Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

NOV 1 M.

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 08-138249

54. **TÍTULO** Nuevos compuestos

51. **CLASIFICACIÓN INTERNACIONAL** (51) C07D481/04

71. **SOLICITANTE** AStraZeneca AB

DOMICILIO

74. **APODERADO** I. IAN RAISBECK

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

OlarteRaisbeck

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-138249- -00000-0000
Fecha: 2008-12-30 17:39:57 Dep: 2020 NUECREACIONI
Tra: 11, PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1001

PETITORIO - FORMULARIO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000241**

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-151 85 Södertalje
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: World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10.
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: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA DJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2007/002490 Fecha Julio 5, 2007

Publicación Internacional No. WO 2008/003958 Fecha Enero 10, 2008

(6) **Título (54)** NUEVOS COMPUESTOS (Ver folio Todo)

Clasificación Internacional (51) C07D 487/04, A61K 31/522

Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Julio 6, 2006	60/818,878

(9) **Comprobante de pago No.** 08-99,681 **Fecha** Diciembre 23, 2008

(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.
- [ ] 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).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [x] 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.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

LISTA DE INVENTORES

PCT/GB2007/002490

Christopher Thomas HALSALL,
AstraZeneca R & D Alderley,
Ardeley Park, Macclesfield Cheshire
SK10 4TG
Gran Bretaña
Nacionalidad: Britanico

David Alan RUDGE,
AstraZeneca R & D Alderley,
Ardeley Park, Macclesfield Cheshire
SK10 4TG
Gran Bretaña
Nacionalidad: Británico

Iain SIMPSON,
AstraZeneca R & D Alderley,
Ardeley Park, Macclesfield Cheshire
SK10 4TG
Gran Bretaña
Nacionalidad: Británico

Richard Andrew WARD,
AstraZeneca R & D Alderley,
Ardeley Park, Macclesfield Cheshire
SK10 4TG
Gran Bretaña
Nacionalidad: Británico

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 99,681
FECHA : DICIEMBRE 23 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-138249- -00000-0000
Fecha: 2008-12-30 17:39:57 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1001

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	14443951	23/12/2008	8,092,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
		TOTAL : $	501,000.00

SON: QUINIENTOS UN 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.

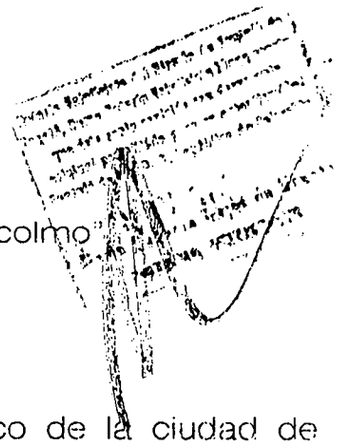
Firma de Agneta S...

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 E.
Licencia No. [illegible]

6

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.

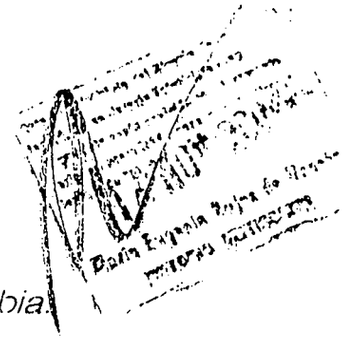
Traductor: Jorge Enrique Sierra Reyes.

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



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

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayda Chalú
Simón Selim
Alexander Agudel
Camilo A. Rodrígue
Lina Mosquer
Catalina Barbastefan

Of Counsel
Guillermo Chalú
Graciela Mel
Jacqueline Chapper
Cruz E. de Moncaleano

Power of Attorney

Poder

The undersigned,

El suscrito,

AstraZeneca AB

domiciled in

domiciliado en

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.

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 OCTOBER 2007

City,Country/Ciudad,País: SÖDERTÄLJE

World Trade Center - Torre A, Calle 100 No. 8A – 37, Piso 10, Bogotá D.C., Colombia
Tel + 57 1 601-7700, Fax + 57 1 601-7799, office@olarteraisbeck.com, www.olarteraisbeck.com

I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm hereby certify that

ANDERS BURÉN

duly authorized to sign for

ASTRAZENECA AB

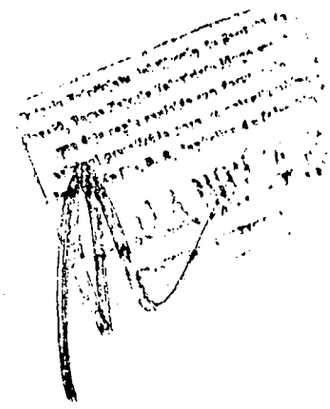
has issued and signed the foregoing document.

Fee 340:- Stockholm 2007-10-26

.Crowns Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Anders Burén
Authorised Signatory



10

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

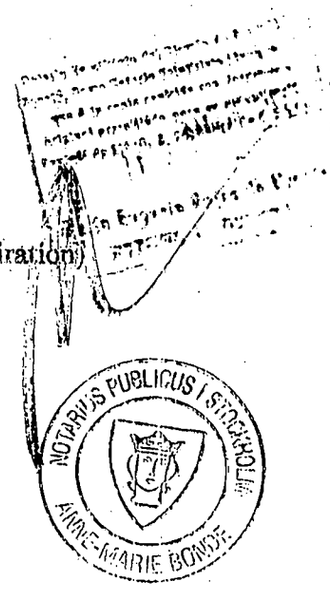
4. Que
con sede principal ubicada en

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)



11

Traducción oficial de un documento cuyo original está en inglés

BOLAGSVERKET

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

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.

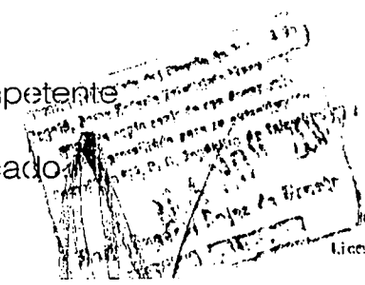
En testimonio de lo anterior, he puesto mi firma y estampado el sello oficial de Bolagsverket en Sundsvall, este día 8 de Agosto del año 2007.

(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



Traductor Oficial
JORGE E. SIERRA REY
Licencia 876 - 1993 Minis

12

- 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 DEYE
Matrícula [illegible]

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

Traductor Oficial
JORGE E. SIERRA R
Licencia 376 - 1993 Min

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

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.

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

16

I, the undersigned, Anne-Marie Bonde, Notary Public of the City of Stockholm

hereby certify that

ANNA-KARIN ÖSTIN

duly authorized to sign for

THE SWEDISH COMPANIES REGISTRATION OFFICE

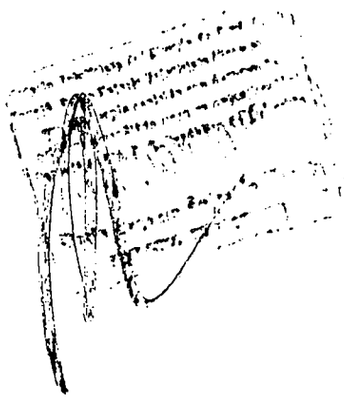
has issued and signed the foregoing document in original of which this is a true copy.

Fee 340:- Crowns

Stockholm 2007-10-26

Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE



11426

The Ministry for Foreign Affairs in Stockholm, hereby certifies that

Ms. Anna-Karin Sjöö

Swedish Companies Registration Office, Sundsvall

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

For Stockholm this 17th day of August 2007

Fee 60:- PAID

Gunilla Kindbom

SIGNATURE OF Agneta Ecklund

AND STAMP OF : Sec MFA

SIGNATURE : Mohamed Hussein

DATE 20-08-07

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2008 (10.01.2008)

PCT

(10) International Publication Number
WO 2008/003958 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/GB2007/002490

(22) International Filing Date: 5 July 2007 (05.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/818,878 6 July 2006 (06.07.2006) US

(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-SE-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)*: **HALSALL, Christopher, Thomas** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **RUDGE, David, Alan** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **SIMPSON, Iain** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **WARD, Richard, Andrew** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

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

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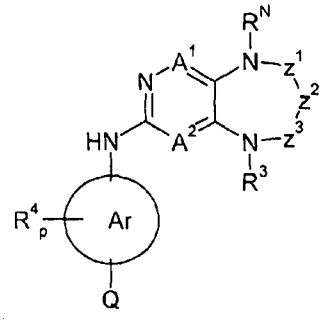
(54) Title: NOVEL COMPOUNDS



(I)

(57) Abstract: There is provided a compound of formula (I):processes for the manufacure thereof, pharmaceutical compoitions thereof and uses in therapy.

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NOVEL COMPOUNDS

The present invention relates to pyrimidine derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy and the treating of conditions mediated by polo-like kinases.

Many of the current treatment regimes for cell proliferation diseases such as cancer and psoriasis utilise compounds that inhibit DNA synthesis. Compounds that inhibit DNA synthesis may often prove to be toxic to many types of cells. However, the marked toxic effect on rapidly dividing cells such as tumour cells is often seen to offer a benefit in light of the general toxic nature of such compounds. Therefore, alternative antiproliferative agents that act by mechanisms other than the inhibition of DNA synthesis may offer the potential for selective targeting of the proliferating cells.

The Cyclin dependent kinase family (Cdks) have long been considered the master regulators of the cell cycle but an increasing number of diverse protein kinases are emerging as critical components of cell cycle progression. Among these are the polo-like kinase family (Plks), serine/threonine kinases that play multiple roles in regulating progress through cell cycle. In man, four distinct family members have been identified. These are Plk1, Plk2 (Snk), Plk3 (Fnk, Prk) and Plk4 (Sak).

The best characterized family member is Plk1 which is conserved from yeast to man and has been implicated in numerous mitotic processes including activation of Cdc25C and Cdk1/Cyclin B at the G2-M transition, centrosome maturation, spindle formation and assembly (Glover et al. 1998, Genes Dev. 12:3777-87; Barr et al 2004, Nat. Rev. Mol. Cell Biol 5:429-441). In the later stages of mitosis Plk1 is involved in separation of sister chromatids, activation of components of the anaphase-promoting complex and septin regulation during cytokinesis (van Vugt & Medema 2005, Oncogene 24:2844-2859).

Plk1 is overexpressed in a broad spectrum of cancer types including breast, colorectal, endometrial, oesophageal, ovarian, prostate, pancreatic, non small cell lung cancers and melanomas (Wolf et al. 1997, Oncogene 14:543-549; Knecht et al. 1999, Cancer Res. 59:2794-2797; Wolf et al. 2000, Pathol. Res. Pract. 196:753-759; Takahashi et al. 2003, Cancer Sci. 94:148-152). The expression of Plk1 often correlates with poor patient prognosis.

The conclusion that Plk1 elevation is a cause and not a consequence of oncogenesis resulted from a study demonstrating that overexpression or constitutive expression of Plk1 induces malignant transformation of mammalian cells, causing tumour formation in nude mice (Smith et al 1997, Biochem. Biophys. Res. Commun 234:397-405)

Therapeutic potential for Plk1 inhibition has been demonstrated in studies employing both antisense oligonucleotides (ASO) and small molecule RNA (siRNA). Reduction in the level of Plk1 results in the inhibition of proliferation of tumour cells and loss of cell viability both *in vivo* and *in vitro* but does not inhibit proliferation of primary cells (Spankuch-Schmitt et al 2002, Oncogene 21: 3162-3171; Elez et al 2003, Oncogene 22:69-80). Microinjection of anti-Plk1 antibodies induced mitotic catastrophe in HeLa tumour cells. These cells displayed abnormal distribution of chromatin and monoastral microtubules while normal fibroblast cells arrested transiently in G2 phase of cell cycle as single mononucleated cells (Lane & Nigg 1996 J.Cell Biol. 135:1701-1713). These results suggest that Plk1 inhibition specifically targets cancer cells with checkpoint defects while cells with intact checkpoint pathways are less affected.

Although the exact functions of the other family members remains largely unknown, silencing of Plk2 in the presence of taxol or nocodazole significantly increases apoptosis suggesting Plk2 may prevent mitotic catastrophe following spindle damage (Burns et al. 2003, Mol Cell Biol 23: 5556-5571). Likewise silencing of Plk4 in mammalian cells induces apoptosis (Li et al. 2005, Neoplasia 7: 312-323) and plk4 null mouse embryos arrest with an increase in mitotic and apoptotic cells (Hudson et al. 2001, Curr Biol 11: 441-446).

Plk3 also appears to play roles in mitosis, like Plk1 it has been reported to phosphorylate Cdc25C, regulate microtubule dynamics and is involved in centrosome function. Overexpression of Plk3 has been observed in both breast and ovarian carcinomas, with little or no expression in adjacent normal tissue. Increased protein level was associated with enhanced mitosis and was significantly linked to reduced median survival time of patients (Weichert et al. 2005, Virchows Arch 446: 442-450; Weichert et al. 2004 Br. J.Cancer 90:815-821).

These findings suggest that pharmacological inhibitors of Plk family members should be of therapeutic value for treatment of proliferative disease including solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In addition Plk

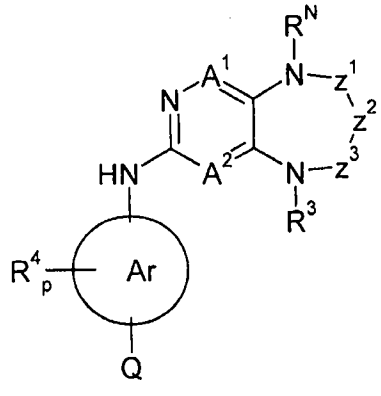
inhibitors should be useful in the treatment of other disorders associated with uncontrolled cellular proliferation.

Pteridinone derivatives are known from the prior art as active substances with an antiproliferative activity. WO 01/019825 and WO 03/020722 describe the use of pteridinone derivatives for the treatment of tumoural diseases.

The resistance of many types of tumours calls for the development of new pharmaceutical compositions for combating tumours.

The aim of the present invention is to provide new compounds having an antiproliferative activity.

According to a first aspect of the present invention there is provided a compound of formula (I):



(I)

wherein

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2

heteroatoms, or an optionally substituted heteroaryl ring comprising 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen or sulphur;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, -OH, -CN, -C=CH, $-C(=O)NH_2$, C_{1-3}alkyl, C_{-1-3}alkylamino, C_{1-3}alkylthio, C_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, -CHO, or $-SO_2Me$

p is 0, 1 or 2;

Q is $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, -(optionally substituted C_{1-3}alkyl)$_g$-$NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ or –(5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur)-L_n-$R^5{}_m$;

g is 0 or 1;

k is 0, 1 or 2;

R^a represents H or an optionally substituted C_{1-6}alkyl group, and R^b represents -L_n-$R^5{}_m$, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a2} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b2} represents -L_n-$R^5{}_m$, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a3} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b3} represents -L_n-$R^5{}_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, or R^{a3} and R^{b3} together

with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a4} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b4} represents $-L_n-R^5_m$, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b5} represents $-L_n-R^5_m$, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a6} represents $-L_n-R^5_m$;

R^{a7} represents $-L_n-R^5_m$;

R^{a8} represents $-L_n-R^5_m$;

R^{a9} represents $-L_n-R^5_m$;

R^{a10} represents $-L_n-R^5_m$;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl, optionally substituted C_{7-12}polycycloalkyl group, optionally substituted C_{7-12}polycycloalkenyl group, optionally substituted C_{5-12}spirocycloalkyl group and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatane, optionally substituted oxogranatane and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group;

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted -C_{1-4}alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{1-4}alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

X^1 is O or S;

X^2 is O, S or H_2;

Ar represents a 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur; and

A^1, A^2 each independently represents N or CH;

and wherein

when Z^1 is C=O, Z^2 is CR^cR^d or NR^e and Z^3 is CR^1R^2;

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group; or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d, or R^1 and R^e together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

or when Z^2 is C=O, Z^1 is $CR^{f2}R^{g2}$ and Z^3 is CR^1R^2;

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^{f2}, R^{g2} each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^{f2} and R^{g2} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^1 and R^3, or R^2 and R^3 together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

or when Z^3 is C=O, Z^2 is $CR^{c3}R^{d3}$ or NR^{e3} and Z^1 is $CR^{f3}R^{g3}$;

R^{c3}, R^{d3} each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^{c3} and R^{d3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^{e3} represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group;

R^{f3}, R^{g3} each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^{f3} and R^{g3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^{c3} and R^{f3}, or R^{d3} and R^{g3}, or R^{c3} and R^{f3} together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom

or when Z^1 is CR^fR^g, Z^2 is CR^cR^d or NR^e and Z^3 is CR^1R^2;

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the

carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group;

R^f, R^g each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d, or R^1 and R^{c3} together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom,

or pharmacologically acceptable salts thereof.

The term alkyl group, including alkyl groups which are a part of other groups, unless otherwise stated, includes branched and unbranched alkyl groups with 1 to 12 carbon atoms. Examples of C_{1-12}alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and dodecyl groups. Unless otherwise stated, the terms propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl and dodecyl include all the possible isomeric forms. For example, the term propyl includes the two isomeric groups n-propyl and iso-propyl, the term butyl includes n-butyl, iso-butyl, sec-butyl and tert-butyl, the term pentyl includes iso-pentyl, neopentyl, etc.

In the above mentioned alkyl groups, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, alkyl groups may be substituted by the following substituents groups: =O; OH; NO_2; CN; $-NH_2$; halogen, for example fluorine or chlorine; optionally substituted C_{1-10}alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted $-OC_{1-3}$alkyl, for example OMe, OEt, $-OCHF_2$, $-OCF_3$; -COOH; $-COO-C_{1-4}$alkyl, for example -COOMe or –COOEt; or $-CONH_2$. "=O" denotes an oxygen atom linked via a double bond. All the hydrogen atoms of the alkyl group may optionally be

replaced by substituent groups, for example a trifluoromethyl group is a methyl group wherein all the hydrogen atoms have been replaced with fluorine atoms.

The term alkyl bridge, unless otherwise stated, includes branched and unbranched alkyl bridging groups with 1 to 5 carbon atoms, for example methylene, ethylene, propylene, butylene and pentylene bridges. Unless otherwise stated, the terms propylene, butylene and pentylene include all the possible isomeric forms. In the aforementioned alkyl bridges, 1 or 2 C-atoms may optionally be replaced by one or more heteroatoms selected from among oxygen, nitrogen or sulphur.

The term alkenyl groups (including those which are a part of other groups), unless otherwise stated, includes branched and unbranched alkylene groups with 2 to 10 carbon atoms comprising at least one carbon-carbon double bond. Examples of C_{2-10}alkenyl groups include ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl nonenyl and decenyl groups. Unless otherwise stated, the abovementioned terms propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl also include all the possible isomeric forms. For example, the term butenyl includes 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl, 2-methyl-1-propenyl, 2-methyl-2-propenyl and 1-ethyl-1-ethenyl.

In the above mentioned alkenyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, alkenyl groups may be substituted by the following substituents groups: =O; OH; NO_2; CN; $-NH_2$; halogen, for example fluorine or chlorine; optionally substituted C_{1-10}alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted $-OC_{1-3}$alkyl, for example OMe, OEt, $-OCHF_2$, $-OCF_3$; -COOH; $-COO-C_{1-4}$alkyl, for example -COOMe or –COOEt; or $-CONH_2$. "=O" denotes an oxygen atom linked via a double bond. All the hydrogen atoms of the alkenyl group may optionally be replaced, for example a trifluoroethylene group is an ethylene group wherein all the hydrogen atoms have been replaced with fluorine atoms.

The term alkynyl groups (including those which are a part of other groups), unless otherwise stated, includes branched and unbranched alkynyl groups with 2 to 10 carbon atoms comprising at least one triple bond. Examples of C_{2-10}alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl and decynyl groups. Unless otherwise stated, the terms propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl

and decynyl also include all the possible isomeric forms. For example, the term butynyl includes 1-butynyl, 2-butynyl, 3-butynyl and 1-methyl-2-propynyl.

In the above mentioned alkynyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, alkynyl groups may be substituted by the following substituents groups: =O; OH; NO_2; CN; $-NH_2$; halogen, for example fluorine or chlorine; optionally substituted C_{1-10}alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted $-OC_{1-3}$alkyl, for example OMe, OEt, $-OCHF_2$, $-OCF_3$; -COOH; $-COO-C_{1-4}$alkyl, for example -COOMe or –COOEt; or $-CONH_2$. "=O" denotes an oxygen atom linked via a double bond. All the hydrogen atoms of the alkynyl group may optionally also be replaced.

The term aryl includes aromatic ring systems with 6 to 14 carbon atoms, said aromatic ring systems comprising one or more rings having from 6 to 14 ring atoms wherein at least one ring is aromatic. Examples of C_{6-14}aryl groups include phenyl (C_6), indenyl (C_9), naphthyl (C_{10}), fluorenyl (C_{13}), anthracyl (C_{14}), and phenanthryl (C_{14}). In the above mentioned aryl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substitutent groups. For example, aryl groups may be substituted by the following substituents groups: OH; NO_2; CN; NH_2; halogen, for example fluorine or chlorine; optionally substituted C_{1-10}alkyl, for example methyl, ethyl, propyl or CF_3; optionally substituted $-OC_{1-3}$alkyl, for example –OMe, –OEt, $OCHF_2$, or OCF_3; -COOH, $-COO-C_{1-4}$alkyl, for example -COOMe or –COOEt, or $-CONH_2$.

The term heteroaryl comprising 1 or 2 nitrogen atoms includes heteroaromatic ring systems with 5 to 14 ring atoms, said heteroaromatic ring systems comprising one or more rings having from 5 to 14 ring atoms wherein at least one ring is aromatic and wherein one or two of the ring atoms are replaced by nitrogen atoms the remaining ring atoms being carbon atoms. Examples of heteroaryl groups wherein up to two carbon atoms are replaced by one or two nitrogen atoms comprising one ring include pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyridinyl and pyrimidinyl groups. Each of the aforementioned examples of heteroaryl rings may optionally also be anellated by a further ring, for example a benzene ring. Examples of heteroaryl groups wherein up to two carbon atoms are replaced by one or two nitrogen atoms comprising two rings include indolyl, benzimidazolyl, quinolinyl, isoquinolinyl and quinazolinyl. In the above mentioned heteroaryl groups, unless otherwise stated, one or more

hydrogen atoms may optionally be replaced by other substituent groups. For example, heteroaryl groups may be substituted by the following substituents groups: F; Cl; Br; OH; OMe; Me; Et; CN; NH_2; $CONH_2$; optionally substituted phenyl; and optionally substituted heteroaryl, for example optionally substituted pyridyl.

The term optionally substituted heteroaryl ring comprising 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen or sulphur includes heteroaromatic ring systems with 5 to 14 ring atoms, said heteroaromatic ring systems comprising one or more rings having from 5 to 14 ring atoms wherein at least one ring is aromatic and wherein one, two or three of the ring atoms are replaced by nitrogen, oxygen or sulphur atoms the remaining ring atoms being carbon atoms. Examples of heteroaryl rings wherein up to three carbon atoms are replaced by nitrogen, oxygen or sulphur comprising one ring include furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiazolyl, thienyl and triazolyl groups. Each of the aforementioned examples of heteroaryl rings may optionally also be anellated by a further ring, for example a benzene ring. Examples of heteroaryl rings wherein up to three carbon atoms are replaced by nitrogen, oxygen or sulphur atoms comprising two rings include indolyl, benzimidazolyl, benzoxazoyl, benzioxazoyl, quinolinyl, isoquinolinyl and quinazolinyl. In the above mentioned heteroaryl rings, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, heteroaryl groups may be substituted by the following substituents groups: F; Cl; Br; OH; OMe; Me; Et; CN; NH_2; $CONH_2$; optionally substituted phenyl; and optionally substituted heteroaryl, for example optionally substituted pyridyl.

The term cycloalkyl groups, unless otherwise stated, includes cycloalkyl groups comprising 1 ring with 3-12 carbon atoms. Examples of C_{3-12}cycoalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl groups. In the abovementioned cycloalkyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, cycloalkyl groups may be substituted by the following substituents groups: =O; OH; NO_2; CN; $-NH_2$; halogen, for example fluorine or chlorine; optionally substituted C_{1-10}alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted $-OC_{1-3}$alkyl, for example OMe, OEt, $-OCHF_2$, $-OCF_3$; -COOH;

-COO-C_{1-4}alkyl, for example -COOMe or –COOEt; or -$CONH_2$. "=O" denotes an oxygen atom linked via a double bond.

The term cycloalkenyl, unless otherwise stated, includes cycloalkenyl groups with 3-12 carbon atoms comprising one ring, said ring comprising at least one carbon-carbon double bond. Examples of C_{3-12}cycloakenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl, cycloundecenyl and cyclododecenyl groups. In the abovementioned cycloalkenyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, cycloalkenyl groups may be substituted by the following substituent groups: =O; OH; NO_2; CN; -NH_2; halogen, for example fluorine or chlorine; optionally substituted C_{1-10}alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted -OC_{1-3}alkyl, for example OMe, OEt, -$OCHF_2$, -OCF_3; -COOH; -COO-C_{1-4}alkyl, for example -COOMe or –COOEt; or -$CONH_2$. "=O" denotes an oxygen atom linked via a double bond.

The terms heterocycloalkyl and heterocycloakenyl, unless otherwise described in the definitions, includes 3- to 12-membered, for example 5-, 6- or 7-membered, heterocycles which may contain 1 to 4 heteroatoms selected from nitrogen, oxygen or sulphur. Heterocycloalkyl denotes a saturated heterocycle, and heterocycloakenyl denotes an unsaturated heterocycle. Examples of heterocycloalkyl or heterocycloakenyl groups include tetrahydrofuran, tetrahydrofuranone, *gamma*-butyrolactone, *alpha*-pyran, *gamma*-pyran, dioxolane, tetrahydropyran, dioxane, dihydrothiophene, thiolan, dithiolan, pyrroline, pyrrolidine, pyrazoline, pyrazolidine, imidazoline, imidazolidine, tetrazole, piperidine, pyridazine, pyrimidine, pyrazine, piperazine, triazine, tetrazine, morpholine, thiomorpholine, diazepan, oxazine, tetrahydro-oxazinyl, isothiazole, and pyrazolidine. In the abovementioned heterocycloalkyl or heterocycloakenyl groups, unless otherwise stated, one or more hydrogen atoms may optionally be replaced by other substituent groups. For example, heterocycloalkyl or heterocycloakenyl groups may be substituted by the following substituents groups: =O; OH; CN; -NH_2; halogen, for example fluorine or chlorine; optionally substituted C_{1-4}alkyl, for example methyl, ethyl, propyl, trifluoromethyl; optionally substituted -OC_{1-3}alkyl, for example OMe, OEt, -$OCHF_2$, -OCF_3; -COOH; -COO-C_{1-4}alkyl, for example -COOMe or -COOEt; or -$CONH_2$. "=O" denotes an oxygen atom linked via a double bond.

The term polycycloalkyl, unless otherwise stated, includes cycloalkyl groups comprising 3 to 12 carbon atoms and comprising 2 or more rings. Examples of polycycloalkyl groups include optionally substituted, bi-, tri-, tetra- or pentacyclic cycloalkyl groups, for example pinane, 2,2,2-octane, 2,2,1-heptane or adamantane.

The term polycycloalkenyl, unless otherwise stated, includes cycloalkenyl groups comprising 7 to 12 carbon atoms and comprising 2 or more rings wherein at least one ring comprises a carbon-carbon double bond. Examples of polycycloalkenyl groups are optionally bridged and/or substituted bi-, tri-, tetra- or pentacyclic cycloalkenyl groups, for example bicycloalkenyl or tricycloalkenyl groups having at least one double bond, such as norbornene.

The term spirocycloalkyl unless otherwise stated, includes spirocycloalkyl groups comprising 5 to 12 carbon atoms and comprising 2 or more rings wherein two rings are joined at a spiro carbon centre. Examples of spirocycloalkyl groups include spiro[4.4]nonyl and spiro[3.4]octyl.

