) en una mezcla de isopropanol (50 mL) y agua (5 mL) fueron agitados bajo una atmósfera de hidrógeno a 20 atmósferas y 70°C durante 15 horas. La reacción fue enfriada hasta la temperatura ambiente, el catalizador eliminado por filtración y el solvente evaporado para dar el producto crudo, el cual fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 2M en metanol para dar 3–(piperidin–4–il)benzoato de etilo (1.190 g, 79%) como un líquido.
m/z = 275 [M+H]+ (aducto de acetonitrilo).

Preparación de 3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]benzoato de etilo

3–(Piperidin–4–il)benzoato de etilo (1.195 g, 5.12 mmol) fue añadido a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (1 g, 4.49 mmol) y DIPEA (1.174 mL, 6.74 mmol) en DMA (10 mL). La solución resultante fue agitada a 125°C durante 2 horas. La mezcla de reacción fue evaporada hasta secarse, redisuelta en DCM y purificada por cromatografía flash en sílice, eluyendo con 50% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse para dar un sólido beige, el cual fue triturado con éter para dar 3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]benzoato de etilo (0.805 g, 42.7%) como un sólido.
1H NMR (399.9 MHz, DMSO–d6) δ 1.33 (3H, t), 1.74 (2H, m), 1.94 (2H, m), 2.99 (1H, m), 3.14 (2H, m), 4.32 (2H, q), 4.44 (2H, m), 7.47 (1H, m), 7.59 (1H, m), 7.67 (1H, d), 7.83 (2H, m), 8.25 (1H, d); m/z = 420 [M+H]+.

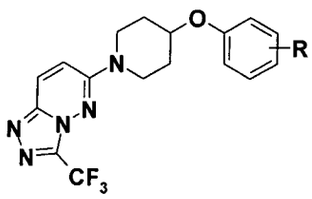
Preparación de ácido 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico

Obtenido en 100% de rendimiento mediante un procedimiento análogo al Ejemplo 512, preparación de los materiales de partida, partiendo de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoato de etilo.

1H NMR (399.9 MHz, DMSO–d6) δ 1.69 – 1.79 (2H, m), 1.94 (2H, m), 2.95 – 3.01 (1H, m), 3.14 (2H, m), 4.44 (2H, m), 7.45 (1H, m), 7.54 – 7.56 (1H, m), 7.67 (1H, d), 7.79 – 7.82 (1H, m), 7.84 (1H, m), 8.25 (1H, d), 12.78 (1H, s); m/z = 392 [M+H]+.

Ejemplos 653–654

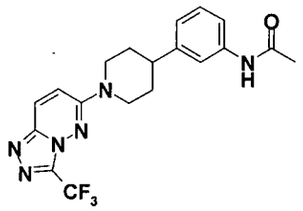
Los siguientes compuestos fueron preparados en 25–37% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (obtenido como se describió en el Ejemplo 412, preparación de los materiales de partida) y el fenol apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
653	2–CF3	δ 1.81 (2H, m), 2.08 (2H, m), 3.69 (2H, m), 3.80 (2H, m), 4.94 (1H, m), 7.11 (1H, m), 7.40 (1H, m), 7.64 (3H, m), 8.26 (1H, d)	432
654	2–CN	δ 1.82 (2H, m), 2.11 (2H, m), 3.65 (2H, m), 3.90 (2H, m), 4.94 (1H, m), 7.12 (1H, m), 7.41 (1H, m), 7.68 (2H, m), 7.75 (1H, m), 8.27 (1H, d)	389

Ejemplo 655

Preparación de N–[3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida

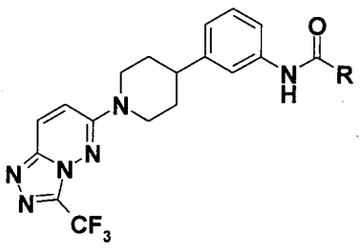


DIPEA (123 µl, 0.70 mmol) fue añadido a 3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]anilina (obtenida como se describió en el Ejemplo 616) (85 mg, 0.23 mmol), ácido acético(16 µl, 0.28 mmol) y HATU (107 mg, 0.28 mmol) en DMA (2 mL). La solución resultante fue agitada a temperatura ambiente durante 2 horas luego purificada por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y acetonitrilo como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para dar N–[3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida (89 mg, 94%) como un sólido.

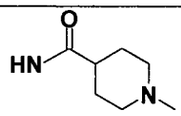
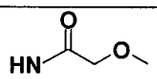
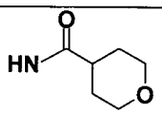
1H NMR (399.9 MHz, DMSO–d6) δ 1.66 (2H, m), 1.91 (2H, m), 2.02 (3H, s), 2.84 (1H, m), 3.13 (2H, m), 4.42 (2H, m), 6.95 (1H, m), 7.22 (1H, m), 7.41 (1H, m), 7.49 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.84 (1H, s); m/z = 405 [M+H]+.

Ejemplos 656–658

Los siguientes compuestos fueron preparados en 71–86% de rendimiento mediante un método análogo al Ejemplo 655, partiendo de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina y el ácido carboxílico apropiado:

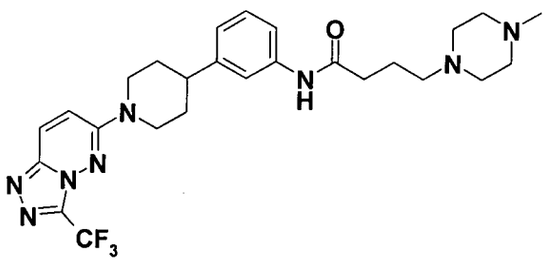


Ej.	NHCOR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+

656		δ 1.68 (6H, m), 1.88 (4H, m), 2.17 (3H, s), 2.25 (1H, m), 2.83 (3H, m), 3.13 (2H, m), 4.42 (2H, m), 6.94 (1H, m), 7.21 (1H, m), 7.42 (1H, m), 7.56 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.77 (1H, s)	488
657		δ 1.67 (2H, m), 1.92 (2H, m), 2.85 (1H, m), 3.14 (2H, m), 3.38 (3H, s), 3.98 (2H, s), 4.43 (2H, m), 6.99 (1H, m), 7.24 (1H, m), 7.53 (1H, m), 7.59 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.64 (1H, s)	435
658		δ 1.66 (6H, m), 1.91 (2H, m), 2.58 (1H, m), 2.84 (1H, m), 3.13 (2H, m), 3.35 (2H, m), 3.91 (2H, m), 4.42 (2H, m), 6.95 (1H, m), 7.22 (1H, m), 7.43 (1H, m), 7.56 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.80 (1H, s)	475

Ejemplo 659

Preparación de 4–(4–metilpiperazin–1–il)–N–[3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]butanamida



1–Metilpiperazina (152 µl, 1.37 mmol) fue añadida a 4–cloro–N–[3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]butanamida (160 mg, 0.343 mmol) y yoduro de sodio (10 mg, 0.069 mmol) en una mezcla de THF (2 mL) y DMA (0.5 mL). La solución resultante fue calentada a 60°C durante 16 horas, luego enfriada y evaporada para dar el producto crudo, el cual fue purificado por cromatografía flash en sílice, eluyendo con un gradiente de 0 – 10% amoniaco 2M en metanol en DCM. Los solventes fueron evaporados, luego la goma resultante triturada con éter y el precipitado filtrado y secado para dar 4–(4–metilpiperazin–1–il)–N–[3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]butanamida (87 mg, 48%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.60 – 1.76 (4H, m), 1.91 (2H, m), 2.12 (3H, s), 2.25 – 2.35 (12H, m), 2.84 (1H, m), 3.13 (2H, m), 4.42 (2H, m), 6.94 (1H, m), 7.21 (1H, m), 7.42 (1H, m), 7.52 (1H, m), 7.67 (1H, d), 8.25 (1H, d), 9.77 (1H, s); m/z = 531 [M+H]+.

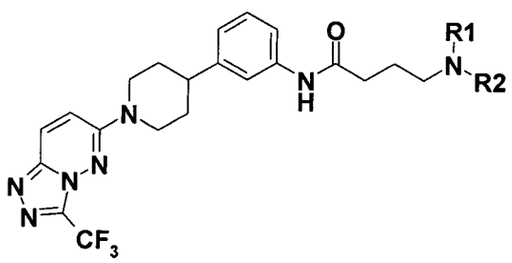
La 4–cloro–N–[3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]butanamida usada como material de partida fue preparada como sigue:

Una solución de cloruro de 4–clorobutirilo (175 mg, 1.24 mmol) en DCM (2 mL) fue añadida en forma de gotas a una suspensión agitada de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina (obtenida como se describió en el Ejemplo 616) (375 mg, 1.03 mmol) y piridina (164 mg, 2.07 mmol) en DCM (3 mL) bajo nitrógeno. La solución resultante fue agitada a temperatura ambiente durante 16 horas. La mezcla de reacción fue diluida con DCM (5 mL), lavada con bicarbonato de sodio saturado (10 mL), secada y el solvente evaporado hasta una goma amarilla, la cual fue triturada con éter para dar 4–cloro–N–[3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]butanamida (480 mg, 99%) como un sólido.

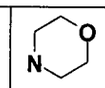
m/z = 467 [M+H]+.

Ejemplos 660–661

Los siguientes compuestos fueron preparados en 5–34% de rendimiento mediante un método análogo al Ejemplo 659, partiendo de 4–cloro–N–[3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]butanamida y la amina apropiada:

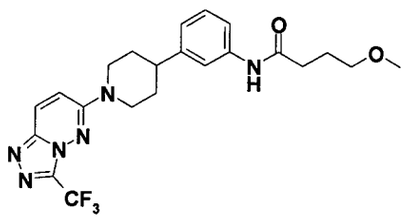


Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
660		δ 1.66 (2H, m), 1.85 – 1.95 (8H, m), 2.40 (2H, t), 2.85 (1H, m), 2.98 – 3.19 (8H, m), 4.43 (2H, m), 6.97 (1H, m), 7.24 (1H, m), 7.43 (1H, m), 7.51 (1H, m), 7.67 (1H, d), 8.26 (1H, d), 9.90 (1H, s)	502

661		δ 1.61 – 1.77 (4H, m), 1.86 (2H, m), 2.27 – 2.40 (8H, m), 2.84 (1H, m), 3.13 (2H, m), 3.59 (4H, m), 4.45 (2H, m), 6.92 (1H, m), 7.22 (1H, m), 7.46 (1H, m), 7.54 (1H, m), 7.69 (1H, d), 8.26 (1H, d), 9.78 (1H, s)	518

Ejemplo 662

Preparación de 4–metoxi–N–[3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]fenil]butanamida



Obtenida en 68% de rendimiento mediante un procedimiento análogo al Ejemplo 655, partiendo de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina y ácido 4–metoxibutanóico.

1H NMR (399.9 MHz, DMSO–d6) δ 1.66 (2H, m), 1.80 (2H, m), 1.91 (2H, m), 2.34 (2H, t), 2.84 (1H, m), 3.13 (2H, m), 3.24 (3H, s), 3.35 (2H, t), 4.42 (2H, m), 6.94 (1H, d), 7.22 (1H, m), 7.42 (1H, d), 7.53 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.81 (1H, s); m/z = 463 [M+H]+.

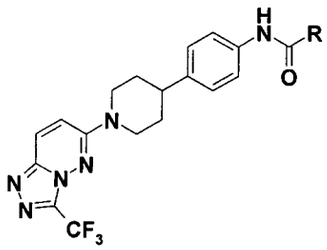
El ácido 4–metoxibutanóico usado como material de partida fue preparado como sigue:

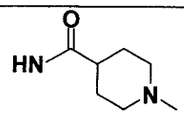
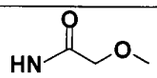
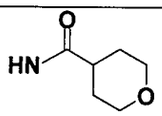
Hidróxido de litio monohidrato (0.381 g, 9.08 mmol) fue añadido a metil 4–metoxibutanoato (1g, 7.57 mmol) en una mezcla de MeOH (20 mL) y agua (10 mL). La suspensión resultante fue agitada a 50°C durante 16 horas. La reacción fue enfriada hasta la temperatura ambiente, el MeOH evaporado y el residuo acuoso diluido con agua (50 mL) y lavado con EtOAc (2 x 50 mL). La capa acuosa fue luego acidificada hasta pH 4 con ácido cítrico 1M y extraída con EtOAc (2 x 50 mL). Los extractos combinados fueron secado sobre $MgSO_4$ y el solvente evaporado para proporcionar ácido 4–metoxibutanóico (0.709 g, 79%) como un líquido.

1H NMR (399.9 MHz, CDCl3) δ 1.91 (2H, m), 2.46 (2H, t), 3.34 (3H, s), 3.44 (2H, t), 10.92 (1H, br s).

Ejemplos 663–665

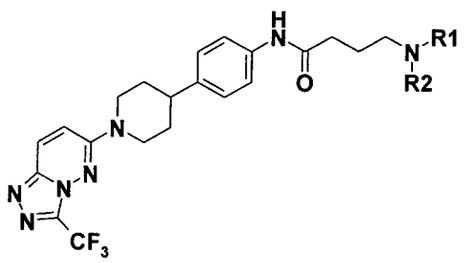
Los siguientes compuestos fueron preparados en 22–68% de rendimiento mediante un método análogo al Ejemplo 655, partiendo de 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina (obtenida como se describió en el Ejemplo 615) y el ácido carboxílico apropiado:

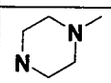


Ej.	NHCOR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
663		δ 1.60 – 1.75 (6H, m), 1.88 (4H, m), 2.18 (3H, s), 2.26 (1H, m), 2.83 (3H, m), 3.10 (2H, m), 4.41 (2H, m), 7.18 (2H, d), 7.52 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.75 (1H, s)	488
664		δ 1.68 (2H, m), 1.89 (2H, m), 2.83 (1H, m), 3.11 (2H, m), 3.38 (3H, s), 3.98 (2H, s), 4.42 (2H, m), 7.21 (2H, d), 7.58 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.66 (1H, s)	435
665		δ 1.67 (6H, m), 1.89 (2H, m), 2.82 (1H, m), 3.11 (2H, m), 3.36 (2H, m), 3.91 (2H, m), 4.41 (2H, m), 7.19 (2H, d), 7.53 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.79 (1H, s), (1H oscurecida por DMSO)	475

Ejemplos 666–668

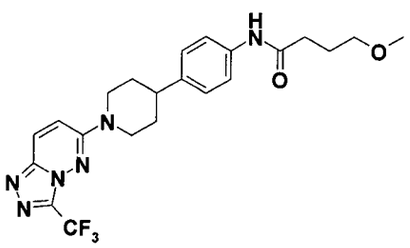
Los siguientes compuestos fueron preparados en 27–68% de rendimiento mediante un método análogo al Ejemplo 659, partiendo de 4–cloro–N–[4–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]fenil]butanamida y la amina apropiada:



Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
666		δ 1.62 – 1.76 (4H, m), 1.88 (2H, m), 2.13 (3H, s), 2.26 – 2.37 (12H, m), 2.81 (1H, m), 3.11 (2H, m), 4.41 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.76 (1H, s)	531
667		δ 1.62 – 1.79 (8H, m), 1.89 (2H, m), 2.33 (2H, m), 2.41 – 2.50 (6H, m), 2.82 (1H, m), 3.11 (2H, m), 4.42 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.80 (1H, s)	502
668		δ 1.62 – 1.78 (4H, m), 1.89 (2H, m), 2.27 – 2.40 (8H, m), 2.82 (1H, m), 3.11 (2H, m), 3.56 (4H, m), 4.41 (2H, m), 7.19 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.78 (1H, s)	518

La 4–cloro–N–[4–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il]fenil]butanamida usada como material de partida fue obtenida en 80% de rendimiento mediante un procedimiento análogo al Ejemplo 659, preparación de los materiales de partida, partiendo de 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina (obtenida como se describió en el Ejemplo 615).
m/z = 467 [M+H]+.

Ejemplo 669

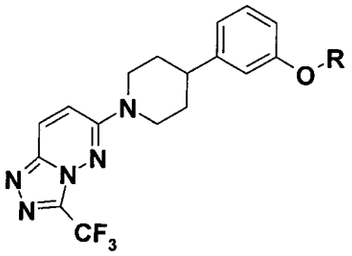


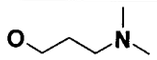
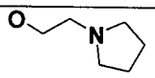
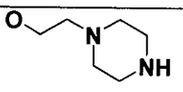
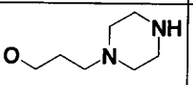
Obtenida en 38% de rendimiento mediante un procedimiento análogo al Ejemplo 655, partiendo de 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina (obtenida como se describió en el Ejemplo 615) y ácido 4–metoxibutanóico (obtenido como se describió en el Ejemplo 662, preparación de los materiales de partida).

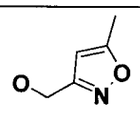
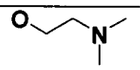
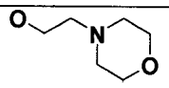
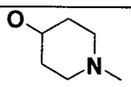
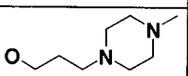
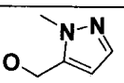
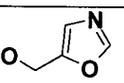
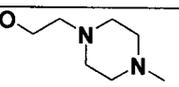
1H NMR (399.9 MHz, DMSO–d6) δ 1.68 (2H, m), 1.80 (2H, m), 1.89 (2H, m), 2.34 (2H, t), 2.82 (1H, m), 3.11 (2H, m), 3.24 (3H, s), 3.35 (2H, t), 4.41 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.80 (1H, s); m/z = 463 [M+H]+.

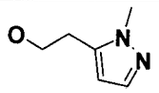
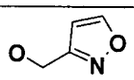
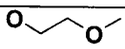
Ejemplos 670–684

Los siguientes compuestos fueron preparados en 17–64% de rendimiento mediante un método análogo al Ejemplo 513, partiendo de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol y el alcohol apropiado:



Ej.	OR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
670		δ 1.71 (2H, m), 1.85 (4H, m), 2.14 (6H, s), 2.35 (2H, t), 2.84 (1H, m), 3.10 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 6.76 (1H, m), 6.83 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	449
671		δ 1.66 – 1.77 (6H, m), 1.90 (2H, m), 2.59 (4H, m), 2.85 (3H, m), 3.11 (2H, m), 4.07 (2H, t), 4.42 (2H, m), 6.78 (1H, m), 6.85 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	461
672		δ 1.72 (2H, m), 1.90 (2H, m), 2.38 (4H, m), 2.65 (6H, m), 2.84 (1H, m), 3.10 (2H, m), 4.05 (2H, t), 4.42 (2H, m), 6.77 (1H, m), 6.84 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	476
673		δ 1.71 (2H, m), 1.86 (4H, m), 2.29 (4H, m), 2.36 (2H, m), 2.67 (4H, m), 2.84 (1H, m), 3.10 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 6.76 (1H, m), 6.83 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	490

674		δ 1.72 (2H, m), 1.91 (2H, m), 2.41 (3H, s), 2.85 (1H, m), 3.11 (2H, m), 4.42 (2H, m), 5.12 (2H, s), 6.32 (1H, s), 6.85 – 6.94 (3H, m), 7.24 (1H, m), 7.67 (1H, d), 8.25 (1H, d)	459
675		δ 1.71 (2H, m), 1.90 (2H, m), 2.21 (6H, s), 2.61 (2H, t), 2.84 (1H, m), 3.10 (2H, m), 4.03 (2H, t), 4.42 (2H, m), 6.78 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	435
676		δ 1.71 (2H, m), 1.90 (2H, m), 2.47 (4H, m), 2.68 (2H, t), 2.84 (1H, m), 3.11 (2H, m), 3.57 (4H, m), 4.07 (2H, t), 4.42 (2H, m), 6.78 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	477
677		δ 1.65 – 1.76 (4H, m), 1.88 – 2.01 (4H, m), 2.42 (3H, s), 2.86 (3H, m), 3.10 (2H, m), 4.44 (3H, m), 6.83 (3H, m), 7.21 (1H, m), 7.66 (1H, d), 8.25 (1H, d), (2H oscurecida por DMSO)	461
678		δ 1.71 (2H, m), 1.87 (4H, m), 2.14 (3H, s), 2.25 – 2.42 (10H, m), 2.84 (1H, m), 3.10 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 6.76 (1H, m), 6.83 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.25 (1H, d)	504
679		δ 1.72 (2H, m), 1.91 (2H, m), 2.86 (1H, m), 3.11 (2H, m), 4.43 (2H, m), 5.22 (2H, s), 6.69 (1H, d), 6.89 (2H, m), 6.95 (1H, m), 7.24 (1H, m), 7.67 (1H, d), 8.25 (1H, d), 8.94 (1H, d)	445
680		δ 1.72 (2H, m), 1.91 (2H, m), 2.86 (1H, m), 3.11 (2H, m), 4.43 (2H, m), 5.17 (2H, s), 6.89 (2H, m), 6.94 (1H, m), 7.24 (1H, m), 7.32 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 8.40 (1H, s)	445
681		δ 1.72 (2H, m), 1.90 (2H, m), 2.14 (3H, s), 2.30 (4H, m), 2.47 (4H, m), 2.66 (2H, t), 2.84 (1H, m), 3.10 (2H, m), 4.05 (2H, t), 4.42 (2H, m), 6.77 (1H, m), 6.84 (2H, m), 7.20 (1H, m), 7.66	490

		(1H, d), 8.24 (1H, d)	
682		δ 1.71 (2H, m), 1.90 (2H, m), 2.81 – 2.88 (3H, m), 3.10 (2H, m), 3.78 (3H, s), 4.07 (2H, t), 4.42 (2H, m), 6.79 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.33 (1H, s), 7.56 (1H, s), 7.66 (1H, d), 8.24 (1H, d)	472
683		δ 1.72 (2H, m), 1.91 (2H, m), 2.86 (1H, m), 3.11 (2H, m), 3.83 (3H, s), 4.43 (2H, m), 5.16 (2H, s), 6.36 (1H, d), 6.90 (2H, m), 6.96 (1H, m), 7.24 (1H, m), 7.37 (1H, d), 7.67 (1H, d), 8.25 (1H, d)	458
684		δ 1.72 (2H, m), 1.90 (2H, m), 2.84 (1H, m), 3.10 (2H, m), 3.31 (3H, s), 3.65 (2H, m), 4.08 (2H, m), 4.42 (2H, m), 6.78 (1H, m), 6.85 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.24 (1H, d)	422

El 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol usado como material de partida fue preparado como sigue:

Preparación de 3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,2,3,6–tetrahidropiridin–4–il]fenol

Obtenido en 72% de rendimiento mediante un procedimiento análogo al Ejemplo 605, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,2,3,6–tetrahidropiridin–4–il trifluorometanosulfonato y ácido 3–hidroxifenilboronico.

1H NMR (399.9 MHz, DMSO–d6) δ 2.63 (2H, m), 3.88 (2H, m), 4.25 (2H, m), 6.24 (1H, m), 6.70 (1H, m), 6.86 (1H, m), 6.92 (1H, m), 7.17 (1H, m), 7.67 (1H, d), 8.29 (1H, d), 9.38 (1H, s); m/z = 362 [M+H]+.

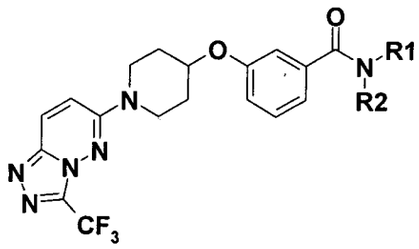
Preparación de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol

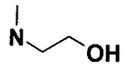
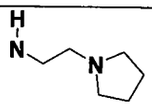
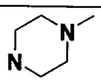
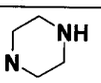
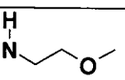
Obtenido en 73% de rendimiento mediante un procedimiento análogo al Ejemplo 610, partiendo de 3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]–1,2,3,6–tetrahidropiridin–4–il]fenol.

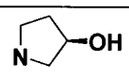
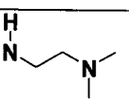
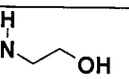
1H NMR (399.9 MHz, DMSO–d6) δ 1.64 – 1.71 (2H, m), 1.89 (2H, m), 2.75 – 2.79 (1H, m), 3.07 – 3.14 (2H, m), 4.39 – 4.42 (2H, m), 6.59 – 6.70 (3H, m), 7.09 (1H, m), 7.66 (1H, d), 8.24 (1H, d), 9.24 (1H, s); m/z = 364 [M+H]+.