The term 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur is a fully unsaturated, aromatic monocyclic ring containing 5 or 6 atoms of which one or more ring atoms is optionally a heteroatom selected from nitrogen, oxygen or sulphur, with the remaining ring atoms being carbon. Examples of a 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur include furyl, imidazolyl, isothiazolyl, isoxazolyl, oxazolyl, phenyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl thiazolyl, thienyl and triazolyl rings.

The term 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms includes optionally substituted C_{3-6}cylcoalkyl and optionally substituted C_{3-6}cylcoalkenyl groups, and optionally substituted 3- to 6-membered heterocylcoalkyl and optionally substituted 3- to 6-membered heterocylcoalkenyl groups each with 1 or 2 heteroatoms.

The term halogen includes fluorine, chlorine, bromine or iodine.

The terms alkyloxy (-OR wherein R is an alkyl), alkenyloxy (-OR wherein R is an alkenyl), alkynyloxy (-OR wherein R is an alkynyl), cycloalkyloxy (-OR wherein R is a cycloalkyl) and heterocycloalkoxy (-OR wherein R is a heterocycloalkyl) denote an –OR

group wherein the respective alkyl, alkenyl, alkynyl, cycloalkyl or heterocycloalkyl group is as hereinbefore described above.

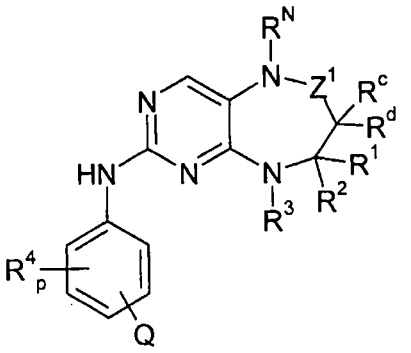
The terms alkylthio, alkylsulphoxo and alkylsulphono denotes an $-S(O)_xR$ group wherein x=0, 1 or 2 respectively and R is an alkyl group as hereinbefore described above.

The term –alkyl-aryl refers to an alkyl group with an aryl substituent. The term -alkyl-cycloalkyl refers to an alkyl group with a cycloakyl substituent. The term –aryl-alkyl refers to an aryl group with an alkyl substituent. The terms alkoxycarbonyl (-(C=O)OR), alkylcarbonyl (-COR) and arylcarbonyl (-COR) refer to a carbonyl group with an alkoxy, alkyl or aryl substituent.

When R^5 represents a substituted morpholinyl, piperidinyl, homopiperidinyl, piperazinyl, piperazinylcarbonyl, pyrrolidinyl, tropenyl, diketomethylpiperazinyl, sulphoxomorpholinyl, sulphonylmorpholinyl, thiomorpholinyl, granatanyl, oxogranatanyl or azacycloheptyl, one or more substituents may be present and are as defined above for R^8.

All the groups mentioned in the definition of R^1 to R^9 may optionally be branched and/or substituted.

According to a second aspect of the present invention there is provided a compound of formula (II):



(II)

wherein

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, -OH, -CN, -C=CH, $-C(=O)NH_2$, C_{1-3}alkyl, C_{-1-3}alkylamino, C_{1-3}alkylthio, C_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, -CHO, or $-SO_2Me$;

p is 0, 1 or 2;

Q is $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, -(optionally substituted C_{1-3}alkyl)$_g$-$NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ or –(5- or 6-membered aromatic or heteroaromatic

ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur)-L_n-$R^5{}_m$;

g is 0 or 1;

k is 0, 1 or 2;

R^a represents H or an optionally substituted C_{1-6}alkyl group, and R^b represents -L_n-$R^5{}_m$, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a2} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b2} represents -L_n-$R^5{}_m$, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a3} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b3} represents -L_n-$R^5{}_m$, -$SO_2NR^{a4}R^{b4}$, -$C(=O)NR^{a5}R^{b5}$, -SO_2R^{a6}, -$C(=O)OR^{a7}$, or R^{a3} and R^{b3} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a4} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b4} represents -L_n-$R^5{}_m$, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b5} represents -L_n-$R^5{}_m$, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a6} represents –L_n-$R^5{}_m$;

R^{a7} represents –L_n-$R^5{}_m$;

R^{a8} represents –L_n-$R^5{}_m$;

R^{a9} represents –L_n-$R^5{}_m$;

R^{a10} represents –L_n-$R^5{}_m$;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted

-C_{2-4}alkyl-C_{6-14}aryl, optionally substituted -C_{6-14}aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and -NR^8R^9;

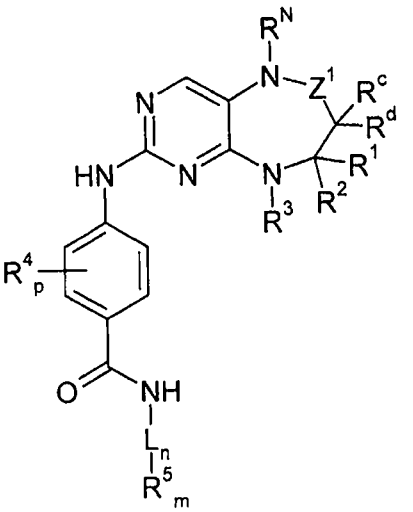
R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group;

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted -C_{1-4}alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{1-4}alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and

Z^1 is C=O or CR^fR^g wherein R^f, R^g each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms,

or pharmacologically acceptable salts thereof.

According to a third aspect of the present invention there is provided a compound of formula (IIa):



(IIa)

wherein

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally

substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, -OH, -CN, -C=CH, $-C(=O)NH_2$, C_{1-3}alkyl, C_{-1-3}alkylamino, C_{1-3}alkylthio, C_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, -CHO, or $-SO_2Me$;

p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted

azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group;

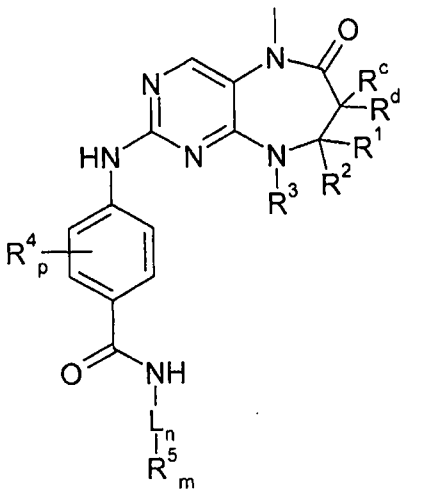
R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted $-C_{1-4}$alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{1-4}$alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and

Z^1 is C=O or CR^fR^g wherein R^f, R^g each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms,

or pharmacologically acceptable salts thereof.

In one embodiment of the second aspect of the invention, Z^1 is C=O or CH_2.

According to a fourth aspect of the present invention there is provided a compound of formula (III):



(III)

wherein

R^1, R^2 each independently represents hydrogen or an optionally substituted C_{1-6}alkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1;

m is 1 or 2;

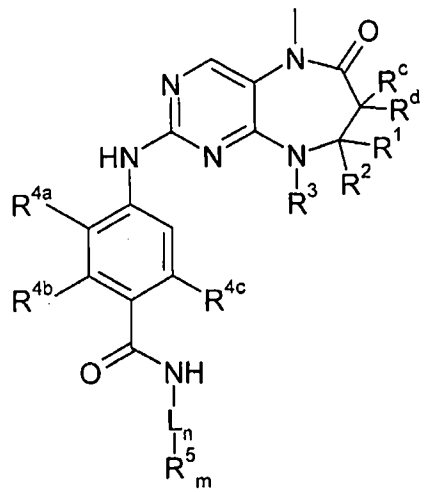
R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group; and

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted -C_{1-4}alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{1-4}alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms,

or pharmacologically acceptable salt thereof.

According to a fifth aspect of the present invention there is provided a compound of formula (IIIa):



(IIIa)

wherein

R^1, R^2 each independently represents hydrogen or an optionally substituted C_{1-6}alkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^{4a}, R^{4b}, R^{4c} each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is the number of $R^{4a, 4b, 4c}$ groups that are not hydrogen and is selected from 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted

C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1;

m is 1 or 2;

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group; and

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted $-C_{1-4}$alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{1-4}$alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms,

or pharmacologically acceptable salt thereof.

In one embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^1 and R^2 may be identical or different and represent hydrogen or a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^1 and R^2 may be identical or different and represent hydrogen or a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^1 and R^2 are different wherein one of R^1 or R^2 represents hydrogen and the other represents a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 together represent a 2- to 5-membered alkyl bridge optionally comprising 1 to 2 heteroatoms selected from oxygen or nitrogen and optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 together represent an ethylene or propylene bridge.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^c and R^d may be identical or different and represent hydrogen or a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^c and R^d may be identical or different and represent hydrogen or a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^c and R^d are different wherein one of R^c or R^d represents hydrogen and the other represents a methyl or ethyl group.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^c and R^d together represent a 2- to 5-membered alkyl bridge optionally comprising 1 to 2 heteroatoms selected from oxygen or nitrogen and optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^c and R^d together represent an ethylene, propylene or butylene bridge.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, at least one of R^1, R^2, R^c, or R^d is hydrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, at least two of R^1, R^2, R^c, or R^d are hydrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and one of R^c or R^d is hydrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and one of R^c or R^d is hydrogen and the other is methyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and R^c and R^d are methyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^2 are hydrogen, and R^c and R^d together represent an ethylene bridge.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^3 represents hydrogen; a C_1-C_{12}alkyl, for example ethyl, propyl, butyl, pentyl or hexyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; a C_2-C_{12}alkenyl, for example C_5-C_7alkenyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_2-C_{12}alkynyl, for example C_5-C_7alkynyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; a C_6-C_{14}aryl, for example phenyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; a C_3-C_{12}cycloalkyl, for example cyclopentyl or cyclohexyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; a C_3-C_{12}cycloalkenyl, for example C_5-C_7cycloalkenyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_7-C_{12}polycycloalkyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino;

C_7-C_{12}polycycloalkenyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_5-C_{12}spirocycloalkyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_3-C_{12}heterocycloalkyl which contains 1 to 2 heteroatoms selected from oxygen, nitrogen or sulphur, for example pyranyl or piperinyl, pyrrolidinyl, pyrazinyl or morpholinyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; and C_3-C_{12}heterocycloalkenyl which contains 1 to 2 heteroatoms selected from oxygen, nitrogen or sulphur, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^3 represents isopropyl, isobutyl, isopentyl, cyclopentyl, phenyl or cyclohexyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^3 represents cyclopentyl,or cyclohexyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^1 and R^3 or R^2 and R^3 together represent a saturated or unsaturated C_3-C_4alkyl bridge optionally comprising 1 heteroatom selected from oxygen or nitrogen.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, when p is 1 or 2, R^4 represents a group selected from among -CN; hydroxyl; -NR^6R^7; halogen, for example chlorine or fluorine; C_1-C_6alkyl, for example methyl, ethyl or propyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_2-C_6alkenyl, for example ethenyl or propenyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_2-C_6alkynyl, for example ethynyl, propynyl or butynyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_1-C_5alkyloxy, for example methoxy, ethoxy or propargyloxy, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_2-C_5alkenyloxy optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$,

C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_2-C_5alkynyloxy optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_1-C_6alkylthio optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_1-C_6alkylsulphoxo optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino and C_1-C_6alkylsulphonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third and fourth aspects, when p is 1, R^4 represents methoxy, methyl, ethoxy, chlorine or fluorine.

In another embodiment, for compounds of the first, second, third, and fourth aspects, when p is 2, each R^4 may be the same or different and selected from methoxy, methyl, ethoxy, ethyl, propargyloxy, chlorine or fluorine.

In another embodiment, for compounds of the first, second, third, and fourth aspects, when p is 2 and when each R^4 is adjacent, both R^4 together with the aromatic ring atoms to which they are attached form a 4- to 7-member unsaturated ring optionally comprising 1 to 2 heteroatoms.

In another embodiment, for compounds of the fifth aspect, when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine.

In another embodiment, for compounds of the fifth aspect, when p is 2, R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine.

In another embodiment, for compounds of the fifth aspect, when p is 2, R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, L represents a linker selected from among C_2-C_{10}alkyl, for example ethyl, propyl, butyl or pentyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_2-C_{10}alkenyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-S(O)$_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_6-C_{14}aryl, for example phenyl,

optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; -C_2-C_4alkyl-C_6-C_{14}aryl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; -C_6-C_{14}aryl-C_1-C_4alkyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_3-C_{12}cycloalkyl, for example cyclohexyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; and heteroaryl which contains 1 or 2 nitrogen atoms optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, when n is 1, L represents an optionally substituted a C_{2-10}alkyl or an optionally substituted C_{3-12}cycloalkyl linker.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, when n is 1, L represents cyclohexyl, $-C(CH_3)_2-CH_2-$ or $-CH_2-C(CH_3)_2-CH_2-$.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, n is 0.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, m is 1.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted granatanyl, optionally substituted oxogranatanyl $-NR^8R^9$ and optionally substituted azacycloheptyl wherein each morpholinyl, piperidinyl, piperazinyl, piperazinylcarbonyl, pyrrolidinyl, tropenyl, diketomethylpiperazinyl, sulphoxomorpholinyl, sulphonylmorpholinyl, thiomorpholinyl, $-NR^8R^9$ and azacycloheptyl is optionally substituted by one or more groups as defined for R^8.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents hydrogen, $-NR^8R^9$ or a piperidinyl, morpholinyl, pyrrolidinyl, sulphoxomorpholiny, piperazinyl, thiomorpholinyl, tropenyl, granatanyl, oxogranatanyl or azacycloheptyl each optionally substituted by one or more groups as defined for R^8.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents piperidinyl optionally substituted by one or more groups as defined for R^8.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents pyrrolidinyl optionally substituted by one or more groups as defined for R^8.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^5 represents granatanyl optionally substituted by one or more groups as defined for R^8.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^6 and R^7 may be identical or different and represent hydrogen or C_1-C_4alkyl, for example methyl or ethyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, the groups R^8 and R^9 may be identical or different and represent hydrogen; a C_1-C_6alkyl, for example methyl, ethyl or propyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; -C_1-C_4alkyl-C_3-C_{10}cycloalkyl, for example -CH_2-cyclopropyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_3-C_{10}cycloalkyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and d-(C_{1-3}alkyl)amino; C_6-C_{14}aryl, for example phenyl, optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; -C_1-C_4alkyl-C_6-C_{14}aryl, for example benzyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; pyranyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; pyridinyl optionally substituted by one or more

substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; pyrimidinyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; pyranyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_1-C_4alkyloxycarbonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_6-C_{14}arylcarbonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_1-C_4alkylcarbonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_6-C_{14} arylmethyloxycarbonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_6-C_{14}arylsulphonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino; C_1-C_4alkylsulphonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino and C_6-C_{14}aryl-C_1-C_4alkylsulphonyl optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^8 represents methyl, ethyl or propyl.

In another embodiment, for compounds of the first, second, third, fourth and fifth aspects, R^9 represents methyl, ethyl or propyl.

In another embodiment, for the compound of formula (I), R^N represents C_{1-3}alkyl.

In another embodiment, for the compound of formula (I), R^N represents methyl or ethyl.

In another embodiment, for the compound of formula (I), Z^1 represents C=O or CR^fR^g.

In another embodiment, for the compound of formula (I), Z^1 represents C=O or CR^fR^g, and Z^2 represents CR^cR^d.

In another embodiment, for the compound of formula (I), Z^1 represents C=O or CH_2.

In another embodiment, for the compound of formula (I), Q represents $-CH_2-NR^{a3}R^{b3}$ or $-C(=X^1)-NR^aR^b$, wherein X^1 is O.

In another embodiment, for the compounds of formula (I), (II), (IIa), (III) or (IIIa), n is 1 and L is an optionally substituted C_{2-10}alkyl linker.

In another embodiment, for the compounds of formula (I), (II), (IIa), (III) or (IIIa), n is 0.

In a further embodiment of the invention there is provided a subset of compounds of formula (III) or (IIIa) wherein R^1 to R^4, R^{4a}, R^{4b}, R^{4c}, R^c, R^d, R^6 and R^7 are as hereinbefore defined; and L represents a linker selected from among optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 1; m denotes 1 or 2; R^5 denotes hydrogen or a group which is bound to L via a nitrogen atom, selected from optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, $-NR^8R^9$ and optionally substituted azacycloheptyl; R^8, R^9 independently represent hydrogen, C_{1-6}alkyl, $-C_{1-4}$alkyl-C_{3-10}cycloalkyl, C_{3-10}cycloalkyl, C_{6-14}aryl, $-C_{1-4}$alkyl-C_{6-14}aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4}alkyloxycarbonyl, C_{6-14}arylcarbonyl, C_{1-4}alkylcarbonyl, C_{6-14}arylmethyloxycarbonyl, C_{6-14}arylsulphonyl, C_{1-4}alkylsulphonyl or C_{6-14}aryl-C_{1-4}alkylsulphonyl, or pharmacologically acceptable salts thereof.

In a still further embodiment of the invention there is provided another subset of compounds of formula (III) or (IIIa) wherein p, R^1 to R^4, R^{4a}, R^{4b}, R^{4c}, R^c, R^d, R^6 and R^7 are as hereinbefore defined; L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes hydrogen or a group which is bound to L via a carbon atom, selected from among piperidinyl, piperazinyl, pyrrolidinyl, piperazinylcarbonyl, tropenyl, morpholinyl, granatanyl, oxogranatanyl and azacycloheptyl each optionally

substituted by one or more groups as defined for R^8; and R^8 independently represent hydrogen, C_{1-6}alkyl, -C_{1-4}alkyl-C_{3-10}cycloalkyl, C_{3-10}cycloalkyl, C_{6-14}aryl, -C_{1-4}alkyl-C_{6-14}aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4}alkyloxycarbonyl, C_{6-14}arylcarbonyl, C_{1-4}alkylcarbonyl, C_{6-14}arylmethyloxycarbonyl, C_{6-14}arylsulphonyl, C_{1-4}alkylsulphonyl or C_{6-14}aryl-C_{1-4}alkylsulphonyl, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein L, m, n, p, R^3 to R^9, R^c and R^d are as hereinbefore defined; and R^1, R^2 each independently represents hydrogen, Me, Et, Pr, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 5- membered cycloalkyl ring, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein L, m, n, p and R^1 to R^9 are as hereinbefore defined; and R^c, R^d each independently represents hydrogen, Me, Et, Pr, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 5- membered cycloalkyl ring, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein L, m, n, p and R^3 to R^9 are as hereinbefore defined; and at least two of R^1, R^2, R^c or R^d are hydrogen.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein L, m, n, p and R^3 to R^9 are as hereinbefore defined; R^1 and R^2 are hydrogen, and one of R^c or R^d is hydrogen.

In a further additional embodiment of the invention there is provided an additional subset of compounds of formula (III) or (IIIa) wherein R^1, R^2, R^c, R^d, m, n and R^5 to R^8 are as hereinbefore defined; and R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl or optionally substituted C_{6-14}aryl group or R^1 and R^3 or R^2 and R^3 together represent a saturated or unsaturated C_{3-4}alkyl bridge optionally comprising 1 or 2 heteroatoms; p is 0 or 1; R^4 represents OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2, F, CL, Br, O-propargyl, O-butynyl, CN, SMe, NMe_2, $CONH_2$, ethynyl, propynyl, butynyl or allyl; and L denotes a linker selected from among optionally substituted phenyl, phenylmethyl, cyclohexyl and branched C_{1-6}alkyl, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl or optionally substituted C_{6-14}aryl group; p is 0 or 1; R^4 represents OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2, F, CL, Br, O-propargyl, O-butynyl, CN, SMe, NMe_2, $CONH_2$, ethynyl, propynyl, butynyl or allyl; L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{2-4}alkyl-C_{6-14}aryl, optionally substituted -C_{6-14}aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes hydrogen or a group, which is bound to L via a carbon atom, selected from among -NR^8R^9, piperidinyl, piperazinyl, pyrrolidinyl, piperazinylcarbonyl, tropenyl, morpholinyl, granatanyl, oxogranatanyl and azacycloheptyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent hydrogen, C_{1-6}alkyl, -C_{1-4}alkyl-C_{3-10}cycloalkyl, C_{3-10}cycloalkyl, C_{6-14}aryl, -C_{1-4}alkyl-C_{6-14}aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4}alkyloxycarbonyl, C_{6-14}arylcarbonyl, C_{1-4}alkylcarbonyl, C_{6-14}arylmethyloxycarbonyl, C_{6-14}arylsulphonyl, C_{1-4}alkylsulphonyl or C_{6-14}aryl-C_{1-4}alkylsulphonyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among -NR^8R^9 and piperidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; p is 0, 1 or

2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (III) wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and granatanyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (IIIa) wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and piperidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (IIIa) wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5

denotes a group selected from among -NR^8R^9 and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

In an additional embodiment of the invention there is provided an additional subset of compounds of formula (IIIa) wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among -NR^8R^9 and granatanyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

In a further aspect of the invention, there is provided a compound selected from any one of the Examples or pharmacologically acceptable salts thereof.

In a further aspect of the invention, there is provided a compound selected from any one of Examples 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451, 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299,

300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453 or pharmacologically acceptable salts thereof.

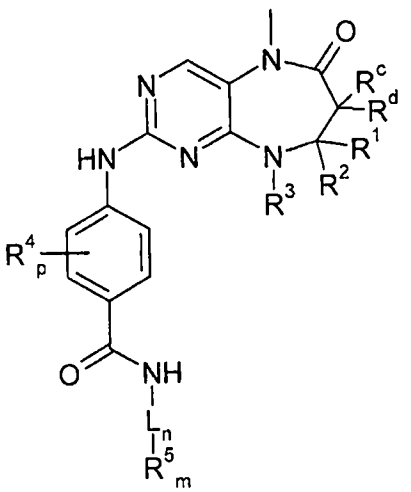
In a further aspect of the invention, there is provided a compound selected from any one of Examples 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453, or pharmacologically acceptable salts thereof.

The compounds according to the first, second, third, fourth and fifth aspects of the invention may be present in the form of the individual optical isomers, mixtures of the individual enantiomers, diastereomers or racemates, in the form of the tautomers and also as solvates and/or in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids, such as for example acid addition salts with hydrohalic acids, for example hydrochloric or hydrobromic acid, or organic acids, such as for example oxalic, fumaric, diglycolic or methanesulphonic acid or metal salts such as a magnesium, calcium, sodium or potassium salt

The compounds of formula (I), (II), (IIa), (III) or (IIIa) above may be converted to a pharmaceutically acceptable salt thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or p-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I), (II), (IIa), (III) or (IIIa) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I), (II), (IIa), (III) or (IIIa) and mixtures thereof including racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention.

The invention also relates to a process for preparing a compound of general formula (III),

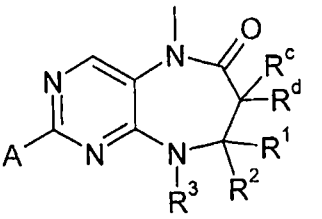


(III)

wherein R^1-R^5, R^c, R^d m, n and L are as hereinbefore defined,

comprising either

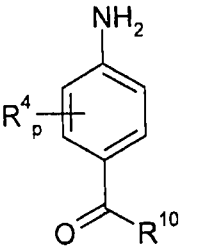
a) reacting a compound of general formula (IV)



(IV)

wherein R^1-R^3 are as hereinbefore defined and A is a leaving group,

with an optionally substituted compound of general formula (V):



(V)

wherein R^4 is as hereinbefore defined; and R^{10} denotes OH, NH-L_m-$R^5{}_n$, OMe, OEt, and when R^{10} denotes OH, OMe or OEt optionally after previous hydrolysis of the ester group -COR^{10}, reacting with an amine of general formula (VI):

$$NH_2\text{-}L_m\text{-}R^5{}_n$$

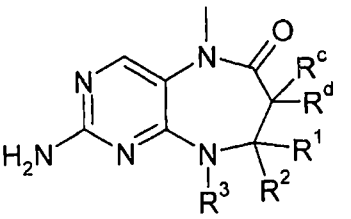
(VI)

wherein R^5 is as hereinbefore defined,

to give a compound of formula (III);

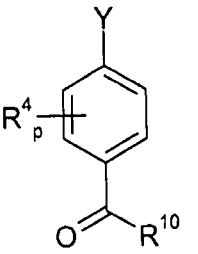
or

b) reacting a compound of general formula (VII)



(VII)

wherein R^1-R^3 are as hereinbefore defined with an optionally substituted compound of general formula (VIII):



(VIII)

wherein Y is a leaving group, p and R^4 are as hereinbefore defined; and R^{10} denotes OH, NH-L_m-$R^5{}_n$, OMe, OEt,

and when R^{10} denotes OH, OMe or OEt optionally after previous hydrolysis of the ester group -COR^{10}, reacting with an amine of general formula (VI):

$$NH_2 - L_m - R^5{}_n$$

(VI)

wherein R^5 is as hereinbefore defined,

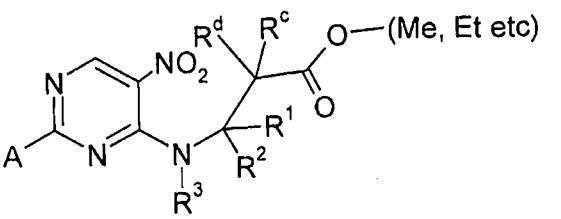
to give a compound of formula (III).

In one embodiment R^{10} is a substituent selected from among OH, NH_2-LR^5, -O-methyl and -O-ethyl.

The term leaving group includes leaving groups such as for example –O-methyl, -SCN, chlorine, bromine, iodine, methanesulphonyl, trifluoromethanesulphonyl or p-toluenesulphonyl. In one embodiment the leaving group A is chlorine.

Methods for the preparation of compounds of Formula (V) are described in WO04/076454 and WO03/020722 and are incorporated herein by reference.

Compounds of Formula (IV) where A is chlorine may also be obtained by the reductive cyclisation of a compound of formula (IX)



(IX)

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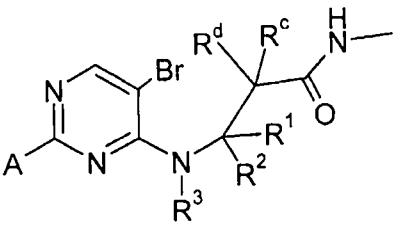
for example by palladium coupling.

Compounds of Formula (IV) may also be obtained by the cyclisation of a compound of formula (X)

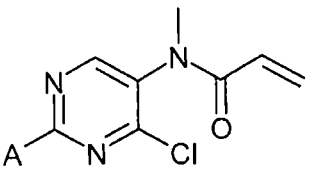


(X)

for example by under catalysis by a suitable palladium couplingcompound and in the presence of a suitable ligand and a suitable base.

Furthermore, compounds of formula (IV) may be obtained by reaction of another compound of general formula (IV), wherein R3 is hydrogen, with an alkyl halide, in a polar solvent, such as, for example, N,N-dimethylacetamide, in the presence of a strong base, such as, for example, sodium hydride.

Still furthermore compounds of formula (IV), where R^c, R^d, R^1 & R^2 are hydrogen, may be obtained by reaction of a compound of formula (XI)



(XI)

with an amine, in the presence of a base, such as triethylamine, and a lewis acid, such as titanium (IV) tetraethoxide.