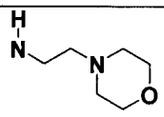
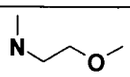
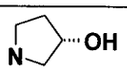
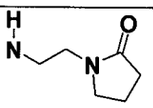
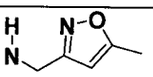
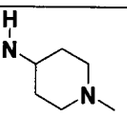
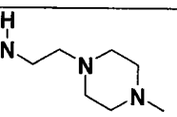
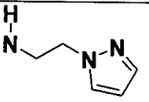
Ejemplos 685–707

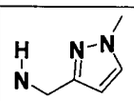
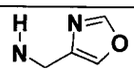
Los siguientes compuestos fueron preparados en 31–95% de rendimiento mediante un método análogo al Ejemplo 512, partiendo de ácido 3–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoico y la amina apropiada:



Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
685		δ 1.74 (2H, m), 2.09 (2H, m), 2.96 (3H, m), 3.46 – 3.65 (6H, m), 3.97 (2H, m), 4.75 (2H, m), 6.96 (1H, m), 7.05 (2H, m), 7.34 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	465
686		δ 1.66 – 1.80 (6H, m), 2.10 (2H, m), 2.48 (4H, m), 2.57 (2H, t), 3.38 (2H, m), 3.56 (2H, m), 3.96 (2H, m), 4.75 (1H, m), 7.17 (1H, m), 7.36 – 7.44 (3H, m), 7.65 (1H, d), 8.26 (1H, d), 8.39 (1H, t)	504
687		δ 1.74 (2H, m), 2.09 (2H, m), 2.27 (3H, s), 2.37 – 2.47 (4H, m), 3.37 – 3.70 (6H, m), 3.97 (2H, m), 4.75 (1H, m), 6.94 (1H, m), 7.00 (1H, m), 7.09 (1H, m), 7.37 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	490
688		δ 1.73 (2H, m), 2.08 (2H, m), 2.60 – 2.75 (4H, m), 3.28 (2H, m), 3.54 (4H, m), 3.98 (2H, m), 4.75 (1H, m), 6.92 (1H, m), 6.98 (1H, m), 7.07 (1H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	476
689		δ 1.76 (2H, m), 2.09 (2H, m), 3.28 (3H, s), 3.44 (4H, m), 3.57 (2H, m), 3.96 (2H, m), 4.76 (1H,	465

		m), 7.18 (1H, m), 7.39 (1H, m), 7.45 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.48 (1H, t)	
690	NMe2	δ 1.73 (2H, m), 2.08 (2H, m), 2.91 (3H, s), 2.98 (3H, s), 3.53 (2H, m), 3.97 (2H, m), 4.75 (1H, m), 6.95 (1H, m), 7.02 (1H, m), 7.07 (1H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	435
691		δ 1.70 – 1.97 (4H, m), 2.08 (2H, m), 3.39 (1H, m), 3.55 (5H, m), 3.96 (2H, m), 4.28 (1H, m), 4.76 (1H, m), 4.95 (1H, m), 7.08 (3H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	477
692		δ 1.69 – 1.89 (6H, m), 2.08 (2H, m), 3.37 (2H, m), 3.47 (2H, m), 3.54 (2H, m), 3.97 (2H, m), 4.75 (1H, m), 7.08 (3H, m), 7.35 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	461
693		δ 1.74 (2H, m), 2.09 (2H, m), 3.32 – 3.67 (10H, m), 3.97 (2H, m), 4.75 (1H, m), 6.97 (1H, m), 7.02 (1H, m), 7.09 (1H, m), 7.37 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	477
694	NHMe	δ 1.75 (2H, m), 2.10 (2H, m), 2.79 (3H, d), 3.56 (2H, m), 3.97 (2H, m), 4.75 (1H, m), 7.16 (1H, m), 7.36 – 7.44 (3H, m), 7.66 (1H, d), 8.26 (1H, d), 8.39 (1H, q)	421
695	NHEt	δ 1.13 (3H, t), 1.75 (2H, m), 2.09 (2H, m), 3.28 (2H, m), 3.57 (2H, m), 3.96 (2H, m), 4.76 (1H, m), 7.17 (1H, m), 7.38 (1H, m), 7.44 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.42 (1H, t)	435
696		δ 1.76 (2H, m), 2.09 (2H, m), 2.22 (6H, s), 2.45 (2H, t), 3.37 (2H, m), 3.57 (2H, m), 3.96 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.37 – 7.44 (3H, m), 7.66 (1H, d), 8.26 (1H, d), 8.36 (1H, t)	478
697		δ 1.76 (2H, m), 2.09 (2H, m), 3.33 (2H, m), 3.55 (4H, m), 3.96 (2H, m), 4.70 (1H, t), 4.76 (1H, m), 7.17 (1H, m), 7.38 (1H, m), 7.45 (2H, m), 7.65	451

		(1H, d), 8.26 (1H, d), 8.39 (1H, t)	
698		δ 1.76 (2H, m), 2.10 (2H, m), 2.45 (4H, m), 3.40 (2H, m), 3.57 (6H, m), 3.96 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.41 (3H, m), 7.65 (1H, d), 8.26 (1H, d), 8.38 (1H, t), (2H oscurecida por DMSO)	520
699		δ 1.74 (2H, m), 2.08 (2H, m), 2.95 (3H, m), 3.21 (2H, m), 3.33 – 3.62 (7H, m), 3.97 (2H, m), 4.74 (1H, m), 6.94 (1H, m), 7.00 (1H, m), 7.06 (1H, m), 7.35 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	479
700		δ 1.70 – 1.96 (4H, m), 2.08 (2H, m), 3.38 (1H, m), 3.54 (5H, m), 3.97 (2H, m), 4.28 (1H, m), 4.76 (1H, m), 4.95 (1H, m), 7.08 (3H, m), 7.36 (1H, m), 7.65 (1H, d), 8.26 (1H, d)	477
701		δ 1.76 (2H, m), 1.91 (2H, m), 2.10 (2H, m), 2.19 (2H, m), 3.39 (6H, m), 3.56 (2H, m), 3.98 (2H, m), 4.75 (1H, m), 7.17 (1H, m), 7.39 (3H, m), 7.66 (1H, d), 8.26 (1H, d), 8.47 (1H, t)	518
702		δ 1.76 (2H, m), 2.10 (2H, m), 2.38 (3H, s), 3.57 (2H, m), 3.96 (2H, m), 4.46 (2H, d), 4.76 (1H, m), 6.16 (1H, s), 7.20 (1H, m), 7.41 (1H, m), 7.48 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 9.03 (1H, t)	502
703		δ 1.60 (2H, m), 1.76 (4H, m), 1.97 (2H, m), 2.09 (2H, m), 2.19 (3H, s), 2.79 (2H, m), 3.57 (2H, m), 3.73 (1H, m), 3.95 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.38 (1H, m), 7.44 (2H, m), 7.65 (1H, d), 8.19 (1H, d), 8.26 (1H, d)	504
704		δ 1.75 (2H, m), 2.10 (2H, m), 2.24 (3H, s), 2.40 – 2.51 (10H, m), 3.38 (2H, m), 3.56 (2H, m), 3.96 (2H, m), 4.76 (1H, m), 7.18 (1H, m), 7.40 (3H, m), 7.65 (1H, d), 8.26 (1H, d), 8.35 (1H, t)	533
705		δ 1.75 (2H, m), 2.09 (2H, m), 3.56 (2H, m), 3.64 (2H, m), 3.97 (2H, m), 4.31 (2H, t), 4.74 (1H, m), 6.23 (1H, m), 7.18 (1H, m), 7.39 (3H, m), 7.46	501

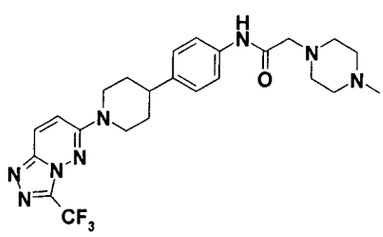
		(1H, m), 7.66 (1H, d), 7.70 (1H, m), 8.27 (1H, d), 8.53 (1H, t)	
706		δ 1.76 (2H, m), 2.09 (2H, m), 3.57 (2H, m), 3.79 (3H, s), 3.96 (2H, m), 4.41 (2H, d), 4.76 (1H, m), 6.13 (1H, d), 7.17 (1H, m), 7.38 (1H, m), 7.48 (2H, m), 7.58 (1H, d), 7.65 (1H, d), 8.26 (1H, d), 8.85 (1H, t)	501
707		δ 1.75 (2H, m), 2.10 (2H, m), 3.57 (2H, m), 3.96 (2H, m), 4.38 (2H, d), 4.76 (1H, m), 7.18 (1H, m), 7.39 (1H, m), 7.48 (2H, m), 7.65 (1H, d), 7.97 (1H, s), 8.26 (1H, d), 8.32 (1H, s), 8.90 (1H, t)	488

El ácido 3–[[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]oxi]benzoico usado como material de partida fue preparado en 2 pasos en 38% de rendimiento total mediante un método análogo al Ejemplo 412, preparación de los materiales de partida, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol y 4–hidroxi benzoato de metilo.

1H NMR (399.9 MHz, DMSO–d6) δ 1.74 – 1.78 (2H, m), 2.06 – 2.11 (2H, m), 3.54 – 3.60 (2H, m), 3.93 – 3.99 (2H, m), 4.78 (1H, m), 7.27 – 7.30 (1H, m), 7.44 (1H, m), 7.51 – 7.57 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 12.97 (1H, s); m/z = 408 [M+H]+.

Ejemplo 708

Preparación de 2–(4–metilpiperazin–1–il)–N–[4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida



1–Metilpiperazina (140 µl, 1.27 mmol) fue añadida a 2–cloro–N–[4–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida (139 mg, 0.317 mmol) y yoduro de sodio (10 mg, 0.063 mmol) en una mezcla de THF (2 mL) y DMA (0.5 mL). La solución resultante fue calentada a 60°C durante 2 horas, luego enfriada y evaporada para dar el producto crudo el cual fue purificado por HPLC

preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para dar 2–(4–metilpiperazin–1–il)–N–[4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida (111 mg, 70%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.68 (2H, m), 1.89 (2H, m), 2.17 (3H, s), 2.37 (4H, m), 2.83 (1H, m), 3.11 (4H, m), 4.42 (2H, m), 7.21 (2H, d), 7.54 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.58 (1H, s), (4H oscurecida por DMSO); m/z = 503 [M+H]+.

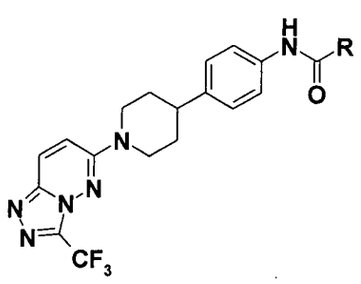
La 2–cloro–N–[4–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida usada como material de partida fue preparada como sigue:

Una solución de cloruro de cloroacetil (140 mg, 1.24 mmol) en DCM (2 mL) fue añadida en forma de gotas a una suspensión agitada de 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina (obtenida como se describió en el Ejemplo 615) (375 mg, 1.03 mmol) y piridina (164 mg, 2.07 mmol) en DCM (3 mL) bajo nitrógeno. La solución resultante fue agitada a temperatura ambiente durante 2 horas. El precipitado resultante fue recogido por filtración, lavado con DCM (2 mL) y secado al vacío para dar 2–cloro–N–[4–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida (418 mg, 92%) como un sólido.

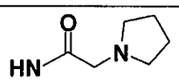
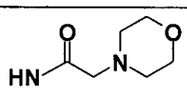
m/z = 439 [M+H]+.

Ejemplos 709–710

Los siguientes compuestos fueron preparados en 41–61% de rendimiento mediante un método análogo al Ejemplo 708, partiendo de 2–cloro–N–[4–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida y la amina apropiada:

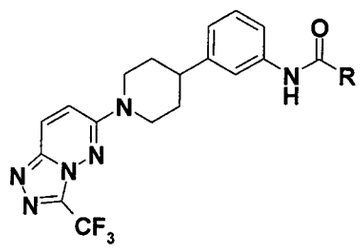


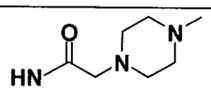
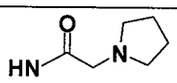
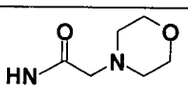
Ej.	NHCOR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+

709		δ 1.63 – 1.76 (6H, m), 1.89 (2H, m), 2.59 (4H, m), 2.83 (1H, m), 3.11 (2H, m), 3.22 (2H, s), 4.42 (2H, m), 7.20 (2H, d), 7.56 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.60 (1H, s)	474
710		δ 1.68 (2H, m), 1.89 (2H, m), 2.55 (4H, m), 2.83 (1H, m), 3.11 (4H, m), 3.64 (4H, m), 4.42 (2H, m), 7.21 (2H, d), 7.55 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.64 (1H, s)	490

Ejemplos 711–713

Los siguientes compuestos fueron preparados en 26–33% de rendimiento mediante un método análogo al Ejemplo 708, partiendo de 2–cloro–N–[3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida y la amina apropiada:

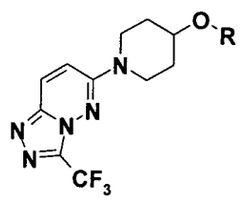


Ej.	NHCOR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
711		δ 1.68 (2H, m), 1.92 (2H, m), 2.17 (3H, s), 2.37 (4H, m), 2.85 (1H, m), 3.12 (4H, m), 4.43 (2H, m), 6.98 (1H, m), 7.24 (1H, m), 7.50 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 9.58 (1H, s), (4H oscurecida por DMSO)	503
712		δ 1.63 – 1.77 (6H, m), 1.92 (2H, m), 2.58 (4H, m), 2.85 (1H, m), 3.13 (2H, m), 3.22 (2H, s), 4.43 (2H, m), 6.97 (1H, m), 7.23 (1H, m), 7.53 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 9.59 (1H, s)	474
713		δ 1.68 (2H, m), 1.91 (2H, m), 2.56 (4H, m), 2.85 (1H, m), 3.13 (4H, m), 3.64 (4H, m), 4.43 (2H, m), 6.98 (1H, m), 7.24 (1H, m), 7.52 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 9.64 (1H, s), (4H parcialmente oscurecida por DMSO)	490

La 2–cloro–N–[3–[1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenil]acetamida usada como material de partida fue preparada en 100% de rendimiento mediante un método análogo al Ejemplo 708, preparación de los materiales de partida, partiendo de 3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]anilina (obtenida como se describió en el Ejemplo 616) y cloruro de cloroacetilo. m/z = 439 [M+H]+.

Ejemplos 714–723

Los siguientes compuestos fueron preparados en 15–48% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (obtenida como se describió en el Ejemplo 412, preparación de material de partida) y el hidroxi heterociclo apropiado:

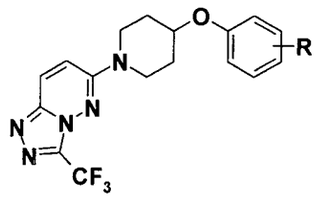


Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
714	5–cloropirimidin–2–il	δ 1.82 (2H, m), 2.14 (2H, m), 3.55 (2H, m), 3.99 (2H, m), 5.24 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.73 (2H, s)	400
715	2–cloropiridin–3–il	δ 1.81 (2H, m), 2.09 (2H, m), 3.64 (2H, m), 3.89 (2H, m), 4.88 (1H, m), 7.41 (1H, m), 7.65 (1H, d), 7.75 (1H, m), 8.01 (1H, m), 8.26 (1H, d)	399
716	6–cloropiridin–2–il	δ 1.78 (2H, m), 2.12 (2H, m), 3.56 (2H, m), 3.97 (2H, m), 5.24 (1H, m), 6.84 (1H, m), 7.10 (1H, m), 7.65 (1H, d), 7.78 (1H, m), 8.26 (1H, d)	399
717	2–bromopiridin–3–il	δ 1.83 (2H, m), 2.07 (2H, m), 3.69 (2H, m), 3.85 (2H, m), 4.90 (1H, m), 7.42 (1H, m), 7.67 (2H, m),	443

		8.00 (1H, m), 8.27 (1H, d)	
718	piridin–3–il	δ 1.75 (2H, m), 2.10 (2H, m), 3.53 (2H, m), 3.98 (2H, m), 4.78 (1H, m), 7.35 (1H, m), 7.49 (1H, m), 7.65 (1H, d), 8.19 (1H, m), 8.26 (1H, d), 8.35 (1H, m)	365
719	5–trifluorometilpiridin–2–il	δ 1.81 (2H, m), 2.14 (2H, m), 3.55 (2H, m), 4.00 (2H, m), 5.40 (1H, m), 7.02 (1H, d), 7.66 (1H, d), 8.07 (1H, m), 8.26 (1H, d), 8.59 (1H, m)	433
720	6–cloropiridin–3–il	δ 1.74 (2H, m), 2.10 (2H, m), 3.52 (2H, m), 3.97 (2H, m), 4.78 (1H, m), 7.45 (1H, d), 7.59 (1H, m), 7.65 (1H, d), 8.19 (1H, d), 8.26 (1H, d)	399
721	5–bromopiridin–2–il	δ 1.76 (2H, m), 2.11 (2H, m), 3.52 (2H, m), 3.99 (2H, m), 5.26 (1H, m), 6.84 (1H, d), 7.65 (1H, d), 7.91 (1H, m), 8.26 (1H, d), 8.30 (1H, d)	443
722	5–bromopiridin–3–il	δ 1.74 (2H, m), 2.10 (2H, m), 3.52 (2H, m), 3.99 (2H, m), 4.85 (1H, m), 7.65 (1H, d), 7.85 (1H, m), 8.25 – 8.36 (3H, m)	443
723	3–bromopiridin–2–il	δ 1.82 (2H, m), 2.10 (2H, m), 3.67 (2H, m), 3.89 (2H, m), 5.40 (1H, m), 6.97 (1H, m), 7.65 (1H, d), 8.05 (1H, m), 8.18 (1H, m), 8.26 (1H, d)	443

Ejemplos 724–725

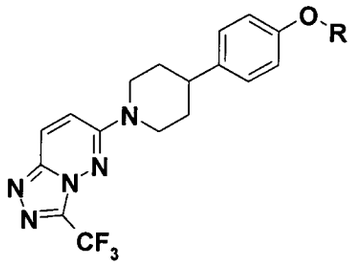
Los siguientes compuestos fueron preparados en 18–26% de rendimiento mediante un método análogo al Ejemplo 447, partiendo de 1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–ol (obtenido como se describió en el Ejemplo 412, preparación de los materiales de partida) y el fenol apropiado:

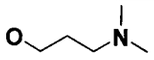
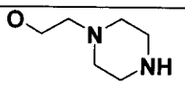
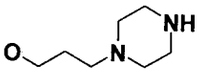


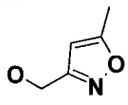
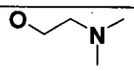
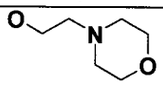
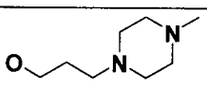
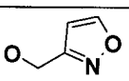
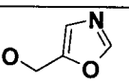
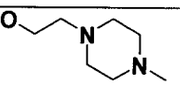
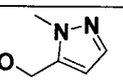
Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
724	4–Cl	δ 1.72 (2H, m), 2.07 (2H, m), 3.52 (2H, m), 3.96 (2H, m), 4.68 (1H, m), 7.05 (2H, d), 7.34 (2H, d), 7.64 (1H, d), 8.25 (1H, d)	398
725	3–Cl	δ 1.72 (2H, m), 2.08 (2H, m), 3.53 (2H, m), 3.96 (2H, m), 4.75 (1H, m), 7.00 (2H, m), 7.12 (1H, m), 7.32 (1H, m), 7.64 (1H, d), 8.25 (1H, d)	398

Ejemplos 726–736

Los siguientes compuestos fueron preparados en 7–51% de rendimiento mediante un método análogo al Ejemplo 513, partiendo de 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol y el alcohol apropiado:



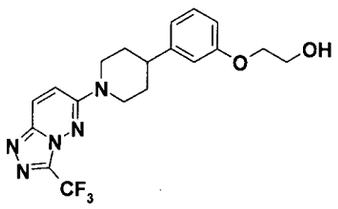
Ej.	OR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
726		δ 1.66 (2H, m), 1.79 – 1.91 (4H, m), 2.14 (6H, s), 2.34 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 3.96 (2H, t), 4.41 (2H, m), 6.85 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	449
727		δ 1.66 (2H, m), 1.88 (2H, m), 2.39 (4H, m), 2.63 (2H, t), 2.68 (4H, m), 2.81 (1H, m), 3.10 (2H, m), 4.03 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	476
728		δ 1.66 (2H, m), 1.85 (4H, m), 2.38 (6H, m), 2.78 – 2.84 (5H, m), 3.10 (2H, m), 3.97 (2H, t), 4.41 (2H, m), 6.85 (2H, d), 7.17 (2H, d), 7.66	490

		(1H, d), 8.24 (1H, d)	
729		δ 1.67 (2H, m), 1.88 (2H, m), 2.41 (3H, s), 2.82 (1H, m), 3.10 (2H, m), 4.41 (2H, m), 5.11 (2H, s), 6.31 (1H, s), 6.95 (2H, d), 7.20 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	459
730		δ 1.66 (2H, m), 1.88 (2H, m), 2.22 (6H, s), 2.61 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 4.01 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	435
731		δ 1.66 (2H, m), 1.88 (2H, m), 2.47 (4H, m), 2.68 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 3.58 (4H, m), 4.06 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	477
732		δ 1.66 (2H, m), 1.80 – 1.90 (4H, m), 2.15 (3H, s), 2.25 – 2.42 (10H, m), 2.81 (1H, m), 3.10 (2H, m), 3.96 (2H, t), 4.41 (2H, m), 6.85 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	504
733		δ 1.67 (2H, m), 1.89 (2H, m), 2.82 (1H, m), 3.10 (2H, m), 4.41 (2H, m), 5.20 (2H, s), 6.68 (1H, d), 6.97 (2H, d), 7.21 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 8.94 (1H, d)	445
734		δ 1.67 (2H, m), 1.89 (2H, m), 2.82 (1H, m), 3.10 (2H, m), 4.41 (2H, m), 5.15 (2H, s), 6.97 (2H, d), 7.20 (2H, d), 7.32 (1H, s), 7.66 (1H, d), 8.24 (1H, d), 8.40 (1H, s)	445
735		δ 1.66 (2H, m), 1.88 (2H, m), 2.15 (3H, s), 2.31 (4H, m), 2.46 (4H, m), 2.66 (2H, t), 2.81 (1H, m), 3.10 (2H, m), 4.03 (2H, t), 4.41 (2H, m), 6.87 (2H, d), 7.17 (2H, d), 7.66 (1H, d), 8.24 (1H, d)	490
736		δ 1.68 (2H, m), 1.89 (2H, m), 2.82 (1H, m), 3.10 (2H, m), 3.83 (3H, s), 4.42 (2H, m), 5.14 (2H, s), 6.36 (1H, d), 6.99 (2H, d), 7.21 (2H, d),	458

		7.37 (1H, d), 7.66 (1H, d), 8.24 (1H, d)	

Ejemplo 737

Preparación de 2–[3–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenoxi]etanol

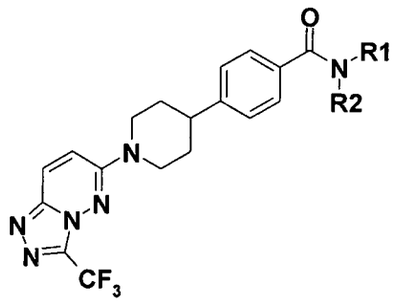


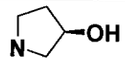
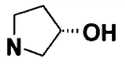
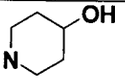
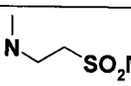
DIAD (0.081 mL, 0.41 mmol) fue añadido en forma de gotas a 3–[1–[3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]fenol (obtenida como se describió en el Ejemplo 670, Preparación de material de partida) (125 mg, 0.34 mmol), trifenilfosfina (108 mg, 0.41 mmol) y 2–(tetrahidro–2H–piran–2–iloxi)etanol (60.4 mg, 0.41 mmol) en THF (3 mL) bajo nitrógeno. La mezcla resultante fue agitada a temperatura ambiente durante 4 horas, luego añadida a una columna SCX. El producto crudo fue eluido de la columna usando amoniaco 2M en metanol y los solventes fueron evaporados. El producto crudo fue purificado por cromatografía flash en sílice, gradiente en elusión 80 a 100% EtOAc en isohexano. Las fracciones que contienen el producto fueron evaporadas, luego además purificadas por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 2–(3–(1–(3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazin–6–il)piperidin–4–il)fenoxi)etanol (74 mg, 53%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.71 (2H, m), 1.91 (2H, m), 2.85 (1H, m), 3.11 (2H, m), 3.70 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 4.80 (1H, t), 6.78 (1H, m), 6.84 (2H, m), 7.21 (1H, m), 7.66 (1H, d), 8.24 (1H, d); m/z = 408 [M+H]+.

Ejemplos 738–741

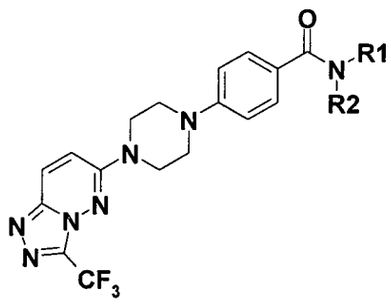
Los siguientes compuestos fueron preparados en 78–89% de rendimiento mediante un método análogo al Ejemplo 512, partiendo de ácido 4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzoico y la amina apropiada:

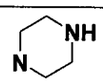
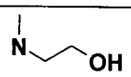
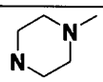
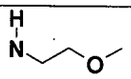
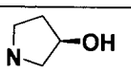
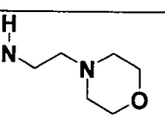


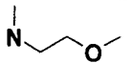
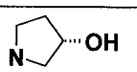
Ej.	NR1R2	1H NMR (399.1 MHz, DMSO–d6)	m/z [M+H]+
738		δ 1.68 – 1.95 (6H, m), 2.93 (1H, m), 3.13 (2H, m), 3.33 – 3.42 (1H, m), 3.47 – 3.62 (3H, m), 4.22 – 4.32 (1H, m), 4.44 (2H, m), 4.88 – 4.98 (1H, m), 7.34 (2H, d), 7.46 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	461
739		δ 1.68 – 1.96 (6H, m), 2.93 (1H, m), 3.13 (2H, m), 3.35 – 3.42 (1H, m), 3.47 – 3.62 (3H, m), 4.22 – 4.32 (1H, m), 4.44 (2H, m), 4.88 – 4.98 (1H, m), 7.34 (2H, d), 7.46 (2H, m), 7.67 (1H, d), 8.25 (1H, d)	461
740		δ (373K) 1.38 (2H, m), 1.75 (4H, m), 1.97 (2H, m), 3.18 (4H, m), 3.75 (3H, m), 4.39 (3H, m), 7.31 (4H, m), 7.56 (1H, d), 8.14 (1H, d)	475
741		δ 1.73 (2H, m), 1.94 (2H, m), 2.90 – 3.17 (9H, m), 3.48 (2H, t), 3.85 (2H, m), 4.44 (2H, m), 7.36 (4H, s), 7.67 (1H, d), 8.25 (1H, d)	511

Ejemplos 742–752

Los siguientes compuestos fueron preparados en 39–84% de rendimiento mediante un método análogo al Ejemplo 512, partiendo de ácido 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]benzoico y la amina apropiada:



Ej.	NR1R2	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
742		δ 2.67 (4H, m), 3.41 (8H, m), 3.78 (4H, m), 7.02 (2H, d), 7.30 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	461
743		δ 2.98 (3H, s), 3.41 (6H, m), 3.55 (2H, m), 3.78 (4H, m), 4.79 (1H, t), 7.02 (2H, d), 7.35 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	450
744		δ 2.20 (3H, s), 2.30 (4H, m), 3.42 (4H, m), 3.49 (4H, m), 3.78 (4H, m), 7.03 (2H, d), 7.31 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	475
745		δ 3.27 (3H, s), 3.39 – 3.47 (8H, m), 3.78 (4H, m), 7.03 (2H, d), 7.69 (1H, d), 7.78 (2H, d), 8.27 (1H, t), 8.31 (1H, d)	450
746	NMe2	δ 2.97 (6H, s), 3.42 (4H, m), 3.78 (4H, m), 7.02 (2H, d), 7.34 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	420
747		δ 1.77 – 1.95 (2H, m), 3.29 (1H, m), 3.42 – 3.66 (7H, m), 3.78 (4H, m), 4.27 (1H, m), 4.95 (1H, m), 7.02 (2H, d), 7.46 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	462
748		δ 1.83 (4H, m), 3.43 (8H, m), 3.78 (4H, m), 7.01 (2H, d), 7.47 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	446
749		δ 3.42 (4H, m), 3.50 (4H, m), 3.59 (4H, m), 3.78 (4H, m), 7.03 (2H, d), 7.34 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	462
750		δ 2.39 – 2.46 (6H, m), 3.36 (2H, m), 3.46 (4H, m), 3.57 (4H, m), 3.78 (4H, m), 7.03 (2H, d), 7.69 (1H, d), 7.76 (2H, d), 8.16 (1H, t), 8.31 (1H, d)	505

751		δ 2.97 (3H, s), 3.24 (3H, s), 3.41 (4H, m), 3.50 (4H, m), 3.78 (4H, m), 7.02 (2H, d), 7.32 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	464
752		δ 1.76 – 1.95 (2H, m), 3.29 (1H, m), 3.42 – 3.66 (7H, m), 3.78 (4H, m), 4.27 (1H, m), 4.96 (1H, m), 7.02 (2H, d), 7.46 (2H, d), 7.69 (1H, d), 8.31 (1H, d)	462

El ácido 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]benzoico usado como material de partida fue preparado como sigue:

Preparación de 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]benzoato de etilo

DIPEA (2.348 mL, 13.48 mmol) fue añadido a 6–cloro–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (2 g, 8.99 mmol) y 4–(piperazin–1–il)benzoato de etilo (2.316 g, 9.89 mmol, CAS 80518–57–6) en DMF (20 mL). La solución resultante fue agitada a 80°C durante 2 horas. La mezcla de reacción fue enfriada hasta la temperatura ambiente, luego evaporada hasta secarse y redisuelta en DCM (150 mL) y lavada con agua (100 mL). La capa orgánica fue secada sobre MgSO4, filtrada y evaporada para proporcionar el producto crudo el cual fue triturado con éter. El sólido fue recogido por filtración y secado al vacío para dar 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]benzoato de etilo (3.40 g, 90%) como un sólido.
1H NMR (399.9 MHz, DMSO–d6) δ 1.30 (3H, t), 3.54 (4H, m), 3.79 (4H, m), 4.26 (2H, q), 7.04 (2H, d), 7.66 (1H, d), 7.83 (2H, d), 8.30 (1H, d); m/z = 421 [M+H]+.

Preparación de ácido 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]benzoico

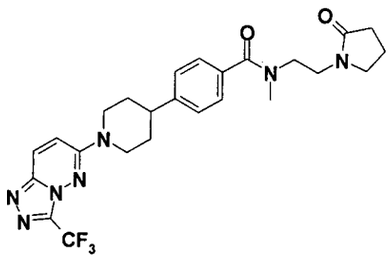
Hidróxido de litio monohidrato (0.373 g, 8.90 mmol) fue añadida a 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]benzoato de etilo (3.40 g, 8.09 mmol) en una mezcla de MeOH (60 mL) y agua (30 mL). La suspensión resultante fue agitada a 50°C durante 16 horas. Además hidróxido de litio monohidrato (0.373 g, 8.90 mmol) fue añadido, la temperatura fue aumentada hasta 65 °C y la suspensión fue agitada durante unas 6 horas adicionales. La mezcla de reacción fue enfriada hasta la temperatura ambiente y el MeOH evaporado. Los residuos fueron disueltos en agua (200 mL) y filtrada. El filtrado fue acidificado con ácido cítrico 1M hasta que la precipitación cesó, y el

precipitado fue recogido por filtración, lavado con agua y secado al vacío para proporcionar 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]benzoico ácido (3.17 g, 100%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 3.52 (4H, m), 3.79 (4H, m), 7.03 (2H, d), 7.67 (1H, d), 7.81 (2H, d), 8.30 (1H, d), 12.20 (1H, s); m/z = 393 [M+H]+.

Ejemplo 753

Preparación de N–metil–N–[2–(2–oxopirrolidin–1–il)etil]–4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzamida

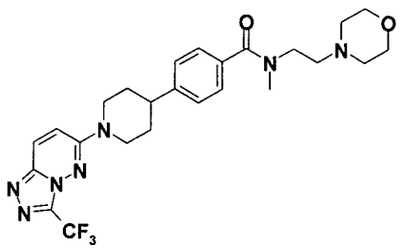


Una solución de N–[2–(2–oxopirrolidin–1–il)etil]–4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzamida (obtenida como se describió en el Ejemplo 639) (150 mg, 0.30 mmol) en DMF (2 mL) fue añadida en forma de gotas a una suspensión agitada de hidruro de sodio (60% en mineral oil) (13.16 mg, 0.33 mmol) en DMF (1 mL) bajo nitrógeno. La suspensión resultante fue agitada a temperatura ambiente durante 5 minutos, luego yodometano (0.028 mL, 0.45 mmol) fue añadido y la mezcla fue agitada a temperatura ambiente durante unos 10 minutos adicionales. La reacción fue apagada con MeOH (0.5 mL) y purificada por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar N–metil–N–[2–(2–oxopirrolidin–1–il)etil]–4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzamida (84 mg, 55%) como un sólido.

1H NMR (399.9 MHz, DMSO–d6) δ 1.67 – 1.94 (6H, m), 2.17 (2H, m), 2.87 – 2.98 (4H, m), 3.12 (2H, m), 3.44 (4H, m), 3.62 (2H, m), 4.44 (2H, m), 7.25 – 7.35 (4H, m), 7.68 (1H, d), 8.26 (1H, d); m/z = 516 [M+H]+.

Ejemplo 754

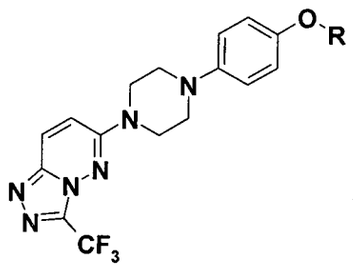
Preparación de N–metil–N–(2–morfolin–4–iletil)–4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzamida

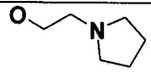
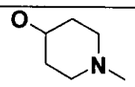
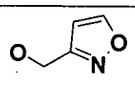


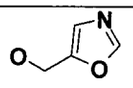
Obtenida en 74% de rendimiento mediante un método análogo al Ejemplo 753, partiendo de N–(2–morfolin–4–iletil)–4–[1–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperidin–4–il]benzamida (obtenida como se describió en el Ejemplo 638).
1H NMR (399.9 MHz, DMSO–d6) δ 1.72 (2H, m), 1.92 (2H, m), 2.14 (2H, m), 2.41 (4H, m), 2.88 – 2.97 (4H, m), 3.13 (2H, m), 3.43 – 3.59 (6H, m), 4.44 (2H, m), 7.33 (4H, m), 7.68 (1H, d), 8.26 (1H, d); m/z = 518 [M+H]+.

Ejemplos 755–758

Los siguientes compuestos fueron preparados en 9–24% de rendimiento mediante un método análogo al Ejemplo 514, partiendo de 4–[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]fenol y el alcohol apropiado:

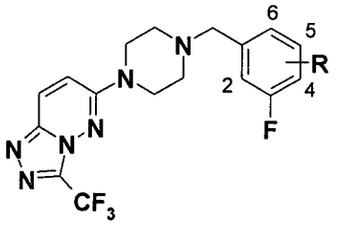


Ej.	OR	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
755		δ 1.70 (4H, m), 2.58 (4H, m), 2.82 (2H, m), 3.17 (4H, m), 3.76 (4H, m), 4.02 (2H, m), 6.87 (2H, d), 6.97 (2H, d), 7.69 (1H, d), 8.30 (1H, d)	462
756		δ 1.61 (2H, m), 1.89 (2H, m), 2.19 (5H, m), 2.64 (2H, m), 3.17 (4H, m), 3.75 (4H, m), 4.23 (1H, m), 6.87 (2H, d), 6.96 (2H, d), 7.69 (1H, d), 8.30 (1H, d)	462
757		δ 3.19 (4H, m), 3.76 (4H, m), 5.17 (2H, s), 6.69 (1H, d), 6.97 (4H, m), 7.69 (1H, d), 8.30 (1H, d),	446

		8.95 (1H, d)	
758		δ 3.19 (4H, m), 3.76 (4H, m), 5.11 (2H, s), 6.97 (4H, m), 7.31 (1H, s), 7.69 (1H, d), 8.30 (1H, d), 8.41 (1H, s)	446

Ejemplos 759–768

Los siguientes compuestos fueron preparados en 15–49% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:

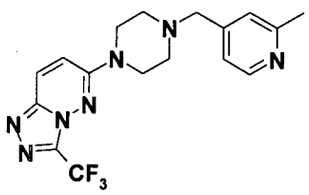


Ej.	R	1H NMR (400.1 MHz, DMSO–d6)	m/z [M+H]+
759	5–Cl	δ 2.52 – 2.56 (4H, m), 3.59 (2H, s), 3.62 – 3.66 (4H, m), 7.18 – 7.22 (1H, m), 7.29 (1H, s), 7.32 – 7.36 (1H, m), 7.59 (1H, d), 8.26 (1H, d)	415
760	5–CF3	δ 2.53 – 2.57 (4H, m), 3.62 – 3.66 (4H, m), 3.68 (2H, s), 7.56 – 7.61 (4H, m), 8.26 (1H, d)	449
761	2–CF3	δ 2.54 – 2.58 (4H, m), 3.60 – 3.64 (4H, m), 3.73 (2H, s), 7.38 – 7.44 (1H, m), 7.58 – 7.61 (2H, m), 7.69 – 7.72 (1H, m), 8.27 (1H, d)	449
762	6–CF3	δ 2.57 – 2.61 (4H, m), 3.65 – 3.69 (4H, m), 3.72 (2H, s), 7.32 – 7.36 (1H, m), 7.61 (1H, d), 7.64 – 7.67 (1H, m), 7.80 – 7.83 (1H, m), 8.27 (1H, d)	449
763	2,5–F	δ 2.55 – 2.58 (4H, m), 3.62 – 3.65 (4H, m), 3.67 (2H, d), 7.17 – 7.20 (1H, m), 7.45 – 7.48 (1H, m), 7.59 (1H, d), 8.26 (1H, d)	417
764	2,6–F	δ 2.55 – 2.59 (4H, m), 3.59 – 3.63 (4H, m), 3.71 (2H, s), 7.15 – 7.18 (1H, m), 7.48 – 7.53 (1H, m), 7.57 (1H, d), 8.24 (1H, d)	417
765	6–	δ 2.59 – 2.63 (4H, m), 3.42 (3H, s), 3.62 – 3.66 (4H,	459

	SO2Me	m), 3.96 (2H, s), 7.43 – 7.47 (1H, m), 7.56 – 7.59 (1H, m), 7.62 (1H, d), 8.04 – 8.08 (1H, m), 8.28 (1H, d)	
766	2,4–F	δ 2.54 – 2.58 (4H, m), 3.60 – 3.64 (6H, m), 7.30 – 7.34 (2H, m), 7.59 (1H, d), 8.25 (1H, d)	417
767	4,5–F	δ 2.53 – 2.56 (4H, m), 3.56 (2H, s), 3.61 – 3.65 (4H, m), 7.28 – 7.32 (2H, m), 7.60 (1H, d), 8.26 (1H, d)	417
768	2–Cl	δ 2.59 – 2.63 (4H, m), 3.62 – 3.66 (4H, m), 3.69 (2H, s), 7.35 – 7.42 (3H, m), 7.60 (1H, d), 8.26 (1H, d)	415

Ejemplo 769

Preparación de 6–[4–[(2–metilpiridin–4–il)metil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

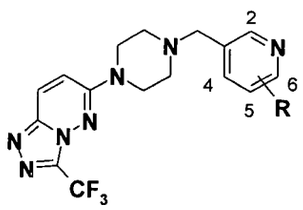


Obtenida en 61% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 2–metilpiridina–4–carboxaldehido.

1H NMR (399.9 MHz, DMSO–d6) δ 2.47 (3H, s), 2.54 – 2.58 (4H, m), 3.55 (2H, s), 3.62 – 3.66 (4H, m), 7.15 – 7.17 (1H, m), 7.22 (1H, s), 7.59 (1H, d), 8.26 (1H, d), 8.39 – 8.40 (1H, m); m/z = 378 [M+H]+.

Ejemplos 770–777

Los siguientes compuestos fueron preparados en 19–69% de rendimiento mediante el Método Sintético General 5 partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:

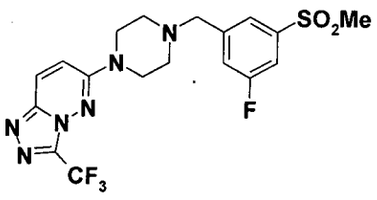


Ej.	R	1H NMR (400.1 MHz, DMSO–d6)	m/z [M+H]+

770	5–Cl	δ 2.54 – 2.58 (4H, m), 3.62 – 3.65 (6H, m), 7.59 (1H, d), 7.89 (1H, t), 8.26 (1H, d), 8.51 (1H, d), 8.56 (1H, d)	398
771	4–CF3	δ 2.56 – 2.60 (4H, m), 3.62 – 3.66 (4H, m), 3.76 (2H, s), 7.60 (1H, d), 7.74 (1H, d), 8.27 (1H, d), 8.78 (1H, d), 8.99 (1H, s)	432
772	2–Me	δ 2.53 – 2.57 (7H, m), 3.54 (2H, s), 3.60 – 3.64 (4H, m), 7.19 – 7.22 (1H, m), 7.60 (1H, d), 7.65 (1H, d), 8.26 (1H, d), 8.35 – 8.37 (1H, m)	378
773	4–Cl	δ 2.58 – 2.62 (4H, m), 3.61 – 3.65 (4H, m), 3.70 (2H, s), 7.56 (1H, d), 7.60 (1H, d), 8.26 (1H, d), 8.47 (1H, d), 8.66 (1H, s)	398
774	5–Br	δ 2.49 – 2.53 (4H, m), 3.60 – 3.90 (6H, m), 7.54 – 7.57 (1H, m), 7.63 (1H, d), 8.04 – 8.06 (1H, m), 8.34 (1H, d), 8.43 (1H, s)	442
775	2–OMe	δ 2.54 (2H, d), 2.56 (1H, t), 3.59 – 3.62 (3H, m), 3.64 (3H, d), 3.85 (3H, s), 7.33 (1H, q), 7.59 (1H, d), 8.14 (1H, d), 8.21 – 8.22 (1H, m), 8.26 (1H, d)	394
776	6–Me	δ 2.46 (3H, s), 2.52 – 2.55 (4H, m), 3.54 (2H, s), 3.60 – 3.63 (4H, m), 7.23 – 7.24 (1H, m), 7.57 – 7.63 (2H, m), 8.25 (1H, d), 8.39 (1H, s)	378
777	2–CF3	δ 2.56 – 2.60 (4H, m), 3.62 – 3.66 (4H, m), 3.75 (2H, s), 7.61 (1H, d), 7.73 – 7.76 (1H, m), 8.26 – 8.29 (2H, m), 8.65 – 8.66 (1H, m)	432

Ejemplo 778

Preparación de 6–[4–[3–fluoro–5–(metilsulfonil)bencil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 45% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 3–fluoro–5–metilsulfonilbenzaldehido.

1H NMR (399.9 MHz, DMSO–d6) δ 2.55 – 2.59 (4H, m), 3.30 (3H, s), 3.63 – 3.67 (4H, m), 3.70 (2H, s), 7.58 – 7.62 (2H, m), 7.70 – 7.73 (1H, m), 7.77 (1H, d), 8.26 (1H, d); m/z = 459 [M+H]+.

El 3–fluoro–5–metilsulfonilbenzaldehido usado como material de partida fue preparado como sigue:

Preparación de [3–fluoro–5–(metilsulfonil)fenil]metanol

La sal de sodio del ácido metanosulfínico (748 mg, 7.33 mmol) fue añadida a (3–bromo–5–fluorofenil)metanol (501 mg, 2.44 mmol) y yoduro de cobre(I) (0.248 mL, 7.33 mmol) en DMSO (12 mL) bajo nitrógeno. La mezcla resultante fue agitada a 90°C durante 3 días. La mezcla de reacción fue diluida con EtOAc (300 mL), luego filtrada. El filtrado fue lavado secuencialmente con agua (200 mL) y salmuera saturada (2 x 200 mL). La capa orgánica fue secada sobre Na_2SO_4, filtrada y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente en elusión 70 a 100% EtOAc en isohexano. Las fracciones puras fueron evaporadas hasta secarse para proporcionar [3–fluoro–5–(metilsulfonil)fenil]metanol (240 mg, 48.1%) como un sólido blanco.

1H NMR (399.9 MHz, CDCl3) δ 2.49 (1H, t), 3.07 (3H, s), 4.79 (2H, d), 7.36 – 7.40 (1H, m), 7.51 – 7.54 (1H, m), 7.72 (1H, s); m/z = 203 [M–H]–.

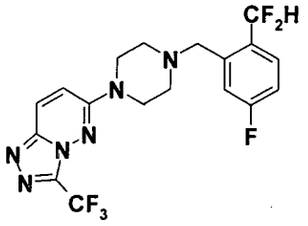
Preparación de 3–fluoro–5–metilsulfonilbenzaldehido

1,1,1–Triacetoxi–1,1–dihidro–1,2–benziodoxol–3(1H)–ona (530 mg, 1.21 mmol) fue añadida en una porción a [3–fluoro–5–(metilsulfonil)fenil]metanol (225 mg, 1.10 mmol) en DCM (20 mL) a 22°C. La solución resultante fue agitada a temperatura ambiente durante 2 horas. La mezcla de reacción fue diluida con DCM (50 ml) y vertida en bicarbonato de sodio acuoso saturado (30 mL) que contiene tiosulfato de sodio (1219 mg, 7.71 mmol). La suspensión resultante fue agitada durante 10 minutos antes de separar las capas. La capa orgánica fue lavada con agua (1 x 50 mL), secada sobre MgSO4 y evaporada para proporcionar el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente en elusión 30 a 40% EtOAc en isohexano. Las

fracciones puras fueron evaporadas hasta secarse para proporcionar 3–fluoro–5–(metilsulfonil)benzaldehído (168 mg, 75%) como un sólido blanco.
1H NMR (399.9 MHz, CDCl3) δ 3.13 (3H, s), 7.85 – 7.88 (1H, m), 7.91 – 7.93 (1H, m), 8.26 (1H, t), 10.07 (1H, d); m/z = 201 [M–H]–.

Ejemplo 779

Preparación de 6–[4–[2–(difluorometil)–5–fluorobencil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 61% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 2–difluorometil–5–fluorobenzaldehido.
1H NMR (399.9 MHz, DMSO–d6) δ 2.55 – 2.59 (4H, m), 3.60 – 3.64 (4H, m), 3.70 (2H, s), 7.26 – 7.32 (1H, m), 7.36 (1H, t), 7.36 – 7.41 (1H, m), 7.60 (1H, d), 7.67 – 7.71 (1H, m), 8.26 (1H, d); m/z = 431 [M+H]+.