Compounds of formula (VII) may also be obtained by the reaction of a compound of formula (IV), wherein A is as hereinbefore defined, but typically chloro,

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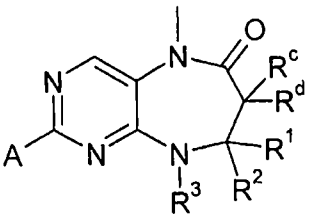
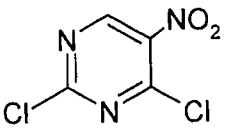


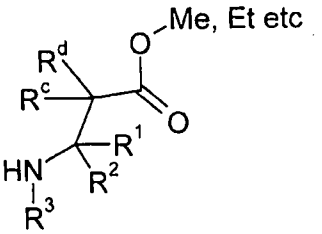
(IV)

with ammonia or a suitably protected equivalent.

Compounds of Formula (IX), wherein A is chlorine, may also be obtained by reaction of 5-nitro-2,4-dichloropyrimidinee



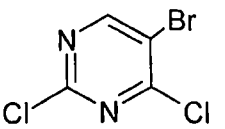
with an amine of Formula (XII)



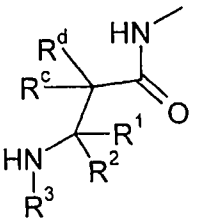
(XII)

for example by heating in the presence of a base, such as potassium carbonate, in a polar organic solvent such as acetone.

Compounds of Formula (IX), wherein A is chlorine, may also be obtained by reaction of 5-bromo-2,4dichloropyrimide



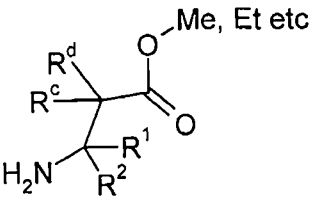
with an amine of Formula (XIII)



(XIII)

for example by heating in the presence of a base, such as triethylamine, in a polar organic solvent such as acetonitrile.

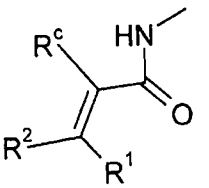
Compounds of Formula (XII), may also be obtained by reaction of esters of an appropriately substituted 3-amino-propanoic acid (XIV)



(XIV)

with a ketone or aldehyde, in the presence of a suitable reducing agent, such as, for example, sodium triacetoxyborohydride..

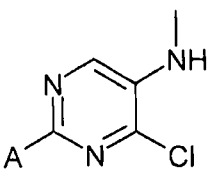
Compounds of Formula (XIII), may also be obtained by reaction of amides of propenoic acid (XV)



(XV)

with an amine.

Compounds of formula (XI) may also be obtained by the reaction of a compound of formula (XVI),



(XVI)

with a compound of formula (XVII),

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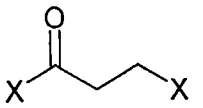
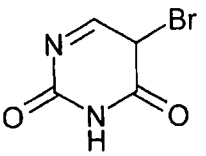


(XVII)

wherein X is a leaving group, typically a halogen, such as chloro, in the presence of a base, such as triethylamine, in an organic solvent, such as dichloromethane.

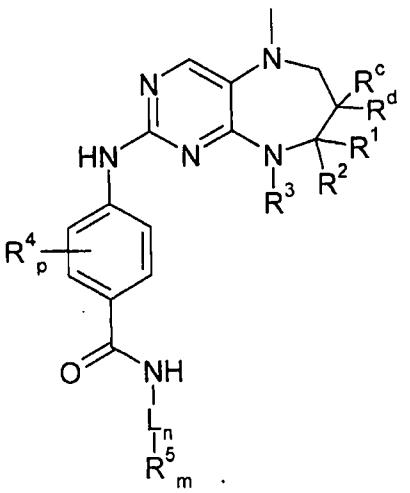
A compound of formula (XVI) may also be obtained by the sequential reaction of 5-bromouracil,



with i) methylamine, in a polar solvent, such as ethanol and;

ii) a chlorinating agent, such as phosphorous oxychloride as for instance exemplified in Journal of Medicinal Chemistry (1966), 9(1), 121-6.

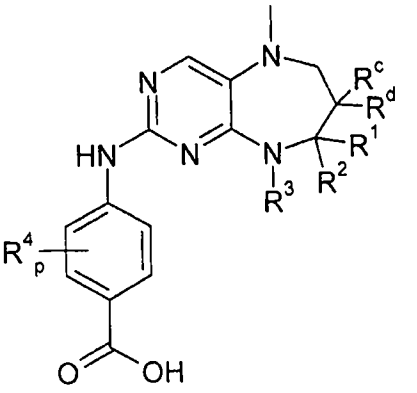
The invention also relates to a process for preparing a compound of general formula (XVIII),



(XVIII)

wherein R^1-R^5, R^c, R^d m, n and L are as hereinbefore defined,

comprising reacting a compound of general formula (XIX)



(XIX)

with an amine of general formula (VI):

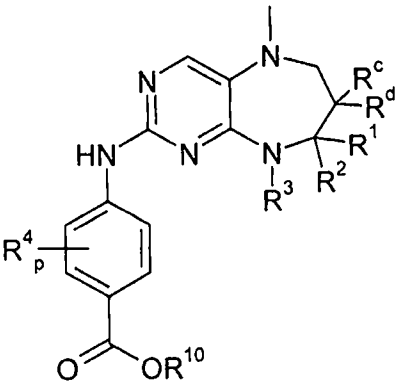
$$NH_2\text{–}L_m\text{-}R^5{}_n$$

(VI)

wherein L and R^5 are as hereinbefore defined.

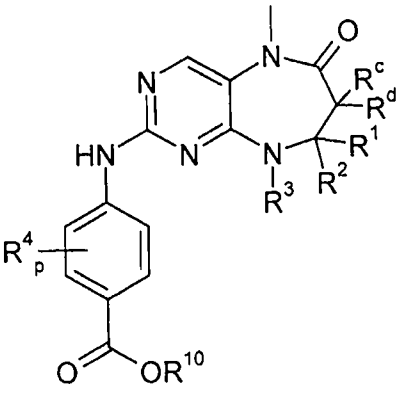
Compounds of formula (XIX) may be obtained by hydrolysis of the corresponding esters.

Esters of general formula (XX)



(XX)

may be obtained by the reduction of a compound of formula (XXI)



(XXI)

which may be prepared as described above.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I), (II), (IIa), (III) or (IIIa) may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley Interscience (19911999) and 'Protecting Groups', 3rd edition, P. J. Kocienski, Thieme (2005).

The invention further relates to compounds of formula (I), (II), (IIa), (III) or (IIIa) for use as pharmaceutical compositions.

In one embodiment of the invention, compounds of formula (I), (II), (IIa), (III) or (IIIa) are of use as pharmaceutical compositions with an antiproliferative activity.

The invention also relates to the use of a compound of formula (I), (II), (IIa), (III) or (IIIa) for preparing a pharmaceutical composition for the treatment and/or prevention of cancer, infections, inflammatory and autoimmune diseases.

These findings suggest that pharmacological inhibitors of Plk should be of therapeutic value for treatment of proliferative disease including solid tumours such as carcinomas and sarcomas and the leukaemias and lymphoid malignancies. In addition Plk inhibitors should

be useful in the treatment of other disorders associated with uncontrolled cellular proliferation.

One aspect of the current invention therefore relates to the use of one or more of the compounds of formula (I), (II), (IIa), (III) or (IIIa) in the treatment of disorders characterised by excessive or anomalous cell proliferation.

Such diseases include for example: viral infections such as HIV and Kaposi's sarcoma; inflammatory and autoimmune diseases such as colitis, rheumatoid arthritis, Alzheimer's disease, glomerulonephritis and wound healing; bacterial, fungal and parasitic infections such as malaria and emphysema; dermatological diseases such as psoriasis; bone diseases; cardiovascular diseases such as restenosis and cardiomyopathy. The compounds in the present invention may be used for the prevention, short- or long-term treatment of the above-mentioned diseases, also in combination with other active substances used for the same indications.

The invention also relates to a method of treating and/or preventing cancer, infections, inflammatory and autoimmune diseases, characterised in that a patient is given an effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa).

The invention also relates to pharmaceutical preparations, containing as active substance one or more compounds of general formula (I), (II), (IIa), (III) or (IIIa), or the physiologically acceptable salts thereof, optionally combined with conventional excipients and/or carriers.

The compounds of formula (I), (II) and (III) have activity as pharmaceuticals, in particular as modulators or inhibitors of Plk activity, and may be used in the treatment of proliferative and hyperproliferative diseases/conditions, examples of which include the following cancers:

(1) carcinoma, including that of the bladder, brain, breast, colon, kidney, liver, lung, ovary, pancreas, prostate, stomach, cervix, colon, thyroid and skin;

(2) hematopoietic tumours of lymphoid lineage, including acute lymphocytic leukaemia, B cell lymphoma and Burketts lymphoma;

(3) hematopoietic tumours of myeloid lineage, including acute and chronic myelogenous leukaemias and promyelocytic leukaemia;

(4) tumours of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; and

(5) other tumours, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma.

In one embodiment, the compounds of formula (I), (II) and (III) are useful in the treatment of tumours of the lung, breast and prostate.

Thus, the present invention provides a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treating cancer which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

The invention still further provides a method of modulating polo-like kinase (Plk) activity which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

The invention still further provides the use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

The invention still further provides the use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating polo-like kinase (Plk) activity.

The compounds of formula (I), (II) and (III), and pharmaceutically acceptable salts thereof, may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I), (II), (IIa), (III) or (IIIa) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99%w (per cent by weight), more preferably from 0.05 to 80%w, still more preferably from 0.10 to 70%w, and even more preferably from 0.10 to 50%w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc;

preservative agents such as ethyl or propyl p-hydroxybenzoate and anti oxidants such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p- hydroxybenzoate, anti oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

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

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil in water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally occurring gums such as gum acacia or gum tragacanth, naturally occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non toxic parenterally acceptable diluent or solvent, for example a solution in 1,3 butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic purposes of a compound of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In general, a compound of the invention will be administered so that a daily dose in the range, for example, from 0.5 mg to 75 mg active ingredient per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, from 0.5 mg to 30 mg active ingredient per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, from 0.5 mg to 25 mg active ingredient per kg body weight will generally be used. Also, for example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active ingredient.

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.

The anti cancer treatment defined hereinbefore may be applied as a sole therapy or may involve, in addition to the compound of the invention, conventional surgery or 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 cisplatin, 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 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 5*-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) and 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 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 platelet-derived growth factor family such as imatinib, inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006)), inhibitors of cell signalling through MEK and/or AKT kinases, inhibitors of the hepatocyte growth factor family, c-kit inhibitors, abl 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 VEGF receptor tyrosine kinase inhibitors such as 4-(4-bromo-2-fluoroanilino)-6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazoline (ZD6474; Example 2 within WO 01/32651), 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), vatalanib (PTK787; WO 98/35985) and SU11248 (sunitinib; WO 01/60814), 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 avb3 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) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) 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;

(ix) 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; and

(x) other inhibitors of cell cycle such as Eg5, Chk1 or PARP inhibitors.

Examples

The invention will now be further described with reference to the following illustrative examples in which, unless stated otherwise:

(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 18-25°C;

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

(iii) chromatography means flash chromatography on silica gel;

(iv) SCX-2 cartridges are Ion Exchange SPE columns where the stationary phase is polymeric propylsulfonic acid. These are used to isolate amines.

(v) in general, the course of reactions was followed by TLC or LCMS and reaction times are given for illustration only;

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

(vii) 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;

(viii) 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 400 MHz or 500MHz, in $CDCl_3$, DMSO-d_6 or DMSO-d6 + d_4-AcOH unless otherwise indicated;

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

(x) solvent ratios are given in volume:volume (v/v) terms; and

(xi) Mass spectra (MS) data was generated on an LCMS system where the HPLC component comprised generally either a Agilent 1100 or Waters Alliance HT (2790 & 2795) equipment and was run on a Phemonenex Gemini C18 5mm, 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 using an equivalent solvent system with methanol instead of acetonitrile), 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 mode;

(xii) Micorwave irradiation of reaction mixtures was performed using Emrys Optimiser instrument;

(xiii) the following abbreviations have been used:

AcOH	acetic acid
$CDCl_3$	deuterochloroform
DCM	dichloromethane
DIPEA	*N,N*-diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	hexadeuterodimethylsulfoxide
EtOH	ethanol

EtOAc	ethyl acetate
HATU	2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate.
HPLC	high performance liquid chromatography
MeCN	acetonitrile
MeOH	methanol
MeI	methyl iodide
MS	mass spectroscopy
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
SCX-2	ion exchange SPE column (polymeric propylsulfonic acid stationery phase)
THF	terahydrofuran
TFA	Trifluoroacetic acid
XANTPHOS	9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

Example 1:

4-[(2-Cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-*N*-(1-methyl-4-piperidyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 99 mg, 0.34 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 93 mg, 0.35 mmol) and *p*-toluenesulfonic acid (167 mg, 0.88 mmol) were dissolved in (*R*/S)-4-methyl-2-pentanol (8 mL) and heated at reflux under a blanket of nitrogen for 24 h. The reaction mixture was cooled and loaded onto an SCX-2 column then washed with MeOH (15 mL). The crude compound was eluted from the SCX-2 column with NH_3 (40mL, 7M in MeOH) and the volatiles were removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient: 0-10% NH_3 [7M in MeOH] in DCM), afforded the title compound (159 mg, 89%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.26 (t, 5H), 1.56 - 1.83 (m, 9H), 2.04 (s, 3H), 2.20 - 2.29 (m, 3H), 2.64 - 2.71 (m, 2H), 2.85 - 2.95 (m, 2H), 3.29 (s, 3H), 3.68 - 3.71 (m, 2H), 4.12 (q, 1H), 4.90 (quintet, 1H), 5.95 (d, 1H), 7.24 (dd, 1H), 7.42 (s, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.51 (d, 1H); MS m/z 508 $[M+H]^+$.

Example 2:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-*N*-(1-methyl-4-piperidyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 86 mg, 0.31 mmol), 4-amino-*N*-(1-methyl-4-piperidyl)benzamide (Intermediate 4; 72 mg, 0.31 mmol) and *p*-toluene sulfonic acid (146 mg, 0.76 mmol) were dissolved in 4-methyl-2-pentanol (5 mL) and refluxed under an atmosphere of nitrogen for 18 hrs. The reaction mixture was loaded onto an SCX-2 column then washed with MeOH (15 mL). The crude compound was eluted from the SCX-2 column with NH_3 (40 mL, 7M in MeOH) and the volatiles were removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient: 0-10% NH_3 [7M in MeOH] in DCM) then by preparative HPLC (Sunfire prep RP18, 19 x 100 mm column, eluting with a gradient of 0.1% solution of TFA in H_2O and a 0.1% solution of TFA in MeCN). The product fractions were then loaded onto an SCX-2 column then washed with MeOH (10 mL). The product was eluted from the SCX-2 column with NH_3 (30 mL, 7M in MeOH) and the volatiles removed under reduced pressure to give the title compound (38.5 mg, 26%) as a solid.

^{1}H NMR (399.9 MHz, DMSO-d_6) δ_H 1.58 - 1.78 (10H, m), 1.92 - 2.04 (4H, m), 2.21 (3H, s), 2.58 - 2.60 (2H, m), 2.79 - 2.83 (2H, m), 3.18 (3H, s), 3.60 - 3.65 (2H, m), 3.71 - 3.79 (1H, m), 4.81 - 4.89 (1H, m), 7.76 (2H, d), 7.82 (2H, d), 7.99 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 478 $[M+H]^+$.

Example 3:

4-[(4*R*/*S*)-(2-Cyclopentyl-4,6-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-*N*-(1-methyl-4-piperidyl)benzamide

(4*R*/*S*)-10-Chloro-2-cyclopentyl-4,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 5; 106 mg, 0.36 mmol), 4-amino-*N*-(1-methyl-4-

piperidyl)benzamide (WO06018220; 95 mg, 0.36 mmol) and *p*-toluene sulphonic acid (170 mg, 0.89 mmol) were dissolved in (*R/S*)-4-methyl-2-pentanol (6 mL) and refluxed under a blanket of nitrogen for 24 hrs. The reaction mixture was cooled to ambient temperature and loaded onto an SCX-2 column and then washed with MeOH (40 mL). The crude compound was eluted from the SCX-2 column with NH_3 (40 mL, 7M in MeOH) and the volatiles removed under reduced pressure. The crude material was then purified by column chromatography (SiO_2, eluent gradient: 0-10% NH_3 [7M in MeOH] in DCM) then by preparative HPLC (Sunfire prep RP18, 19 x 100 mm column, eluting with a gradient composing of a 0.1% solution of TFA in H_2O and a 0.1% solution of TFA in MeCN). The product fractions were loaded onto an SCX-2 column then washed with MeOH (10 mL). The product was eluted from the SCX-2 column with NH_3 (30 mL, 7M in MeOH) and the volatiles removed under reduced pressure to give the title compound (43.9 mg, 23%) as a solid.

^1H NMR (400 MHz, DMSO-d6) δ_H 1.04 (d, 3H), 1.51 - 1.84 (m, 12H), 1.99 - 2.13 (m, 3H), 2.81 - 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quintet, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 522 $[M+H]^+$.

Example 4:

4-[(2-Cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

To a solution of 4-[(9-cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoic acid (Intermediate 6; 240 mg, 0.60 mmol) and N-[(dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yloxy)methylene]-N-methylmethanaminium hexafluorophosphate (275 mg, 0.72 mmol) in DMA (10 mL) was added 1-methylpiperidin-4-amine (82 mg, 0.72 mmol) and DIPEA (210 uL, 1.20 mmol), and the reaction stirred at ambient temperature for 2 hr. The reaction mixture was loaded onto an SCX-2 column and washed with MeOH (20 mL). The crude product was then eluted from the SCX-2 column with NH_3 (40 mL, 7M in MeOH) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient: 5-10% MeOH in DCM) afforded the title compound (160 mg, 54%) as a solid.

^{1}H NMR (400 MHz, DMSO-d6) δ_H 1.65 (m, 10H), 1.94 (m, 6H), 2.21 (s, 3H), 2.71 (s, 3H), 2.82 (d, 2H), 3.00 (t, 2H), 3.48 (m, 2H), 3.94 (s, 3H), 4.86 (m, 1H), 7.36 (s, 1H), 7.46 (m, 2H), 7.53 (s, 1H), 8.02 (d, 1H), 8.46 (d, 1H); MS m/z 494 $[M+H]^+$.

Example 5:

4-[(2,6-Dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-*N*-(1-methyl-4-piperidyl)benzamide

10-Chloro-2,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 9; 185 mg, 0.82 mmol), 4-amino-3-methoxy-*N*-(1-methyl-4-piperidyl)benzamide (215 mg, 0.82 mmol) and *p*-toluenesulphonic acid (389 mg, 2.05 mmol) in (*R*/S)-4-methyl-2-pentanol (6 mL) were heated at 115 °C for 5 h. The reaction mixture was cooled to ambient temperature then passed through a SCX-2 cartridge and washed with MeOH (40 mL). The crude product was eluted off the SCX-2 cartridge with NH_3 (40 mL, 7M in MeOH). Purification by preparative HPLC (Gemini RP C18 30x100mm, gradient mobile phase: 10-80% MeCN/water + 0.5% NH_3) afforded the title compound (180 mg, 48%) as a foam.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.60 (m, 2H), 1.78 (m, 2H), 1.90 (tr, 2H), 2.19 (s, 3H), 2.62 (tr, 2H), 2.79 (d, 2H), 3.09 (s, 3H), 3.20 (s, 3H), 3.73 (m, 3H), 3.95 (s, 3H), 7.51 (m, 2H), 7.75 (m, 1H), 8.05 (d, 1H), 8.11 (s, 1H), 8.48 (d, 1H); MS m/z 454 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 5 utilising the appropriate pyrimidine derivative (Intermediates 10 – 13) as the electrophile and 4-amino-3-methoxy-*N*-(1-methyl-4-piperidyl)benzamide (WO06/018220) as the aniline:

Example 6:

3-Methoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-*N*-(1-methyl-4-piperidyl)benzamide

Example 7:

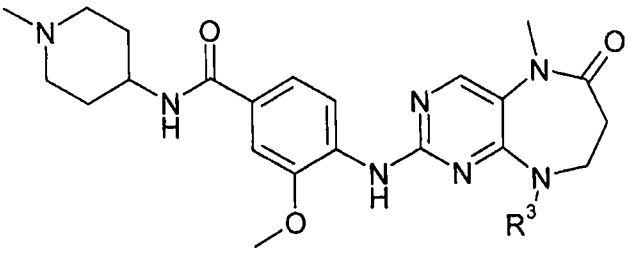
3-Methoxy-4-[[6-methyl-2-(3-methylbutyl)-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-*N*-(1-methyl-4-piperidyl)benzamide

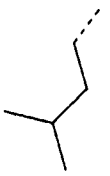
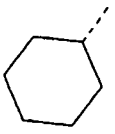
Example 8:

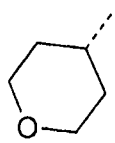
4-[(2-Cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-*N*-(1-methyl-4-piperidyl)benzamide

Example 9:

3-Methoxy-4-[[6-methyl-2-(oxan-4-yl)-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-*N*-(1-methyl-4-piperidyl)benzamide



Example	R^3	^{1}H NMR (400 MHz, DMSO-d_6)	MS m/z $[M+H]^+$
6		1.25 (d, 6H), 1.60 (m, 2H), 1.77 (m, 2H), 1.95 (tr, 2H), 2.19 (s, 3H), 2.60 (tr, 2H), 2.70 (d, 2H), 3.19 (s, 3H), 3.62 (m, 2H), 3.75 (m, 1H), 3.96 (s, 3H), 4.80 (m, 1H), 7.51 (m, 2H), 7.69 (s, 1H), 8.08 (d, 2H), 8.41 (d, 1H)	482
7		0.92 (d, 6H), 1.58 (m, 5H), 1.76 (m, 2H), 1.93 (tr, 2H), 2.19 (s, 3H), 2.61 (tr, 2H), 2.79 (d, 2H), 3.19 (s, 3H), 3.61 (tr, 2H), 3.71 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.70 (s, 1H), 8.06 (d, 2H), 8.35 (d, 1H)	510
8		1.17 (m, 1H), 1.41 (m, 2H), 1.55-1.90 (m, 11H), 1.95 (tr, 2H), 2.19 (s, 3H), 2.59 (tr, 2H), 2.80 (d, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 3.77 (m, 1H), 4.49 (tr, 1H), 7.49	522

Example	R^3	^{1}H NMR (400 MHz, DMSO-d_6)	MS m/z $[M+H]^+$
		(m, 2H), 7.70 (s, 1H), 8.08 (m, 2H), 8.39 (d, 1H)	
9		1.61 (m, 2H). 1.72-2.00 (m, 7H), 2.20 (s, 3H), 2.61 (tr, 2H), 2.80 (d, 2H), 3.19 (s, 3H), 3.50 (tr, 2H), 3.67 (m, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.02 (dd, 2H), 4.62 (tr,1H), 7.51 (m, 2H), 7.78 (s, 1H), 8.10 (m, 2H), 8.31 (d, 1H)	524

Example 10:

4-[(2-Cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-*N*-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide hydrochloride

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 238 mg, 0.85 mmol), 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 250 mg, 0.85 mmol) and *p*-toluenesulfonic acid (405 mg, 2.13 mmol) were dissolved in (*R*/S)-4-methyl-2-pentanol (4 mL) and heated at reflux for 24 h. The reaction mixture was then cooled and loaded onto an SCX-2 column, which was then washed with MeOH (40 mL). The crude product was washed off the SCX-2 column with NH_3 (50 mL, 7M in MeOH). Purification by column chromatography (SiO_2, eluent gradient: 0-10% NH_3 [7M in methanol] in DCM) give a pale yellow oil. HCl (0.43 uL, 2N in Et_2O, 0.85 mmol) was added to a DCM (5 mL) solution of the yellow oil. Concentration under reduced pressure gave the title compound (188 mg, 40%) as a solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.00 (s, 6H), 1.60 - 1.84 (m, 6H), 2.02 - 2.34 (m, 2H), 2.37 (s, 2H), 2.39 (s, 6H), 2.65 - 2.69 (m, 2H), 3.29 (s, 3H), 3.38 (d, 2H), 3.68 - 3.72 (m, 2H), 3.98 (s, 3H), 4.87 - 4.96 (m, 1H), 7.29 (dd, 1H), 7.51 (d, 1H), 7.67 (s, 1H), 7.95 (s, 1H), 8.51 (d, 1H), 9.14 (t, 1H); MS m/z 524 $[M+H]^+$.

Example 11:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-cyclopropyl-4-piperidyl)-3-methoxy-benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 150 mg, 0.36mmol), 1-cyclopropylpiperidin-4-amine (Intermediate 24, 77 mg, 0.55mmol) and HATU (208 mg, 0.55mmol) were stirred in DMF (92ml). DIPEA (191 mL, 1.09mmol) was added and the mixture stirred at room temperature for 3 h. The mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative HPLC to give the title compound as a pale brown solid (127mg, 66%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.29 (2H, s), 0.43 (2H, d), 1.48 – 1.81 (11H, m), 1.94 (2H, m), 2.24 (2H, t), 2.60 (2H, t), 2.96 (2H, d), 3.18 (3H, s), 3.63 (2H, t), 3.78 (1H, m), 3.95 (3H, s), 4.78 - 4.86 (1H, m), 7.46 - 7.51 (2H, m), 7.73 (1H, s), 8.04 (1H, d), 8.09 (1H, s), 8.39 (1H, d); MS m/z 534 $[M+H]^+$.

Example 12:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(1-piperidyl)ethyl]benzamide

A solution of HATU (147 mg, 0.385 mmol) in DMA (1 mL) was added to a mixture of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 144mg, 0.35 mmol), DIPEA (183uL, 1.05 mmol) and 2-(1-piperidyl)ethanamine (Aldrich, 56 mg 0.44 mmol) in DMA (1 mL). The resulting mixture was stirred at room temperature overnight. The mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative reverse phase HPLC to give the title compound (86mg, 47%)

The following examples were prepared by an analogous process to that used in the preparation of Example 12 utilising the acid described in Example 111 and the appropriate amines.

Example 13:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-morpholin-4-ylethyl)benzamide

Example 14:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

Example 15:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[(1-ethylpyrrolidin-2-yl)methyl]-3-methoxy-benzamide

Example 16:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

Example 17:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(5-diethylaminopentan-2-yl)-3-methoxy-benzamide

Example 18:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-diethylaminoethyl)-3-methoxy-benzamide

Example 19:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

Example 20:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[3-(4-methylpiperazin-1-yl)propyl]benzamide

Example 21:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-dimethylaminobutyl)-3-methoxy-benzamide

Example 22:

N-(1-azabicyclo[2.2.2]oct-8-yl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 23:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(2-oxoimidazolidin-1-yl)ethyl]benzamide

Example 24:

N-(2-acetamidoethyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 25:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(3-morpholin-4-ylpropyl)benzamide

Example 26:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-imidazol-1-ylpropyl)-3-methoxy-benzamide

Example 27:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-imidazol-1-ylethyl)-3-methoxy-benzamide

Example 28:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-dimethylaminopropan-2-yl)-3-methoxy-benzamide

Example 29:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[1-(2-methoxyethyl)-4-piperidyl]benzamide

Example 30:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-diethylaminobutyl)-3-methoxy-benzamide

Example 31:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-imidazol-1-ylbutyl)-3-methoxy-benzamide

Example 32:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(8-oxa-3-azabicyclo[3.2.1]oct-3-yl)ethyl]benzamide

Example 33:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(4-pyrrolidin-1-ylbutyl)benzamide

Example 34:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(4-methylpiperazin-1-yl)ethyl]benzamide

Example 35:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[2-(3,3-difluoropyrrolidin-1-yl)ethyl]-3-methoxy-benzamide

Example 36:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[2-[(3R)-3-fluoropyrrolidin-1-yl]ethyl]-3-methoxy-benzamide

Example 37:

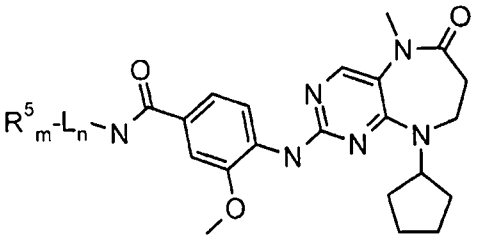
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[2-(4,4-difluoro-1-piperidyl)ethyl]-3-methoxy-benzamide

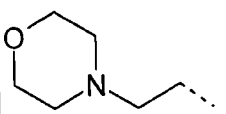
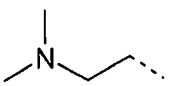
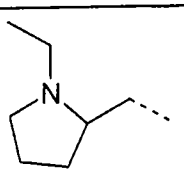
Example 38:

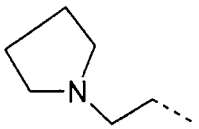
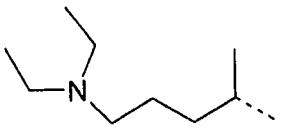
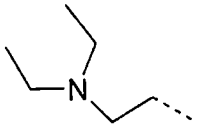
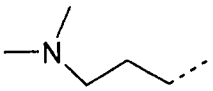
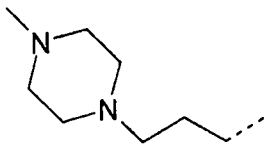
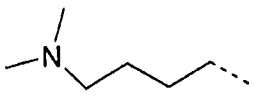
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[3-(pyridin-2-ylamino)propyl]benzamide

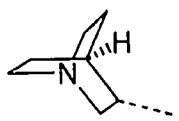
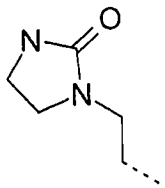
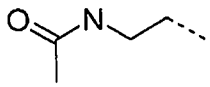
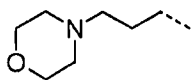
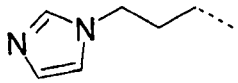
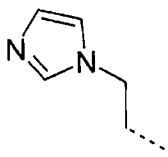
Example 39:

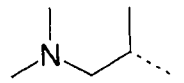
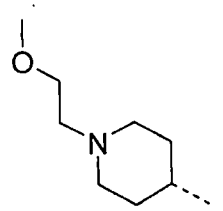
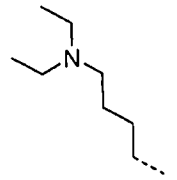
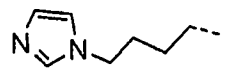
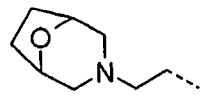
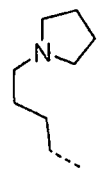
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-3-piperidyl)benzamide

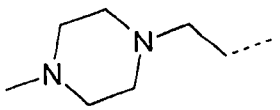
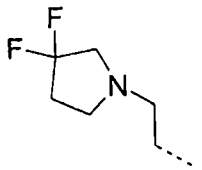
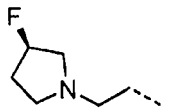
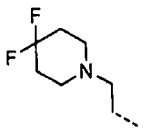
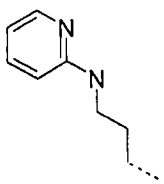
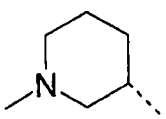


Example	$R^5{}_m$-L_n-	Supplier Or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
13		Aldrich	524	1.88
14		Aldrich	482	2.00
15		Aldrich	522	2.45

Example	$R^5{}_m$-L_n-	Supplier Or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
16		Aldrich	509	2.35
17		Aldrich	553	2.4
18		Aldrich	511	2.2
19		Aldrich	497	1.99
20		ABCR	552	1.74
21		ABCR	511	2.07

Example	R^5_m-L_n-	Supplier Or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
22		Aldrich	521	1.97
23		Maybridge	524	1.73
24		Aldrich	497	1.7
25		ABCR	539	1.87
26		Aldrich	520	1.87
27		ABCR	506	1.79

Example	R^5_m-L_n-	Supplier Or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
28		Aldrich	497	2.03
29		Chemstep	553	1.96
30		Frinton	539	2.33
31		Asinex	534	1.91
32		US3856783	551	2.07
33		Matrix	537	2.27

Example	R^5_m-L_n-	Supplier Or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
34		Matrix	538	1.74
35		WO2005097750	545	2.2
36		US2005209274	527	2.02
37		Fluorochem	559	2.29
38		US2003069236	546	2.18
39		Fluorochem	509	2.03

The following examples were prepared by an analogous process to that used in the preparation of Example 12 utilising the acid described in Example 111 and the appropriate

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BOC- protected amines. Prior to SCX purification the reaction mixture was treated with 4N HCl in dioxane (1 mL) and stirred at room temperature for 24 hr. The reaction mixtures were absorbed onto SCX columns, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative HPLC to give the title compounds

Example 40:

N-(4-aminobutyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 41:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(4-piperidyl)benzamide

Example 42:

N-(3-aminopropyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 43:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-methylaminoethyl)benzamide

Example 44:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(3-methylaminopropyl)benzamide

Example 45:

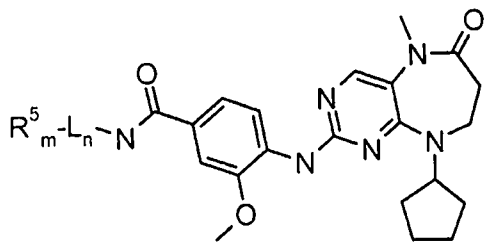
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-pyrrolidin-3-yl-benzamide

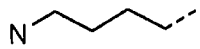
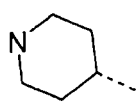
Example 46:

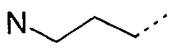
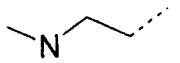
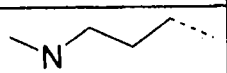
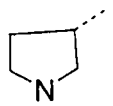
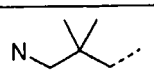
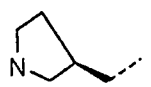
N-(3-amino-2,2-dimethyl-propyl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 47:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[[(3R)-pyrrolidin-3-yl]methyl]benzamide



Example	$R^5{}_m$-L_n-	Supplier or Source of BOC-Protected Amine	MS m/z $[M+H]^+$	Retention time (Minutes)
40		Fluka	482	2.02
41		Aldrich	494	2.02

Example	R^5_m-L_n-	Supplier or Source of BOC-Protected Amine	MS m/z $[M+H]^+$	Retention time (Minutes)
42		Aldrich	468	1.97
43		ABCR	468	1.9
44		ABCR	482	2.26
45		ABCR	480	2.02
46		ABCR	496	2.16
47		ABCR	494	2.47

Example 48:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 211 mg, 0.75 mmol) and 4-amino-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide (Intermediate 27, 211 mg, 0.75 mmol) were combined with p-TSA (357 mg, 1.88 mmol) in 4-methyl-2-pentanol (1 mL) and heated to 150 °C for 18 hr. The cooled reaction mixture was diluted with methanol and water (approx 50 mL) and loaded onto a 50 g SCX-2 cartridge washing with methanol (100 mL) and eluting with 7 *N* methanolic ammonia (100 mL). The concentrated solution was purified by reversed phase HPLC. The title compound was obtained as a beige solid (178 mg, 45%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.50 - 1.81 (m, 10H), 1.90 - 2.00 (m, 4H), 2.16 (s, 3H), 2.58 - 2.61 (m, 2H), 2.72 (br d, 2H), 3.17 (s, 3H), 3.63 - 3.65 (m, 2H), 3.68 - 3.75 (m, 1H), 3.92 (s, 3H), 4.83 (quintet, 1H), 7.19 (d, 1H), 7.79 - 7.82 (m, 2H), 8.11 (s, 1H), 8.33 (d, 1H); MS m/z 526 $[M+H]^+$.

Example 49:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-propan-2-yl-4-piperidyl)benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 100mg, 0.24 mmol), N-Isopropyl-4-aminopiperidine (ABCR, 42 mg, 0.29 mmol), HATU (111 mg, 0.29mmol) and DIPEA (127 uL, 0.73 mmol) and DMF (3 mL) were combined and stirred at room temperature for 3 hours. The solvent was evaporated and the residue partitioned between DCM (10 mL) and water (10 mL). The organic phase was added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH and solvents evaporated. The residue was taken up in DCM and purified on silica, eluting with a gradient of 0 – 5% MeOH / DCM followed by 5% then 10% and finally 15% MeOH / DCM. Fractions containing product were combined and evaporated to give the tile compound as a white solid (45 mg, 35%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ0.99 (d, 6H), 1.55 - 1.73 (m, 8H), 2.00 (m, 4H), 2.27 (m, 2H), 2.60 (m, 2H), 2.69 (m, 1H), 2.81 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.92 (m, 4H), 4.83

(m, 1H), 5.82 (d, 1H), 7.14 (m, 1H), 7.35 (d, 1H), 7.59 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 50:

tert-butyl 4-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]piperidine-1-carboxylate

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 113 mg, 0.27 mmol), tert-butyl 4-aminopiperidine-1-carboxylate (ABCR, 50mg, 0.25 mmol), HATU (114 mg, 0.3 mmol) and DIPEA (130 uL, 0.75 mmol) and DMF (3 mL) were combined and stirred at room temperature for 3 hours. Solvent was evaporated and the residue partitioned between DCM (25 mL) and sat. aq. Bicarb. (25 mL) and gravity filtered through a PTFE cup. The organic phase was added to a silica column and eluted with a shallow gradient of 0 – 10% MeOH / DCM. Fractions containing product were combined and evaporated to a yellow gum to which ether was added and re-evaporated to give the title compound as an orange solid. (89mg, 55%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ1.37 (m, 11H), 1.53 - 1.71 (m, 6H), 1.97 (m, 4H), 2.60 (m, 2H), 2.86 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.91 (s, 3H), 4.05 (m, 3H), 4.83 (m, 1H), 5.83 (d, 1H), 7.15 (m, 1H), 7.35 (m, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 594 $[M+H]^+$.

Example 51:

Benzyl (1S,5R)-6-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 113 mg, 0.27 mmol), benzyl (1S,5R)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate (Intermediate 30; 50 mg, 0.25 mmol), HATU (114 mg, 0.3 mmol) and DIPEA (130 uL, 0.75 mmol) and DMF (3 mL) were combined and stirred at room temperature for 3 hours. Solvent was evaporated and the residue partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), gravity filtered through

a PTFE cup and solvents evaporated. The residue was taken up in DCM and purified on silica eluting with a gradient of 0 – 5% MeOH / DCM. Fractions containing product were combined and evaporated. The resultant material was purified by reversed phase HPLC. ^{1}H NMR (400.132 MHz, CDCl3) δ1.64 (m, 8H), 1.97 (m, 2H), 2.58 (m, 3H), 3.22 (s, 3H), 3.46 (m, 2H), 3.62 (m, 2H), 3.78 (m, 2H), 3.90 (s, 3H), 4.82 (m, 1H), 5.05 (s, 2H), 6.08 (s, 1H), 7.12 (m, 1H), 7.26 (m, 5H), 7.34 (d, 1H), 7.61 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 626 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 51 utilising the acid described in Example 111 and the appropriate amines.

Example 52:

tert-butyl (3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]pyrrolidine-1-carboxylate

Amine available from Chempacific

^{1}H NMR (400.132 MHz, CDCl3) δ1.41 (s, 9H), 1.63 (m, 3H), 1.94 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 3.26 (m, 4H), 3.43 (m, 2H), 3.65 (m, 3H), 3.91 (s, 3H), 4.59 (m, 1H), 4.84 (m, 1H), 6.01 (d, 1H), 7.15 (m, 5H), 7.35 (d, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 8.45 (d, 1H); MS m/z 580 $[M+H]^+$.

Example 53:

tert-butyl (3S)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]pyrrolidine-1-carboxylate

Amine available from Chempacific

^{1}H NMR (400.132 MHz, $CDCl_3$) δ1.41 (s, 9H), 1.64 (m, 6H), 1.93 (m, 3H), 2.19 (m, 1H), 2.60 (m, 2H), 3.26 (m, 4H), 3.43 (m, 2H), 3.65 (m, 3H), 3.91 (s, 3H), 4.59 (m, 1H), 4.84 (m,

1H), 6.02 (d, 1H), 7.15 (m, 1H), 7.35 (d, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 8.45 (d, 1H); MS m/z 580 $[M+H]^+$.

Example 54:

Benzyl 4-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]piperidine-1-carboxylate

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111 , 350 mg, 0.85 mmol), Benzyl 4-aminopiperidine-1-carboxylate (ABCR, 219 mg, 0.94 mmol), HATU (388 mg, 1.02 mmol) and DIPEA (445 uL, 2.55 mmol) and DMF (5 mL) were combined and stirred at room temperature for 3 hours. Solvent was evaporated and the residues partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), gravity filtered through a PTFE cup and solvents evaporated. The residue was taken up in DCM and purified on silica eluting with a gradient of 0 – 5% MeOH / DCM. Fractions containing product were combined and evaporated. To give the title compound as an orange solid.

^{1}H NMR (400.132 MHz, $CDCl_3$) δ1.38 (m, 2H), 1.62 (m, 6H), 1.97 (m, 4H), 2.60 (m, 2H), 2.94 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.91 (s, 3H), 4.11 (m, 3H), 4.83 (m, 1H), 5.07 (s, 2H), 5.82 (d, 1H), 7.14 (m, 1H), 7.27 (m, 5H), 7.34 (d, 1H), 7.61 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 628 $[M+H]^+$.

Example 55:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-pyrrolidin-3-yl]benzamide

tert-butyl (3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]pyrrolidine-1-carboxylate (630 mg, 1 mmol) was dissolved in DCN (10 mL), TFA (10 mL) added and stirred at room temperature for 2 hr. The reaction mixture was added to a 10 g SCX-2 column pre wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) then the crude product eluted with 2M ammonia in MeOH and solvents evaporated. The residue was taken up in DCM and purified on silica eluting with a gradient of 0 – 10% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated

to a gum, ether was added and re-evaporated to give the title compound as a solid. (300 mg, 74%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ1.62 (m, 8H), 1.98 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 2.89 (m, 2H), 3.06 (m, 1H), 3.17 (m, 1H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.53 (m, 1H), 4.83 (m, 1H), 6.24 (d, 1H), 7.19 (m, 1H), 7.37 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 480 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 56 utilising the BOC-protected material described in Example 54.

Example 56:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3S)-pyrrolidin-3-yl]benzamide

^{1}H NMR (400.132 MHz, CDCl3) δ1.62 (m, 8H), 1.98 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 2.85 (m, 1H), 2.91 (m, 1H), 3.06 (m, 1H), 3.17 (m, 1H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.53 (m, 1H), 4.83 (m, 1H), 6.24 (d, 1H), 7.19 (m, 1H), 7.37 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 480 $[M+H]^+$.

Example 57:

N-[(1S,5R)-3-azabicyclo[3.1.0]hex-6-yl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Benzyl (1S,5R)-6-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]-3-azabicyclo[3.1.0]hexane-3-carboxylate (Example 51, 357mg, 0.57 mmol) was dissolved in MeOH (30 mL) and passed through the H-cube at 50 °C on full hydrogen mode at 1 mL per minute. The solution added to a 10 g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH. The basic fractions were evaporated and the residue dissolved in DCM and purified on silica eluting with a gradient of 0 – 10% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to a gum to which ether was added and re-evaporated to give the title compound as a cream solid. (172 mg, 42%).

^{1}H NMR (400.132 MHz, CDCl3) δ1.64 (m, 8H), 1.97 (m, 2H), 2.60 (m, 3H), 2.91 (m, 2H), 3.17 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.82 (m, 1H), 6.02 (s, 1H), 7.13 (m, 1H), 7.35 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 492 $[M+H]^+$.

Example 58:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-diethylaminocyclohexyl)-3-methoxy-benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111_, 100 mg, 0.24 mmol), N,N-diethylcyclohexane-1,4-diamine (ABChem, 46 mg, 0.28 mmol), HATU (111 mg, 0.29mmol) and DIPEA (127 uL, 0.73 mmol) and DMF (3 mL) were combined and stirred at room temperature for overnight. Solvent was evaporated and the residues partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), gravity filtered through a PTFE cup, solvent evaporated and the residue purified by reverse phase HPLC to give the title compound as a cream solid (114mg, 83%)

MS m/z 564 [M+H]+. Retention Time 2.20 minutes

The following examples were prepared by an analogous process to that used in the preparation of Example 58 utilising the appropriate amines

Example 59:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

Amine available from Chontech

^{1}H NMR (399.902 MHz, CDCl3) δ1.03 (m, 2H), 1.30 (m, 2H), 1.54 (m, 2H), 1.60 - 1.80 (m, 6H), 1.98 (m, 2H), 2.05 (m, 2H), 2.53 (m, 5H), 2.67 (m, 2H), 3.09 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 4.90 (m, 1H), 5.78 (d, 1H), 7.23 (m, 1H), 7.44 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.49 (d, 1H); MS m/z 548 [M+H]+.

Example 60:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide

Amine available from ABChem

MS m/z 536 [M+H]+. Retention Time 1.92 minutes

Example 61:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(4-piperidyl)benzamide (Example 41; 80 mg, 0.16 mmol), Ethyl Bromide (ABCR, 13 uL, 0.18 mmol), Triethylamine (0.45 uL, 0.32 mmol) and DMF (3 mL) were combined and heated by microwave irradiation at 75 °C for 1 hr and thenat 80 °C for 30 minutes. The reaction mixture was purified by reverse phase HPLC to give the title compound as a white solide (56 mg, 66%)

^{1}H NMR (399.902 MHz, CDCl3) δ1.10 (t, 3H), 1.53 - 1.80 (m, 8H), 2.09 (m, 6H), 2.44 (m, 2H), 2.67 (m, 2H), 2.92 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 4.00 (m, 4H), 4.90 (m, 1H), 5.90 (d, 1H), 7.22 (m, 1H), 7.42 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 522 [M+H]+.

Example 62:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

To 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-pyrrolidin-3-yl]benzamide (Example 55, 140 mg, 0.29 mmol) dissolved in THF (2 mL) was added acetic acid (17uL, 0.29 mmol) followed by aqueous formaldehyde (1 mL). The reaction mixture was stirred at room temperature for 30 mins and sodium triacetoxyborohydride (100 mg, 0.47 mmol) added and the reaction mixture stirred for a further 2 hrs. The solvent was evaporated and the residue neutralised with sat. aq. sodium bicarbarbonate and extracted with DCM (2 x 5ml), gravity filtered through a PTFE cup and solvent evaporated. The resultant material was purified by reverse phase HPLC to give the title compound as a white solid (97mg, 67%)

^{1}H NMR (399.902 MHz, CDCl3) δ1.60 - 1.80 (m, 7H), 2.05 (m, 2H), 2.22 (m, 1H), 2.38 (s, 3H), 2.44 (m, 1H), 2.55 (m, 1H), 2.67 (m, 2H), 2.77 (m, 1H), 2.96 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.69 (m, 1H), 4.91 (m, 1H), 6.45 (d, 1H), 7.27 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 494 [M+H]+.

The following example was prepared by an analogous process to that used in the preparation of Example 62 utilising the pyrrolidine analogue from Example 56

Example 63:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3S)-1-methylpyrrolidin-3-yl]benzamide

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.60 - 1.80 (m, 7H), 2.05 (m, 2H), 2.22 (m, 1H), 2.38 (s, 3H), 2.44 (m, 1H), 2.55 (m, 1H), 2.67 (m, 2H), 2.77 (m, 1H), 2.96 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.68 (m, 1H), 4.91 (m, 1H), 6.45 (d, 1H), 7.27 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 494 [M+H]+.

Example 64:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1S,5R)-3-methyl-3-azabicyclo[3.1.0]hex-6-yl]benzamide

To N-[(1S,5R)-3-azabicyclo[3.1.0]hex-6-yl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide (Example 57, 114 mg, 0.23 mmol) dissolved in THF (2 mL) was added acetic acid (13 uL, 0.23 mmol) (material came out of solution), followed by aqueous formaldehyde (0.5 mL, material all dissolved again). The reaction mixture was stirred at room temperature for 30 mins and sodium triacetoxyborohydride (100 mg, 0.47 mmol) added and the reaction mixture stirred for a further 2 hrs. The solvent was evaporated and the residue neutralised with sat. aq. sodium bicarbonate and extracted with DCM (15 mL), filtered through a PTFE cup and evaporated. The resultant material was purified by reverse phase HPLC.

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.56 - 1.80 (m, 8H), 2.04 (m, 2H), 2.30 (s, 3H), 2.39 (m, 2H), 2.66 (m, 2H), 3.12 (m, 1H), 3.17 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 3.96 (s, 3H), 4.89

(m, 1H), 6.06 (s, 1H), 7.18 (m, 1H), 7.43 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.48 (d, 1H); MS m/z 506 [M+H]+.

Example 65:

Methyl (1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylate

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 1.1 g, 2.7 mmol), methyl (1S,3R)-3-aminocyclopentane-1-carboxylate (Intermediate 31; 528 mg, 2.94 mmol), HATU (1.22 g, 3.22 mmol) and DIPEA (1.86 mL, 10.68 mmol) and DMF (10 mL) were combined and stirred at room temperature overnight. Solvent was evaporated and the residue partitioned between saturated sodium carbonate and DCM then gravity filtered through a PTFE cup. The organic phase was passed through a silica pad eluting with EtOAc. Fractions containing product were combined and evaporated to give a brown gum which was dissolved in MeOH and added to a 50g SCX-2 column pre-wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and product eluted with 2M ammonia in MeOH. Solvent was evaporated to a yellow gum, ether was added then re-evaporated to give the title compound as a yellow foam (1.21 g, 84%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.62 (m, 2H), 1.75 (m, 4H), 1.95 (m, 4H), 2.02 - 2.22 (m, 4H), 2.67 (m, 2H), 3.02 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.72 (s, 3H), 3.99 (s, 3H), 4.60 (m, 1H), 4.91 (m, 1H), 7.25 (m, 1H), 7.38 (m, 1H), 7.49 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.53 (d, 1H); MS m/z 537 [M+H]+.

Example 66:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[2-(dipropan-2-ylamino)ethyl]-3-methoxy-benzamide

A solution of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 100 mg, 0.24 mmol), DIPEA (0.127 mL, 0.73 mmol) and HATU (120 mg, 0.32 mmol) in DMF (2 mL) was stirred at ambient temperature for 10 mins. The pale brown solution was add to N,N-dipropan-2-

ylethane-1,2-diamine (ABCR, 43 mg, 0.3 mmol) and the resulting solution stirred at ambient temperature for 18 hours. The reaction solution was purified by reverse phase HPLC to give the title compound as a white solid (43 mg, 33%); MS m/z 538 [M+H]+. Retention Time 2.49 mins.

The following examples were prepared by an analogous process to that used in the preparation of Example 66, utilising the appropriate amines. NMR data was obtained on a selection of compounds as indicated.

Example 67:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-pyridin-4-yl-benzamide

Example 68:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(3-pyrrolidin-1-ylpropyl)benzamide

Example 69:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[3-(1-piperidyl)propyl]benzamide

Example 70:

N-[3-(azepan-1-yl)propyl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

Example 71:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1S,5R)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]benzamide

Example 72:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1,2,2,6,6-pentamethyl-4-piperidyl)benzamide

Example 73:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[1-(1-piperidyl)propan-2-yl]benzamide

Example 74:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-pyridin-3-yl-benzamide

Example 75:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-methyl-2-(1-piperidyl)propyl]benzamide

Example 76:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(pyridin-3-ylmethyl)benzamide

Example 77:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(4-methoxyphenyl)benzamide

Example 78:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-diethylaminopropyl)-3-methoxy-benzamide

1H NMR (400.132 MHz, DMSO-d_6) δ 0.95 (t, 6H), 1.66 (m, 8H), 1.94 (m, 2H), 2.45 (m, 6H), 2.59 (m, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.94 (s, 3H), 4.81 (m, 1H), 7.45 (d, 2H), 7.48 (s, 1H), 7.73 (s, 1H), 8.08 (s, 1H), 8.38 (s, 1H), 8.38 (d, 2H)

Example 79:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(1-methylpyrrolidin-2-yl)ethyl]benzamide

Example 80:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(pyridin-4-ylmethyl)benzamide

Example 81:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-methyl-1-pyrrolidin-1-yl-propan-2-yl)benzamide

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.37 (s, 6H), 1.67 (m, 10H), 1.94 (m, 2H), 2.60 (m, 6H), 2.78 (s, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.94 (s, 3H), 4.80 (m, 1H), 7.37 (d, 1H), 7.42 (s, 1H), 7.48 (s, 1H), 7.72 (s, 1H), 8.08 (s, 1H), 8.36 (d, 1H)

Example 82:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[[(2S)-1-(cyclopropylmethyl)pyrrolidin-2-yl]methyl]-3-methoxy-benzamide

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.01 (m, 2H), 0.34 (m, 2H), 0.80 (m, 1H), 1.59 (m, 10H), 1.84 (m, 2H), 1.96 (m, 1H), 2.12 (m, 1H), 2.50 (m, 3H), 2.64 (m, 1H), 3.01 (m, 2H), 3.08 (s, 3H), 3.32 (m, 1H), 3.53 (m, 2H), 3.84 (s, 3H), 4.71 (m, 1H), 7.36 (d, 1H), 7.39 (s, 1H), 7.63 (s, 1H), 7.98 (s, 1H), 8.12 (t, 1H), 8.28 (d, 1H)

Example 83:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.29 (s, 2H), 0.51 (s, 2H), 1.66 (m, 10H), 1.94 (m, 2H), 2.43 (s, 2H), 2.51 (m, 4H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (d, 2H), 3.63 (m, 2H), 3.95 (s, 3H), 4.82 (m, 1H), 7.38 (d, 1H), 7.47 (s, 1H), 7.74 (s, 1H), 8.09 (s, 1H), 8.38 (d, 1H), 8.49 (t, 1H).