El 2–difluorometil–5–fluorobenzaldehido usado como material de partida fue preparado como sigue:

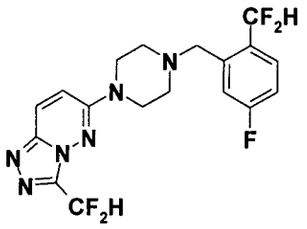
Complejo de cloruro de isopropilmagnesio– cloruro de litio en THF (1M, 21.46 mL, 21.46 mmol) fue añadido a 2–bromo–1–(difluorometil)–4–fluorobenceno (4.39 g, 19.51 mmol) en THF (120 mL), enfriado hasta –20°C bajo nitrógeno. La solución resultante fue agitada a –20°C durante 1 hora. N,N–Dimetilformamida (1.813 mL, 23.41 mmol) fue añadida, y la mezcla fue agitada durante 1 hora adicional, manteniendo la temperatura en el rango de –15 a –20 °C. La mezcla se dejó calentar hasta la temperatura ambiente, luego ácido clorhídrico 2M (100 mL) fue añadido y la mezcla fue extraída con EtOAc (150 mL). La capa orgánica fue lavada con bicarbonato de sodio saturado (120 mL) y concentrada para producir el producto crudo. El producto crudo fue purificado por cromatografía flash en sílice, gradiente en elusión 5 a 10% EtOAc en isohexano. Las fracciones puras fueron

evaporadas hasta secarse para proporcionar 2–(difluorometil)–5–fluorobenzaldehido (1.250 g, 36.8%) como un líquido incoloro.

1H NMR (399.9 MHz, CDCl3) δ 7.26 (1H, t), 7.37 – 7.43 (1H, m), 7.63 – 7.67 (1H, m), 7.78 – 7.82 (1H, m), 10.19 (1H, d); m/z = 173 [M–H]–.

Ejemplo 780

Preparación de 3–(difluorometil)–6–[4–[2–(difluorometil)–5–fluorobencil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina

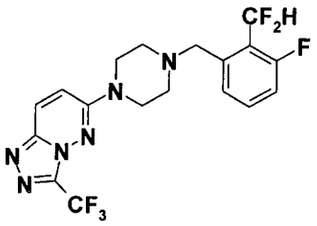


Obtenida en 58% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 248–263, preparación de los materiales de partida) y 2–difluorometil–5–fluorobenzaldehido (obtenida como se describió en el Ejemplo 779, preparación de los materiales de partida).

1H NMR (399.9 MHz, DMSO–d6) δ 2.54 – 2.57 (4H, m), 3.60 – 3.63 (4H, m), 3.70 (2H, s), 7.27 – 7.31 (1H, m), 7.36 (1H, t), 7.36 – 7.41 (1H, m), 7.51 – 7.53 (1H, m), 7.53 (1H, t), 7.67 – 7.71 (1H, m), 8.19 (1H, d); m/z = 413 [M+H]+.

Ejemplo 781

Preparación de 6–[4–[2–(difluorometil)–3–fluorobencil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



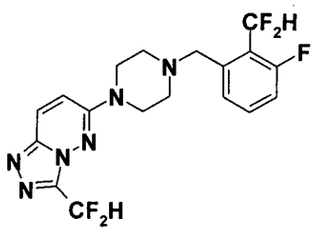
Obtenida en 33% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 2–difluorometil–3–fluorobenzaldehido.

1H NMR (399.9 MHz, DMSO–d6) δ 2.57 – 2.57 (4H, m), 3.56 – 3.60 (4H, m), 3.73 (2H, s), 7.28 – 7.32 (2H, m), 7.42 (1H, t), 7.55 – 7.60 (2H, m), 8.26 (1H, d); m/z = 431 [M+H]+.

El 2–difluorometil–3–fluorobenzaldehido usado como material de partida fue obtenido en 32% de rendimiento mediante un método análogo al Ejemplo 779, preparación de los materiales de partida, partiendo de 1–bromo–2–(difluorometil)–3–fluorobenceno.
1H NMR (399.9 MHz, CDCl3) δ 7.20– 7.43 (2H, m), 7.61 – 7.67 (1H, m), 7.86 (1H, d), 10.38 – 10.48 (1H, m); m/z = 173 [M–H]–.

Ejemplo 782

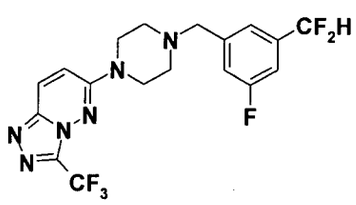
Preparación de 3–(difluorometil)–6–[4–[2–(difluorometil)–3–fluorobencil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



Obtenida en 39% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 248–263, preparación de los materiales de partida) y 2–difluorometil–3–fluorobenzaldehido (obtenida como se describió en el Ejemplo 781, preparación de los materiales de partida).
1H NMR (399.9 MHz, DMSO–d6) δ 2.52 – 2.56 (4H, m), 3.56 – 3.60 (4H, m), 3.73 (2H, s), 7.28 – 7.32 (2H, m), 7.34 – 7.57 (4H, m), 8.20 (1H, d); m/z = 413 [M+H]+.

Ejemplo 783

Preparación de 6–[4–[3–(difluorometil)–5–fluorobencil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina



Obtenida en 73% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 3–difluorometil–5–fluorobenzaldehido.

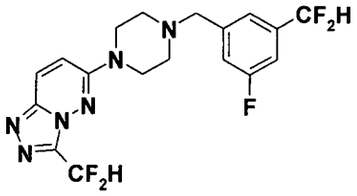
1H NMR (399.9 MHz, DMSO–d6) δ 2.53 – 2.58 (4H, m), 3.62 – 3.66 (6H, m), 7.07 (1H, t), 7.33 – 7.43 (3H, m), 7.60 (1H, d), 8.26 (1H, d); m/z = 431 [M+H]+.

El 3–difluorometil–5–fluorobenzaldehido usado como material de partida fue obtenido en 44% de rendimiento mediante un método análogo al Ejemplo 779, Preparación de material de partida, partiendo de 1–bromo–3–(difluorometil)–5–fluorobenceno.

1H NMR (399.9 MHz, CDCl3) δ 6.72 (1H, t), 7.49 – 7.52 (1H, m), 7.68 – 7.71 (1H, m), 7.83 (1H, d), 10.03 (1H, d); m/z = 173 [M–H]–.

Ejemplo 784

Preparación de 3–(difluorometil)–6–[4–[3–(difluorometil)–5–fluorobencil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina

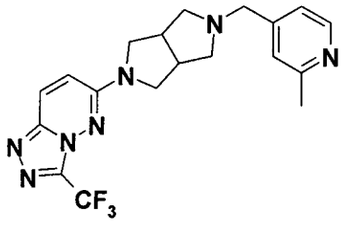


Obtenida en 66% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 248–263, preparación de los materiales de partida) y 3–difluorometil–5–fluorobenzaldehido (obtenida como se describió en el Ejemplo 783, preparación de los materiales de partida).

1H NMR (399.9 MHz, DMSO–d6) δ 2.53 – 2.57 (4H, m), 3.61 – 3.65 (6H, m), 7.07 (1H, t), 7.33 – 7.67 (5H, m), 8.19 (1H, d); m/z = 413 [M+H]+.

Ejemplo 785

Preparación de 6–[5–[(2–metilpiridin–4–il)metil]hexahidropirrolo[3,4–c]pirrol–2(1H)–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

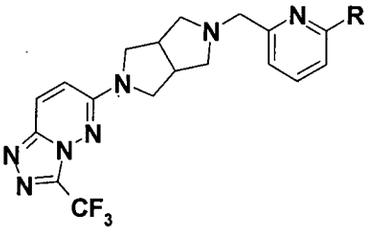


Obtenida en 47% de rendimiento mediante el Método Sintético General 10, partiendo de 6–[(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)]–[1,2,4]triazolo[4,3–b]piridazina y 2–metilpiridina–4–carboxaldehido.

1H NMR (399.9 MHz, DMSO–d6) δ 2.43 (3H, s), 2.55 – 2.63 (4H, m), 2.97 – 2.99 (2H, m), 3.41 – 3.44 (2H, m), 3.57 (2H, s), 3.73 – 3.78 (2H, m), 7.10 (1H, d), 7.15 (1H, s), 7.32 (1H, d), 8.23 (1H, d), 8.34 (1H, d); m/z = 404 [M+H]+.

Ejemplos 786–787

Los siguientes compuestos fueron preparados en 22–57% de rendimiento mediante el Método Sintético General 10, partiendo de 6–[(hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil)]–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:

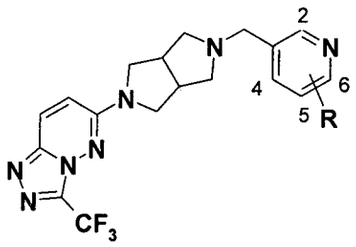


Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
786	H	δ 2.61 – 2.67 (4H, m), 2.96 – 3.00 (2H, m), 3.39 – 3.42 (2H, m), 3.71 (2H, s), 3.74 – 3.79 (2H, m), 7.23 – 7.26 (1H, m), 7.31 (1H, d), 7.39 (1H, d), 7.71 – 7.75 (1H, m), 8.22 (1H, d), 8.47 – 8.49 (1H, m)	390
787	Br	δ 2.62 – 2.68 (4H, m), 2.97 – 3.00 (2H, m), 3.40 – 3.44 (2H, m), 3.69 (2H, s), 3.75 – 3.79 (2H, m), 7.31 (1H, d), 7.45 (1H, d), 7.51 (1H, d), 7.71 (1H, t), 8.22 (1H, d)	469

825

Ejemplos 788–805

Los siguientes compuestos fueron preparados en 12–86% de rendimiento mediante el Método Sintético General 10, partiendo de 6–[hexahidropirrolo[3,4–c]pirrol–2(1H)–il)–3–(trifluorometil]–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:



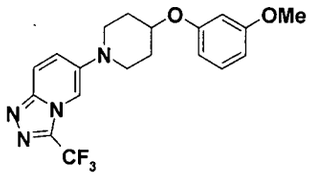
Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
788	2–OMe	δ 2.56 – 2.65 (4H, m), 2.95 – 2.99 (2H, m), 3.40 – 3.44 (2H, m), 3.56 (2H, s), 3.73 – 3.78 (2H, m), 3.86 (3H, s), 6.93 – 6.96 (1H, m), 7.32 (1H, d), 7.63 – 7.66 (1H, m), 8.04 – 8.05 (1H, m), 8.22 (1H, d)	420
789	5–F	δ 2.58 – 2.64 (4H, m), 2.96 – 3.00 (2H, m), 3.40 – 3.44 (2H, m), 3.67 (2H, s), 3.73 – 3.77 (2H, m), 7.31 (1H, d), 7.60 – 7.64 (1H, m), 8.22 (1H, d), 8.39 (1H, d), 8.46 (1H, d)	408
790	2–Cl	δ 2.63 – 2.70 (4H, m), 2.98 – 3.01 (2H, m), 3.41 – 3.44 (2H, m), 3.70 (2H, s), 3.75 – 3.80 (2H, m), 7.32 (1H, d), 7.39 – 7.42 (1H, m), 7.88 – 7.90 (1H, m), 8.23 (1H, d), 8.29 – 8.31 (1H, m)	424
791	6–Cl	δ 2.54 – 2.62 (4H, m), 2.96 – 2.98 (2H, m), 3.36 – 3.41 (2H, m), 3.62 (2H, s), 3.72 – 3.77 (2H, m), 7.30 (1H, d), 7.44 – 7.47 (1H, m), 7.76 – 7.78 (1H, m), 8.22 (1H, d), 8.32 (1H, d)	424
792	2–Cl, 5–F	δ 2.63 – 2.68 (4H, m), 2.98 – 3.01 (2H, m), 3.42 – 3.46 (2H, m), 3.70 (2H, s), 3.75 – 3.80 (2H, m), 7.32 (1H, d), 7.79 – 7.82 (1H, m), 8.23 (1H, d), 8.36 (1H, d)	442
793	6–OMe	δ 2.53 – 2.60 (4H, m), 2.95 – 2.98 (2H, m), 3.36 – 3.40 (2H, m), 3.52 (2H, s), 3.71 – 3.75 (2H, m), 3.83 (3H, s), 6.75 (1H, d), 7.30 (1H, d), 7.59 – 7.62 (1H,	420

		m), 8.05 (1H, d), 8.22 (1H, d)	
794	5–Br	δ 2.53 – 2.56 (2H, m), 2.60 – 2.65 (2H, m), 2.95 – 2.99 (2H, m), 3.39 – 3.43 (2H, m), 3.63 (2H, s), 3.71 – 3.76 (2H, m), 7.31 (1H, d), 7.94 (1H, t), 8.22 (1H, d), 8.49 (1H, d), 8.59 (1H, d)	468
795	5–Br, 2–F	δ 2.53 – 2.59 (2H, m), 2.65 – 2.69 (2H, m), 2.96 – 2.99 (2H, m), 3.40 – 3.44 (2H, m), 3.64 (2H, s), 3.71 – 3.75 (2H, m), 7.31 (1H, d), 8.10 – 8.13 (1H, m), 8.22 (1H, d), 8.27 – 8.29 (1H, m)	486
796	2–Br	δ 2.62 – 2.68 (4H, m), 2.99 – 3.01 (2H, m), 3.40 – 3.44 (2H, m), 3.67 (2H, s), 3.76 – 3.80 (2H, m), 7.32 (1H, d), 7.41 – 7.44 (1H, m), 7.82 – 7.85 (1H, m), 8.22 (1H, d), 8.26 – 8.28 (1H, m)	468
797	5–OMe	δ 2.54 – 2.63 (4H, m), 2.97 – 2.99 (2H, m), 3.41 – 3.44 (2H, m), 3.61 (2H, s), 3.71 – 3.76 (2H, m), 3.79 (3H, s), 7.26 (1H, s), 7.31 (1H, d), 8.10 (1H, d), 8.17 – 8.18 (1H, m), 8.22 (1H, d)	420
798	6–Br	δ 2.53 – 2.62 (4H, m), 2.96 – 2.98 (2H, m), 3.36 – 3.41 (2H, m), 3.59 (2H, s), 3.72 –3.75 (2H, m), 7.30 (1H, d), 7.57 – 7.60 (1H, m), 7.66 – 7.68 (1H, m), 8.22 (1H, d), 8.31 (1H, d)	468
799	2–Me	δ 2.46 (3H, s), 2.56 – 2.62 (4H, m), 2.96 – 2.98 (2H, m), 3.38 – 3.41 (2H, m), 3.58 (2H, s), 3.73 – 3.77 (2H, m), 7.14 – 7.17 (1H, m), 7.30 (1H, d), 7.58 – 7.61 (1H, m), 8.22 (1H, d), 8.30 – 8.31 (1H, m)	404
800	4–Cl	δ 2.59 – 2.63 (2H, m), 2.66 – 2.70 (2H, m), 2.97 – 2.99 (2H, m), 3.39 – 3.43 (2H, m), 3.72 – 3.76 (4H, m), 7.31 (1H, d), 7.51 (1H, d), 8.22 (1H, d), 8.43 (1H, d), 8.58 (1H, s)	424
801	4–Br	δ 2.61 – 2.68 (4H, m), 2.97 – 2.99 (2H, m), 3.40 – 3.44 (2H, m), 3.73 – 3.76 (4H, m), 7.31 (1H, d), 7.67 (1H, d), 8.22 (1H, d), 8.31 (1H, d), 8.54 (1H, s)	469
802	4–CF3	δ 2.60 – 2.64 (4H, m), 2.97 – 3.00 (2H, m), 3.36 –	458

		3.41 (3H, m), 3.75 – 3.78 (2H, m), 3.79 (2H, s), 7.31 (1H, d), 7.68 (1H, d), 8.22 (1H, d), 8.73 (1H, d), 8.89 (1H, s)	
803	4–OMe	δ 2.53 – 2.68 (4H, m), 2.96 – 2.99 (2H, m), 3.41 – 3.44 (2H, m), 3.62 (2H, s), 3.71 – 3.75 (2H, m), 3.84 (3H, s), 7.02 (1H, d), 7.31 (1H, d), 8.22 (1H, d), 8.33 – 8.36 (2H, m)	420
804	5–Cl	δ 2.54 – 2.58 (2H, m), 2.60 – 2.65 (2H, m), 2.97 – 2.99 (2H, m), 3.41 – 3.44 (2H, m), 3.64 (2H, s), 3.72 – 3.76 (2H, m), 7.31 (1H, d), 7.82 (1H, t), 8.22 (1H, d), 8.46 – 8.47 (1H, m), 8.51 (1H, d)	424
805	2–CF3	δ 2.60 – 2.64 (4H, m), 2.97 – 3.00 (2H, m), 3.38 – 3.41 (2H, m), 3.76 – 3.79 (4H, m), 7.32 (1H, d), 7.66 – 7.69 (1H, m), 8.14 (1H, d), 8.23 (1H, d), 8.61 (1H, d)	458

Ejemplo 806

Preparación de 6–[4–(3–metoxifenoxi)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–a]piridina



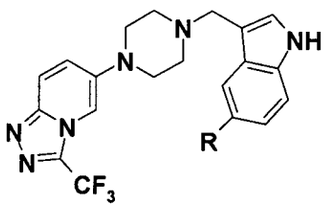
Una mezcla de 6–bromo–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina (obtenida como se describió en el Método Sintético General 9, preparación de los materiales de partida) (100 mg, 0.38 mmol) y hidrocloruro de 4–(3–metoxifenoxi)piperidina (110 mg, 0.45 mmol), rac–2,2'–bis(difenilfosfino)–1,1'–binaftil (17.56 mg, 0.03 mmol) y tert–butóxido de sodio (0.161 mL, 1.32 mmol) fue suspendida en xilenos (5 mL), luego degasificada y purgada con nitrógeno. Bis(dibencilidenoacetona)paladio (11 mg, 0.02 mmol) fue añadido, y la mezcla fue sellada en un tubo de microondas. La reacción fue calentada hasta 100°C durante 20 minutos en el reactor de microondas y enfriada hasta la temperatura ambiente. La mezcla de reacción fue diluida con EtOAc (25 mL) y lavada con agua (25 mL). La capa orgánica fue purificada por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 7M en metanol y las

fracciones puras fueron evaporadas hasta secarse para proporcionar el producto crudo. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–(3–metoxifenoxi)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–a]piridina (45.0 mg, 30.5 %) como un sólido blanco.

1H NMR (399.9 MHz, DMSO–d6) δ 1.77 – 1.83 (2H, m), 2.07 – 2.12 (2H, m), 3.11 – 3.17 (2H, m), 3.47 – 3.53 (2H, m), 3.74 (3H, s), 4.59 – 4.63 (1H, m), 6.51 – 6.55 (2H, m), 6.54 – 6.59 (1H, m), 7.20 (1H, t), 7.59 (1H, s), 7.75 – 7.78 (1H, m), 7.94 (1H, d); m/z = 393 [M+H]+.

Ejemplos 807–809

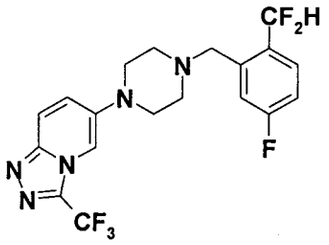
Los siguientes compuestos fueron preparados en 61–70% de rendimiento mediante el Método Sintético General 9, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina y el indol–3–carboxaldehido apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
807	H	δ 2.56 – 2.60 (4H, m), 3.16 – 3.19 (4H, m), 3.72 (2H, s), 6.97 – 7.01 (1H, m), 7.06 – 7.10 (1H, m), 7.28 (1H, d), 7.36 (1H, d), 7.51 (1H, s), 7.66 – 7.69 (1H, m), 7.71 – 7.74 (1H, m), 7.92 (1H, d), 10.96 (1H, s)	401
808	F	δ 2.55 – 2.59 (4H, m), 3.16 – 3.20 (4H, m), 3.69 (2H, s), 6.90 – 6.95 (1H, m), 7.34 – 7.37 (2H, m), 7.38 – 7.42 (1H, m), 7.51 (1H, s), 7.71 – 7.74 (1H, m), 7.92 (1H, d), 11.07 – 11.08 (1H, m)	419
809	CN	δ 2.56 – 2.60 (4H, m), 3.17 – 3.21 (4H, m), 3.76 (2H, s), 7.43 – 7.45 (1H, m), 7.51 – 7.56 (3H, m), 7.71 – 7.74 (1H, m), 7.92 (1H, d), 8.20 (1H, t), 11.57 (1H, d)	426

Ejemplo 810

Preparación de 6–[4–[2–(difluorometil)–5–fluorobencil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–a]piridina

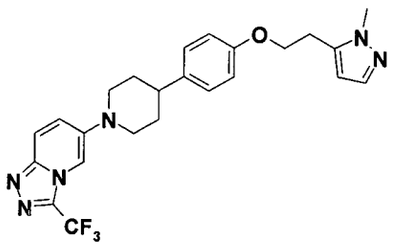


Obtenida en 39% de rendimiento mediante el Método Sintético General 9, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina y 2–difluorometil–5–fluorobenzaldehido (obtenido como se describió en el Ejemplo 779, preparación de los materiales de partida).

1H NMR (399.9 MHz, DMSO–d6) δ 2.56 – 2.60 (4H, m), 3.18 – 3.22 (4H, m), 3.72 (2H, s), 7.28 – 7.32 (1H, m), 7.37 (1H, t), 7.37 – 7.41 (1H, m), 7.54 (1H, s), 7.68 – 7.75 (2H, m), 7.94 (1H, d); m/z = 430 [M+H]+.

Ejemplo 811

Preparación de 6–[4–[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–a]piridina



4–[4–[2–(1–Metil–1H–pirazol–5–il)etoxi]fenil]piperidina (69 mg, 0.24 mmol), 6–bromo–3–(trifluorometil)–[1,2,4]triazolo[4,3–a]piridina (obtenida como se describió en el Método Sintético General 9, preparación de los materiales de partida) (65 mg, 0.24 mmol), rac–2,2'–bis(difenilfosfino)–1,1'–binaftil (11.41 mg, 0.02 mmol) y tert–butóxido de sodio (0.060 mL, 0.49 mmol) fueron suspendidos en xilenos (5 mL), luego degasificados y purgados con nitrógeno. Bis(dibencilidenoacetona)paladio (7.02 mg, 0.01 mmol) fue añadido, y la mezcla fue sellada en un tubo de microondas. La reacción fue calentada hasta 110°C durante 30 minutos en el reactor de microondas y enfriada hasta la temperatura ambiente. La mezcla de reacción fue diluida con EtOAc (25 mL), y lavada con agua (25

mL). La capa acuosa fue extraída con EtOAc adicional (25 mL). Las capas orgánicas separadas fueron purificadas por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 7M en metanol y las fracciones puras fueron evaporadas hasta secarse para proporcionar el producto crudo. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, 5µ sílice, diámetro 19 mm, longitud 100 mm), usando mezclas decrecientemente polares de agua (que contienen 1% amoniaco) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar 6–[4–[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–a]piridina (22.00 mg, 19.14 %) como una goma incolora.

1H NMR (399.9 MHz, DMSO–d6) δ 1.75 – 1.82 (2H, m), 1.84 – 1.90 (2H, m), 2.66 – 2.70 (1H, m), 2.80 – 2.85 (4H, m), 3.79 (3H, s), 3.80 – 3.83 (2H, s), 4.06 (2H, t), 6.90 (2H, d), 7.21 (2H, d), 7.34 (1H, s), 7.57 (2H, s), 7.77 – 7.80 (1H, m), 7.94 (1H, d); m/z = 471 [M+H]+.

La 4–[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperidina usada como material de partida fue preparada como sigue:

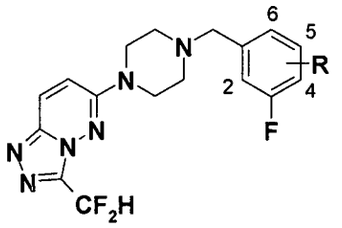
DIAD (64.8 µl, 0.33 mmol) fue añadido a 4–(piperidin–4–il)fenol (CAS 263139–27–1, 53 mg, 0.30 mmol), 2–(1–metil–1H–pirazol–5–il)etanol (obtenida como se describió en la Sol. Int. WO 2007017222, producto intermedio1) (37.7 mg, 0.30 mmol) y trifenilfosfina (86 mg, 0.33 mmol) en DCM (3 mL) a 20°C bajo nitrógeno. La mezcla resultante fue agitada a 22°C durante 3 días. La mezcla de reacción fue purificada por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando amoniaco 7M en metanol y las fracciones puras fueron evaporadas hasta secarse para proporcionar 4–[4–[2–(1–metil–1H–pirazol–5–il)etoxi]fenil]piperidina (85 mg, 96%) como una aceite amarillo.

m/z = 286 [M+H]+.

Ejemplos 812–820

Los siguientes compuestos fueron preparados en 11–72% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–

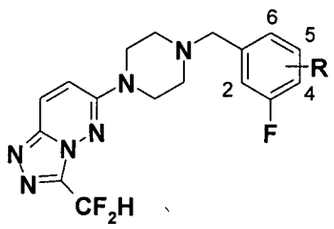
[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 248–263, preparación de los materiales de partida) y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
812	2–CF3	δ 2.54 (4H, t), 3.54 (4H, t), 3.66 (2H, s), 6.96 (1H, d), 7.02 – 7.07 (1H, m), 7.05 (1H, t), 7.39 – 7.45 (2H, m), 7.83 (1H, d)	432
813	5–Cl	δ 2.59 (4H, t), 3.54 (2H, s), 3.64 (4H, t), 7.00 – 7.26 (5H, m), 7.91 (1H, d)	398
814	5–CF3	δ 2.61 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.03 (1H, d), 7.13 (1H, t), 7.25 (1H, d), 7.31 (1H, d), 7.42 (1H, s), 7.91 (1H, dd)	432
815	6–Cl	δ 2.67 (4H, t), 3.64 – 3.67 (6H, m), 6.94 (1H, td), 7.04 (1H, d), 7.13 (1H, t), 7.26 – 7.35 (2H, m), 7.91 (1H, d)	398
816	6–CF3	δ 2.65 (4H, s), 3.66 (4H, s), 3.73 (2H, s), 7.03 – 7.07 (2H, m), 7.13 (1H, t), 7.59 (1H, d), 7.65 (1H, dd), 7.92 (1H, d)	432
817	2,6–F	δ 2.68 (4H, s), 3.63 (4H, t), 3.81 (2H, s), 6.83 – 6.89 (1H, m), 7.00 (1H, d), 7.08 – 7.16 (1H, m), 7.12 (1H, t), 7.89 (1H, d)	400
818	4,5–F	δ 2.59 (4H, s), 3.50 (2H, s), 3.64 (4H, s), 6.95 – 7.05 (3H, m), 7.15 (1H, t), 7.92 (1H, d)	399
819	6–SO2Me	δ 2.73 – 2.81 (4H, m), 3.31 (3H, s), 3.65 (4H, t), 4.07 (2H, s), 7.04 (1H, d), 7.12 (1H, t), 7.18 – 7.23 (1H, m), 7.36 (1H, s), 7.94 (1H, d), 8.15 (1H, dd)	441
820	2,5–F	δ 2.58 – 2.71 (4H, m), 3.56 – 3.72 (6H, m), 6.80 – 6.91 (1H, m), 6.95 – 7.03 (1H, m), 7.02 (1H, d), 7.13 (1H, t), 7.91 (1H, d)	400

Ejemplos 821–823

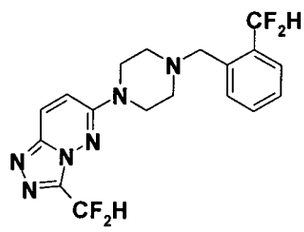
Los siguientes compuestos fueron preparados en 19–45% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 248–263, preparación de los materiales de partida) y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
821	4,6–F	δ 3.18 – 3.80 (10H, m), 7.41 – 7.67 (4H, m), 8.21 (1H, d)	400
822	2–Cl	δ 3.38 – 4.41 (10H, m), 7.47 – 7.54 (4H, m), 7.56 (1H, t), 8.27 (1H, d)	397
823	2,4–F	δ 3.39 – 4.25 (10H, m), 7.34 – 7.69 (4H, m), 8.28 (1H, d)	399

Ejemplo 824

Preparación de 3–(difluorometil)–6–[4–[2–(difluorometil)bencil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



Obtenida en 70% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en los Ejemplos 248–263, preparación de los materiales de partida) y 2–difluorometilbenzaldehido.

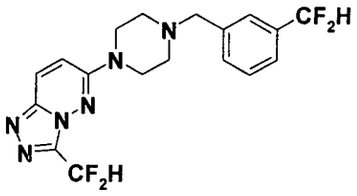
1H NMR (399.9 MHz, CDCl3) δ 2.51 (4H, t), 3.53 (4H, t), 3.62 (2H, s), 6.95 (1H, d), 7.05 (1H, t), 7.18 (1H, t), 7.27 – 7.37 (3H, m), 7.59 (1H, t), 7.83 (1H, d); m/z = 396 [M+H]+.

El 2–difluorometilbenzaldehido usado como material de partida fue obtenido en 19% de rendimiento mediante un método análogo al Ejemplo 779, preparación de los materiales de partida, partiendo de 1–bromo–2–(difluorometil)benceno.

1H NMR (399.9 MHz, CDCl3) δ 7.36 (1H, t), 7.61 – 7.68 (2H, m), 7.75 (1H, d), 7.87 (1H, d), 10.12 (1H, s); m/z = 155 (M–H)–.

Ejemplo 825

Preparación de 3–(difluorometil)–6–[4–[3–(difluorometil)bencil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



Obtenida en 20% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina y 3–difluorometilbenzaldehido.

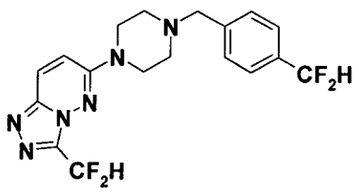
1H NMR (399.9 MHz, CDCl3) δ 2.53 (4H, t), 3.55 – 3.57 (6H, m), 6.58 (1H, t), 6.95 (1H, d), 7.06 (1H, t), 7.36 – 7.44 (4H, m), 7.83 (1H, d); m/z = 396 [M+H]+.

El 3–difluorometilbenzaldehido usado como material de partida fue obtenido en 10% de rendimiento mediante un método análogo al Ejemplo 779, preparación de los materiales de partida, partiendo de 1–bromo–3–(difluorometil)benceno.

1H NMR (399.9 MHz, CDCl3) δ 6.66 (1H, t), 7.59 (1H, t), 7.72 (1H, d), 7.94 (1H, d), 7.97 (1H, s), 10.01 (1H, s)

Ejemplo 826

Preparación de 3–(difluorometil)–6–[4–[4–(difluorometil)bencil]piperazin–1–il][1,2,4]triazolo[4,3–b]piridazina



Obtenida en 20% de rendimiento mediante el Método Sintético General 5, partiendo de 3–(difluorometil)–6–(piperazin–1–il)–[1,2,4]triazolo[4,3–b]piridazina y 4–difluorometilbenzaldehido.

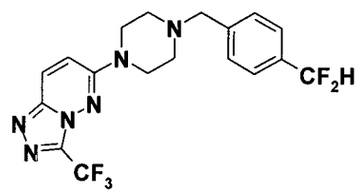
1H NMR (399.9 MHz, CDCl3) δ 2.54 – 2.69 (4H, m), 3.55 – 3.72 (6H, m), 6.65 (1H, t), 7.02 (1H, d), 7.12 (1H, t), 7.43 – 7.52 (4H, m), 7.91 (1H, d); m/z = 396 [M+H]+.

El 4–difluorometilbenzaldehido usado como material de partida fue obtenido en 34% de rendimiento mediante un método análogo al Ejemplo 779, preparación de los materiales de partida, partiendo de 1–bromo–3–(difluorometil)benceno.

1H NMR (399.9 MHz, CDCl3) δ 6.71 (1H, t), 7.69 (2H, d), 7.98 (2H, d), 10.08 (1H, s); m/z = 155 [M–H]–.

Ejemplo 827

Preparación de 6–[4–[4–(difluorometil)bencil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

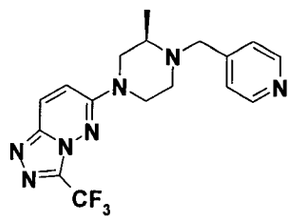


Obtenida en 23% de rendimiento mediante el Método Sintético General 5, partiendo de 6–(piperazin–1–il)–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y 4–difluorometilbenzaldehido (obtenida como se describió en el Ejemplo 826, Preparación de material de partida).

1H NMR (399.9 MHz, CDCl3) δ 2.57 – 2.70 (4H, m), 3.61 – 3.73 (6H, m), 6.65 (1H, t), 7.05 (1H, d), 7.45 – 7.51 (4H, m), 7.93 (1H, d); m/z = 414 [M+H]+.

Ejemplos 828

Preparación de 6–[(3R)–3–metil–4–(piridin–4–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina

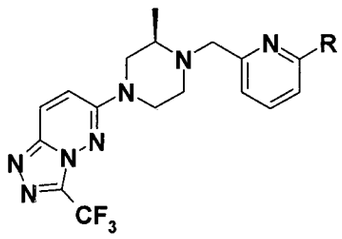


Obtenida en 58% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(3R)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 564, preparación de los materiales de partida) y piridina–4–carboxaldehido.

1H NMR (399.9 MHz, CDCl3) δ 1.21 (3H, d), 2.34 (1H, ddd), 2.66 – 2.73 (1H, m), 2.81 (1H, ddd), 3.15 (1H, dd), 3.29 (1H, d), 3.37 (1H, ddd), 3.81 – 3.91 (2H, m), 4.04 (1H, d), 7.05 (1H, d), 7.32 (2H, d), 7.93 (1H, dd), 8.57 (2H, dd); m/z = 378 [M+H]+.

Ejemplos 829–830

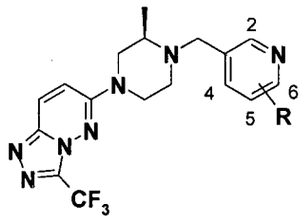
Los siguientes compuestos fueron preparados en 19–28% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(3R)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
829	H	δ 1.22 – 1.33 (3H, m), 2.37 – 2.58 (1H, m), 2.66 – 2.84 (1H, m), 2.84 – 3.01 (1H, m), 3.08 – 3.27 (1H, m), 3.30 – 3.62 (2H, m), 3.84 – 3.94 (2H, m), 4.16 (1H, d), 7.05 (1H, d), 7.18 – 7.23 (1H, m), 7.44 – 7.52 (1H, m), 7.69 (1H, t), 7.92 (1H, d), 8.58 (1H, dd)	378
830	Br	δ 1.21 (3H, d), 2.42 – 2.52 (1H, m), 2.66 – 2.81 (1H, m), 2.89 – 2.91 (1H, m), 3.13 (1H, t), 3.37 (1H, t), 3.58 (1H, d), 3.87 (2H, d), 4.07 (1H, d), 7.05 (1H, d), 7.38 (1H, d), 7.48 – 7.56 (2H, m), 7.93 (1H, d)	456

Ejemplos 831–836

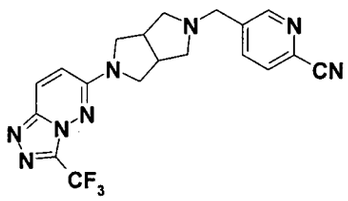
Los siguientes compuestos fueron preparados en 8–30% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(3R)–3–metilpiperazin–1–il]–3–(trifluorometil)–[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:–



Ej.	R	1H NMR (399.9 MHz, CDCl3)	m/z [M+H]+
831	6–CF3	δ 1.24 (3H, d), 2.36 (1H, t), 2.67 – 2.81 (2H, m), 3.17 (1H, t), 3.34 – 3.40 (2H, m), 3.81 – 3.90 (2H, m), 4.11 (1H, d), 7.05 (1H, dd), 7.67 (1H, d), 7.86 – 7.92 (1H, m), 7.93 (1H, d), 8.71 (1H, s)	446
832	2–Cl	δ 1.22 (3H, d), 2.45 (1H, t), 2.71 – 2.87 (2H, m), 3.17 (1H, t), 3.39 (1H, t), 3.48 (1H, d), 3.86 (2H, t), 4.03 (1H, d), 7.06 (1H, d), 7.85 – 7.95 (2H, m), 8.26 – 8.36 (1H, m) (1H oscurecida por CHCl3)	412
833	6–Cl	δ 1.20 – 1.27 (3H, m), 2.25 – 2.41 (1H, m), 2.69 – 2.78 (2H, m), 3.09 – 3.20 (1H, m), 3.26 – 3.34 (2H, m), 3.80 – 3.88 (2H, m), 4.00 – 4.03 (1H, m), 7.04 (1H, d), 7.31 – 7.36 (1H, m), 7.64 – 7.71 (1H, m), 7.93 (1H, d), 8.35 (1H, d)	412
834	6–OMe	δ 1.24 (3H, d), 2.25 – 2.30 (1H, m), 2.59 – 2.69 (1H, m), 2.79 – 2.82 (1H, m), 3.12 (1H, t), 3.22 (1H, d), 3.27 – 3.35 (1H, m), 3.79 – 3.87 (2H, m), 3.94 (3H, s), 3.94 – 3.99 (1H, m), 6.74 (1H, d), 7.04 (1H, d), 7.57 – 7.59 (1H, m), 7.91 (1H, d), 8.07 (1H, s)	409
835	5–Br, 2–F	δ 1.21 – 1.24 (3H, m), 2.39 – 2.47 (1H, m), 2.68 – 2.80 (1H, m), 2.85 – 2.87 (1H, m), 3.11 – 3.20 (1H, m), 3.39 – 3.42 (2H, m), 3.82 – 3.97 (3H, m), 7.06 (1H, d), 7.94 (1H, d), 7.99 – 8.08 (1H, m), 8.18 (1H, s)	475
836	5–F	δ 1.16 (3H, d), 2.22 – 2.35 (1H, m), 2.65 – 2.76 (2H, m), 3.04 – 3.16 (1H, m), 3.25 – 3.34 (2H, m), 3.75 – 3.83 (2H, m), 3.99 (1H, d), 6.98 (1H, d), 7.34 – 7.49 (1H, m), 7.86 (1H, d), 8.33 (2H, s)	397

Ejemplo 837

Preparación de 5–[[5–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]hexahidropirrolo[3,4–c]pirrol–2(1H)–il]metil]piridina–2–carbonitrilo

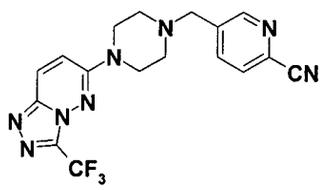


Obtenido en 76% de rendimiento mediante un método análogo al Ejemplo 307, partiendo de 6–[5–[(6–bromopiridin–3–il)metil]hexahidropirrolo[3,4–c]pirrol–2(1H)–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 797).

1H NMR (399.9 MHz, CDCl3) δ 2.63 - 2.70 (4H, m), 3.43 (2H, dd), 3.45 (2H, s), 3.71 (2H, s), 3.83 (2H, dd), 6.87 (1H, d), 7.65 (1H, d), 7.78 (1H, d), 7.91 (1H, d), 8.65 (1H, s); m/z = 416 [M+H]+.

Ejemplo 838

Preparación de 5–[[4–[3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazin–6–il]piperazin–1–il]metil]piridina–2–carbonitrilo



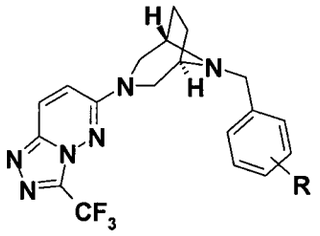
Obtenido en 49% de rendimiento mediante un método análogo al Ejemplo 307, partiendo de 6–[4–[(6–bromopiridin–3–il)metil]piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 374).

1H NMR (399.9 MHz, CDCl3) δ 2.58 - 2.69 (4H, m), 3.60 - 3.75 (6H, m), 7.06 (1H, d), 7.70 (1H, d), 7.83 - 7.90 (1H, m), 7.95 (1H, d), 8.71 (1H, s); m/z = 390 [M+H]+.

Ejemplos 839–841

Los siguientes compuestos fueron preparados en 62–77% de rendimiento mediante el Método Sintético General 5, partiendo de 6–[(1R,5S)–3,8–diazabiciclo[3.2.1]oct–3–il]–3–

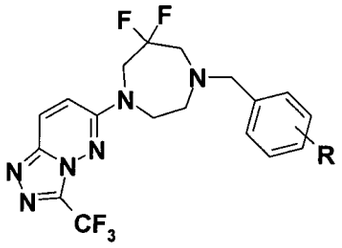
(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina (obtenida como se describió en el Ejemplo 553, preparación de los materiales de partida) y el aldehído apropiado:



Ej.	R	1H NMR (399.9 MHz, DMSO–d6)	m/z [M+H]+
839	4–F	δ 1.64 (2H, m), 2.00 – 2.04 (2H, m), 3.16 – 3.19 (2H, m), 3.58 (2H, s), 3.81 – 3.84 (2H, m), 7.14 – 7.18 (2H, m), 7.43 – 7.47 (2H, m), 7.50 (1H, d), 8.24 (1H, d)	407
840	3–CN	δ 1.65 – 1.67 (2H, m), 2.02 – 2.05 (2H, m), 3.20 – 3.23 (2H, m), 3.33 (2H, d), 3.67 (2H, s), 3.82 – 3.85 (2H, m), 7.51 (1H, d), 7.55 – 7.59 (1H, m), 7.73 – 7.76 (1H, m), 7.77 – 7.79 (1H, m), 7.86 (1H, s), 8.25 (1H, d)	414
841	4–CN	δ 1.65 – 1.68 (2H, m), 2.01 – 2.04 (2H, m), 3.19 – 3.22 (2H, m), 3.31 – 3.34 (2H, m, parcialmente oscurecida por pico del solvente), 3.71 (2H, s), 3.82 – 3.86 (2H, m), 7.51 (1H, d), 7.63 – 7.65 (2H, m), 7.80 – 7.83 (2H, m), 8.25 (1H, d)	414

Ejemplos 842–844

Los siguientes compuestos fueron preparados en 42–55% de rendimiento mediante un método análogo al Ejemplo 563, partiendo de 6–(6,6–difluoro–1,4–diazepan–1–il)–3–(trifluorometil)[1,2,4]triazolo[4,3–b]piridazina y el aldehído apropiado:

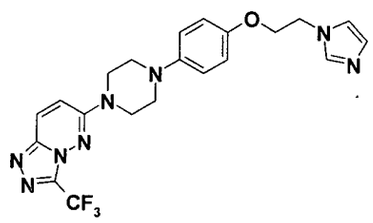


Ej.	R	1H NMR (500 MHz, DMSO–d6)	m/z [M+H]+
842	3–F	δ 2.84–2.91 (m, 2H), 3.06–3.16 (m, 2H), 3.78 (s, 2H), 3.80–3.87 (m, 2H), 4.29–4.38 (m, 2H), 6.95–7.05 (m,	431

		3H), 7.16–7.22 (m, 1H), 7.62 (d, 1H), 8.32 (d, 1H)	
843	4–CN	δ 2.83–2.89 (m, 2H), 3.07–3.17 (m, 2H), 3.79–3.85 (m, 2H), 3.85 (s, 2H), 4.29–4.38 (m, 2H), 7.39 (d, 2H), 7.58 (d, 2H), 7.62 (d, 1H), 8.33 (d, 1H)	438
844	3–CN	δ 2.84–2.91 (m, 2H), 3.06–3.17 (m, 2H), 3.82 (s, 2H), 3.82–3.86 (m, 2H), 4.29–4.39 (m, 2H), 7.33 (dd, 1H), 7.53 (d, 1H), 7.59–7.66 (m, 2H), 7.68 (s, 1H), 8.32 (d, 1H)	438

Ejemplo 845

Preparación de 6-[4-[4-[2-(1H-imidazol-1-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

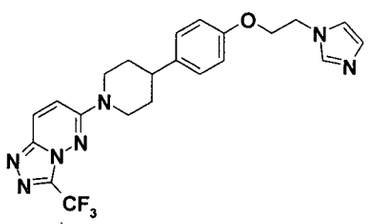


Se obtuvo con un 6% de rendimiento por un método análogo al del Ejemplo 514, partiendo de 4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenol y 1-(2-hidroxietil)imidazol.

1H NMR (399.9 MHz, DMSO-d6) δ 3.18 (4H, t), 3.76 (1H, t), 4.18 (2H, t), 4.33 (2H, t), 6.82-6.99 (5H, m), 7.26 (1H, s), 7.53-7.72 (2H, m), 8.29 (1H, d); m/z = 459 [M+H]+.

Ejemplo 846

Preparación de 6-[4-[4-[2-(1H-imidazol-1-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

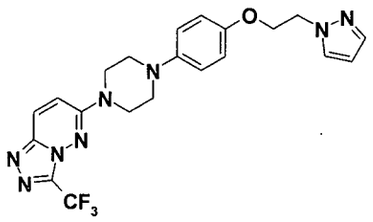


Se obtuvo con un 38% de rendimiento por un método análogo al del Ejemplo 513, partiendo de 4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-1-il]fenol y 1-(2-hidroxietil)imidazol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.58-1.73 (2H, m), 1.86 (2H, d), 2.76-2.88 (1H, m), 3.04-3.17 (2H, m), 4.18-4.29 (2H, m), 4.32-4.47 (4H, m), 6.83-6.93 (3H, m), 7.15-7.27 (3H, m), 7.62-7.70 (2H, m), 8.26 (1H, d); m/z = 458 [M+H]+.

Ejemplo 847

Preparación de 6-[4-[4-[2-(1H-pirazol-1-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina



Hidruro sódico (60% dispersión en aceite, 16.97 mg, 0.42 mmol) fue añadido a 1H-pirazol (28.9 mg, 0.42 mmol) en DMF (2 mL) a 20°C en atmósfera de nitrógeno. La suspensión resutlante fue agitada a 20°C durante 20 minutos. 6-[4-[4-(2-Bromoetoxi)fenil]piperazin-1-il]-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (100 mg, 0.21 mmol) fue añadido y la reacción fue agitada a 20°C durante 1 hora. Se añadió entonces agua (25 mL) y el precipitado resultante fue filtrado, lavado con éter y secado durante la noche al vacío a 50°C para dar 6-[4-[4-[2-(1H-pirazol-1-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (66.0 mg, 68 %) como un sólido amarillo pálido.

1H NMR (399.9 MHz, DMSO-d6) δ 3.17 (4H, t), 3.73 (4H, t), 4.27 (2H, t), 4.46 (2H, t), 6.25 (1H, d), 6.84 (2H, d), 6.96 (2H, d), 7.48 (1H, d), 7.68 (1H, d), 7.79 (1H, d), 8.29 (1H, d); m/z = 459 [M+H]+.

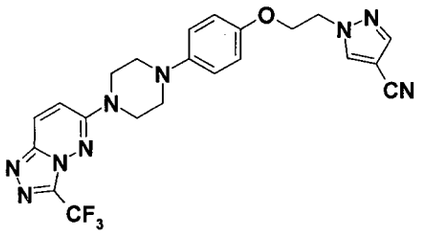
El 6-[4-[4-(2-bromoetoxi)fenil]piperazin-1-il]-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina de partida fue preparado como se indica a continuación:

DIAD (1.625 mL, 8.25 mmol) se añadió a 4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenol (obtenido como se describe en el Ejemplo 514, preparación de los reactivos de partida) (3.01 g, 8.25 mmol), 2-bromoetanol (0.645 mL, 9.08 mmol) y trifenilfosfina (2.165 g, 8.25 mmol) en THF (150 mL) a 20°C en atmósfera de nitrógeno. La solución resultante fue agitada a 20°C durante 16 horas. El producto crudo fue purificado por cromatografía sobre gel de sílice ultrarápida, con un gradiente de elución de 0 a 3% de MeOH en DCM para dar 6-[4-[4-(2-bromoetoxi)fenil]piperazin-1-il]-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (0.765 g, 19.67 %) como un sólido amarillo pálido.