Example 84:

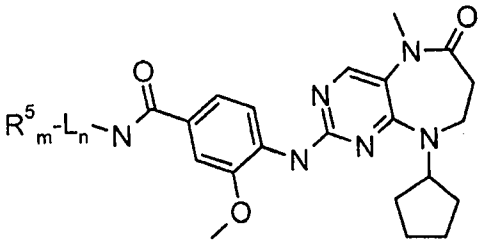
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(1-methyl-3-piperidyl)methyl]benzamide

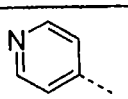
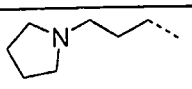
^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.92 (m, 1H), 1.44 (m, 1H), 1.73 (m, 10H), 1.94 (m, 2H), 2.13 (s, 3H), 2.64 (m, 5H), 3.15 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.49 (m, 2H), 7.73 (s, 1H), 8.08 (s, 1H), 8.32 (t, 1H), 8.38 (d, 1H)

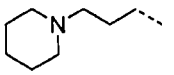
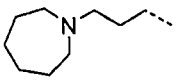
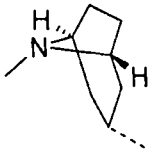
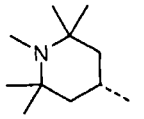
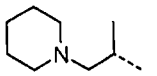
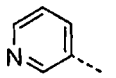
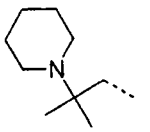
Example 85:

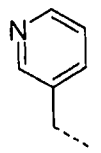
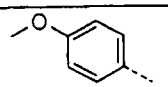
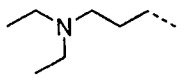
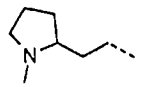
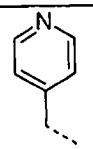
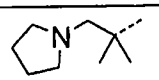
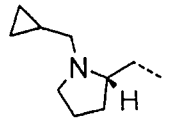
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[2-(1-methyl-2-piperidyl)ethyl]benzamide

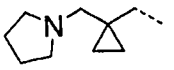
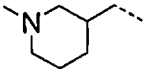
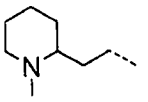
^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.45 (m, 14H), 1.95 (m, 4H), 2.21 (s, 3H), 2.59 (m, 2H), 2.76 (m, 1H), 3.17 (s, 3H), 3.31 (m, 2H), 3.63 (m, 2H), 3.94 (s, 3H), 4.81 (m, 1H), 7.46 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.35 (t, 1H), 8.38 (d, 1H)



Example	$R^5{}_m$-L_n-	Supplier or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
67		Aldrich	488	1.97
68		ABCR	522	2.01

Example	R^5_m-L_n-	Supplier or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
69		ABCR	536	2.17
70		ABCR	550	2.33
71		Flurochem	534	1.85
72		ABCR	564	2.28
73		Journal of the Chemical Society (1947), p 1511-13.	536	2.31
74		Aldrich	488	1.96
75		Matrix	550	2.67

Example	R^5_m-L_n-	Supplier or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
76		Aldrich	502	1.81
77		Aldrich	517	2.35
78		Aldrich	524	2.11
79		Aldrich	522	1.83
80		Aldrich	502	1.73
81		Flurochem	536	2.64
82		Intermediate 32	548	2.85

Example	$R^5{}_m$-L_n-	Supplier or Source	MS m/z $[M+H]^+$	Retention time (Minutes)
83		Intermediate 33	548	3.01
84		Chembridge	522	2.19
85		Chembridge	536	2.39

Example 86:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-tert-butyl-4-piperidyl)benzamide

A solution of N-[(1S,5R)-3-azabicyclo[3.1.0]hex-6-yl]-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide (Example 57, 250mg, 0.61mmol), 1-tert-butylpiperidin-4-amine (Activate, 96mg, 0.61mmol), HATU (349mg, 0.92mmol) and DIPEA (321uL, 1.83mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was loaded on to an SCX-3 column pre-wet with methanol. The column was washed with methanol and then with 2% 7N ammonia/methanol to elute the crude product. The product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a white solid (137mg, 40.8%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.04 (9H, s), 1.55 (2H, s), 1.62 - 1.63 (3H, m), 1.73 (3H, d), 1.80 (2H, d), 1.95 (2H, t), 2.10 (2H, t), 2.60 (2H, t), 3.01 (2H, d), 3.18 (3H, s), 3.62 -3.64

(2H, t), 3.72 (1H, m), 3.95 (3H, s), 4.79 - 4.84 (1H, m), 7.46 (1H, d), 7.50 (1H, d), 7.73 (1H, s), 8.02 (1H, d), 8.09 (1H, s), 8.39 (1H, d); MS m/z 549[M+H]+.

Example 87:

(1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylic acid

To a solution of Methyl (1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylate (Example 65, 1.21 g, 2.25 mmol) in 4:1 THF / water (20 mL) was added lithium hydroxide (472 mg, 11.25 mmol) and the reaction mixture stirred at room temperature overnight. The solvent was evaporated and the residue diluted with water. 1M citric acid was added until precipitation ceased (pH 3 – 4) and the resultant suspension stirred for 20 minutes. The resulting cream precipitate was filtered off, washed with water followed by isohexane and dried under vacuum to yield the title compound (1.08 g, 92%)

^{1}H NMR (399.902 MHz, DMSO-d_6) δ1.62 - 1.95 (m, 12H), 2.07 (m, 1H), 2.59 (m, 3H), 2.72 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.28 (m, 1H), 4.81 (m, 1H), 7.51 (m, 2H), 7.74 (s, 1H), 8.09 (s, 1H), 8.38 (d, 1H), 8.85 (s, 1H); MS m/z 523 [M+H]+.

Example 88:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-[(1R,3S)-3-(dimethylcarbamoyl)cyclopentyl]-3-methoxy-benzamide

A solution of (1S,3R)-3-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoyl]amino]cyclopentane-1-carboxylic acid (Example 87, 100 mg, 0.19 mmol), HATU (80 mg, 0.21 mmol) and DIPEA (100 uL, 0.73 mmol) in DMF (3 mL) was stirred at room temperature for 10 minutes. Dimethylamine solution in THF (1 mL) was added and the reaction mixture stirred at room temperature overnight. Solvent was evaporated and the

resultant marterial purified by reverse phase HPLC to yield the title compound as a yellow solid (80 mg, 86%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ1.62 (m, 2H), 1.75 (m, 4H), 1.84 (m, 2H), 2.06 (m, 6H), 2.67 (m, 2H), 2.99 (s, 3H), 3.11 (s, 3H), 3.31 (m, 4H), 3.69 (m, 2H), 3.99 (s, 3H), 4.58 (m, 1H), 4.91 (m, 1H), 7.53 (m, 2H), 7.67 (s, 1H), 7.93 (s, 1H), 8.44 (d, 1H), 8.51 (d, 1H); MS m/z 550 [M+H]+.

Example 89:

N-cyclohexyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino] benzamide

A solutiom of 4-amino-N-cyclohexyl-benzamide (TimTec, 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140mg, 0.5mmol) and p-toluenesulphonic acid monohydrate(238mg, 1.25mmol) in 4-methyl-2-pentanol (3ml) was heated at 140°C for 3h. The mixture was allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto an SCX-3 column and washed with methanol. The product with eluted with ammonia/methanol and the product containing fractions were concentrated. Purification by preparative, reverse phase chromatography (Note 1) gave the title compound as a white solid (35mg, 15%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.11 – 1.19 (1H, m), 1.26 - 1.37 (4H, m), 1.60 – 1.85 (11H, m), 1.97 - 2.01 (2H, m), 2.59 (2H, m), 3.18 (3H, s), 3.62 - 3.65 (2H, m), 3.72 – 1.76 (1H, m), 4.85 (1H, m), 7.75 - 7.81 (4H, m), 7.93 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 463 [M+H]+.

Example 90:

N-cyclohexyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

A solution of HATU (147 mg, 0.385 mmol) in DMA (1 mL) was added to a mixture of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111, 144mg, 0.35 mmol), DIPEA (183 uL, 0.385 mmol) and Cyclohexylamine (Aldrich, 44 mg, 0.44 mmol) in DMA (1 mL). The resulting mixture

was stirred at room temperature overnight. The mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated *in vacuo*. The resultant material was purified by preparative reverse phase HPLC to yield the title compound as a white solid (7 mg, 4%).

m/z 493 [M+H]+. Retention Time 2.57 minutes

Example 91:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-me thoxy-N-methyl-benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111_, 100mg, 0.24 mmol), 2M Methylamine in THF (365 uL, 0.73 mmol), HATU (111 mg, 0.29mmol) and DIPEA (127 uL, 0.73 mmol) and DMF (3 mL) were combined and stirred at ambient temperature overnight. Solvent was evaporated and the residue partitioned between DCM (2 mL) and sat. aq. Bicarb. (2 mL), and gravity filtered through a PTFE cup. The organic phase was added to a silica column, eluting with a gradient of 0 – 10% MeOH / DCM and solvent evaporated from product containing fractions. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solid. (45 mg, 44 %)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ1.62 (m, 6H), 1.98 (m, 2H), 2.60 (m, 2H), 2.95 (d, 3H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.83 (m, 1H), 6.00 (d, 1H), 7.17 (m, 1H), 7.37 (d, 1H), 7.59 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 454 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 91 utilising Ammonium Chloride and 3 additional equivalents of DIPEA and collecting the product as a solid precipitated from the work-up procedure with DCM and saturated aqueous Sodium Bicarbonate solution.

Example 92:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

^{1}H NMR (400.132 MHz, DMSO-d_6) δ1.73 (m, 6H), 2.00 (m, 2H), 2.64 (m, 2H), 3.23 (s, 3H), 3.68 (m, 2H), 3.99 (s, 3H), 4.86 (m, 1H), 7.22 (s, 1H), 7.57 (m, 2H), 7.78 (s, 1H), 7.92 (s, 1H), 8.13 (s, 1H), 8.44 (d, 1H); MS m/z 411 [M+H]+.

The following examples were prepared by an analogous process to that used in the preparation of **Example 66,** utilising the appropriate amines. NMR data was obtained on compounds when indicated.

Example 93:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-propyl-benzamide

Example 94:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(cyclopropylmethyl)-3-methoxy-benzamide

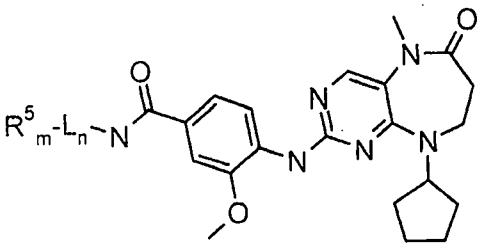
Example 95:

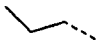
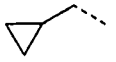
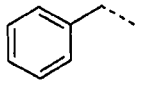
4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-propan-2-yl-benzamide

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.19 (d, 6H), 1.67 (m, 6H), 1.95 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.12 (m, 1H), 4.82 (m, 1H), 7.49 (m, 2H), 7.72 (s, 1H), 8.04 (d, 1H), 8.08 (s, 1H), 8.38 (d, 1H)

Example 96:

N-benzyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide



Example	R^5_m-L_n-	Supplier Or Source	MS m/z [M+H]+	Retention time (Minutes)
93		Aldrich	453	2.04
94		Aldrich	465	2.09
5		Aldrich	453	2.04
96		ABCR	501	2.31

Example 97:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-N-cyclohexyl-benzamide (TimTec, 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100mg, 0.36 mmol), the 4-aminobenzamide (Aldrich, 59 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) were heated together in 4-methyl-2-pentanol (4ml) at 120^{0}C for 22 hours. The reaction was cooled to ambient temperature and passed down a 5g SCX-2 column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and solvent evaporated. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solid (37 mg, 27%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.67 (m, 6H), 1.97 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 4.84 (m, 1H), 7.08 (s, 1H), 7.77 (s, 1H), 7.79 (s, 4H), 8.08 (s, 1H), 9.46 (s, 1H); MS m/z 381 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 66 utilising the appropriate amine.

Example 98:

N-cyclobutyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzamide

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.67 (m, 8H), 1.95 (m, 2H), 2.09 (m, 2H), 2.23 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.43 (m, 1H), 4.82 (m, 1H), 7.48 (m, 2H), 7.72 (s, 1H), 8.09 (s, 1H), 8.41 (m, 2H); MS m/z 465 $[M+H]^+$.

Example 99:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-phenyl-benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), 4-amino-3-methoxy-N-phenyl-benzamide (Apin, 104 mg, 0.43 mmol) and p-toluenesulphonic acid monohydrate (137 mg, 0.72 mmol) were vortexed and heated together in 4-methyl-2-pentanol (4 mL) at 100^{0}C for 24 hours.. The crude reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with MeOH. The column was washed with MeOH and the product eluted with 2M NH3/MeOH. Solvent was evaporated and the resultant material was purified by reverse phase HPLC to yield the title compound as a white solid (64 mg, 36 %). MS m/z 487 $[M+H]^+$. Retention Time 3.81 minutes

Example 100:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-propan-2-yl-benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 134mg, 0.48mmol), 4-amino-N-propan-2-yl-benzamide (Butt Park, 86 mg, 0.48 mmol) and p-toluenesulphonic acid monohydrate (227 mg, 1.19 mmol) in 4-methyl-2-pentanol (4 mL) were heated at 140°C for 2h. The reaction mixture was loaded onto an SCX-3 column pre-wet with methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydate and then eluted with 2% 7N ammonia/methanol.. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a white solid (121 mg, 60%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.17 (6H, d), 1.63 (4H, m), 1.74 (2H, m), 1.97 – 1.99 (2H, d), 2.58 – 2.61 (2H, t), 3.18 (3H, s), 3.62 – 3.65 (2H, t), 4.07 – 4.13 (1H, m), 4.85 (1H, m), 7.71 – 7.82 (4H, m), 7.95 – 7.97 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 423 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 100 utilising the appropriate aniline.

Example 101:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-phenyl-benzamide

Amine available from **Aldrich**

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.64 - 1.67 (4H, m), 1.72 - 1.75 (2H, m), 1.99 (2H, m), 2.60 (2H, t), 3.19 (3H, s), 3.63 (2H, t), 4.87 (1H, m), 7.09 (1H, t), 7.35 (2H, m), 7.76 - 7.79 (2H, d), 7.90 (4H, s), 8.11 (1H, s), 9.55 (1H, s), 10.00 (1H, s); MS m/z 423 $[M+H]^+$.

Example 102:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-methyl-benzamide

Amine available from **TimTec**

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.63 (4H, m), 1.70 – 1.74 (2H, m), 1.97 (2H, m), 2.58 – 2.61 (2H, t), 2.78 (3H, d), 3.18 (3H, s), 3.62 – 3.65 (2H, t), 4.84 (1H, m), 7.75 (2H, d), 7.81 (2H, d), 8.09 (1H, s), 8.20 (1H, d), 9.46 (1H, s); MS m/z 395 $[M+H]^+$.

Example 103:

6-cyclopentyl-9-[[2-methoxy-4-(2-pyrrolidin-1-ylethylamino)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140 mg, 0.5 mmol) 2-methoxy-N'-(2-pyrrolidin-1-ylethyl)benzene-1,4-diamine (Intermediate 35, 141 mg, 0.6 mmol), and p-toluenesulphonic acid monohydrate (227 mg, 1.19 mmol) in 4-methyl-2-pentanol (4 mL) were heated by microwave irradiation at 160 °C for 1 hour. The reaction mixture was absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and the material produced was purified by normal phase chromatography using 0-10% ammonia/methanol to yield the title compound as a solid (100 mg, 42 %).
^{1}H NMR (500.13 MHz, DMSO-d6) ä 1.55 - 1.62 (4H, m), 1.68 - 1.75 (6H, m), 1.85 - 1.92 (2H, m), 2.54 - 2.56 (6H, m), 2.67 (2H, t), 3.15 - 3.19 (5H, m), 3.58 - 3.60 (2H, m), 3.80 (3H, s), 4.64 - 4.71 (1H, m), 4.87 (1H, t), 6.19 (1H, dd), 6.36 (1H, d), 7.12 (1H, s), 7.67 (1H, d), 7.93 (1H, s); MS m/z 480 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 103, utilising the appropriate aniline. NMR data is recorded where obtained.

Example 104:

6-cyclopentyl-9-[[2-methoxy-4-[methyl-(1-methyl-4-piperidyl)amino]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 105:

6-cyclopentyl-9-[[2-methoxy-4-[4-(2-methoxyethyl)piperazin-1-yl]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 106:

6-cyclopentyl-9-[[2-methoxy-4-[4-(1-piperidyl)-1-piperidyl]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 107:

6-cyclopentyl-9-[[4-(2-dimethylaminoethylamino)-2-methoxy-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.55 - 1.76 (7H, m), 1.99 - 2.02 (2H, m), 2.31 (6H, s), 2.60 - 2.66 (4H, m), 3.19 (2H, t), 3.27 (3H, s), 3.64 - 3.68 (2H, m), 3.85 (3H, s), 4.80 - 4.88 (1H, m), 6.23 - 6.26 (1H, m), 6.29 (1H, d), 7.09 (1H, s), 7.88 (1H, s), 8.03 (1H, d).

Example 108:

9-[[4-(4-cyclohexylpiperazin-1-yl)-2-methoxy-phenyl]amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

1H NMR (400.13 MHz, $CDCl_3$) δ 1.10 - 1.37 (4H, m), 1.55 - 1.78 (8H, m), 1.81 - 1.89 (2H, m), 1.95 - 2.05 (4H, m), 2.44 (1H, s), 2.65 - 2.67 (2H, m), 2.85 (4H, s), 3.24 (4H, s), 3.28 (3H, s), 3.66 - 3.69 (2H, m), 3.89 (3H, s), 4.82 - 4.91 (1H, m), 6.54 - 6.57 (2H, m), 7.24 (1H, s), 7.90 (1H, s), 8.19 (1H, d)

Example 109:

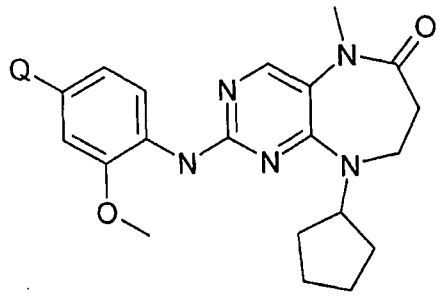
6-cyclopentyl-9-[[2-methoxy-4-(4-methyl-1,4-diazepan-1-yl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

1H NMR (400.13 MHz, $CDCl_3$) δ 1.53 - 1.78 (6H, m), 1.97 - 2.08 (4H, m), 2.42 (3H, s), 2.62 - 2.68 (4H, m), 2.75 - 2.78 (2H, m), 3.27 (3H, s), 3.50 (2H, t), 3.58 - 3.62 (2H, m), 3.64 - 3.67 (2H, m), 3.87 (3H, s), 4.81 - 4.88 (1H, m), 6.27 (1H, d), 6.28 (1H, s), 7.06 (1H, s), 7.88 (1H, m), 8.02 (1H, d)

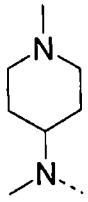
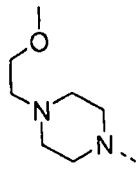
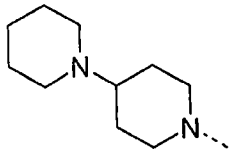
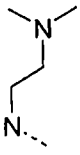
Example 110:

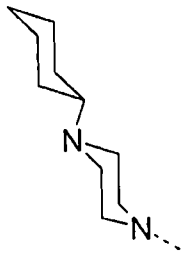
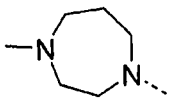
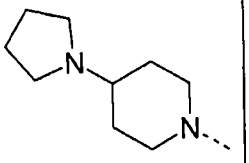
6-cyclopentyl-9-[[2-methoxy-4-(4-pyrrolidin-1-yl-1-piperidyl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

120



5

Example	Q	Source	MS m/z [M+H]+	Retention time (Minutes)
104		Intermediate 36	494	2.10
105		Intermediate 37	510	2.14
106		Intermediate 38	534	2.82
107		Intermediate 39	454	2.00

Example	Q	Source	MS m/z [M+H]+	Retention time (Minutes)
108		Intermediate 40	534	3.49
109		Intermediate 41	480	2.33
110		Intermediate 42	520	2.68

Example 111:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-benzoic acid

To a solution of 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 10.62 g, 36 mmol) and 4-amino-3-methoxybenzoic acid (Aldrich, 6.795 g, 40.7 mmol) in ethanol (150 mL) was added water (450 mL) and conc hydrochloric acid 96 mL, 72 mmol). The mixture was heated under reflux for 36 hours. The reaction was cooled and a brown solid precipitate formed which was filtered, triturated with cold acetonitrile and dried *in vacuo* to give the title compound (10.1 g, 68 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.55 - 1.75 (6H, m), 1.87 - 1.95 (2H, m), 2.71 - 2.75 (2H, m), 3.18 (3H, s), 3.71 - 3.76 (2H, m), 3.95 (3H, s), 4.79 - 4.93 (1H, m), 7.58 - 7.62 (2H, m), 8.19 (1H, d), 8.19 (1H, s), 9.37 (1H, s); MS m/z 412 $[M+H]^+$.

Example 112:

6-cyclopentyl-2-methyl-9-[(2,4,6-trimethoxyphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

2,4,6-trimethoxyaniline (Maybridge, 104 mg, 0.56 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.56 mmol) and p-toluenesulphonic acid monohydrate (268 mg, 1.41 mmol) in 4-methyl-2-pentanol (4 mL) were heated at 140°C for 2h. The reaction solution was loaded on to an SCX-3 column pre-wet with methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydate and then washed with 2% 7N ammonia/methanol to elute the crude product. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a white solid (140mg, 58%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.32 – 1.68 (8H, m), 2.46 – 2.48 (2H, t), 3.13 (3H, s), 3.50 (2H, t), 3.70 (6H, s), 3.79 (3H, s), 4.32 (1H, m), 6.25 (2H, s), 7.37 (1H, s), 7.85 (1H, s); MS m/z 429 $[M+H]^+$.

Example 113:

6-cyclopentyl-9-[[2-methoxy-4-[(1-methyl-4-piperidyl)oxy]phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.53 mmol), 2-methoxy-4-[(1-methyl-4-piperidyl)oxy]aniline (Intermediate 43 (124 mg, 0.53 mmol) and p-toluenesulphonic acid monohydrate (255 mg, 1.34 mmol) heated in 4-methyl-2-pentanol (4 mL) at 140°C for 2h. The reaction solution was loaded on to an SCX-2 column pre-wet with methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydrate and then washed with 2% 7N ammonia/methanol to elute the crude product. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a red gum (189 mg, 82 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.53 – 1.56 (4H, m), 1.60 (2H, d), 1.63 – 1.68 (4H, m), 1.84 (2H, d), 1.92 (2H, d), 2.20 (3H, s), 2.18 – 2.22 (2H, m), 2.63 (2H, t), 3.15 (3H, s), 3.56 –

3.59 (2H, t), 3.81 (3H, s), 4.33 (1H, m), 4.64 (1H, m), 6.49 – 6.52 (1H, m), 6.62 (1H, d), 7.51 (1H, s), 7.82 (1H, d), 7.98 (1H, s); MS m/z 481 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 113 utilising the appropriate aniline indicated.

Example 114:

6-cyclopentyl-9-[[2-methoxy-4-(1-methylpyrrolidin-3-yl)oxy-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Starting aniline - 2-methoxy-4-(1-methylpyrrolidin-3-yl)oxy-aniline Intermediate 45

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.54 (3H, d), 1.58 (1H, s), 1.66 (2H, s), 1.79 – 1.83 (2H, m), 1.85 (1H, s), 2.25 – 2.29 (1H, m), 2.30 (3H, s), 2.43 (1H, m), 2.53 – 2.56 (2H, t), 2.61 – 2.65 (1H, m), 2.66 – 2.68 (1H, m), 2.69 – 2.70 (1H, m), 2.81 – 2.85 (1H, m), 3.15 (3H, s), 3.56 – 3.59 (2H, m), 3.81 (3H, s), 4.65 (1H,m), 4.86 – 4.89 (1H, m), 6.41 – 6.44 (1H, m), 6.56 (1H, d), 7.51 (1H, s), 7.82 (1H, d), 7.98 (1H, s); MS m/z 467 $[M+H]^+$.

Example 115:

6-cyclopentyl-9-[[2-methoxy-4-(2-morpholin-4-ylethoxy)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Starting aniline - 2-methoxy-4-(2-morpholin-4-ylethoxy)aniline Intermediate 47

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.55 (3H, d), 1.59 (1H, s), 1.67 (2H, s), 1.85 (2H, s), 2.48 (4H, d), 2.53 – 2.56 (2H, t), 2.69 (2H, t), 3.15 (3H, s), 3.59 (2H, d), 3.59 (4H, d), 3.83 (3H, s), 4.08 (2H, t), 4.67 (1H, s), 6.48 – 6.51 (1H, m), 6.63 (1H, d), 7.50 (1H, s), 7.86 (1H, d), 7.98 (1H, s); MS m/z 497 $[M+H]^+$.

Example 116:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-(trifluoromethyl)benzonitrile

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 157 mg, 0.56 mmol), 4-amino-2-methyl-benzonitrile (Aldrich, 95 mg, 0.51 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were

dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (330 mg, 1.01 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (28 mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100°C for 8 h. The mixture was cooled, filtered and the filtrate absorbed onto an SCX-3 column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative reverse phase chromatography to give the title compound as a white solid. (21mg, 10%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.57 - 1.72 (6H, m), 1.92 – 2.00 (2H, m), 2.61 (2H, m), 3.19 (3H, s), 3.64 - 3.66 (2H, m), 4.82 - 4.90 (1H, m), 7.99 - 8.07 (2H, m), 8.16 (1H, s), 8.50 (1H, d), 10.15 (1H, s); MS m/z 431 $[M+H]^+$.

Example 117:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-hydroxyethyl)benzenesulfonamide

4-amino-N-(2-hydroxyethyl)benzenesulfonamide (Maybridge; 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140 mg, 0.5 mmol) and p-toluenesulphonic acid monohydrate (238 mg, 1.25 mmol) were heated at 140°C in 4-methyl-2-pentanol (3 mL) for 3 hours. The mixture was allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto and SCX-3 column and washed with methanol. The product with eluted with ammonia/methanol and the product containing fractions were concentrated. Purification by preparative, reverse phase chromatography gave the title compound as a white solid (122mg, 53%)..

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.59 – 1.74 (6H, d), 1.96 - 2.01 (2H, m), 2.57 - 2.61 (2H, m), 2.78 (2H, q), 3.19 (3H, s), 3.35 - 3.40 (2H, m), 3.62 - 3.65 (2H, m), 4.63 (1H, t), 4.80 - 4.88 (1H, m), 7.33 (1H, t), 7.64 - 7.68 (2H, m), 7.90 - 7.94 (2H, m), 8.11 (1H, s), 9.65 (1H, s); MS m/z 461 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 117 utilising the appropriate aniline available from Aldrich.

Example 118:

6-cyclopentyl-9-[[4-(2-dimethylaminoethoxy)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.55 – 1.71 (6H, m), 1.89 – 1.95 (2H, m), 2.22 (6H, s), 2.55 - 2.57 (2H, m), 2.61 (2H, t), 3.16 (3H, s), 3.58 - 3.61 (2H, m), 4.00 (2H, t), 4.72 - 4.81 (1H, m), 6.82 - 6.86 (2H, m), 7.56 - 7.60 (2H, m), 8.01 (1H, s), 8.95 (1H, s); MS m/z 425 $[M+H]^+$.

Example 119:

N-[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]acetamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), N-(4-aminophenyl)acetamide (Aldrich, 64 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 120^{0}C for 22 hours. The reactions were cooled to ambient temperature and then passed down a 5g SCX-2 column pre-wet with methanol. The products were eluted with 2M NH3/MeOH and the solvent evaporated. The resukltatn material was purified by reverse phase HPLC to yield the title compound as a white solids (22 mg, 16%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.64 (m, 6H), 1.94 (m, 2H), 2.01 (s, 3H), 2.56 (m, 2H), 3.16 (s, 3H), 3.60 (m, 2H), 4.78 (m, 1H), 7.43 (d, 2H), 7.61 (d, 2H), 8.02 (s, 1H), 9.06 (s, 1H), 9.74 (s, 1H); MS m/z 495 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 119 utilising the appropriate substituted anilines. NMR analysis was undertaken where indicated.

Example 120:

6-cyclopentyl-9-[(4-methoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.62 (m, 6H), 1.92 (m, 2H), 2.55 (m, 2H), 3.16 (s, 3H), 3.59 (m, 2H), 3.60 (s, 2H), 3.72 (s, 3H), 4.76 (m, 1H), 6.83 (d, 2H), 7.59 (d, 2H), 8.00 (s, 1H), 8.93 (s, 1H)

Example 121:

6-cyclopentyl-2-methyl-9-[(4-morpholin-4-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.63 (m, 6H), 1.92 (m, 2H), 2.55 (m, 2H), 3.02 (m, 4H), 3.15 (s, 3H), 3.59 (m, 2H), 3.74 (m, 4H), 4.76 (m, 1H), 6.85 (d, 2H), 7.56 (d, 2H), 7.99 (s, 1H), 8.89 (s, 1H); MS m/z 423 $[M+H]^+$.

Example 122:

6-cyclopentyl-9-[(4-dimethylaminophenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 123:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzenesulfonamide

Example 124:

9-[(1-acetyl-2,3-dihydroindol-5-yl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 125:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-methoxyethyl)benzenesulfonamide

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.66 (m, 6H), 1.96 (m, 2H), 2.59 (m, 2H), 2.88 (m, 2H), 3.17 (s, 3H), 3.18 (s, 3H), 3.30 (m, 2H), 3.63 (m, 2H), 4.83 (m, 1H), 7.44 (t, 1H), 7.66 (d, 2H), 7.91 (d, 2H), 8.10 (s, 1H), 9.64 (s, 1H)

Example 126:

9-[(3-chloro-4-morpholin-4-yl-phenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

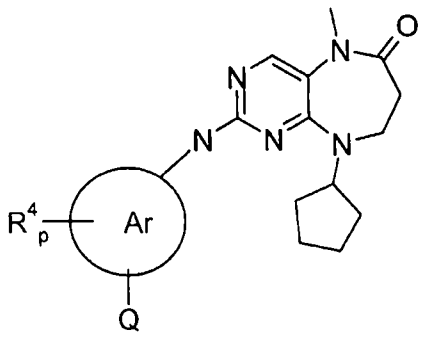
Example 127:

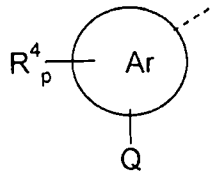
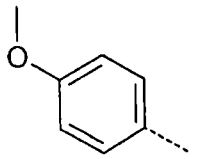
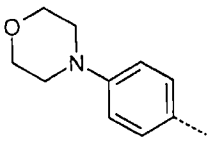
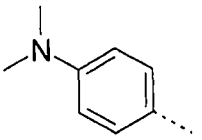
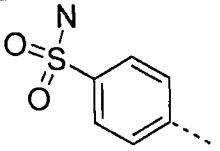
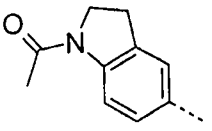
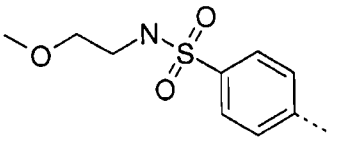
6-cyclopentyl-2-methyl-9-[(4-methylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

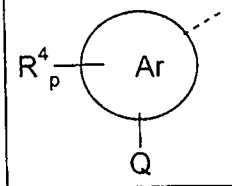
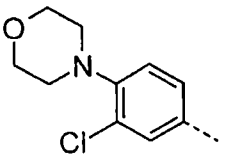
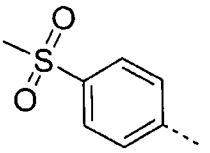
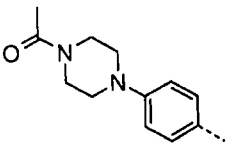
^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.67 (m, 6H), 1.98 (m, 2H), 2.60 (m, 2H), 3.15 (s, 3H), 3.18 (s, 3H), 3.64 (m, 2H), 4.85 (m, 1H), 7.77 (d, 2H), 7.98 (d, 2H), 8.11 (s, 1H), 9.74 (s, 1H)

Example 128:

9-[[4-(4-acetylpiperazin-1-yl)phenyl]amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one



Example		Supplier or Source	MS m/z $[M+H]^+$	Retention Time (Minutes)
120		Aldrich	368	2.16
121		Aldrich	423	1.95
122		Aldrich	381	3.14
123		ABCR	417	2.6
124		Flurochem	421	2.75
125		WO2005/116025	475	2.81

Example		Supplier or Source	MS m/z [M+H]+	Retention Time (Minutes)
126		Flurochem	457	3.26
127		Flurochem	416	2.78
128		Flurochem	464	2.65

Example 129:

6-cyclopentyl-2-methyl-9-[(3,4,5-trimethoxyphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

3,4,5-trimethoxyaniline (Aldrich, 104 mg, 0.56 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.56 mmol) and p-toluenesulphonic acid monohydrate (268 mg, 1.41 mmol) were heated at 140°C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction solution was loaded onto an SCX-3 column pre-wet methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydate and then washed with 2% 7N ammonia/methanol to elute the crude product. The product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a purple solid (130mg, 54%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.50 – 1.52 (2H, m), 1.57 – 1.61 (2H, m), 1.70 (2H, m), 1.95 (2H, m), 2.55 – 2.58 (2H, t), 3.17 (3H, s), 3.59 (2H, t), 3.63 (3H, s), 3.76 (6H, s), 4.86 (1H, d), 7.09 (2H, s), 8.04 (1H, s), 8.97 (1H, s); MS m/z 429 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 129 utilising the appropriate substituted anilines available as indicated.

Example 130:

6-cyclopentyl-2-methyl-9-[(2,3,4-trimethoxyphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Substituted aniline available from **Apin**

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.53 - 1.56 (2H, m), 1.58 (2H, d), 1.67 - 1.68 (2H, m), 1.88 (2H, t), 2.55 - 2.57 (2H, m), 3.16 (3H, s), 3.58 - 3.60 (2H, t), 3.79 (3H, s), 3.78 - 3.82 (6H, s), 4.69 (1H, m), 6.74 (1H, d), 7.70 (2H, t), 8.00 (1H, s); MS m/z 429 $[M+H]^+$.

Example 131:

9-[[4-chloro-3-(hydroxymethyl)phenyl]amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Substituted aniline available from **Aldrich**

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.60 (3H, d), 1.62 - 1.62 (1H, m), 1.67 (2H, d), 1.96 (2H, s), 2.53 - 2.59 (2H, t), 3.17 (3H, s), 3.60 - 3.63 (2H, t), 4.53 (2H, d), 4.88 (1H, m), 5.27 (1H, t), 7.24 (1H, d), 7.62 - 7.65 (1H, m), 7.96 (1H, d), 8.05 (1H, s), 9.31 (1H, s); MS m/z 402 $[M+H]^+$.

Example 132:

6-cyclopentyl-2-methyl-9-[(2-pyridin-3-yl-1H-benzoimidazol-5-yl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 134 mg, 0.50 mmol), 2-pyridin-3-yl-1H-benzoimidazol-5-amine (Flurochem, 117 mg, 0.55 mmol) and cesium carbonate (328 mg, 1.00 mmol) were added to dioxane (4

mL) and the suspension bubbled with nitrogen for 10 minutes. Bis(dibenzylideneacetone)palladium (28 mg, 0.03 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were added and the mixture heated to 110 °C overnight. The mixture was filtered and the filtrate purified by column chromatography with a 5% 7N ammonia in methanol/DCM solvent system. Product containing fractions were combined and evaporated to give the title compound as a solid (73 mg, 32 %)

^{1}H NMR (499.8 MHz, DMSO-d_6 @ 373K) δ1.64 (4H, m), 1.73 (2H, m), 2.00 (2H, m), 2.53 - 2.56 (2H, t), 3.21 (3H, s), 3.62 - 3.65 (2H, t), 4.82 – 4.85 (1H, m), 7.53 - 7.55 (3H, m), 8.04 (2H, s), 8.45 (1H, d), 8.64 - 8.65 (1H, m), 8.71 (1H, s), 9.32 (1H, d), 12.51 (1H, s); MS m/z 455 $[M+H]^+$.

Example 133:

N-[[4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]methyl]pyridine-2-carboxamide

N-[(4-aminophenyl)methyl]pyridine-2-carboxamide (Intermediate 49: 114mg, 0.5mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 141 mg, 0.5 mmol) and p-toluenesulphonic acid monohydrate (239 mg, 1.25 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140°C for 2hours. The mixture was cooled and diluted with methanol / DCM and absorbed on to an SCX-3 column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and puriried by preparative reverse phase chromatography to give the title compound as a white solid (63mg, 27%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.54 – 1.71 (6H, m), 1.89 – 1.96 (2H, m), 2.56 – 2.58 (2H, m), 3.16 (3H, s), 3.59 – 3.61 (2H, m), 4.44 (2H, d), 4.79 (1H, m), 7.23 (2H, d), 7.60 – 7.63 (1H, m), 7.65 – 7.67 (2H, m), 7.99 – 8.08 (3H, m), 8.64 – 8.66 (1H, m), 9.13 (1H, s), 9.18 (1H, t); MS m/z 472 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 133 utilising the appropriate substituted anilines available from ABCR

Example 134:

6-cyclopentyl-2-methyl-9-[[4-(1-piperidylsulfonyl)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.34 – 1.39 (2H, m), 1.52 – 1.75 (10H, m), 1.94 – 2.00 (2H, m), 2.57 – 2.61 (2H, m), 2.87 (4H, t), 3.19 (3H, s), 3.62 – 3.65 (2H, m), 4.84 (1H, m), 7.59 (2H, d), 7.94 – 7.96 (2H, m), 8.11 (1H, s), 9.71 (1H, s); MS m/z 485 $[M+H]^+$.

Example 135:

6-cyclopentyl-2-methyl-9-[[4-(2-morpholin-4-ylethoxy)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.54 – 1.72 (6H, m), 1.89 – 1.95 (2H, m), 2.48 (4H, m), 2.66 – 2.70 (2H, m), 2.68 – 2.69 (2H, m), 3.16 (3H, s), 3.59 (6H, m), 4.05 (2H, t), 4.76 (1H, m), 6.84 – 6.87 (2H, m), 7.57 – 7.60 (2H, m), 8.01 (1H, s), 8.95 (1H, s); MS m/z 467 $[M+H]^+$.

Example 136:

tert-butyl N-[[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]methyl]carbamate

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 155 mg, 0.55 mmol), tert-butyl N-[(3-aminophenyl)methyl]carbamate (Chembasics, 111 mg, 0.50 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were dissolved in 1,4-dioxane (7.5 mL) Caesium carbonate (326 mg, 1.0 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (28 mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100°C for 8h. The mixture was cooled, filtered and the filtrate absorbed onto an SCX-3 column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by normal phase chromatography (1% methanol/DCM) to give the title compound as a white solid (57 mg, 24 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.41 (9H, s), 1.59 - 1.71 (6H, m), 1.96 (2H, m), 2.58 (2H, m), 3.17 (3H, s), 3.61 (2H, m), 4.09 (2H, d), 4.85 (1H, m), 6.80 (1H, d), 7.18 (1H, t), 7.30 (1H, t), 7.57 (1H, d), 7.62 (1H, s), 8.04 (1H, s), 9.16 (1H, s); MS m/z 467 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 136 utilising the appropriate substituted aniline available from Flurochem.

Example 137:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-methyl-isoindole-1,3-dione

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.61 – 1.77 (6H, m), 1.95 - 1.98 (2H, m), 2.61 - 2.63 (2H, m), 3.04 (3H, s), 3.20 (3H, s), 3.65 - 3.68 (2H, m), 4.78 (1H, m), 7.39 (1H, d), 7.74 (1H, t), 8.16 (1H, s), 8.81 (1H, d), 9.14 (1H, s); MS m/z 421 $[M+H]^+$.

Example 138:

N-[2-[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methoxy-phenyl]ethyl]acetamide

N-[2-(3-amino-4-methoxy-phenyl)ethyl]acetamide (Compound 4- Organic Process Research & Development 2004, 8, 628-642, 108 mg, 0.5 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 140 mg, 0.5 mmol) and p-toluenesulphonic acid monohydrate (238 mg, 1.25 mmol) were heated at 140°C in 4-methyl-2-pentanol (3 mL) for 3 hours. The mixture was allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto an SCX-3 column and washed with methanol. The product with eluted with ammonia/methanol and the product containing fractions were concentrated. Purification by preparative, reverse phase chromatography gave the title compound as a white solid (45 mg, 20 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.55 - 1.70 (6H, m), 1.79 (3H, s), 1.93 - 1.96 (2H, m), 2.56 - 2.59 (2H, m), 2.64 (2H, t), 3.17 (3H, s), 3.20 - 3.26 (2H, m), 3.61 - 3.63 (2H, m), 3.86 (3H, s), 4.85 (1H, m), 6.78 - 6.81 (1H, m), 6.95 (1H, d), 7.55 (1H, s), 7.86 (1H, t), 8.05 (1H, s), 8.12 (1H, d); MS m/z 453 $[M+H]^+$.

Example 139:

6-cyclopentyl-9-[(2-methoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

2-methoxyaniline (Aldrich, 22 mg, 0.18 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 50 mg, 0.18 mmol) and p-toluenesulphonic acid monohydrate (84 mg, 0.44 mmol) were heated in 4-methyl-2-pentanol (1 mL) at 135°C for 24 hours. The mixture was cooled and diluted with methanol / DCM and absorbed on to an SCX-3 column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and puriried by preparative reverse phase chromatography to give the title compound as a white solid (42 mg, 64 %). MS m/z 368 $[M+H]^+$, Retention Time 2.61 mins.

The following examples were prepared by an analogous process to that used in the preparation of Example 139, utilising the appropriate substituted anilines available as indicated.

Example 140:

6-cyclopentyl-9-[(2-ethoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 141:

6-cyclopentyl-2-methyl-9-[(2-methylsulfanylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 142:

6-cyclopentyl-9-[(2-hydroxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 143:

6-cyclopentyl-9-[(2-ethylphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 144:

9-[(2-benzoylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 145:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzenesulfonamide

Example 146:

6-cyclopentyl-2-methyl-9-[(2-phenoxyphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 147:

9-[(2-bromophenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 148:

6-cyclopentyl-2-methyl-9-[(2-phenylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 149:

6-cyclopentyl-2-methyl-9-[(2-methylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 150:

6-cyclopentyl-2-methyl-9-[(2-propan-2-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 151:

9-[(2-butylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 152:

6-cyclopentyl-2-methyl-9-[[2-(1-piperidyl)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 153:

6-cyclopentyl-2-methyl-9-[[2-(4-tert-butylphenoxy)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 154:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-ethyl-benzenesulfonamide

Example 155:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-methyl-benzenesulfonamide

Example 156:

6-cyclopentyl-2-methyl-9-[[2-(2-morpholin-4-ylethylamino)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 157:

9-[(2-benzylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 158:

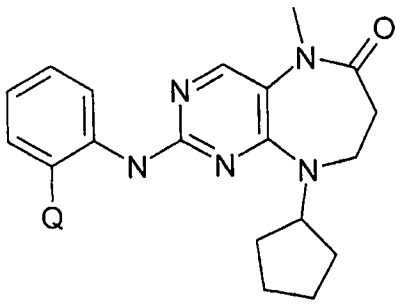
6-cyclopentyl-2-methyl-9-[(2-pyrrol-1-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

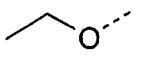
Example 159:

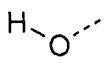
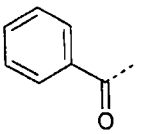
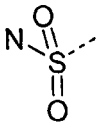
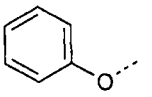
6-cyclopentyl-2-methyl-9-[[2-(4-methylphenoxy)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

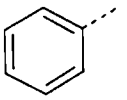
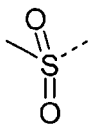
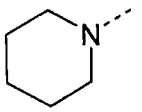
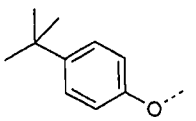
Example 160:

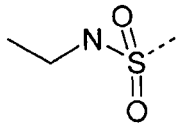
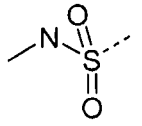
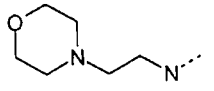
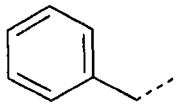
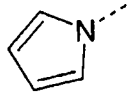
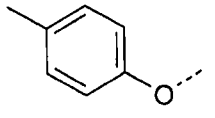
6-cyclopentyl-2-methyl-9-[[2-(morpholin-4-ylmethyl)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

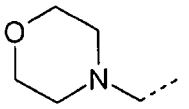


Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
140		Aldrich	382	2.81
141		Aldrich	384	2.76

Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
142		Aldrich	354	2.01
143		Aldrich	366	2.7
144		Aldrich	442	3.11
145		Aldrich	417	1.99
146		Aldrich	430	3.11
147		Aldrich	418	2.82

Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
148		ABCR	414	3
149		Enamine	416	2.38
150		Aldrich	380	2.81
151		ABCR	394	3.07
152		ABCR	421	3.4
153		Tim Tec	486	3.73

Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
154		Farmaco, Edizione Scientifica (1957), 12 41-8	445	2.5
155		Zelinsky	431	2.38
156		Journal of the American Chemical Society (1948), 70 416	466	2.26
157		Aldrich	428	2.99
158		Aldrich	401	2.84
159		Tim Tec	444	3.31

Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
160		Maybridge	437	2.73

Example 161:

6-cyclopentyl-9-[(3-methoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

3-methoxyaniline (Aldrich, 22 mg, 0.18 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, (50 mg, 0.18 mmol), and p-toluene sulphonic acid (84 mg, 0.44 mmol) were combined in 4-methyl-2-pentanol (1 mL). The solution was heated at reflux under a blanket of nitrogen for 12 hours. The reaction mixture was cooled and passed through an SCX-2 column washed with methanol. The crude product were washed off with 7N ammonia in methanol and then concentrated *in vacuo*. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solid. (39 mg, 59%); MS m/z 368 $[M+H]^+$, Retention Time 2.46 mins.

The following examples were prepared by an analogous process to that used in the preparation of Example 161 utilising the appropriate substituted anilines available as indicated.

Example 162:

6-cyclopentyl-9-[(3-ethoxyphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 163:

6-cyclopentyl-2-methyl-9-[(3-methylsulfanylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 164:

3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzonitrile

Example 165:

9-[(3-acetylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 166:

6-cyclopentyl-9-[(3-ethylphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 167:

3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

Example 168:

6-cyclopentyl-9-[(3-ethynylphenyl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 169:

9-[(3-benzoylphenyl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 170:

3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzenesulfonamide

Example 171:

6-cyclopentyl-2-methyl-9-[(3-phenylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 172:

6-cyclopentyl-2-methyl-9-[(3-methylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 173:

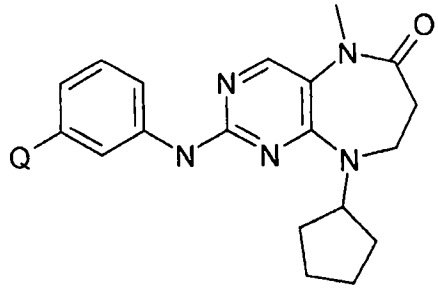
6-cyclopentyl-9-[[3-(hydroxymethyl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Example 174:

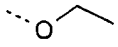
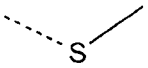
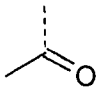
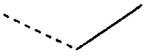
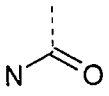
6-cyclopentyl-2-methyl-9-[(3-propan-2-ylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

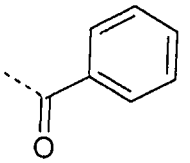
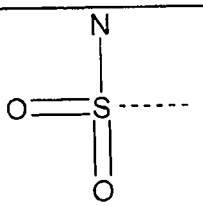
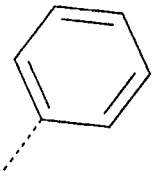
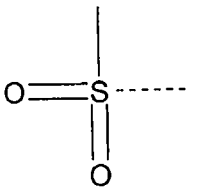
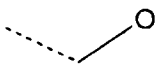
Example 175:

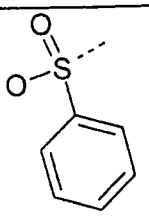
N-[2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]benzenesulfonamide



Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)

Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
162		Aldrich	382.23	2.63
163		Aldrich	384.19	2.65
164		Aldrich	363.18	2.4
165		Aldrich	380.23	2.3
166		Aldrich	366.21	2.78
167		Aldrich	381.2	1.78

Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
168		Aldrich	362.17	2.57
169		Aldrich	442.3	2.72
170		ABCR	417.21	1.87
171		ABCR	414.26	2.94
172		Enamine	416.21	2.09
173		Aldrich	368.16	1.96

Example	Q	Substituted Aniline Supplier or Source	MS m/z $[M+H]^+$	RetentionTime (Minutes)
174		ABCR	380.26	2.92
175		Journal of the Chemical Society (1938), 899-905.	492.19	1.61

Example 176:

N-[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methoxy-phenyl]acetamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), N-(3-amino-4-methoxy-phenyl)acetamide (Aldrich, 77 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) heated together in 4-methyl-2-pentanol (4ml) at 120°C for 22 hours. The reactions were cooled to ambient temperature and then passed down a 5g SCX-2 column pre-wet with methanol. The column was eluted with 2M NH3/MeOH and the solvent evaporated . The resultant material was purified by reverse phase HPLC to give the title compound as a white solid (46 mg, 30%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.58 (m, 6H), 1.88 (m, 2H), 1.99 (s, 3H), 2.56 (m, 2H), 3.17 (s, 3H), 3.59 (m, 2H), 3.83 (s, 3H), 4.85 (m, 1H), 6.93 (d, 1H), 7.05 (d, 1H), 7.56 (s, 1H), 8.02 (s, 1H), 8.37 (s, 1H), 9.68 (s, 1H); MS m/z 425 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 176 utilising the appropriate substituted anilines available from Aldrich

Example 177:

N-[3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]phenyl]acetamide

MS m/z 395 $[M+H]^+$. Retention Time 2.65 mins

Example 178:

6-cyclopentyl-9-[[5-(hydroxymethyl)-2-methyl-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

MS m/z 382 $[M+H]^+$. Retention Time 2.76 mins

Example 179:

6-cyclopentyl-9-[[3-(2-hydroxyethyl)phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 134 mg, 0.48 mmol), 2-(3-aminophenyl)ethanol (ABChem Inc, 92 mg, 0.48 mmol) and p-toluenesulphonic acid monohydrate (227 mg, 1.19 mmol) were heated at 140°C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction solution was loaded onto an SCX-3 column pre-wet with Methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydate and then washed with 2% 7N ammonia/methanol to elute the crude product. Fraction containing products were evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a white solid (92 mg, 50 %). ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.59 – 1.60 (4H, m), 1.69 – 1.71 (2H, m), 1.96 – 1.98 (2H, m), 2.53 – 2.59 (2H, t), 2.69 (2H, t), 3.18 (3H, s), 3.60 (2H, t), 3.62 (2H, t), 4.62 (1H, s), 4.87 (1H, ms), 6.77 (1H, d), 7.14 (1H, t), 7.46 – 7.49 (1H, m), 7.66 (1H, t), 8.04 (1H, s), 9.10 (1H, s); MS m/z 382 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 183 utilising the appropriate substituted aniline available from sources as indicated

Example 180:

6-cyclopentyl-2-methyl-9-[[3-(2-morpholin-4-ylethoxy)phenyl]amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

Substituted aniline available from **ABCR**

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.61 (4H, d), 1.71 (2H, s), 1.97 (2H, s), 2.48 (4H, m), 2.59 (2H, t), 2.68 (2H, t), 3.17 (3H, s), 3.59 (4H, m), 3.62 (2H, m), 4.05 (2H, t), 4.80 – 4.90 (1H, m), 6.49 - 6.52 (1H, d), 7.13 (1H, t), 7.20 (1H, d), 7.51 (1H, t), 8.05 (1H, s), 9.13 (1H, s); MS m/z 467 $[M+H]^+$.

Example 181:

3-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methoxy-N-(1-methyl-4-piperidyl)benzamide

Synthetic route for substituted aniline available from WO06/018220

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.48 – 1.62 (8H, m), 1.71 – 1.77 (2H, d), 1.80 – 2.00 (4H, m), 2.17 (3H, s), 2.56 (2H, t), 2.77 (2H, d), 3.17 (3H, s), 3.59 (2H, t), 3.71 (1H, m), 3.91 (3H, s), 4.74 – 4.79 (1H, m), 7.05 (1H, d), 7.48 - 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, d), 8.04 (1H, s), 8.57 (1H, d); MS m/z 509 $[M+H]^+$.

Example 182:

6-cyclopentyl-9-[[5-(3-dimethylaminopyrrolidin-1-yl)-2-methoxy-phenyl]amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 150 mg, 0.53 mmol), 1-(3-amino-4-methoxy-phenyl)-N,N-dimethyl-pyrrolidin-3-amine (Intermediate 50; 141 mg, 0.53 mmol) and p-toluenesulphonic acid monohydrate (255 mg, 1.34 mmol) were combined and heated in 4-methyl-2-pentanol (4 mL) at 140°C for 2 hours. The reaction mixture was loaded onto a 20g SCX-2 column was pre-wet with methanol. The column was washed with methanol twice to remove p-Toluene Sulphonic

acid and then washed twice with 2% 7N ammonia/methanol to elute the crude product.. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as a white solid (140mg, 51.6%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.48 – 1.62 (8H, m), 1.71 – 1.77 (2H, d), 1.80 – 2.00 (4H, m), 2.17 (3H, s), 2.56 (2H, t), 2.77 (2H, d), 3.17 (3H, s), 3.59 (2H, t), 3.71 (1H, m), 3.91 (3H, s), 4.74 – 4.79 (1H, m), 7.05 (1H, d), 7.48 - 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, d), 8.04 (1H, s), 8.57 (1H, d); MS m/z 508 $[M+H]^+$.

Example 183:

6-cyclopentyl-2-methyl-9-[(3-morpholin-4-ylsulfonylphenyl)amino]-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1,150 mg, 0.53 mmol), 3-(morpholinosulphonyl)aniline (Fluorochem; 130 mg, 0.53 mmol) and p-toluenesulphonic acid monohydrate (255 mg, 1.34 mmol) were combined and heated at 140°C in 4-methyl-2-pentanol (4 mL) for 2 hours. The mixture was cooled and methanol and dichloromethane added to dissolve the solid that formed. The mixture was absorbed on to an SCX –3 column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated to give a white crystalline solid. This was suspended in methanol and filtered off and dried at 140°C under vacuum in a desiccator to give the title compound as a white crystalline solid (200mg, 77%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.57 – 1.70 (6H, m), 1.94 - 2.00 (2H, m), 2.57 - 2.60 (2H, m), 2.88 (4H, m), 3.18 (3H, s), 3.61 - 3.66 (6H, m), 4.91 (1H, m), 7.22 - 7.25 (1H, m), 7.53 (1H, t), 7.99 - 8.02 (1H, m), 8.09 (1H, s), 8.23 (1H, t), 9.57 (1H, s)

MS m/z 487 $[M+H]^+$.

Example 184:

3-chloro-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 52, 100 mg, 0.35 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 124 mg, 0.44 mmol) and p-toluenesulphonic acid monohydrate

(168 mg, 0.88 mmol) were heated at 140°C in 4-methyl-2-pentanol (2.5 mL) for 3 hours. The mixture was allowed to cool causing a solid to form. Methanol and DCM were added to give a solution that was absorbed onto and SCX-3 column and washed with methanol. Elution of the product with ammonia / methanol, concentration and column chromatography (2% 7N ammonia in methanol/DCM) gave material that was further purified by reverse phase HPLC to give the title compound as a white foam (87 mg, 47 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.54 - 1.69 (6H, m), 1.86 - 1.89 (2H, m), 2.44 (6H, m), 2.59 (2H, m), 3.18 (3H, s), 3.37 - 3.42 (2H, m), 3.57 - 3.63 (6H, m), 4.69 - 4.77 (1H, m), 7.78 - 7.81 (1H, m), 7.97 (1H, d), 8.09 (1H, s), 8.20 (1H, s), 8.27 (1H, d), 8.40 (1H, t); MS m/z 528 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 184 utilising 4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide Intermediate 55.

Example 185:

3-chloro-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.55 - 1.68 (8H, m), 1.77 (2H, s), 1.86 - 1.98 (4H, m), 2.18 (3H, s), 2.59 (2H, m), 2.78 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.69 - 3.77 (1H, m), 4.73 (1H, m), 7.79 - 7.82 (1H, m), 8.00 (1H, d), 8.09 (1H, s), 8.19 (2H, d), 8.26 (1H, d); MS m/z 512 $[M+H]^+$.