1H NMR (399.9 MHz, $CDCl_3$) δ 3.22 (4H, t), 3.62 (2H, t), 3.79 (4H, t), 4.26 (2H, t), 6.87-6.96 (4H, m), 7.11 (1H, d),7.98 (1H, d); m/z = 473 [M+H]+

Ejemplo 848

Preparación de 1-[2-[4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenoxi]etil]-1H-pirazol-4-carbonitrilo

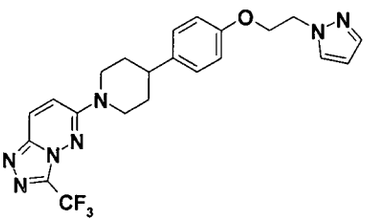


Se obtuvo con un 75% de rendimiento por un método análogo al del Ejemplo 847, partiendo de 6-[4-[4-(2-bromoetoxi)fenil]piperazin-1-il]-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina y 4-cianopirazol.

1H NMR (399.9 MHz, DMSO-d6) δ 3.19 (4H, t), 3.76 (4H, t), 4.32 (2H, t), 4.56 (2H, t), 6.85 (2H, d), 6.97 (2H, d), 7.67 (1H, d), 8.09 (1H, s), 8.29 (1H, d), 8.64 (1H, s); m/z = 484 [M+H]+.

Ejemplo 849

Preparación de 6-[4-[4-[2-(1H-pirazol-1-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina



Se obtuvo con un 67% de rendimiento por un método análogo al del Ejemplo 847, partiendo de 6-[4-[4-(2-bromoetoxi)fenil]piperidin-1-il]-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina y pirazol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.59-1.74 (2H, m), 1.86 (2H, d), 2.76-2.86 (1H, m), 3.07 (2H, t), 4.31 (2H, t), 4.36-4.44 (2H, m), 4.47 (2H, t), 6.25 (1H, d), 6.85 (2H, d), 7.18 (2H, d), 7.46 (1H, d), 7.65 (1H, d), 7.79 (1H, d), 8.24 (1H, d); m/z = 458 [M+H]+.

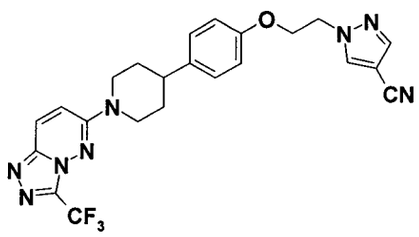
El 6-[4-[4-(2-bromoetoxi)fenil]piperidin-1-il]-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina de partida se obtuvo con un 29% de rendimiento por un método análogo al del Ejemplo 847, preparación de los reactivos de partida, partiendo de

4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-1-il]fenol (obtenido como se describe en el Ejemplo 513, preparación de reactivos de partida).

1H NMR (399.9 MHz, DMSO-d6) δ 1.61-1.74 (2H, m), 1.87 (2H, d), 2.77-2.88 (1H, m), 3.09 (2H, t), 3.79 (2H, t), 4.29 (2H, t), 4.40 (2H, d), 6.89 (2H, d), 7.19 (2H, d), 7.68 (1H, d) ,8.24 (1H, d); m/z = 472 [M+H]+.

Ejemplo 850

Preparación de 1-[2-[4-[4-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-1-il]fenoxi]etil]-1H-pirazol-4-carbonitrilo

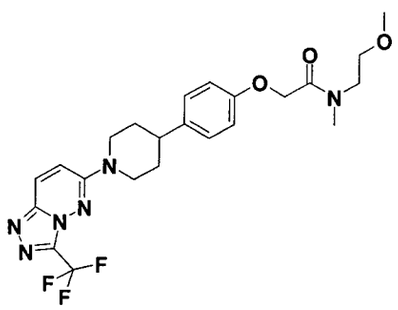


Se obtuvo con un 50% de rendimiento por un método análogo al del Ejemplo 847, partiendo de 6-[4-[4-(2-bromoetoxi)fenil]piperidin-1-il]-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (obtenida como se describe en el Ejemplo 849, preparación de los reactivos de partida) y 4-cianopirazol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.58-1.74 (2H, m), 1.86 (2H, d), 2.76-2.87 (1H, m), 3.11 (2H, t), 4.31-4.47 (4H, m), 4.58 (2H, t), 6.86 (2H, d), 7.17 (2H, d), 7.68 (1H, d), 8.07 (1H, s), 8.23 (1H, d), 8.65 (1H, s); m/z = 484 [M+H]+.

Ejemplo 851

Preparación de N-(2-metoxietil)-N-metil-2-[4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-yl]fenoxi]acetamida



N-(2-metoxietil)metilamina (25 mg, 0.28 mmol) fue añadido a ácido 2-[4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acético (100 mg, 0.24 mmol), HATU (108 mg, 0.28 mmol) y DIPEA (0.124 mL, 0.71 mmol) en DMF (2 mL). La solución resultante fue agitada a temperatura ambiente durante 3 horas y luego fue purificada por HPLC preparativa (columna Waters XBridge Prep C18 OBD, sílice de 5µ,

diámetro de19 mm y longitud de100 mm), utilizando mezclas de polaridad decreciente de agua (conteniendo 1% de amoniaco) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado fueron evaporadas a sequedad para dar N-(2-metoxietil)-N-metil-2-[4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetamida (26 mg, 22%).

1H NMR (499.8 MHz, DMSO-d6) δ 1.69 (2H, m), 1.93 (2H, m), 2.83 (1H, m), 3.14 (2H, m), 3.28 (3H, s), 3.48 (4H, m), 4.37 (2H, m), 4.72 (2H, s), 6.86 (2H, d), 7.16 (2H, d), 7.55 (1H, d), 8.13 (1H, d), 3H oculatado por la señal del agua; m/z = 493 [M+H]+.

El ácido 2-[4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetic de partida fue preparado como se indica a continuación:

Preparación de 2-[4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetato de metilo

2-Bromoacetato de metilo (0.418 mL, 4.42 mmol) fue añadido a 4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenol (obtenido como se describe en el Ejemplo 513, preparación de los reactivos de partida) (1.07 g, 2.94 mmol) y carbonato potásico (0.814 g, 5.89 mmol) en DMF (20 mL). La suspensión resultante fue agitada a temperatura ambiente 16 horas. La mezcla de reacción fue evaporada a sequedad y luego se añadió agua (50 mL) y la agitación continuó durante 20 minutos. El precipitado resultante fue recogido mediante filtración, lavado con agua, depués con éter, y secado para dar 2-[4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetato de metilo (1.290 g, 100%).

1H NMR (399.9 MHz, DMSO-d6) δ 1.67 (2H, m), 1.88 (2H, m), 2.81 (1H, m), 3.09 (2H, m), 3.70 (3H, s), 4.42 (2H, m), 4.77 (2H, s), 6.86 (2H, d), 7.19 (2H, d), 7.67 (1H, d), 8.25 (1H, d); m/z = 436 [M+H]+.

Preparación de ácido 2-[4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acético

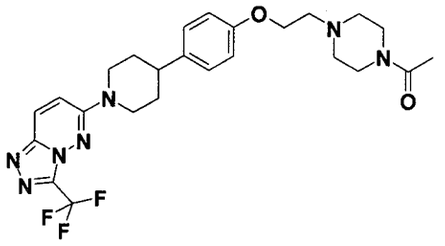
Monohidrato de hidróxido de litio (0.622 g, 14.81 mmol) fue añadido a 2-[4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetato (1.29 g, 2.96 mmol) en una mezcla de THF (20 mL), agua (10 mL) y MeOH (5 mL). La mezcla resultante fue agitada a temperatura ambiente durante 16 horas. Los solventes fueron entonces evaporados y los residuos fueron suspendidos en agua y adificados a pH 4 con ácido cítrico 1M. El precipitado resultante fue recogido mediante filtración, lavado con agua y secado para dar ácido 2-[4-[1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acético (1.020 g, 82%).

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1H NMR (399.9 MHz, DMSO-d6) δ 1.66 (2H, m), 1.88 (2H, m), 2.78 (1H, m), 3.09 (2H, m), 4.17 (2H, s), 4.41 (2H, m), 6.74 (2H, d), 7.12 (2H, d), 7.66 (1H, d), 8.23 (1H, d); m/z = 422 [M+H]+.

Ejemplo 852

Preparación de 6-[4-[4-[2-(4-acetilpiperazin-1-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

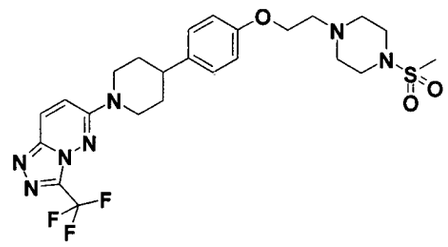


Una solución de cloruro de acetilo (0.029 mL, 0.40 mmol) en DCM (0.5 mL) fue añadida gota a gota a 6-[4-[4-(2-piperazin-1-iletoxi)fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (obtenida como se describe en el Ejemplo 727) (160 mg, 0.34 mmol) y trietilamina (0.094 mL, 0.67 mmol) en DCM (1 mL) enfriada a 0 °C en atmósfera de nitrógeno. La solución resultante fue agitada a 0°C durante 5 minutos luego se dejó calentar a temperatura ambiente y se agitó durante 15 minutos. La mezcla de reacción fue diluida con agua (2 mL), se hizo pasar a través de un cartucho de separación de fases y la fase orgánica fue evaporada para dar el producto crudo. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, sílice de 5µ, diámetro de19 mm y longitud de100 mm), utilizando mezclas de polaridad decreciente de agua (conteniendo 1% de amoniaco) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado fueron evaporadas a sequedad para dar 6-[4-[4-[2-(4-acetilpiperazin-1-il)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (60.0 mg, 35%).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 2.00 (2H, m), 2.08 (3H, s), 2.53 - 2.59 (4H, m), 2.75 - 2.84 (3H, m), 3.12 (2H, m), 3.48 (2H, m), 3.63 (2H, m), 4.10 (2H, t), 4.37 (2H, m), 6.87 (2H, d), 7.13 (3H, m), 7.92 (1H, d); m/z = 518 [M+H]+.

Ejemplo 853

Preparación de 6-[4-[4-[2-[4-(metilsulfonil)piperazin-1-il]etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

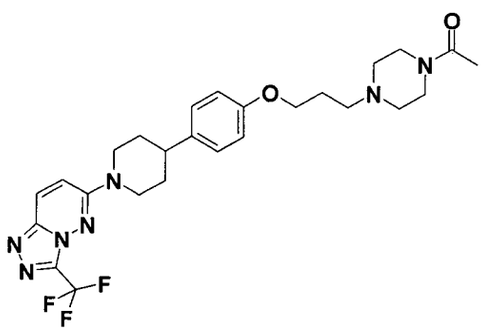


Una solución de cloruro de matanosulfonilo (0.034 mL, 0.44 mmol) en DCM (0.5 mL) fue añadida gota a gota a 6-[4-[4-(2-piperazin-1-iletoxi)fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (obtenida como se describe en el Ejemplo 727) (175 mg, 0.37 mmol) y trietilamina (0.103 mL, 0.74 mmol) en DCM (1 mL) enfriada a 0°C en atmósfera de nitrógeno. La solución resultante fue agitada a 0°C durante 5 minutos, luego se dejó calentar a temperatura ambiente y se agitó durante 15 minutos más. La mezcla de reacción fue diluida con agua (2 mL), se hizo pasar a través de un cartucho de separación de fases y la fase orgánica fue evaporada para dar el producto crudo. El producto crudo fue purificado por HPLC preparativa (columna Waters XBridge Prep C18 OBD, sílice de 5µ, diámetro de 19 mm y longitud de 100 mm), utilizando mezclas de polaridad decreciente de agua (conteniendo 1% de amoniaco) y MeCN como eluyentes. Las fracciones que contenían el compuesto deseado fueron evaporadas a sequedad para dar 6-[4-[4-[2-[4-(metilsulfonil)piperazin-1-il]etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (122 mg, 60%).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 2.00 (2H, m), 2.70 (4H, m), 2.75 - 2.83 (4H, m), 2.86 (2H, t), 3.12 (2H, m), 3.26 (4H, m), 4.09 (2H, t), 4.37 (2H, m), 6.86 (2H, d), 7.13 (3H, m), 7.92 (1H, d); m/z = 554 [M+H]+.

Ejemplo 854

Preparación de 6-[4-[4-[3-(4-acetilpiperazin-1-il)propoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina



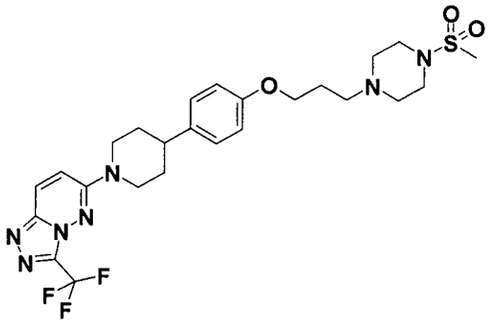
Se obtuvo con un 28% de rendimiento por un método análogo al del Ejemplo 852, partiendo de 6-[4-[4-(3-piperazin-1-ilpropoxi)fenil]piperidin-1-il]-3-

(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (obtenida como se describe en el Ejemplo 728).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 1.92 - 2.02 (4H, m), 2.08 (3H, s), 2.44 (4H, m), 2.54 (2H, t), 2.78 (1H, m), 3.11 (2H, m), 3.46 (2H, m), 3.62 (2H, m), 4.01 (2H, t), 4.37 (2H, m), 6.86 (2H, d), 7.13 (3H, m), 7.92 (1H, d); m/z = 532 [M+H]+.

Ejemplo 855

Preparación de 6-[4-[4-[3-[4-(metilsulfonil)piperazin-1-il]propoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina

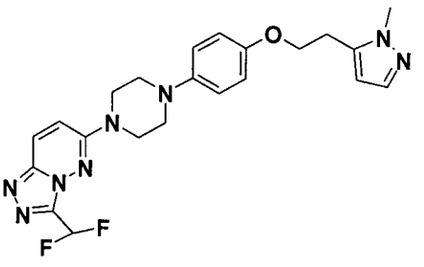


Se obtuvo con un 31% de rendimiento por un método análogo al del Ejemplo 853, partiendo de 6-[4-[4-(3-piperazin-1-ilpropoxi)fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina (obtenida como se describe en el Ejemplo 728).

1H NMR (399.9 MHz, CDCl3) δ 1.76 (2H, m), 1.92 - 2.01 (4H, m), 2.57 (6H, m), 2.74 - 2.82 (4H, m), 3.11 (2H, m), 3.25 (4H, m), 4.00 (2H, t), 4.37 (2H, m), 6.85 (2H, d), 7.12 (3H, m), 7.93 (1H, d); m/z = 568 [M+H]+.

Ejemplo 856

Preparación de 3-(difluorometil)-6-[4-[4-[2-(1-metil-1H-pirazol-5-il]etoxi]fenil]piperazin-1-il)[1,2,4]triazolo[4,3-b]piridazina



Se obtuvo con un 32% de rendimiento por un método análogo al del Ejemplo 514, partiendo de 4-[4-[3-(difluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenol.

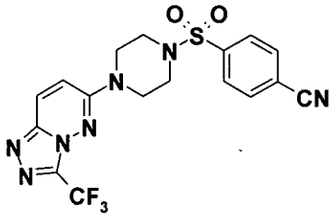
1H NMR (399.9 MHz, DMSO-d6) δ 3.07 (2H, t), 3.17 (4H, m), 3.75 (4H, m), 3.79 (3H, s), 4.15 (2H, t), 6.14 (1H, d), 6.88 (2H, d), 6.97 (2H, d), 7.31 (1H, d), 7.43 - 7.69 (2H, m), 8.22 (1H, d); m/z = 455 [M+H]+.

El 4-[4-[3-(difluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]fenol utilizado como reactivo de partida fue preparado con un 95% de rendimiento por un método análogo al del Ejemplo 514, preparación de los reactivos de partida, partiendo de 3-(difluorometil)[1,2,4]triazolo[4,3-b]piridazina (obtenida como se describe en el Método Sintético General 1, preparación de los reactivos de partida).

1H NMR (399.9 MHz, DMSO-d6) δ 3.11 (4H, m), 3.74 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.43 - 7.69 (2H, m), 8.22 (1H, d), 8.87 (1H, s); m/z = 347 [M+H]+.

Ejemplo 857

Preparación de 4-[4-[3-(trifluorometil)-[1,2,4]triazolo[3,4-f]piridazin-6-il]piperazin-1-il]sulfonilbenzonitrilo

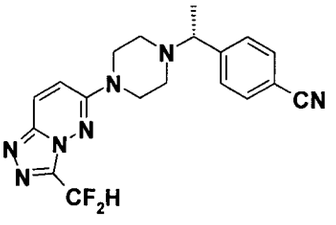


Se obtuvo con un 32% de rendimiento mediante un procedimiento análogo al Ejemplo 394, partiendo de cloruro de 4-cianobencenosulfonilo y 6-(piperazin-1-il)-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina.

1H NMR (399.9 MHz, DMSO-d6) δ 3.07 (4H, m), 3.64 (4H, m), 7.46 (1H, d), 7.89 (2H, d), 8.06 (2H, d), 8.18 (1H, d); m/z = 438 [M+H]+.

Ejemplo 858

Preparación de 4-[(1R)-1-[4-[3-(difluorometil)-[1,2,4]triazolo[3,4-f]piridazin-6-il]piperazin-1-il]etil]benzonitrilo

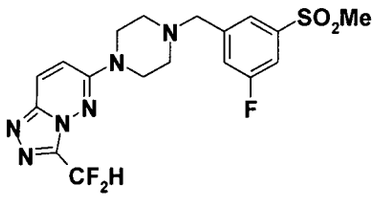


Se obtuvo con un 35% de rendimiento mediante un procedimiento análogo al Ejemplo 307, partiendo de 6-[4-[(1R)-1-(4-bromofenil)etil]piperazin-1-il]-3-(difluorometil)-[1,2,4]triazolo[4,3-b]piridazina (obtenida como se describe en el Ejemplo 270).

1H NMR (399.9 MHz, CDCl3) δ 1.39 (3H, d), 2.48 - 2.53 (2H, m), 2.62 - 2.68 (2H, m), 3.49 (1H, q), 3.54 - 3.64 (4H, m), 7.00 (1H, d), 7.12 (1H, t), 7.47 - 7.49 (2H, m), 7.62 - 7.65 (2H, m), 7.89 (1H, d); m/z = 384 [M+H]+.

Ejemplo 859

Preparación de 3-(difluorometil)-6-{4-[3-fluoro-5-(metilsulfonil)bencil]piperazin-1-il}[1,2,4]triazolo[4,3-b]piridazina

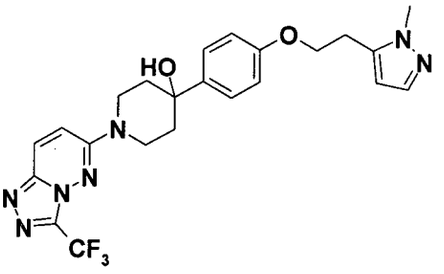


Se obtuvo con un 55% de rendimiento mediante el Método Sintético General 5, partiendo de 6-cloro-3-difluorometil-[1,2,4]triazolo[4,3-b]piridazina y 3-fluoro-5-metilsulfonilbenzaldehído (obtenido como se describe en el Ejemplo 778, preparación de materiales de partida).

1H NMR (399.9 MHz, DMSO) δ 2.53 - 2.57 (4H, m), 3.30 (3H, s), 3.62 - 3.66 (4H, m), 3.70 (2H, s), 7.51 - 7.54 (1H, m), 7.53 (1H, t), 7.58 - 7.60 (1H, m), 7.70 - 7.73 (1H, m), 7.77 (1H, d), 8.18 - 8.21 (1H, m); m/z = 441 [M+H]+.

Ejemplo 860

Preparación de 4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol



Se agregó DIAD (0.311 mL, 1.58 mmol) gota a gota a 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol (500 mg, 1.32 mmol), 2-(1-metil-1H-pirazol-5-il)etanol (obtenido como se describe en el Ejemplo 513, preparación de materiales de partida) (249 mg, 1.98 mmol) y trifenilfosfina (519 mg, 1.98 mmol) en THF (10 mL) en atmósfera de nitrógeno. La suspensión resultante se agitó a temperatura ambiente durante 16 horas, posteriormente los solventes se evaporaron para obtener el producto crudo. El producto crudo se purificó por cromatografía flash en sílice eluyendo con EtOAc seguido de un gradiente de 3 a 5% de MeOH en DCM. Las fracciones puras se

evaporaron a sequedad para obtener un sólido que se recristalizó con éter, se filtró y se secó para obtener 4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol (464 mg, 72.2%) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 1.72 (2H, m), 1.99 (2H, m), 3.09 (2H, t), 3.43 (2H, m), 3.79 (3H, s), 4.18 (4H, m), 5.12 (1H, s), 6.13 (1H, d), 6.90 (2H, d), 7.30 (1H, d), 7.41 (2H, d), 7.65 (1H, d), 8.23 (1H, d); m/z = 488 [M+H]+.

El 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol de partida se preparó como se indica a continuación:-

Preparación de 4-[4-(benciloxi)fenil]-4-hidroxipiperidine-1-carboxilato de bencilo

Se agregó n-butillitio (1.6M en hexano, 42.9 ml, 107.18 mmol) gota a gota a 1-(benciloxi)-4-bromobenceno (28.2 g, 107.18 mmol, CAS 6793-92-6) en THF (367 ml) a -78°C en el transcurso de un periodo de 15 minutos en atmósfera de nitrógeno. La solución resultante se agitó a -78°C durante 1 hora, posteriormente se agregó 4-oxopiperidin-1-carboxilato de bencilo (20 g, 85.74 mmol) en THF (122 ml) gota a gota. La mezcla resultante se agitó a -78°C durante 10 minutos, posteriormente se dejó calentar hasta temperatura ambiente y se agitó durante 16 horas. La mezcla de reacción se evaporó a sequedad y se neutralizó con cloruro de amonio saturado (50 mL), posteriormente se extrajo con EtOAc (500 mL). La capa orgánica se secó con $MgSO_4$, se filtró y evaporó para obtener el producto crudo. El producto crudo se purificó por cromatografía flash en sílice con un gradiente de elución de 1 a 100% de EtOAc en isohexano. Las fracciones puras se evaporaron a sequedad para obtener el producto crudo. El producto crudo se purificó además por cromatografía flash en sílice con un gradiente de elución de 0 a 3% de MeOH en DCM. Las fracciones puras se evaporaron a sequedad para obtener 4-[4-(benciloxi)fenil]-4-hidroxipiperidin-1-carboxilato de bencilo (13.49 g, 30.1%) como una goma.

1H NMR (399.9 MHz, DMSO-d6) δ 1.58 (2H, m), 1.80 (2H, m), 3.27 (2H, m), 3.71 (1H, m), 3.92 (2H, m), 5.10 (4H, m), 6.95 (2H, m), 7.39 (12H, m); m/z = 416 [M-H]+.

Preparación de 4-(4-hidroxifenil)piperidin-4-ol

Se agregó paladio al 10 % sobre carbono (3.44 g, 3.23 mmol) a 4-[4-(benciloxi)fenil]-4-hidroxipiperidin-1-carboxilato de bencilo (13.49 g, 32.31 mmol) en MeOH (146 mL). La mezcla resultante se agitó a temperatura ambiente durante 20 horas en atmósfera de hidrógeno. La mezcla de reacción se filtró y evaporó para obtener el producto crudo. El material crudo se trituró con DCM (100 mL) y MeOH (50 mL) para obtener un sólido que

se recogió por filtración y se secó al vacío para obtener 4-(4-hidroxifenil)piperidin-4-ol (4.16 g, 66.6%).

1H NMR (399.9 MHz, DMSO-d6) δ 1.50 (2H, m), 1.73 (2H, m), 2.70 (2H, m), 2.90 (2H, m), 4.52 (1H, s), 6.69 (2H, m), 7.25 (2H, m), 9.21 (1H, s); m/z = 192 [M-H]+.

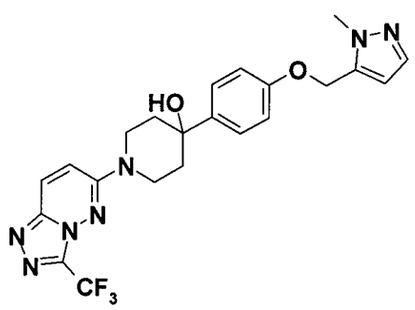
Preparación de 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol

Se agregó DIPEA(1.174 mL, 6.74 mmol) a 6-cloro-3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazina (1 g, 4.49 mmol) y 4-(4-hidroxifenil)piperidin-4-ol (0.955 g, 4.94 mmol) en DMF (10 mL). La solución resultante se agitó a 80°C durante 1 hora. La mezcla de reacción se enfrió hasta temperatura ambiente, posteriormente se evaporó a sequedad. Los residuos se recristalizaron con agua y el sólido resultante se recogió por filtración, se lavó con más agua seguida de éter, luego se secó al vacío para obtener 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol (1.680 g, 99 %) como un sólido.

1H NMR (399.9 MHz, DMSO-d6) δ 1.72 (2H, m), 1.95 (2H, m), 3.42 (2H, m), 4.17 (2H, m), 5.01 (1H, s), 6.70 (2H, d), 7.28 (2H, d), 7.65 (1H, d), 8.23 (1H, d), 9.20 (1H, s); m/z = 380 [M+H]+.

Ejemplo 861

Preparación de 4-[4-[(1-metil-1H-pirazol-5-il)metoxi]fenil]-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol



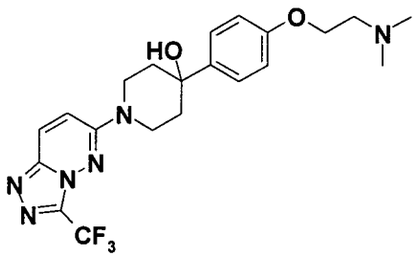
Se obtuvo con un 76% de rendimiento mediante un método análogo al Ejemplo 860, partiendo de 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol y 2-(1-metil-1H-pirazol-5-il)metanol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.73 (2H, d), 1.95-2.07 (2H, m), 3.39-3.50 (2H, m), 3.83 (3H, s), 4.19 (2H, d), 5.13 (1H, s), 5.17 (2H, s), 6.37 (1H, d), 7.00 (2H, d), 7.38 (1H, d), 7.44 (2H, d), 7.66 (1H, d), 8.12 (1H, d); m/z = 474 [M+H]+.

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Ejemplo 862

Preparación de 4-[4-[2-(dimetilamino)etoxi]fenil]-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol

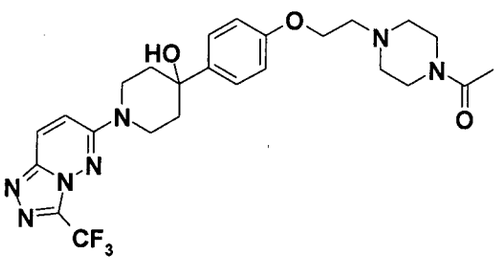


Se obtuvo con un 74% de rendimiento mediante un método análogo al Ejemplo 860, partiendo de 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol y 2-(dimetilamino)etanol.

1H NMR (399.9 MHz, DMSO-d6) δ 1.73 (2H, d), 1.95-2.06 (2H, m), 2.23 (6H, s), 2.61 (2H, t), 3.88-3.49 (2H, m), 4.04 (2H, t), 4.18 (2H, d), 5.11 (1H, s), 6.89 (2H, d), 7.39 (2H, d), 7.66 (1H, d), 8.23 (1H, d); m/z = 451 [M+H]+.

Ejemplo 863

Preparación de 4-[4-[2-(4-acetilpiperazin-1-il)etoxi]fenil]-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol

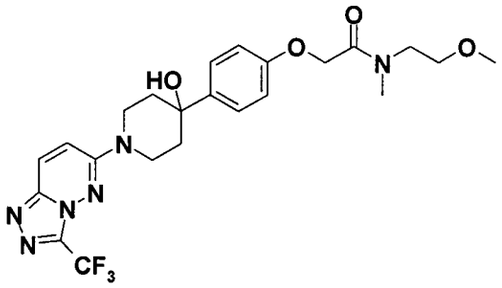


Se obtuvo con un 55% de rendimiento mediante un método análogo al Ejemplo 860, partiendo de 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol y 2-(4-acetilpiperazin-1-il)etanol (obtenido como se describe en la Solicitud Internacional PCT WO2003064413, Ejemplo 28, preparación de materiales de partida).

1H NMR (499.8 MHz, DMSO-d6, espectro registrado a 100°C) δ 1.79 (2H, d), 1.97-2.07 (8H, m), 2.75 (2H, t), 3.39-3.48 (7H, m), 4.08-4.16 (4H, m), 6.89 (2H, d), 7.41 (2H, d), 7.55 (1H, d), 8.12 (1H, d); m/z = 534 [M+H]+.

Ejemplo 864

Preparación de 2-[4-[4-hidroxi-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]-N-(2-metoxietil)-N-metilacetamida



Se agregó DIPEA (0.321 mL, 1.94 mmol) al ácido 2-[4-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acético (283 mg, 0.65 mmol), N-(2-metoxietil)metilamina (63 mg, 0.71 mmol) y HATU (270 mg, 0.71 mmol) en DMF (5 mL) a 20°C en atmósfera de nitrógeno. La solución resultante se agitó a 20°C durante 4 horas. Posteriormente, se agregó agua (50 mL) y la mezcla se extrajo con DCM (2 x 50 mL). Los extractos orgánicos combinados se secaron (Na_2SO_4), filtraron y evaporaron para obtener un aceite naranja. El producto crudo se purificó por cromatografía flash en sílice eluyendo con un gradiente de 0 a 100% de EtOAc en isohexano, seguido de 0 a 10% de MeOH en EtOAc. Las fracciones puras se evaporaron a sequedad, luego se recristalizaron con isohexano, se filtraron y secaron para obtener 2-[4-[4-hidroxi-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]-N-(2-metoxietil)-N-metilacetamida (161 mg, 48.9%) como un sólido blanco.

1H NMR (499.8 MHz, DMSO-d6, espectro registrado a 100°C) δ 1.79 (2H, d), 1.98-2.06 (2H, m), 2.89-2.99 (6H, m), 3.47-3.54 (6H, m), 3.46-3.54 (6H, m), 4.12 (2H, d), 4.71-4.79 (3H, m), 6.87 (2H, d), 7.39 (2H, d), 7.54 (1H, d), 8.12 (1H, d); m/z = 509 [M+H]+.

El ácido 2-[4-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acético de partida se preparó como se indica a continuación:-

Preparación de 2-[4-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetato de metilo

2-Bromoacetato de metilo (0.121 mL, 1.28 mmol) se agregó a 4-(4-hidroxifenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol (323 mg, 0.85 mmol) y carbonato de potasio (235 mg, 1.70 mmol) en DMF (5 mL). La suspensión resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se evaporó a sequedad, luego se agregó agua (50 mL) y la mezcla se agitó durante 20 minutos. El precipitado resultante se recogió por filtración, se lavó con agua seguida de éter y se secó

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para obtener 2-[4-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetato de metilo (384 mg, 100%) como un sólido beis.
1H NMR (399.9 MHz, $CDCl_3$) δ 1.93 (2H, d), 2.08-2.18 (2H, m), 3.58 (2H, t), 3.82 (3H, s), 4.14 (2H, d), 4.65 (2H, s), 6.91 (2H, d), 7.13 (1H, d), 7.42 (2H, d), 7.92 (1H, d); m/z = 452 [M+H]+.

Preparación de ácido 2-[4-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acético

Se agregó hidróxido de litio monohidrato (177 mg, 4.21 mmol) a 2-[4-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acetato (380 mg, 0.84 mmol) en una mezcla de THF (7 mL), agua (3.5 mL) y MeOH (3.5 mL). La mezcla resultante se agitó a temperatura ambiente durante 16 horas. Los solventes se evaporaron, posteriormente los residuos se suspendieron en agua y se acidificaron hasta pH 4 con ácido cítrico 1M. El precipitado resultante se recogió por filtración, se lavó con agua y se secó para obtener ácido 2-[4-[4-hidroxi-1-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]fenoxi]acético (297 mg, 81%) como un sólido blanco.
1H NMR (399.9 MHz, DMSO-d6) δ 1.73 (2H, d), 1.95-2.06 (2H, m), 3.43 (2H, t), 4.18 (2H, d), 4.67 (2H, s), 5.1
4 (1H, s), 6.87 (2H, d), 7.42 (2H, d), 7.67 (1H, d), 8.23 (1H, d), 12.94 (1H, bs); m/z = 438 [M+H]+.

Lista de las Figuras

Figura 1: Patrón de difracción de rayos X en polvo para la Forma Anhidra A de 4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol cuando se mide utilizando radiación CuKa.

Figura 2: Patrón de difracción de rayos X en polvo para la Forma Anhidra A de N-(2-metoxietil)-N-metil-4-[1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il]benzamida cuando se mide utilizando radiación CuKa.

Figura 3: Patrón de difracción de rayos X en polvo para la Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-yl)etoxi]fenil]piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina cuando se mide utilizando radiación CuKa.

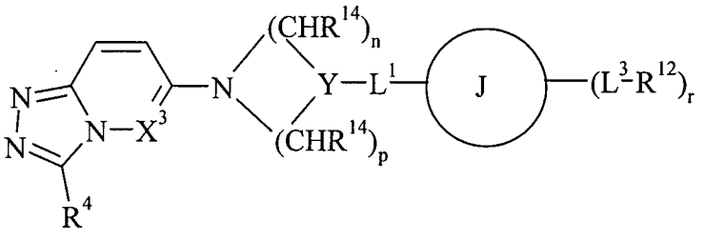
Figura 4: Patrón de difracción de rayos X en polvo para la Forma Anhidra A de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina cuando se mide utilizando radiación CuKa.

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Figura 5: Patrón de difracción de rayos X en polvo para el fumarato de 6-[4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina cuando se mide utilizando radiación CuKa.

Reivindicaciones

1. Un compuesto de Fórmula (Ic), o una sal farmacéuticamente aceptable del mismo, para su uso como un medicamento:



(Ic)

donde

X^3 representa CH o N;

R^4 representa haloC_{1-4}alquil;

Y representa CH, COH o N;

R^{14}, de manera idéntica o diferente en cada aparición, representa hidrógeno o metil;

n y p independientemente representan 1 ó 2;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$,-S-, -S(O)- o $-S(O)_2-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S;

un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S; o

un sistema de anillos heteroaril de 9 ó 10 miembros bicíclico que comprende 1, 2, 3, 4 ó 5 heteroátomos independientemente seleccionados de O, N o S;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

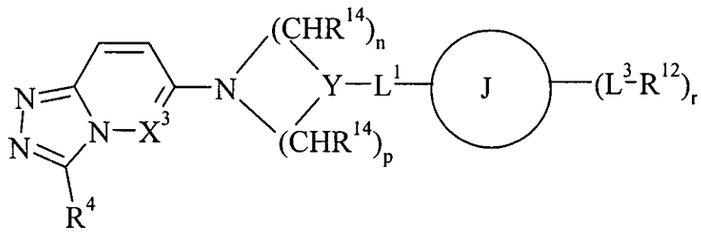
un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o –C(O)$NR^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil; y

r representa 0, 1, 2 ó 3.

2. Un compuesto de Fórmula (Ic), o una sal farmacéuticamente aceptable del mismo, para su uso en el tratamiento del cáncer de próstata:



(Ic)

donde

X^3 representa CH o N;

R^4 representa haloC_{1-4}alquil;

Y representa CH, COH o N;

R^{14}, de manera idéntica o diferente en cada aparición, representa hidrógeno o metil;

n y p independientemente representan 1 ó 2;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S;

un anillo heteroaril de 5 ó 6 miembros monocíclico que comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S; o

un sistema de anillos heteroaril de 9 ó 10 miembros bicíclico que comprende 1, 2, 3, 4 ó 5 heteroátomos independientemente seleccionados de O, N o S;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

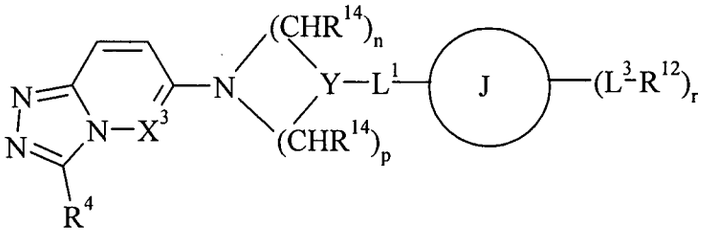
un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi,

C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o –C(O)$NR^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil; y

r representa 0, 1, 2 ó 3.

3. Un compuesto de Fórmula (Ic), o una sal farmacéuticamente aceptable del mismo:



(Ic)

wherein

donde

X^3 representa CH o N;

R^4 representa haloC_{1-4}alquil;

Y representa CH, COH o N;

R^{14}, de manera idéntica o diferente en cada aparición, representa hidrógeno o metil;

n y p independientemente representan 1 ó 2;

L^1 representa un enlace directo, $-(CR^9R^{10})_t-$, $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$, $-N(R^{11})-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^9 y R^{10}, de manera idéntica o diferente en cada aparición, representan hidrógeno o metil;

q, de manera idéntica o diferente en cada aparición, representa 0, 1, 2 ó 3;

t representa 1, 2 ó 3;

v, de manera idéntica o diferente en cada aparición, representa 0, 1 ó 2;

J representa:

aril;

un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado;

furanil, imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro-2*H*-piranil, pirazolil, piridazinil, piridinil, pirrolil o tiadiazolil; o

un sistema de anillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno, 1 ó 2 átomos de oxígeno , 1 átomo de azufre, o 1 átomo de nitrógeno y 1 átomo de azufre;

L^3 representa un enlace directo, $-(CR^9R^{10})_t-$, $-C(O)N(R^{11})-(CH_2)_q-$, $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, $-O-(CH_2)_q-$, $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$, $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$, -S-, -S(O)- o $-S(O)_2-$;

R^{11} representa hidrógeno o metil;

R^{12} representa:

halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, carboxi, C_{1-6}alcoxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, amino, N–C_{1-4}alquilamino o N,N–di–C_{1-4}alquilamino;

aril, donde el anillo aril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

un anillo heteroaril de 5 ó 6 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heteroaril está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13}; o

un anillo heterocíclico de 4, 5, 6 ó 7 miembros monocíclico el cual comprende 1, 2, 3 ó 4 heteroátomos independientemente seleccionados de O, N o S y donde el anillo heterocíclico está opcionalmente sustituido por 1, 2 ó 3 sustituyentes seleccionados de R^{13};

R^{13} representa amino, halo, C_{1-6}alquil, C_{2-6}alquenil, C_{2-6}alquinil, C_{1-6}alcoxi, C_{2-6}alcanoil, C_{1-6}alcoxiC_{1-6}alquil, carboxi, ciano, oxo, fluoroC_{1-6}alquil, hidroxi, hidroxiC_{1-6}alquil, C_{1-6}alquilsulfanil, C_{1-6}alquilsulfinil, C_{1-6}alquilsulfonil, N–C_{1-4}alquilamino, N,N–di–C_{1-4}alquilamino o $-C(O)NR^{14}R^{15}$ donde R^{14} y R^{15} independientemente representan hidrógeno o metil;

r representa 1, 2 ó 3 cuando J representa aril;

r representa 0 cuando J representa un anillo carbocíclico de 3 a 6 miembros monocíclico totalmente saturado; y

r representa 0, 1, 2 ó 3 cuando J representa furanil, imidazolil, isotiazolil, morfolinil, oxadiazolil, oxazolil, isoxazolil, oxetanil, tetrahidro-2*H*-piranil, pirazolil, piridazinil, piridinil, pirrolil, tiadiazolil o o un sistema de anillos heteroaril de 9 miembros bicíclico que comprende 1 ó 2 átomos de nitrógeno, 1 ó 2 átomos de oxígeno, 1 átomo de azufre, o 1 átomo de nitrógeno y 1 átomo de azufre;

con la condición de que el compuesto de Fórmula (Ic) sea distinto de:

4–{4–[3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazin–6–il]piperazin–1–il}fenol;

6–[4–(piridin–3–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(2–fluorobencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;

6–[4–(imidazo[1,2–*a*]piridin–2–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(3,4–dimetoxibencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(1*H*–indol–3–il)piperidin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–{4–[2–(3,5–dimetoxifenil)etil]piperidin–1–il}–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(4–metoxibencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(3–clorobencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(4–clorobencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(2–metilbencil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(piridin–4–ilmetil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(2,6–dimetilfenil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(4–metoxifenil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6–[4–(3–clorofenil)piperazin–1–il]–3–(trifluorometil)[1,2,4]triazolo[4,3–*b*]piridazina;
6-[4-(4-fluorofenil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina; o
6-{4-[(2,6-difluorofenil)sulfonil]piperazin-1-il}-3-(trifluorometil)[1,2,4]triazolo[4,3-*b*]piridazina.

4. Un compuesto de acuerdo con la Reivindicación 3, o una sal farmacéuticamente aceptable del mismo, donde X^3 representa N.

5. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 ó 4 o una sal farmacéuticamente aceptable del mismo, donde R^4 representa difluorometil, trifluorometil o cloro(difluoro)metil.

6. Un compuesto de acuerdo con la Reivindicación 3 ó 4, o una sal farmacéuticamente aceptable del mismo, donde R^4 representa trifluorometil.

7. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 6, o una sal farmacéuticamente aceptable del mismo, donde R^{14} representa hidrógeno.

8. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 7, o una sal farmacéuticamente aceptable del mismo, donde n y p ambos representan 2.

9. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 8, o una sal farmacéuticamente aceptable del mismo, donde Y representa CH o COH.

10. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 9, o una sal farmacéuticamente aceptable del mismo, donde Y representa N.

11. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 10, o una sal farmacéuticamente aceptable del mismo, donde L^1 representa un enlace directo.

12. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 11, o una sal farmacéuticamente aceptable del mismo, donde J representa fenil, piridinil, indolil, indazolil o pirrolopiridinil.

13. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 12, o una sal farmacéuticamente aceptable del mismo, donde L^3 representa $-C(O)N(R^{11})-(CH_2)_q-$, $-NR^{11}C(O)-(CH_2)_q-$, $-C(O)-(CH_2)_q-$, o $-O-(CH_2)_q-$.

14. Un compuesto de acuerdo con la Reivindicación 13, o una sal farmacéuticamente aceptable del mismo, donde R^{11} representa metil.

15. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 14, o una sal farmacéuticamente aceptable del mismo, donde R^{12} representa fluoro, cloro, metil, metoxi, difluorometil, trifluorometil, ciano, hidroxi, metilsulfonil, dimetilamino, pirrolidinil, piperidinil, piperazinil, morfolinil o pirazolil.

16. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 15, o una sal farmacéuticamente aceptable del mismo, donde R^{13} representa metil, oxo o hidroxi.

17. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 16, o una sal farmacéuticamente aceptable del mismo, donde r representa 1.

18. Un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 16, o una sal farmacéuticamente aceptable del mismo, donde J no representa aril y r representa 0.

19. Un compuesto de acuerdo con la Reivindicación 3 seleccionado de:

4-[[4-[3-(trifluorometil)-[1,2,4]triazolo[4,3-b]piridazin-6-il]piperazin-1-il]metil]benzonitrilo;

3-(trifluorometil)-6-[4-[[3-(trifluorometil)fenil]metil]piperazin-1-il]-[1,2,4]triazolo[4,3-b]piridazina;

4-piridin-3-il-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol;

3-(difluorometil)-6-{4-[(1R)-1-(4-fluorofenil)etil]piperazin-1-il}[1,2,4]triazolo[4,3-b]piridazina;

4-(4-fluorofenil)-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol;

N-(2-metoxietil)-N-metil-4-{1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il}benzamida;

N-(2-hidroxietil)-N-metil-4-{1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il}benzamida;

6-(4-{4-[(4-metilpiperazin-1-il)carbonil]fenil}piperidin-1-il)-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

N-[2-(2-oxopirrolidin-1-il)etil]-4-{1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il}benzamida;

6-[4-(1H-indazol-3-ilmetil)piperazin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

N-(2-metoxietil)-N-metil-3-({1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il}oxi)benzamida;

2-morfolin-4-il-N-(4-{1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il}fenil)acetamida;

6-(4-{4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil}piperidin-1-il)-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

6-{4-[2-(difluorometil)-5-fluorobencil]piperazin-1-il}-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

6-{4-[(6-metilpiridin-3-il)metil]piperazin-1-il}-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

6-[4-(1H-pirrolo[2,3-b]piridin-3-il)piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

6-[4-(5-metoxi-1H-indol-3-il)piperidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

1-[(4-{1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il}fenil)carbonil]piperidin-4-ol;

N-metil-N-[2-(metilsulfonil)etil]-4-{1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-il}benzamida;

6-[3-(4-metoxifenoxi)azetidin-1-il]-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina;

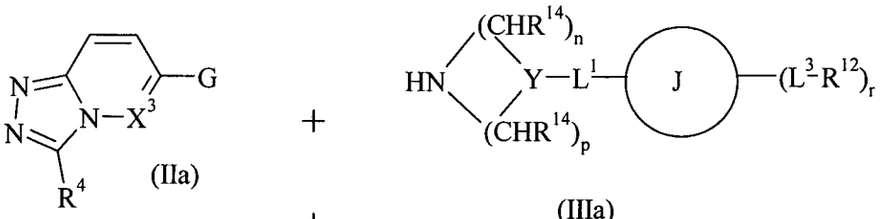
6-(4-{4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil}piperazin-1-il)-3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazina; y

4-[4-[2-(1-metil-1H-pirazol-5-il)etoxi]fenil]-1-[3-(trifluorometil)[1,2,4]triazolo[4,3-b]piridazin-6-il]piperidin-4-ol;

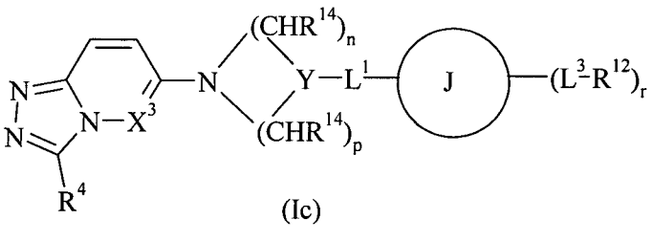
y sales farmacéuticamente aceptables de los mismos.

20. Una composición farmacéutica la cual comprende un compuesto de acuerdo con cualquiera de las Reivindicaciones 3 a 19, o una sal farmacéuticamente aceptable del mismo, en asociación con un diluyente o portador farmacéuticamente aceptable.

21. Un proceso para la preparación de compuestos de Fórmula (Ic) que comprende reaccionar un compuesto de Fórmula (IIa), donde G representa halógeno y R^4 y X^3 son como los definidos aquí anteriomente en relación con la Fórmula (Ic), con una amina de Fórmula (IIIa), donde J, Y, L^1, L^3, R^{12}, R^{14}, n, p y r son como los definidos aquí anteriomente en relación con la Fórmula (Ic):



(IIa) (IIIa)



(Ic)

y a partir de entonces, si fuera necesario:

(i) convertir un grupo funcional de un compuesto de la invención en otro grupo funcional;

(ii) introducir un grupo funcional nuevo en un compuesto de la invención;

(iii) eliminar cualquiera de los grupos protectores;

(iv) para compuestos de la invención en forma de un enantiómero simple separar un compuesto racémico de la invención en enantiómeros separados;

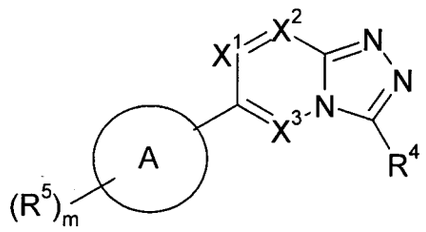
(v) preparar una sal farmacéuticamente aceptable del mismo; y/o

(vi) preparar una forma cristalina del mismo.

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RESUMEN

La invención se refiere a los compuestos bicíclicos de Fórmula I



(I)

donde los números enteros X^1, X^2, X^3, el Anillo A, R^4, R^5 y m son como los definidos en la descripción. La presente invención también se relaciona con procesos para la preparación de tales compuestos, composiciones farmacéuticas que los contienen y su uso en la fabricación de un medicamento para su uso en la prevención o tratamiento de afecciones asociadas con el receptor de andrógeno.