Example 186:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-hydroxy-N-(1-methyl-4-piperidyl)benzamide

To pyridine (1 mL) was cautiously added conc HCl (1 mL) . The mixture was heated at 200^{0}C until no more water was evolved. The mixture was cooled and 4-[(2-Cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-(1-

methyl-4-piperidyl)benzamide (Example 1, 100 mg, 0.2 mmol) was added and the solution reheated and stirred at 200°C for 30 minutes. The solution was cooled and water added followed by pH adjustment to neutral neutral pH by addition of NaHCO3.

The aqueous solution was adsorbed on an SCX-3 column pre-wet with MeOH. The column was washed with MeOH and water and MeOH. Product was removed from the column by addition of NH3/MeOH (2N). Combined fractions were evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a gum which on trituration with DCM / hexane gave an amorphous solid (17 mg, 17 %)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.50-1.85 (m, 10H), 1.85-2.10 (m, 4H), 2.20 (s, 3H), 2.55-2.68 (m, 2H), 2.70-2.85 (m, 2H), 3.20 (s, 3H), 3.55-3.70 (m, 2H), 3.60-3.80 (m, 1H), 4.75-4.90 (m, 1H), 7.28-7.35 (d, 1H), 7.38 (s, 1H), 7.83 (s, 1H), 7.95-8.05 (d, 1H), 8.08 (s, 1H), 8.13-8.23 (d, 1H), 10.2-10.5 (bs, 1H); MS m/z 494 $[M+H]^+$.

Example 187:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2,6-difluoro-N-(1-methyl-4-piperidyl)benzamide

10-amino-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 57, 75 mg, 0.29 mmol), 4-bromo-2,6-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 58, 105 mg, 0.31 mmol) and caesium carbonate (187 mg, 0.57 mmol) were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Bis(dibenzylideneacetone)palladium (16 mg, 0.028 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (15 mg, 0.026 mmol) were added and the mixture heated to 100 °C overnight. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with DCM and the filtrate added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH and evaporated to a brown gum. The resultant material was purified by reverse phase HPLC to yield the title compound as a cream solid (107 mg, 73%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.59 (m, 4H), 1.72 (m, 4H), 2.04 (m, 4H), 2.16 (m, 2H), 2.29 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.29 (s, 3H), 3.70 (m, 2H), 4.01 (m, 1H), 4.86 (m, 1H), 5.83 (d, 1H), 7.10 (s, 1H), 7.28 (s, 1H), 7.31 (s, 1H), 7.93 (s, 1H); MS m/z 514 $[M+H]^+$.

Example 188:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59, 87 mg, 0.32 mmol) and caesium carbonate (211 mg, 0.65 mmol) were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Bis(dibenzylideneacetone)palladium (11 mg, 0.019 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (17 mg, 0.029 mmol) were added and the mixture heated to 100 °C overnight. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with DCM and the filtrate added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), washed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH and evaporated to a brown gum. The resultant material was purified by reverse phase HPLC to yield the title compound as a white solid (34 mg, 19%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.60 (m, 4H), 1.75 (m, 4H), 2.05 (m, 4H), 2.17 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.30 (s, 3H), 3.71 (m, 2H), 4.01 (m, 1H), 4.88 (m, 1H), 6.59 (m, 1H), 7.29 (m, 1H), 7.82 (m, 1H), 7.96 (s, 1H), 8.46 (m, 1H); MS m/z 515 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 188 utilising 4-amino-2-fluoro-N-(1-methyl-4-piperidyl)benzamide Intermediate 61.

Example 189:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-2-fluoro-N -(1-methyl-4-piperidyl)benzamide

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.59 (m, 4H), 1.73 (m, 4H), 2.05 (m, 4H), 2.18 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.29 (s, 3H), 3.70 (m, 2H), 4.03 (m, 1H), 4.88 (m, 1H), 6.56 (m, 1H), 7.12 (m, 2H), 7.87 (m, 1H), 7.94 (s, 1H), 8.01 (m, 1H); MS m/z 496 $[M+H]^+$.

Example 190:

methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-hydroxy-benzoate

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 180 mg, 0.64 mmol) and methyl 3-hydroxy-4-aminobenzoate (ABCR, 123 mg, 0.73 mmol) was taken up in ethanol (4 mL) and water (12 mL). To this was added concentrated hydrochloric acid (36%; 130 µl). The reaction was heated to 80°C and stirred overnight.. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~30 mL with water and the solution basified to pH 9 by addition of a few drops of aq. Ammonia. The resultant mixture was extracted with DCM (2 x 50 mL). A solid persisted at the phase boundary. This solid was collected by suction filtration and dried to give the title compound as a purple/grey solid (64 mg).

Combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to a pink/brown solid which was taken up in small amount (~5 mL) of DCM and sonicated for 5 minutes. The solid was then collected by suction filtration and dried to give the title compound as a dusky pink solid (79 mg)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56 - 1.75 (m, 6H), 1.94 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.80 (s, 3H), 4.82 (m, 1H), 7.44 (m, 2H), 7.84 (s, 1H), 8.09 (s, 1H), 8.35 (d, 1H), 10.53 (s, 1H); MS m/z 412 $[M+H]^+$.

Example 191:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

A solution of 4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 108mg, 0.43mmol) in EtOH (2 mL) was added to 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol). Water (6 mL) was added followed by concentrated hydrochloric acid (36%, 70 ul) and the solution heated at 80^{0}C for 28 hours and then left to cool over the weekend. The reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with methanol. Product was eluted with 2M NH3/MeOH. Solvent evaporation gave crude product as a gum which was purified by reverse phase HPLC to yield the title compound as a white solid (71 mg, 40 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.68 (m, 6H), 1.97 (m, 2H), 2.44 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (m, 2H), 3.58 (m, 4H), 3.63 (m, 2H), 4.84 (m, 1H), 7.77 (m, 4H), 8.08 (s, 1H), 8.16 (t, 1H), 9.45 (s, 1H); MS m/z 494 $[M+H]^+$.

Example 192:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-diethylaminoethyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1, 100 mg, 0.36 mmol), 4-amino-N-(2-diethylaminoethyl)benzamide (Timtec, 101 mg, 0.43 mmol) and p-toluenesulphonic acid (137 mg, 0.72 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 100^{0}C for 24 hours. The crude reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with MeOH. The column was washed with MeOH and the product eluted with 2M NH3/MeOH. Solvent evaporation gave material that was purified by reverse phase HPLC to yield the title compound as a white solid (123 mg, 71 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.98 (t, 6H), 1.66 (m, 6H), 1.96 (m, 2H), 2.52 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.30 (s, 2H), 3.63 (m, 2H), 4.84 (m, 1H), 7.73 (d, 2H), 7.80 (d, 2H), 8.08 (s, 1H), 8.12 (t, 1H), 9.45 (s, 1H); MS m/z 480 $[M+H]^+$.

Example 193:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methyl-N-(1-methyl-4-piperidyl)benzamide

A solution of 4-amino-3-methyl-N-(1-methyl-4-piperidyl)benzamide (Intermediate 63, 53 mg, 0.214 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]u ndeca-8,10,12-trien-5-one (Intermediate 1, 60 mg, 0.214 mmol) and p-toluenesulphonic acid monohydrate (102 mg, 0.535 mmol) in 4-methyl-2-pentanol (4 mL) was heated at 100 °C. overnight. The reaction was cooled to room temperature (solid formed) dissolved in MeOH and added to a 2g SCX-2 column pre-wet with MeOH (2 column volumes). The column was washed with MeOH (2 column volumes) and then product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant material was taken up in DCM and purified on silica eluting with a gradient of 0 – 10% MeOH / DCM then 10% MeOH / DCM. Fractions containing product were combined and evaporated to a clear gum to which ether was added and re-evaporated to a white solid which was further purified by b reverse phase HPLC.

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.54 - 1.70 (m, 6H), 1.75 (m, 2H), 2.02 (m, 4H), 2.17 (m, 2H), 2.31 (s, 3H), 2.37 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.29 (s, 3H), 3.68 (m, 2H), 3.99 (m, 1H), 4.85 (m, 1H), 5.86 (d, 1H), 6.79 (s, 1H), 7.59 (m, 2H), 7.92 (s, 1H), 8.32 (d, 1H); MS m/z 492 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 193 utilising 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide Intermediate 65

Example 194:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-fluoro-N-(1-methyl-4-piperidyl)benzamide

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.53 - 1.80 (m, 8H), 2.03 (m, 4H), 2.16 (m, 2H), 2.30 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.69 (m, 2H), 3.97 (m, 1H), 4.87 (m, 1H), 5.85 (d, 1H), 7.22 (m, 1H), 7.52 (m, 2H), 7.95 (s, 1H), 8.57 (m, 1H); MS m/z 496 $[M+H]^+$.

Example 195:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-methoxyethoxy)-N-(1-methyl-4-piperidyl)benzamide

To a suspension of 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-(2-methoxyethoxy)benzoic acid (Intermediate 66, 55 mg, 0.12 mmol) in DMF (2 mL) was added DIPEA (42 ul, 0.16 mmol) and the mixture stirred for 5 minutes. HATU (60 mg, 0.16 mmol) was added to the resultant straw coloured solution. The solution was stirred for a further 10 minutes before addition of 4-amino-1-methylpiperidine (18 mg, 0.16 mmol) in DMF (0.5 mL). The reactions was stirred at ambient temperature for 6 hours and the crude reaction mixture waspurified by reverse phase HPLC to afford the title compound as a white solid (50 mg, 76 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.55 - 1.83 (m, 10H), 1.89 - 2.10 (m, 4H), 2.23 (s, 3H), 2.59 (m, 2H), 2.84 (m, 2H), 3.18 (s, 3H), 3.38 (s, 3H), 3.64 (m, 2H), 3.73 - 3.81 (m, 3H), 4.26 (m, 2H), 4.79 (m, 1H), 7.51 (d, 1H), 7.54 (m, 1H), 7.81 (s, 1H), 8.06 (d, 1H), 8.09 (s, 1H), 8.42 (d, 1H); MS m/z 552 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 195 utilising a 2.0M methylamine solution in THF

Example 196:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-methoxyethoxy)-N-methyl-benzamide

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.55 - 1.81 (m, 6H), 2.03 (m, 2H), 2.67 (m, 2H), 3.01 (d, 3H), 3.29 (s, 3H), 3.47 (s, 3H), 3.69 (m, 2H), 3.80 (m, 2H), 4.28 (m, 2H), 4.88 (m, 1H), 6.07 (m, 1H), 7.28 (m, 1H), 7.46 (m, 1H), 7.80 (s, 1H), 7.95 (s, 1H), 8.52 (d, 1H) ; MS m/z 469

Example 197:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)-3-propan-2-yloxy-benzamide

To a solution of 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoic acid (Intermediate 69; 49 mg, 0.11 mmol) in DMF (2 mL) was added DIPEA (42 uL, 0.24 mmol) and HATU (61 mg, 0.16 mmol). The solutions were stirred for 5 minutes before addition of 4-amino-1-methylpiperidine (ABCR, 16 mg, 0.14 mmol). The reaction mixture was stirred, at ambient temperature, overnight.

The crude reaction mixture was purified by reverse phase HPLC to afford the title compound as a white solid (29 mg, 49%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 (d, 6H), 1.54 - 1.80 (m, 10H), 1.94 (m, 4H), 2.17 (s, 3H), 2.59 (m, 2H), 2.78 (m, 2H), 3.18 (s, 3H), 3.64 (m, 2H), 3.74 (m, 1H), 4.78 (m, 2H), 7.48 (m, 1H), 7.52 (m, 1H), 7.67 (s, 1H), 8.04 (d, 1H), 8.08 (s, 1H), 8.41 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 198:

N-cyclohexyl-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-dimethylaminoethoxy)benzamide

To a stirred solution of Methyl 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-(2-dimethylaminoethoxy)benzoate (Intermediate 72; 41 mg, 0.08 mmol) in Ethanol (2 mL) was added a solution of lithium hydroxide (8 mg, 0.33 mmol) in water (1 mL). The reaction was heated at 100°C by microwave irradiation with stirring, for 30 minutes, cooled, evaporated and the residue diluted with water (5 mL). The resultant solution was treated with a few drops of 2M HCl (aq.) so as to adjust pH to 2-3. The aqueous solution was evaporated to dryness to give the carboxylic acid as a pale yellow gum, which was dissolved in DMF (1 mL) and treated with DIPEA (25 µL, 0.14 mmol) and HATU (40 mg. 0.11 mmol). Cyclohexylamine (11 µL, 0.10 mmol) was added and reaction mixture left to stir, at ambient temperature, overnight.

The crude reaction mixture was purified by reverse phase HPLC to afford the title compound as an off white solid (14 mg, 32 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.10 - 1.37 (m, 6H), 1.55 - 1.99 (m, 12H), 2.28 (s, 6H), 2.59 (m, 2H), 2.65 (t, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.77 (m, 1H), 4.21 (t, 2H), 4.80 (m, 1H), 7.50 (m, 1H), 7.55 (m, 1H), 7.98 (d, 1H), 8.09 (s, 1H), 8.39 (m, 1H), 8.41 (s, 1H); MS m/z 551 $[M+H]^+$.

Example 199:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide

To a solution of 4-amino-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide (Intermediate 74, 104 mg, 0.33 mmol) 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]u ndeca-8,10,12-trien-5-one (Intermediate 1, 91 mg, 0.32 mmol) in anhydrous 1,4-dioxane (4 mL) was added caesium carbonate (222 mg ,0.68 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes, prior to addition of Tris(dibenzylideneacetone) palladium (II) (21 mg, 0.07 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (21 mg, 0.11 mmol). The reaction was heated by microwave irradiation at 150°C for 60 minutes.Further portions of 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (19 mg) & Tris(dibenzylideneacetone) palladium (II (25 mg) added and mixture heated on hot plate at 100°C overnight. The reaction mixture was cooled and diluted to 10 mL with DCM. Insoluble material was filtered and the filter cake washed with DCM. Evaporation to dryness of filtrate afforded a brown gum, which was taken up in methanol and poured onto an SCX-2 cartridge (5g, Silicycle). The Cartridge was washed with methanol (~75 mL) before eluting products with 2M ammonia in methanol (~50 mL). The ammoniacal fraction was evaporated to afford a brown gum which was purified by reverse phase HPLC to yield the title compound as a white solid (25 mg, 4 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.51 - 1.97 (m, 14H), 2.17 (s, 3H), 2.59 (m, 2H), 2.78 (m, 2H), 3.18 (s, 3H), 3.62 (m, 2H), 3.74 (m, 1H), 4.74 (m, 1H), 7.86 (m, 2H), 8.08 (s, 1H), 8.25 (d, 1H), 8.30 (d, 1H), 8.57 (s, 1H) MS m/z 562 $[M+H]^+$.

Example 200:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-ethoxy-N-(1-methyl-4-piperidyl)benzamide

A solution of HATU (63 mg, 0.165 mmol) in DMA (1 mL) was added to a mixture 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-ethoxy-benzoic acid (Intermediate 75, 64 mg, 0.15 mmol), DIPEA (79 uL, 0.45 mmol) and the amine in DMA (1 mL). The resulting mixture was stirred at room temperature overnight. The reaction mixture was added to an SCX-3 column pre-wet with Methanol, washed with methanol and product eluted with Ammonia in Methanol. Product containing fractions were evaporated and the resultant material purified by column chromatography, eluting with 0-10% 7*N* methanolic ammonia in DCM, to give the title compound as clear glass (64 mg, 82 %) ^{1}H NMR (399.9 MHz, $CDCl_3$) δ1.51 (3H, t), 1.61 - 1.82 (8H, m), 2.03 - 2.09 (2H, m), 2.21 - 2.29 (4H, m), 2.38 (3H, s), 2.67 - 2.70 (2H, m), 2.90 - 2.93 (2H, m), 3.31 (3H, s), 3.70 - 3.73 (2H, m), 4.00 - 4.08 (1H, m), 4.22 (2H, q), 4.92 (1H, quin), 6.07 (1H, d), 7.27 (1H, dd), 7.42 (1H, d), 7.72 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 522 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 200 utilising the appropriate amines available from Aldrich

Example 201:

N-(1-azabicyclo[2.2.2]oct-8-yl)-4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-ethoxy-benzamide

^{1}H NMR (399.9 MHz, $CDCl_3$) δ1.51 (3H, t), 1.55 - 1.89 (10H, m), 2.06 - 2.03 (6H, m), 2.67 - 2.70 (2H, m), 2.84 - 2.97 (4H, m), 3.07 - 3.13 (1H, m), 3.31 (3H, s), 3.44 - 3.50 (1H, m), 3.70 - 3.73 (2H, m), 4.20 - 4.26 (1H, m), 4.22 (2H, q), 4.91 (1H, quin), 6.55 (1H, d), 7.34 (1H, dd), 7.47 (1H, d), 7.72 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 533 $[M+H]^+$.

Example 202:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-dimethylaminoethyl)-3-ethoxy-benzamide

^{1}H NMR (399.9 MHz, $CDCl_3$) δ1.52 (3H, t), 1.62 - 1.82 (6H, m), 2.04 - 2.09 (2H, m), 2.39 (6H, s), 2.64 - 2.71 (4H, m), 3.31 (3H, s), 3.58 - 3.62 (2H, m), 3.70 - 3.73 (2H, m), 4.24 (2H, q), 4.92 (1H, quin), 7.01 (1H, s), 7.38 (1H, dd), 7.49 (1H, d), 7.71 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 494 $[M+H]^+$.

Example 203:

3-chloro-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 76, 100mg, 0.39mmol) and 4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 79; 127 mg, 0.47 mmol) were suspended in 4-methyl-2-pentanol (3 mL) and p-toluenesulphonic acid monohydrate (74 mg, 0.97 mmol) added. The mixture was heated at 140°C for 4 hours The mixture was cooled causing a white solid to formed. The whole mixture was diluted with MeOH to give a solution which was absorbed on to an SCX-3 column, washed with methanol and eluted with ammonia/methanol. Concentration and column chromatography (1-2-3-5% NH_3 in MeOH/DCM) of the product containing fractions gave the title compound as a white solid (58mg, 31%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.23 (6H, d), 1.54 - 1.64 (2H, m), 1.75 - 1.78 (2H, m), 1.91 - 1.97 (2H, m), 2.18 (3H, s), 2.60 (2H, m), 2.78 (2H, d), 3.18 (3H, s), 3.61 (2H, m), 3.69 - 3.75 (1H, m), 4.72 - 4.78 (1H, m), 7.81 - 7.84 (1H, m), 7.99 (1H, d), 8.09 (2H, d), 8.21 (1H, d), 8.32 (1H, d); MS m/z 486 $[M+H]^+$.

Example 204:

3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzoic acid

10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 76; 739 mg, 2.9 mmol) , 4-amino-3-methoxy-benzoic acid (Aldrich, 534 mg, 3.2 mmol), 4:1 Water / Etanol (6 mL) and concentrated aqueous hydrochloric acid (0.485 mL, 5.8 mmol)were combined and heated at reflux overnight under nitrogen. The reaction mixture was cooled to room temperature and filtered. The filter cake was washed with water followed

by diethylether to give the title compound as an off white solid as the Hydrochloride salt (673 mg, 55 %)

^{1}H NMR (399.9 MHz, DMSO-d_6) : δ_H : 1.25 (d, 6H), 2.73(m, 2H), 3.19 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.89 (m, 1H), 7.59 (s, 1H), 7.67 (d, 1H), 8.20 (m, 2H), 9.55 (s, 1H); MS m/z 386 $[M+H]^+$.

Example 205:

3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-[2-(1-piperidyl)ethyl]benzamide

To a solution of the hydrochloride salt of 3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzoic acid (Example 204; 127 mg, 0.33 mmol) and 1-(2-aminoethyl)piperidine (Aldrich, 54uL, 0.38 mmol) and DIPEA (157 uL , 0.9 mmol) in anhydrous DMA (10 mL) at room temperature under nitrogen was added HATU (126 mg, 0.33 mmol) as a solid and the resulting solution stirred at room temperature overnight. The reaction mixture was loaded onto a SCX-3 column pre-wet with Methanol and the column washed with Methanol. The column was eluted with Ammonia in Methanol and produict containing fractions evaporated. The resultant material was dissolved in dichloromethane and chromatographed with 2-5-10-20% methanol/dichloromethane followed by 7N ammonia/methanol. Evaporation of product containing fractions gave a yellow foam foam which was purified by reverse phase HPLC to yield the title compound as an off white gum (75 mg, 46 %)

^{1}H NMR (399.9 MHz, DMSO-d_6) : δ_H : 1.25 (d, 6H), 1.39 (m, 2H), 1.50 (m, 6H), 2.40 (m, 6H), 2.60 (m, 2H), 3.19 (s, 3H), 3.37 (m, 2H), 3.61 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.49 (m, 2H), 7.69 (s, 1H), 8.07 (s, 1H), 8.22 (tr, 1H), 8.41 (m, 1H); MS m/z 496 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 205 utilising the appropriate amines available from Aldrich or Matrix

Example 206:

N-(1-azabicyclo[2.2.2]oct-8-yl)-3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

Example 207:

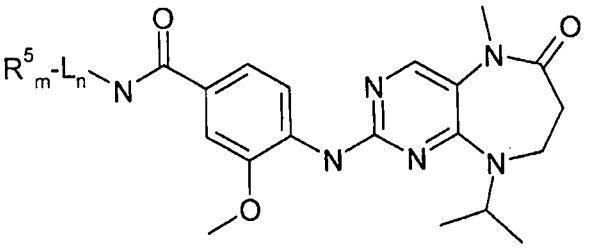
N-(2-dimethylaminoethyl)-3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

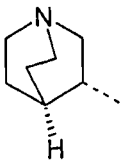
Example 208:

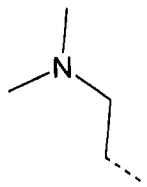
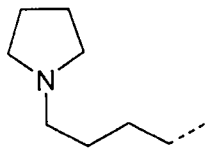
N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

Example 209:

3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(4-pyrrolidin-1-ylbutyl)benzamide



Example	$R^5{}_m$-L_n-	^{1}H NMR (400 MHz, DMSO-d_6)	MS m/z $[M+H]^+$
206		δ_H: 1.23 (d, 6H), 1.30 (m, 1H), 1.60 (m, 2H), 1.85 (m, 2H), 2.60 (m, 2H), 2.70 (m, 4H), 2.90 (m, 1H), 3.11 (m, 1H), 3.20 (s, 3H), 3.62 (m, 2H), 3.95 (m, 4H), 4.81 (m, 1H), 7.49 (s, 1H), 7.56 (d, 1H), 7.30 (s, 1H), 8.06 (m, 2H), 8.42 (d, 1H);	494
207		δ_H: 1.23 (d, 6H), 2.19 (s, 6H), 2.40 (tr, 2H), 2.60 (m, 2H), 3.18 (s, 3H), 3.36 (m , 2H), 3.61 (d, 2H), 3.96 (s, 3H), 4.81 (m, 1H), 7.50 (m, 2H), 7.69 (s, 1H), 8.07 (s, 1H), 8.24 (tr, 1H),	456

Example	R^5_m-L_n-	^{1}H NMR (400 MHz, DMSO-d_6)	MS m/z $[M+H]^+$
		8.41 (d, 1H);	
208		δ_H: 0.89 (s, 6H), 1.25 (d, 6H), 2.20 (s, 2H), 2.29 (s, 6H), 2.61 (m, 2H), 3.20 (m, 5H), 3.61 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.46 (m, 2H), 7.70 (s, 1H), 8.08 (s, 1H), 8.41 (m, 2H)	498
209		δ_H: 1.26 (d, 6H), 1.52 (m, 4H), 1.68 (m, 4H), 2.40 (m, 6H), 2.60 (m, 2H), 3.18 (s, 3H), 3.30 (m, 2H), 3.60 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.50 (m, 2H), 7.69 (s, 1H), 8.09 (s, 1H), 8.31 (tr, 1H), 8.41 (d, 1H)	510

Example 210:

4-[(6-ethyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-ethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one Intermediate 81; 180 mg, 0.75 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220, 198 mg, 0.75 mmol) and p-toluenesulphonic acid (357 mg, 1.88 mmol) were heated in 4-methyl-2-pentanol (3 mL) to 140 °C for 18 hours. The reaction mixture was allowed to cool to room temperature and loaded onto a 10 g SCX-2 cartridge, washing with methanol (10 mL), water (10 mL) and methanol (10 mL) before the product was eluted off with 7 N methanolic ammonia which on evaporation of product containing fractions provided a brown oil which was purified by flash silica chromatography (Companion, 40 g, 0-10% methanolic ammonia/DCM) to give a pale yellow glass which was

further purified by reverse phase HPLC to yield the title compound as a white solid (192 mg, 49 %).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.24 (t, 3H), 1.60 (qd, 2H), 1.73 - 1.81 (m, 2H), 1.95 (td, 2H), 2.18 (s, 3H), 2.62 - 2.64 (m, 2H), 2.79 (br d, 2H), 3.18 (s, 3H), 3.62 (q, 2H), 3.70 - 3.79 (m, 3H), 3.96 (s, 3H), 7.49 - 7.53 (m, 2H), 7.70 (s, 1H), 8.05 - 8.08 (m, 2H), 8.41 (d, 1H); MS m/z 468 $[M+H]^+$.

Example 211:

3-methoxy-4-[[2-methyl-6-(2-methylpropyl)-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-6-methyl-2-(2-methylpropyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 84; 65 mg, 0.24 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220, 57 mg, 0.24 mmol) and p-toluene sulphonic acid (110 mg, 0.58 mmol) were taken up in 4-methyl-2-pentanol (1 mL) and heated to 160°C by microwave irradiation for 1 hour. The reaction mixture was diluted with methanol (5 mL) and water (2 mL) and resultant solution poured onto an SCX-3 cartridge (2 g). The cartridge was washed with methanol (~30 mL) before eluting products with 2M ammonia methanol (~20 mL). The Ammoniacal fraction was evaporated to give an amber gum which was purified by reverse phase HPLC to yield the title compound as a colourless glass (scratches down to a white solid) (80 mg, 75 %).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 (d, 6H), 1.60 (m, 2H), 1.77 (m, 2H), 1.94 (m, 2H), 2.11 (m, 1H), 2.17 (s, 3H), 2.64 (m, 2H), 2.78 (m, 2H), 3.19 (s, 3H), 3.50 (d, 2H), 3.68 – 3.79 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.70 (s, 1H), 8.07 (d, 1H), 8.08 (s, 1H), 8.34 (m, 1H); MS m/z 496 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 211 utilising the appropriate Chloropyrimidines indicated

Example 212A:

4-[(6-butan-2-yl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

Chloropyrimidine used - 2-butan-2-yl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one Intermediate 87

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 (t, 3H), 1.23 (d, 3H), 1.49 - 1.70 (m, 4H), 1.77 (m, 2H), 1.95 (t, 2H), 2.18 (s, 3H), 2.55 - 2.68 (m, 2H), 2.79 (m, 2H), 3.18 (s, 3H), 3.50 (m, 1H), 3.62 (m, 1H), 3.74 (m, 1H), 3.95 (s, 3H), 4.63 (m, 1H), 7.48 - 7.52 (m, 2H), 7.68 (s, 1H), 8.05 - 8.08 (m, 2H), 8.38 (m, 1H); MS m/z 496 $[M+H]^+$.

Example 212B:

4-[(6-cyclobutyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

Chloropyrimidine used - 10-chloro-2-cyclobutyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one Intermediate 90

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.55 - 1.80 (m, 6H), 1.95 (m, 2H), 2.10 (m, 2H), 2.18 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 2.79 (m, 2H), 3.18 (s, 3H), 3.66 (m, 2H), 3.74 (m, 1H), 3.95 (s, 3H), 4.52 (m, 1H), 7.49 (m, 1H), 7.53 (m, 1H), 7.74 (s, 1H), 8.06 (d, 1H), 8.14 (s, 1H), 8.45 (d, 1H); MS m/z 494 $[M+H]^+$.

Example 213:

4-[[6-(cyclopropylmethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

Chloropyrimidine used 10-chloro-2-(cyclopropylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one Intermediate 93

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.30 (m, 2H), 0.52 (m, 2H), 1.17 (m, 1H), 1.60 (m, 2H), 1.77 (m, 2H), 1.95 (m, 2H), 2.17 (s, 3H), 2.65 (m, 2H), 2.79 (m, 2H), 3.19 (s, 3H), 3.51 (d, 2H), 3.69 - 3.81 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.71 (s, 1H), 8.06 (d, 1H), 8.09 (s, 1H), 8.39 (m, 1H); MS m/z 494 $[M+H]^+$.

Example 214:

3-methoxy-4-[(2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-[(2,4-dimethoxyphenyl)methyl]-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 96; 80 mg, 0.23 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 52 mg, 0.20 mmol) and p-toluene sulphonic acid (110 mg, 0.58 mmol) were taken up in 4-methyl-2-pentanol (1.5 mL) and heated at 160°C by microwave irradiation for 1 hour. The reaction mixture was dissolved in methanol (5 mL) and water (~5 mL) and poured directly onto an SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~ 30 mL), before elution of products with 2M ammonia in methanol (~30 mL). Evaporation of ammoniacal fraction gave a brown gum which was purified by reverse phase HPLC to yield the title compound as a white solid (9 mg, 10 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60 (m, 2H), 1.77 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.61 (m, 2H), 2.78 (m, 2H), 3.21 (s, 3H), 3.54 (m, 2H), 3.73 (m, 1H), 3.95 (s, 3H), 7.47 (m, 2H), 7.58 (m, 2H), 8.05 (d, 1H), 8.10 (s, 1H), 8.52 (m, 1H); MS m/z 440 $[M+H]^+$.

Example 215:

4-[(6-benzyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

2-benzyl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 99; 42 mg, 0.14 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 33 mg, 0.13 mmol) and p-toluene sulphonic acid monohydrate (54 mg, 0.28 mmol) were taken up in 4-methyl-2-pentanol (1.5 mL) and heated at 160°C by microwave irradiation for 1 hour. The reaction mixture was dissolved in methanol (5 mL) and water (~5 mL) and poured directly onto an SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~ 30 mL), before elution of products with 2M ammonia in methanol (~30 mL). Evaporation of the ammoniacal fraction gave an amber film which was purified by reverse phase HPLC to yield the title compound as an off-white solid (33 mg, 48 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.57 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.68 (m, 2H), 2.77 (m, 2H), 3.22 (s, 3H), 3.59 - 3.77 (m, 3H), 3.91 (s, 3H), 4.87 (s, 2H), 7.24 - 7.38 (m, 6H), 7.43 (m, 1H), 7.71 (s, 1H), 8.01 (d, 1H), 8.14 (d, 1H), 8.15 (s, 1H); MS m/z 531 $[M+H]^+$.

Example 216:

3-methoxy-4-[[2-methyl-6-[(2-methyl1,3-thiazol-4-yl)methyl]-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-6-methyl-2-[(2-methyl-1,3-thiazol-4-yl)methyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 101; 58 mg, 0.18 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 49 mg, 0.19 mmol) and p-toluene sulphonic acid (70 mg, 0.37 mmol) were taken up in 4-methyl-2-pentanol (2 mL) and heated to 160°C in microwave by microwave irradiation for 1 hour. The reaction mixture was dissolved in methanol (5 mL) and water (~5 mL) and poured directly onto an SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~ 30 mL), before elution of products with 2M ammonia in methanol (~30 mL). Evaporation of the ammoniacal fraction gave an amber film which was purified by reverse phase HPLC to yield the title compound as an off white solid (43 mg, 26 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 (m, 2H), 1.76 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.67 (s, 3H), 2.72 (m, 2H), 2.77 (m, 2H), 3.21 (s, 3H), 3.68 - 3.77 (m, 3H), 3.92 (s, 3H), 4.85 (s, 2H), 7.23 (m, 1H), 7.29 (m, 1H), 7.44 (d, 1H), 7.71 (s, 1H), 8.04 (d, 1H), 8.08 (d, 1H), 8.13 (s, 1H); MS m/z 551 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 216 utilising the appropriate Chloropyrimidines indicated

Example 217:

4-[[6-(cyclobutylmethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

Chloropyrimidine used - 10-chloro-2-(cyclobutylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 102)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60 (m, 2H), 1.73 - 2.07 (m, 10H), 2.17 (s, 3H), 2.61 (m, 2H), 2.69 - 2.81 (m, 3H), 3.17 (s, 3H), 3.66 - 3.80 (m, 5H), 3.95 (s, 3H), 7.47 - 7.51 (m, 2H), 7.71 (s, 1H), 8.07 (m, 2H), 8.35 (d, 1H); MS m/z 509 $[M+H]^+$.

Example 218:

4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 188mg, 0.75mmol) and 10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 76; 160mg, 0.63mmol) were heated together in 1:3 EtOH:water (8 ml) in the prescence of concentrated hydrochloric acid (126ul) for 24 hours. .The reaction was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and the solvent evaporated to give product as a brown gum. This was purified by reverse phase HPLC to give the title compound a white solid. (125 mg, 42 %)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.25 (d, 6H), 2.44 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (m, 2H), 3.59 (m, 6H), 4.85 (m, 1H), 7.78 (m, 4H), 8.06 (s, 1H), 8.15 (t, 1H), 9.42 (s, 1H); MS m/z 468 $[M+H]^+$.

The following examples were prepared by an analogous process to that used in the preparation of Example 218 utilising the appropriate substituted anilines and Chloropyrimidines as indicated.

Example 219:

3-methoxy-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

Prepared from Intermediate 76 and Intermediate 47.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.29 (d, 6H), 2.49 (m, 6H), 2.52 (s, 3H), 2.65 (m, 2H), 3.44 (m, 2H), 3.65 (m, 6H), 4.00 (s, 3H), 4.87 (m, 1H), 7.54 (m, 2H), 7.74 (s, 1H), 8.12 (s, 1H), 8.32 (t,1H), 8.47 (d, 1H).

Example 220:

3-methoxy-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

Prepared from Intermediate 103 and Intermediate 47.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 2.44 (m, 5H), 2.83 (m, 2H), 3.28 (s, 3H), 3.36 (m, 2H), 3.59 (m, 4H), 3.88 (s, 3H), 4.06 (m, 2H), 6.93 (d, 1H), 7.35 (m, 4H), 7.47 (m, 3H), 7.64 (s, 1H), 8.16 (t, 1H), 8.29 (s, 1H).

Example 221:

3-methoxy-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

Prepared from Intermediate 103 and an intermediate decribed in WO06/018220.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.51 (s, 3H), 2.80 (m, 4H), 3.70 (m, 1H), 3.89 (s, 3H), 4.06 (m, 2H), 6.96 (d, 1H), 7.34 (m, 4H), 7.48 (m, 3H), 7.64 (s, 1H), 7.97 (d, 1H), 8.29 (s, 1H).

Example 222:

N-(3-dimethylamino-2,2-dimethyl-propyl)-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

Prepared from Intermediate 76 and Intermediate 22.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.88 (s, 6H), 1.25 (d, 6H), 2.18 (s, 2H), 2.27 (s, 6H), 2.59 (m, 2H), 3.18 (s, 2H), 3.29 (s, 3H), 3.61 (m, 2H), 4.85 (m, 1H), 7.73 (d, 2H), 7.81 (d, 2H), 8.06 (s, 1H), 8.27 (t, 1H), 9.42 (s, 1H);

Example 223:

N-(3-dimethylamino-2,2-dimethyl-propyl)-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

Prepared from Intermediate 103 and Intermediate 22.

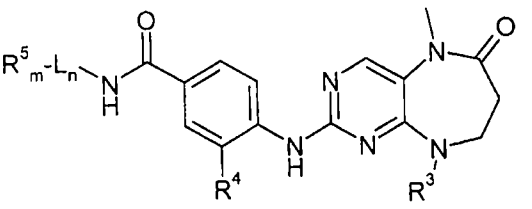
^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.87 (s, 6H), 2.18 (s, 2H), 2.28 (s, 6H), 2.81 (m, 2H), 3.14 (d, 2H), 3.28 (s, 3H), 4.06 (m, 2H), 7.33 (m, 7H), 7.47 (m, 2H), 8.21 (t, 1H), 8.31 (s, 1H), 9.52 (s, 1H).

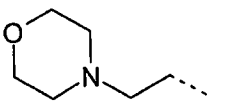
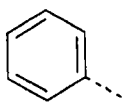
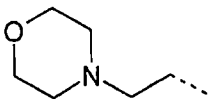
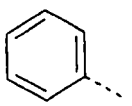
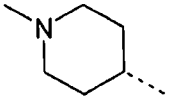
Example 224:

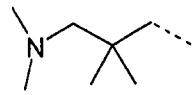
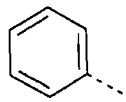
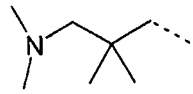
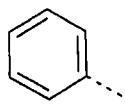
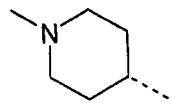
4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

Prepared form Intermediate 103 and Intermediate 4.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56 (m, 2H), 1.72 (m, 2H), 1.93 (m, 2H), 2.16 (s, 3H), 2.78 (m, 4H), 3.28 (s, 3H), 3.68 (m, 1H), 4.05 (m, 2H), 7.29 (m, 5H), 7.45 (m, 4H), 7.87 (d, 1H), 8.31 (s, 1H), 9.49 (s, 1H)



Example	R^3	R^4	$R^5{}_m$-L_n-	MS m/z $[M+H]^+$
219				498
220				532
221				516

Example	R^3	R^4	$R^5{}_m$-L_n-	MS m/z $[M+H]^+$
222		H		468
223		H		502
224		H		486

Example 225:

3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide (Intermediate 107; 99mg, 0.35mmol), 10-chloro-6-methyl-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 103; 99 mg, 0.35 mmol) and p-toluenesulphonic acid monohydrate (165 mg, 0.87 mmol) were heated at 140°C in 4-methyl-2-pentanol (2.5 mL) for 2 hours. The mixture was allowed to cool forming a dark orange clear solution which was loaded onto an SCX-3 column pre-wet with methanol. The column was washed with methanol to remove p-TsOH. and then eluted with 2% 7N ammonia/methanol to give the crude product which was purified by reverse phase HPLC to yield the title compound as a white solid (15 mg, 8 %). ^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.88 (6H, s), 2.17 (2H, s), 2.28 (6H, s), 2.82 - 2.85 (2H, m), 3.16 (2H, d), 4.04 – 4.08 (2H, m), 7.21 - 7.24 (1H, m), 7.28 - 7.30 (1H, m), 7.32 - 7.35 (2H, m), 7.46 (1H, s), 7.48 - 7.50 (1H, m), 7.56 (1H, d), 7.82 (1H, d), 8.02 (1H, s), 8.32 (1H, s), 8.37 (1H, t); MS m/z 537 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 225 utilising the appropriate substituted aniline (Intermediate 52)

Example 226:

3-chloro-4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

^{1}H NMR (399.9 MHz, DMSO-d_6) δ2.41 – 2.47 (6H, m), 2.84 (2H, t), 3.33 - 3.41 (2H, m), 3.59 (4H, t), 4.05 - 4.08 (2H, m), 7.24 - 7.27 (1H, m), 7.31 - 7.35 (3H, m), 7.49 (2H, t), 7.55 (1H, q), 7.85 (1H, d), 8.00 (1H, s), 8.31 (2H, s); MS m/z 537 $[M+H]^+$.

Example 227:

4-[(2-methyl-3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

10-chloro-6-methyl-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 103; 150 mg, 0.52 mmol), 4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 130 mg, 0.52 mmol) and p-toluenesulphonic acid monohydrate (248 mg, 1.30mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140°C for 2 hours. The reaction mixture was cooled and loaded onto an SCX-3 column pre-wet methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydate and then washed with 2% 7N ammonia/methanol to elute the crude product. The product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a white solid (81 mg, 32.2 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 2.41 - 2.44 (6H, m), 2.82 (2H, t), 3.35 (3H, s), 3.38 - 3.39 (2H, t), 3.59 (4H, t), 4.06 - 4.08 (2H, t), 7.26 (1H, s), 7.29 (1H, s), 7.31 - 7.35 (2H, m), 7.34 - 7.34 (1H, m), 7.40 - 7.42 (2H, m), 7.49 (2H, t), 8.05 (1H, t), 8.31 (1H, s), 9.53 (1H, s); MS m/z 503 $[M+H]^+$.

Example 228:

3-chloro-4-[(2-methyl-3-oxo-6-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 76 ;150 mg, 0.59 mmol), 4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 52; 168 mg, 0.59 mmol), and p-toluenesulphonic acid monohydrate (281 mg, 1.47 mmol) were heated in 4-methyl-2-pentanol (4 mL) at 140°C for 2 hours. The reaction mixture was cooled and loaded onto an SCX-3 column pre-wet with Methanol. The column was washed with methanol to remove p-toluenesulphonic acid monohydate and then washed with 2% 7N ammonia/methanol to elute the crude product. Product containing fractions were evaporated and the resultant material purified by reverse phase HPLC to yield the title compound as an orange gum (46 mg, 15.6 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.20 (6H, d), 2.42 - 2.43 (3H, m), 2.44 - 2.49 (2H, m), 2.60 (2H, t), 3.18 (4H, t), 3.39 (2H, q), 3.60 - 3.62 (6H, m), 4.75 (1H, m), 7.80 - 7.82 (1H, m), 7.96 (1H, d), 8.07 (1H, s), 8.12 (1H, s), 8.32 (1H, d), 8.40 (1H, t); MS m/z 503 $[M+H]^+$.

Example 229:

3-methoxy-4-[[6-(2-methoxyethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-(2-methoxyethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 109; 70 mg, 0.26 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 63 mg, 0.26 mmol), and p-toluenesulphonic acid monohydrate (123 mg, 0.65 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C overnight. The reaction was cooled to room temperature and taken up in MeOH and added to a 2g SCX-2 column pre-wet with MeOH (2 column volumes). The column was washed with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant material was dissolved in DCM and purified on silica eluting with a gradient of 0 – 10% MeOH / DCM then 10% MeOH / DCM. Fractions containing product combined and evaporated to a clear gum to which ether was added and re-evaporated and the resultant material purified by reverse phase HPLC to give the title compound as a white solid. (40 mg, 31 %).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.58 (m, 2H), 2.06 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.72 (m, 2H), 2.83 (m, 2H), 3.29 (s, 3H), 3.36 (s, 3H), 3.72 (m, 2H), 3.87 (m, 4H), 4.00 (m,

4H), 5.90 (d, 1H), 7.23 (m, 1H), 7.44 (d, 1H), 7.65 (s, 1H), 7.95 (s, 1H), 8.42 (d, 1H); MS m/z 503 $[M+H]^+$.

Example 230:

3-methoxy-4-[[6-(1-methoxypropan-2-yl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-(1-methoxypropan-2-yl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 112 60 mg, 0.21 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 56 mg, 0.21 mmol), and p-toluenesulphonic acid monohydrate (100 mg, 0.53 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C for 16 hrs. The reacrtion mixture was cooled to room temperature and dissolved in Methanol. The resultant solution was added to a 5g SCX-3 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant residue was dissolved in DCM and purified on silica eluting with a gradient of 5 – 15% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a beige solid. (35 mg, 32%) ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.32 (d, 3H), 1.58 (m, 2H), 2.05 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.83 (m, 2H), 3.29 (s, 3H), 3.36 (s, 3H), 3.51 (m, 1H), 3.62 (m, 1H), 3.73 (m, 2H), 4.00 (m, 4H), 5.00 (m, 1H), 5.90 (d, 1H), 7.23 (m, 1H), 7.43 (m, 1H), 7.65 (s, 1H), 7.94 (s, 1H), 8.47 (d, 1H); MS m/z 503 $[M+H]^+$.

Example 231:

4-[[6-(3-furylmethyl)-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-(3-furylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one one (Intermediate 116; 67 mg, 0.23 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 60 mg, 0.23 mmol), and p-toluenesulphonic acid monohydrate (109 mg, 0.57 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C for 16 hrs.. The reacrtion mixture was cooled to room temperature and dissolved in Methanol. The resultant solution was added to a 5g SCX-3 column pre wet with MeOH (2

column volumes). Flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant residue was dissolved in DCM and purified on silica eluting with a gradient of 0 – 15% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a yellow solid. (50 mg, 42%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.57 (m, 2H), 2.04 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.64 (m, 2H), 2.82 (m, 2H), 3.31 (s, 3H), 3.71 (m, 2H), 3.98 (m, 4H), 4.67 (s, 2H), 5.88 (d, 1H), 6.43 (s, 1H), 7.14 (m, 1H), 7.40 (m, 1H), 7.43 (m, 2H), 7.71 (s, 1H), 7.99 (s, 1H), 8.45 (d, 1H); MS m/z 520 $[M+H]^+$.

Example 232:

4-[(6-cyclopropyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopropyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 117 42mg, 0.16 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 44 mg, 0.216 mmol), and p-toluenesulphonic acid monohydrate (79 mg, 0.41 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C for 16 hrs. The reacrtion mixture was cooled to room temperature and dissolved in methanol. The resultant solution was added to a 5g SCX-3 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and crude product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant residue was dissolved in DCM and purified on silica eluting with a gradient of 0 – 15% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a white solid. (34 mg, 43%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.64 (m, 2H), 0.92 (m, 2H), 1.59 (m, 2H), 2.05 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.67 (m, 2H), 2.86 (m, 3H), 3.26 (s, 3H), 3.82 (m, 2H), 4.00 (m, 4H), 5.90 (d, 1H), 7.22 (m, 1H), 7.44 (d, 1H), 7.82 (s, 1H), 7.99 (s, 1H), 8.76 (d, 1H); MS m/z 503 $[M+H]^+$.

Example 233:

N-cyclohexyl-3-methoxy-4-[[2-methyl-6-(1-methyl-4-piperidyl)-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]benzamide

10-chloro-6-methyl-2-(1-methyl-4-piperidyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 118; 39mg, 0.13 mmol), 4-amino-N-cyclohexyl-3-methoxy-benzamide (Intermediate 119; 31mg, 0.13 mmol) and p-toluenesulphonic acid monohydrate (60 mg, 0.31 mmol) were combined in 4-Methy-2-pentanol (2 mL) and heated at 100 °C for 16 hrs. The reacrtion mixture was cooled to room temperature and dissolved in Methanol and added to a 5g SCX-3 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) then crude product eluted with 2M ammonia in MeOH and solvents evaporated. The resultant material was dissolved in DCM and purified on silica eluting with a shallow (25 column volumes) gradient of 0 – 10% MeOH / DCM. Product containing fractions were combined and evaporated to a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a white solid. (15 mg, 23%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.26 (m, 4H), 1.45 (m, 2H), 1.77 (m, 2H), 1.91 (m, 4H), 2.05 (m, 2H), 2.17 (m, 2H), 2.35 (s, 3H), 2.67 (m, 2H), 3.02 (m, 2H), 3.28 (s, 3H), 3.71 (m, 2H), 3.98 (m, 4H), 4.51 (m, 1H), 5.88 (d, 1H), 7.26 (m, 1H), 7.38 (d, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.45 (d, 1H); MS m/z 522 $[M+H]^+$.

Example 234:

4-[(6-cyclopentyl-2,5-dimethyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopentyl-3,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 120; 25 mg, 0.42 mmol) and), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 112 mg, 0.42 mmol) were combined with p-toluenesulphonic acid monohydrate (202 mg, 1.06 mmol) in 4-methyl-2-pentanol (1 mL) and heated to 150 °C for 2 hr. The cooled reaction mixture was diluted with methanol (approx 50 mL) and loaded onto a 50 g SCX-2 cartridge washing with methanol (100 mL) and eluting

with 7 N methanolic ammonia (100 mL). The concentrated solution was purified by base modified reverse phase HPLC to give the title compound as a white solid (65 mg, 30%)

^{1}H NMR (399.902 MHz, CDCl3) δ 1.29 (d, 3H), 1.54 - 1.89 (m, 9H), 1.95 - 2.23 (m, 6H), 2.32 (s, 3H), 2.56 (dd, 1H), 2.72 (dd, 1H), 2.84 (br d, 2H), 3.31 (s, 3H), 3.98 (s, 3H), 4.00 - 4.07 (m, 1H), 4.63 - 4.71 (m, 1H), 5.91 (d, 1H), 7.23 (dd, 1H), 7.42 (d, 1H), 7.67 (s, 1H), 7.97 (s, 1H), 8.47 (d, 1H); MS m/z 522 $[M+H]^+$.

Example 235:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

A solution of HATU (221 mg, 0.55 mmol) in DMA (10 mL) was added to a mixture of the 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 242; 220 mg, 0.5 mmol), DIPEA(261 uL, 1.5 mmol) and 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 72 mg, 0.62 mmol) in DMA (10 mL). The resulting mixture was stirred at room temperature for 2 hours, then partially purified by SCX. The compound was retrieved from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave the title compound as a pale yellow amorphous solid. (154 mg, 58%)

^{1}H NMR (399.9 MHz, $CDCl_3$) δ1.22 (6H, s), 1.56 - 1.63 (2H, m), 1.72 - 1.93 (6H, m), 1.99 - 2.03 (2H, m), 2.14 (2H, d), 2.41 - 2.45 (2H, m), 2.48 (3H, s), 3.06 - 3.09 (2H, m), 3.32 (3H, s), 3.40 (2H, s), 4.00 (3H, s), 4.10 - 4.14 (1H, m), 5.29 - 5.38 (1H, m), 6.12 (1H, d), 7.28 (1H, dd), 7.44 (1H, d), 7.65 (1H, s), 7.88 (1H, s), 8.52 (1H, d); MS m/z 536 $[M+H]^+$.

Example 236: Example 237:

4-[[(4S)-2-cyclopentyl-4-ethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

and

4-[[(4R)-2-cyclopentyl-4-ethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopentyl-4-ethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5- one (Intermediate 123; 186 mg, 0.6 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 159 mg, 0.6 mmol) were combined with p-toluenesulphonic acid monohydrate (286 mg, 1.5 mmol) in 4-methyl-2-pentanol (01 mL) and at 115°C overnight. The cooled reaction mixture was dissolved in methanol, passed through an SCX-2 column and washed with methanol. The product was eluted off with 7N ammonia/methanol. Product containing fractions were evaporated and the resultant material was purified using base modified reverse phase HPLC to give a mixture of the title compounds as a brown foam (110 mg)

The individual enantiomers were separated by chiral column chromatography to as white foams

Enatiomer 1 (26 mg)

^{1}H NMR (399.9 MHz, DMSO-d6) : δ_H : 0.89 (tr, 3H), 1.31 (m, 2H), 1.50-1.90 (m, 12H), 2.11 (m, 2H), 2.36 (m, 5H), 2.61 (m, 1H), 3.00 (m, 2H), 3.21 (s, 3H), 3.42 (m, 2H), 3.84 (m, 1H), 3.97 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.77 (m, 1H), 8.12 (m, 2H), 8.39 (d, 1H); MS m/z 536 $[M+H]^+$.

Enantiomer 2 (26 mg)

^{1}H NMR (399.9 MHz, DMSO-d6) : δ_H : 0.89 (tr, 3H), 1.31 (m, 2H), 1.50-1.90 (m, 12H), 2.11 (m, 2H), 2.36 (m, 5H), 2.61 (m, 1H), 3.00 (m, 2H), 3.21 (s, 3H), 3.42 (m, 2H), 3.84 (m, 1H), 3.97 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.77 (m, 1H), 8.12 (m, 2H), 8.39 (d, 1H).; MS m/z 536 $[M+H]^+$.

Example 238: Example 239:

4-[[(4S)-2-cyclopentyl-6-methyl-5-oxo-4-propyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

and

4-[[(4R)-2-cyclopentyl-6-methyl-5-oxo-4-propyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopentyl-6-methyl-4-propyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 124; 194 mg, 0.6 mmol), 4-amino-3-methoxy-N-(1-methyl-4-

piperidyl)benzamide (WO06/018220; 159 mg, 0.6 mmol) were combined with p-toluenesulphonic acid monohydrate (286 mg, 1.5 mmol) in 4-methyl-2-pentanol (01 mL) and at 115°C overnight. The cooled reaction mixture was dissolved in methanol, passed through an SCX-2 column and washed with methanol. The product was eluted with 7N ammonia/methanol. Product containing fractions were evaporated and the resultant material purified using basic prep HPLC to give a mixture of the title compounds as a light brown foam (65 mg)

The individual enantiomers were separated by chiral column chromatography to as white foams

Enantiomer 1 (15 mg)

^{1}H NMR (399.9 MHz, DMSO-d6) : δ 0.84 (tr, 3H), 1.29 (m, 3H), 1.50-1.90 (m, 13H), 2.11 (m, 2H), 2.41 (m, 5H), 2.69 (m, 1H), 3.02 (m, 2H), 3.20 (s, 3H), 3.40 (m, 2H), 3.85 (m, 1H), 3.95 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.76 (m, 1H), 8.12 (s, 1H), 8.14 (d, 1H), 8.40 (d, 1H); MS m/z 550 $[M+H]^+$.

Enantiomer 2 (22 mg)

^{1}H NMR (399.9 MHz, DMSO-d6) : δ 0.84 (tr, 3H), 1.29 (m, 3H), 1.50-1.90 (m, 13H), 2.11 (m, 2H), 2.41 (m, 5H), 2.69 (m, 1H), 3.02 (m, 2H), 3.20 (s, 3H), 3.40 (m, 2H), 3.85 (m, 1H), 3.95 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.76 (m, 1H), 8.12 (s, 1H), 8.14 (d, 1H), 8.40 (d, 1H); MS m/z 550 $[M+H]^+$.

Example 240: Example 241:

4-[[(4S)-2-cyclopentyl-4,6-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

and

4-[[(4R)-2-cyclopentyl-4,6-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopentyl-4,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (**Intermediate 125**; 674 mg, 2.29 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 602 mg, 2.29 mmol) and *p*-toluene sulphonic acid (1.09 g, 0.89 mmol) were dissolved in 4-methyl-2-pentanol (15 mL) and refluxed under a blanket of

nitrogen for 24 hours. The reaction mixture was cooled and passed through an SCX-2 column washed with methanol. The crude product was eluted with 7N ammonia in methanol. Product containing fractions were evaporated and the resultant material purified by column chromatography, eluting with 0-10% ammonia methanol (7N) in DCM. The resultant material was purified by base modified reverse phase HPLC to give a mixture of the title compounds as a white solid (480 mg, 40%).

The individual enantiomers were separated by chiral column chromatography to as white gums which were dissolved separately in DCM then passed through SCX-2 columns and washed with methanol. The products were eluted off the columns using 7N ammonia in methanol and concentrated under reduced pressure to yield the enantiomers as white solids.

Enatiomer 1 (118 mg)

^{1}H NMR (399.902 MHz, DMSO-d6) δ 1.04 (d, 3H), 1.51 - 1.84 (m, 12H), 1.99 - 2.13 (m, 3H), 2.81 - 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quintet, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 523 $[M+H]^+$.

Enatiomer 2 (59 mg)

^{1}H NMR (399.902 MHz, DMSO-d6) δ 1.04 (d, 3H), 1.51 - 1.84 (m, 12H), 1.99 - 2.13 (m, 3H), 2.81 - 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quintet, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 523 $[M+H]^+$.

Example 242:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid

To a solution of 10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 126; 616 mg, 2. 0 mmol) and 4-amino-3-methoxybenzoic acid (378 mg, 2.2 