Figure1: X-Ray Powder Diffraction Pattern for 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A when measured using CuKa radiation

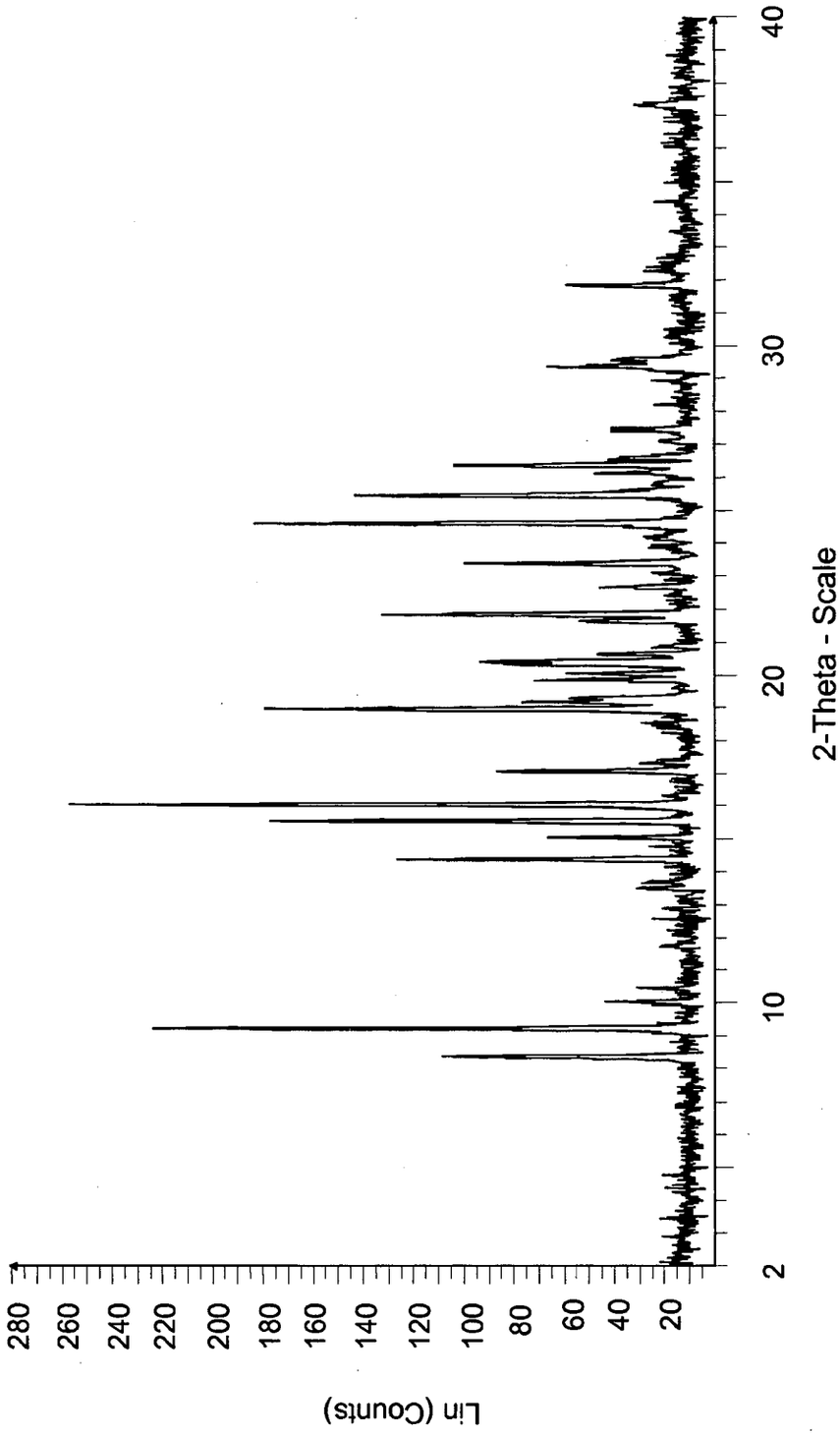


Figure 1

Figure 2: X-Ray Powder Diffraction Pattern for N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A when measured using CuKa radiation

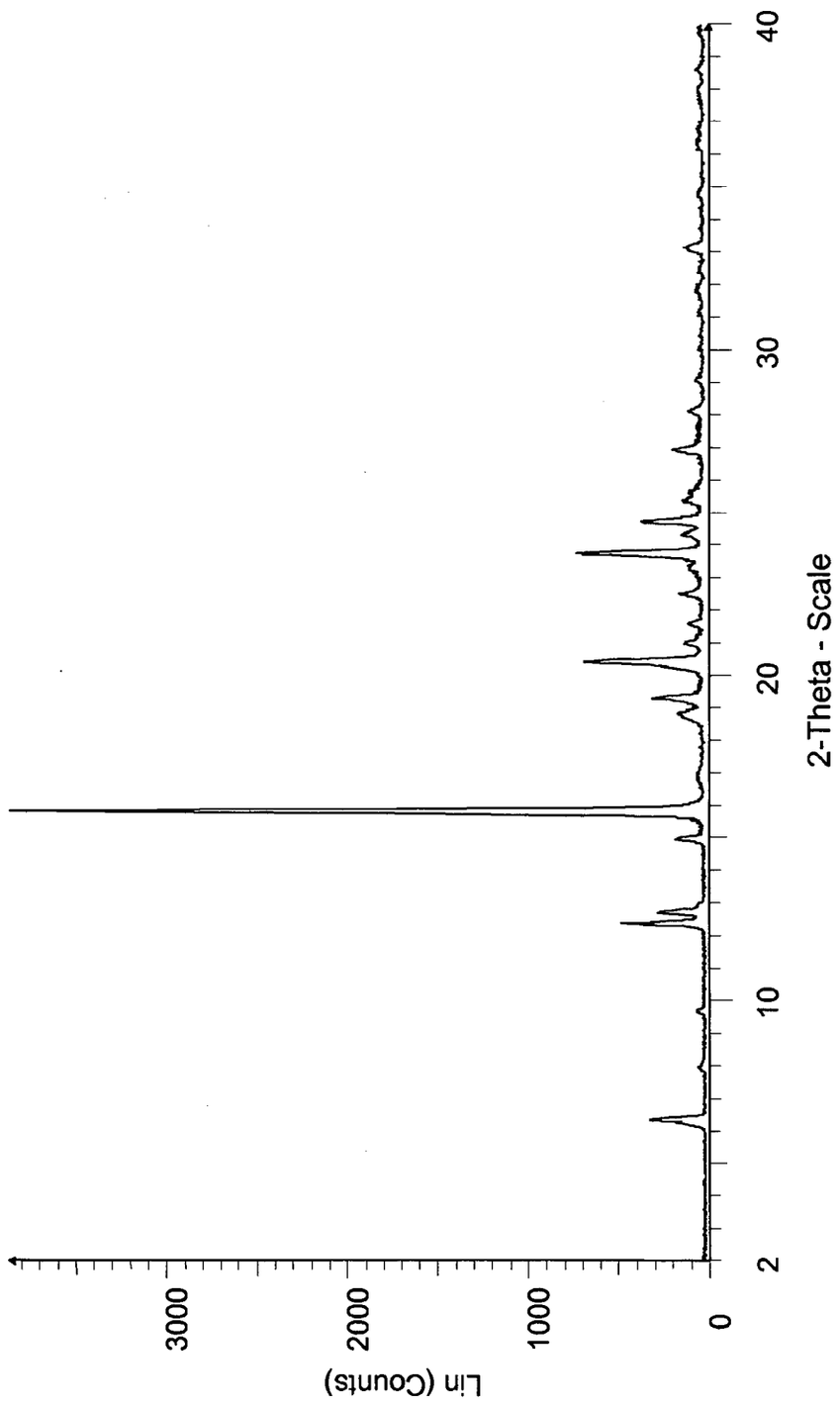


Figure 2

Figure 3: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuKa radiation

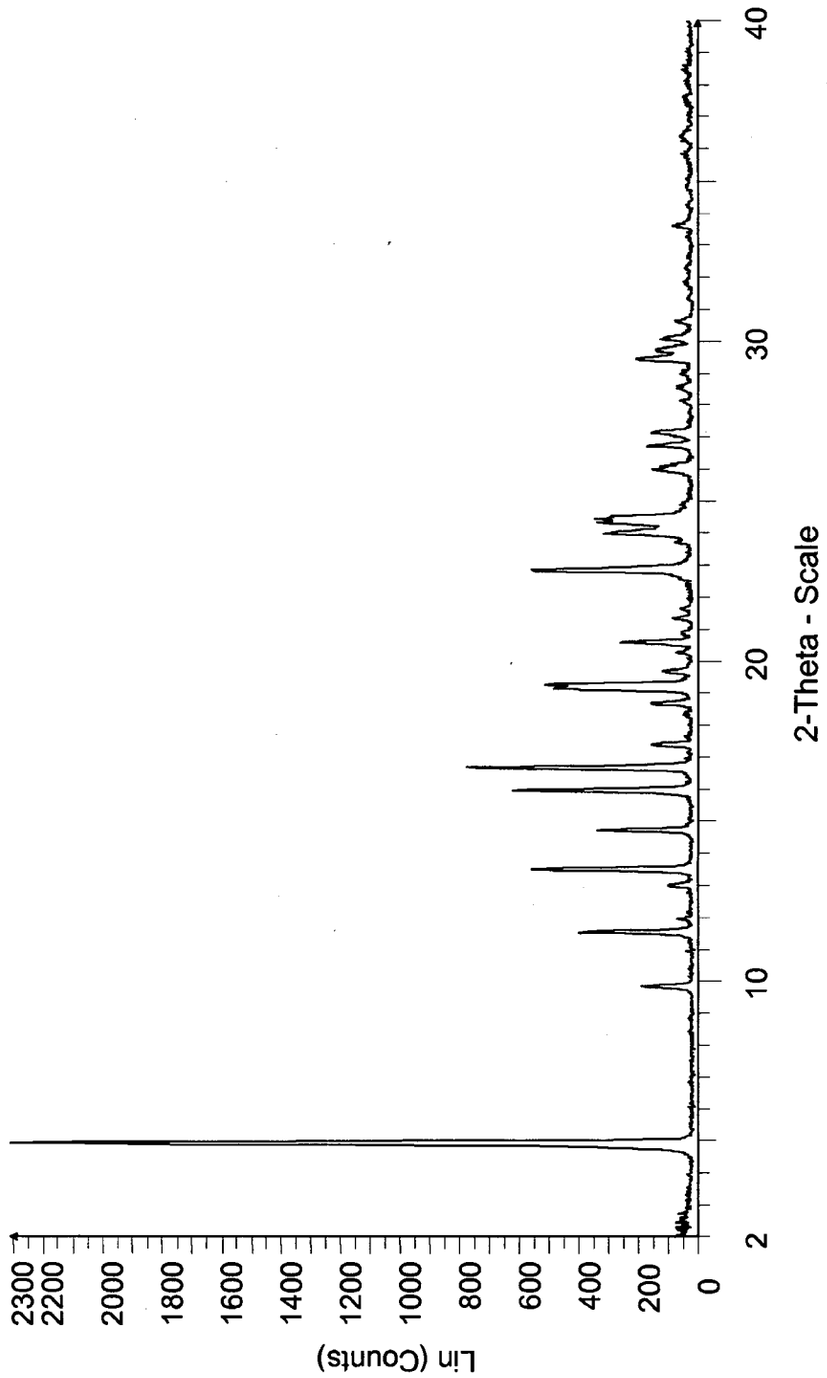


Figure 3

Figure 4: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuKa radiation

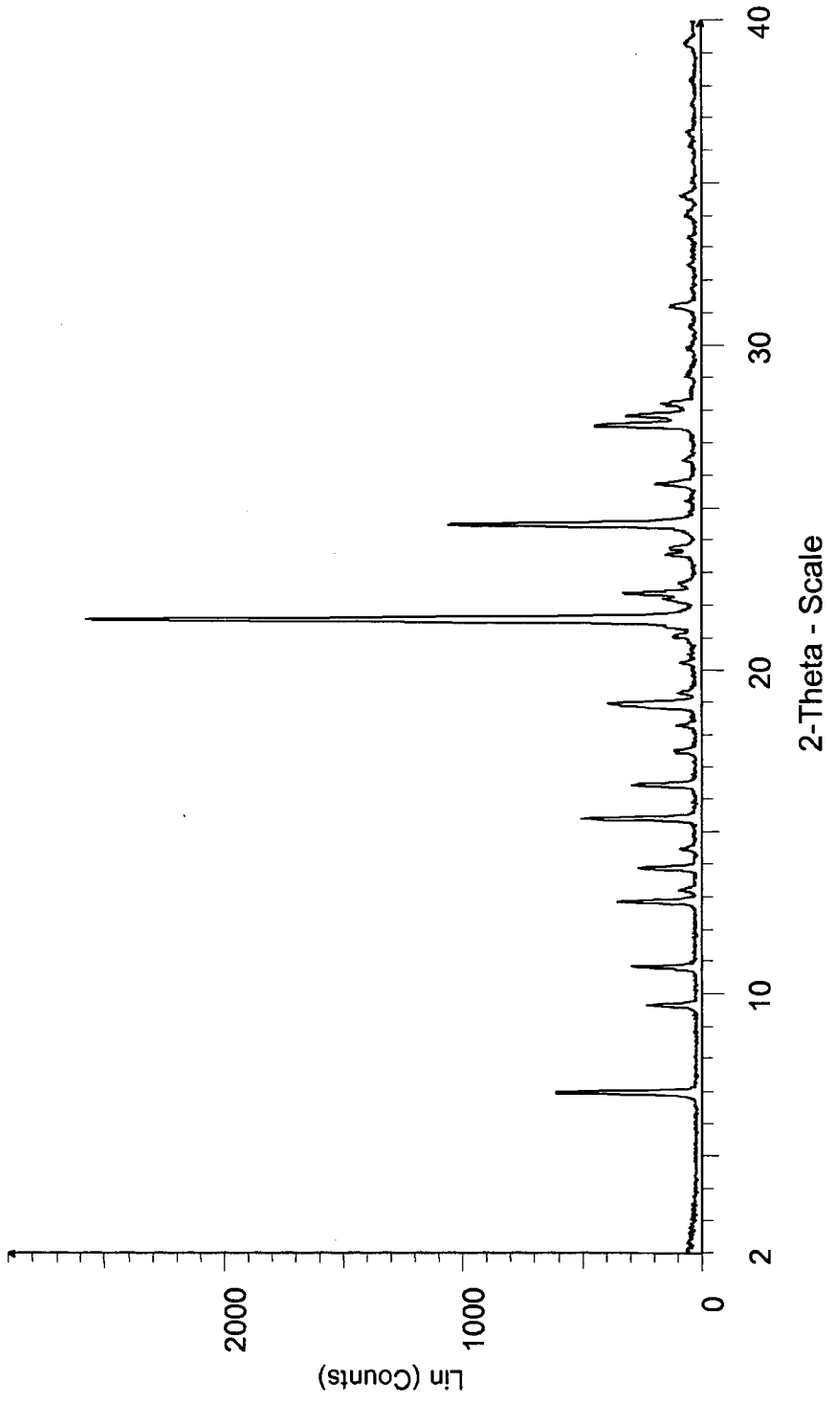


Figure 4

Figure 5: X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate when measured using CuKa radiation

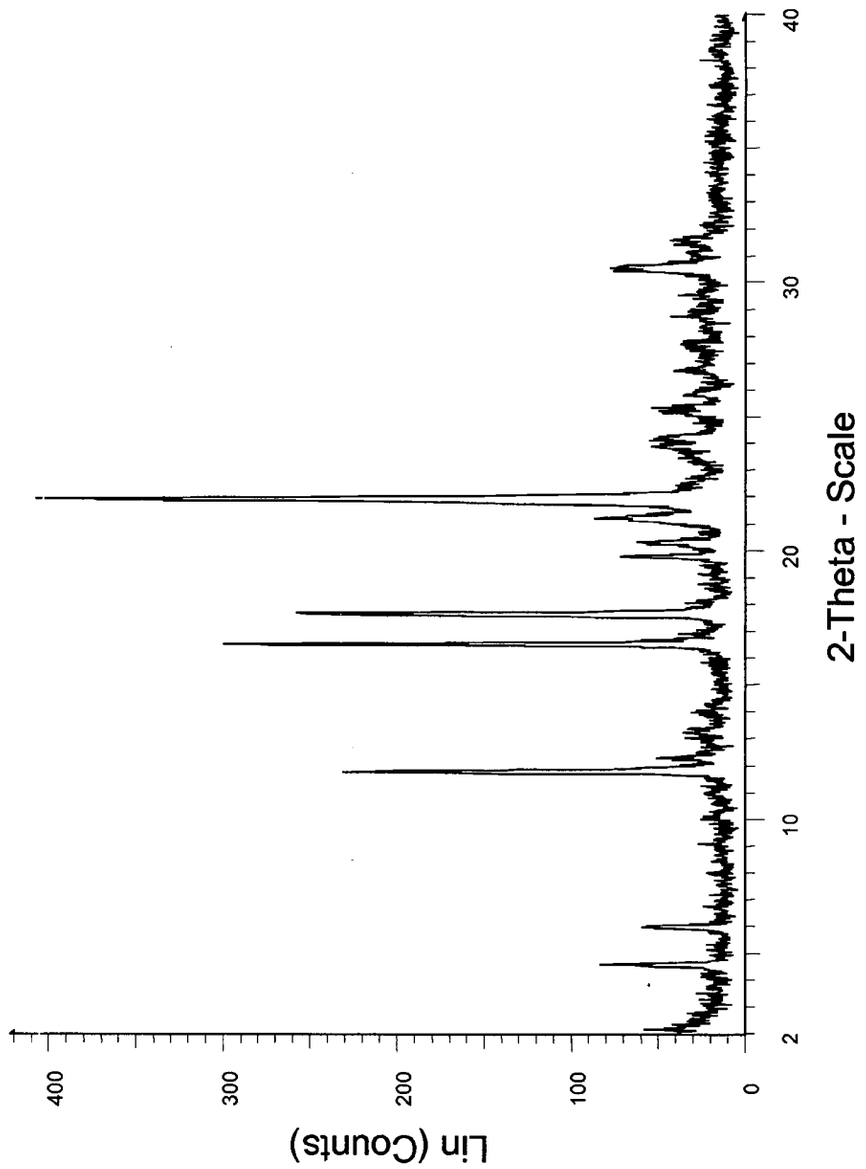


Figure 5

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional N°
PCT/GB2008/051206

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

INV. C07D471/04 C07D487/04 C07D519/00 A61K31/4196 A61K31/437
A61K31/5025 A61P35/00

De acuerdo con la Clasificación Internacional de Patentes (CIP) o según la clasificación nacional y la CPI

B. SECTORES COMPRENDIDOS POR LA BÚSQUEDA

Documentación mínima consultada (sistema de clasificación, seguido de los símbolos de clasificación)
C07D A61K A61P

Otra documentación consultada, además de la documentación mínima, en la medida en que tales documentos formen parte de los sectores comprendidos por la búsqueda

Bases de datos electrónicas consultadas durante la búsqueda internacional (nombre de la base de datos y, si es posible, términos de búsqueda utilizados)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
P,A	WO 2008/109104 A (UNIV CALIFORNIA [US]; KOLB HARTMUTH C [US]; WANG SI [US]; CHERUKUPALLI) 12 de Septiembre de 2008 (2008-09-12) reivindicaciones; ejemplos	1-21
A	WO 2006/039325 A (MERCK & CO INC [US]; COX JASON M [US]; EDMONDSON SCOTT D [US]; HARPER) 13 de Abril de 2006 (2006-04-13) ejemplos	1-21

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☒ En la continuación del recuadro C se relacionan otros documentos.

☒ Los documentos de familias de patentes se indican en el anexo.

* Categorías especiales de documentos citados:

"A" documento que define el estado general de la técnica no considerado como particularmente relevante

"E" documento anterior aunque publicado en la fecha de presentación internacional o en fecha posterior

"L" documento que puede plantear dudas sobre una reivindicación de prioridad o que se cita para determinar la fecha de publicación de otra cita o por una razón especial (como la indicada)

"O" documento que se refiere a una divulgación oral, a una utilización, a una exposición o a cualquier otro medio

"P" documento publicado antes de la fecha de presentación internacional pero con posterioridad a la fecha de prioridad reivindicada

"T" documento ulterior publicado con posterioridad a la fecha de presentación internacional o de prioridad, que no pertenece al estado de la técnica pertinente pero que se cita por permitir la comprensión del principio o teoría que constituye la base de la invención

"X" documento particularmente relevante; la invención reivindicada no puede considerarse nueva o que implique una actividad inventiva por referencia al documento aisladamente considerado

"Y" documento particularmente relevante; la invención reivindicada no puede considerarse que implique una actividad inventiva cuando el documento se asocia a otro u otros documentos de la misma naturaleza, resultando dicha combinación evidente para un experto en la materia

"&" documento que forma parte de la misma familia de patentes

Fecha en que se ha concluido la búsqueda internacional	Fecha de expedición del Informe de Búsqueda Internacional
19 de Marzo de 2009	06/04/2009
Nombre y dirección postal de la Administración encargada de la Búsqueda Internacional Oficina Europea de Patentes, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax. (+31-70) 340-3016	**Funcionario autorizado** Fazzi, Raffaella

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional Nº
PCT/GB2008/051206

C (Continuación). DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría*	Documentos citados, con indicación, si procede, de las partes relevantes	Relevante para las reivindicaciones Nº
A	COX ET AL: "Discovery of 3-aminopiperidines as potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, n.º 16, 17 de Julio de 2007 (2007-07-17), páginas 4579-4583, XP022181870 ISSN: 0960-849X tablas 2-4	1-21

INFORME DE BÚSQUEDA INTERNACIONAL

Información sobre miembros de la familia de patentes

Solicitud internacional Nº
PCT/GB2008/051206

Documento de patente citado en el informe de búsqueda	Fecha de publicación	Miembro(s) de la familia de patentes	Fecha de publicación
WO 2008109104 A	12-09-2008	NINGUNO	
WO 2006039325 A	13-04-2006	AU 2005292134 A1	13-04-2006
		CA 2582447 A1	13-04-2006
		CN 101031300 A	05-09-2007
		EP 1796669 A2	20-06-2007
		JP 2008514716 T	08-05-2008
		US 2008076773 A1	27-03-2008

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/051206

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/04 C07D519/00 A61K31/4196 A61K31/437
A61K31/5025 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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2008/109104 A (UNIV CALIFORNIA [US]; KOLB HARTMUTH C [US]; WANG SI [US]; CHERUKUPALLI) 12 September 2008 (2008-09-12) claims; examples	1-21
A	WO 2006/039325 A (MERCK & CO INC [US]; COX JASON M [US]; EDMONDSON SCOTT D [US]; HARPER) 13 April 2006 (2006-04-13) examples	1-21

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2009	06/04/2009

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	Fazzi, Raffaella

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/051206

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COX ET AL: "Discovery of 3-aminopiperidines as potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 17, no. 16, 17 July 2007 (2007-07-17), pages 4579-4583, XP022181870 ISSN: 0960-894X tables 2-4	1-21

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/051206

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008109104 A	12-09-2008	NONE	
WO 2006039325 A	13-04-2006	AU 2005292134 A1	13-04-2006
		CA 2582447 A1	13-04-2006
		CN 101031300 A	05-09-2007
		EP 1796669 A2	20-06-2007
		JP 2008514716 T	08-05-2008
		US 2008076773 A1	27-03-2008

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-074454- -00000-0000

Fecha: 2010-06-21 16:56:23 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 882

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art.33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA		
	Radicación No.	10 074454
	Solicitud internacional	PCT/GB2008/051206
	Fecha inicio fase nacional	21/07/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10532

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 20 AGO. 2010.
adpa11

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

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
ASTRAZENECA AB

REFERENCIA		
	Radicación No.	10 074454
	Solicitud internacional	PCT/GB2008/051206
	Fecha inicio fase nacional	21/07/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10533

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 20 AGO. 2010.
adpa11

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Call Center 6513240. Línea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia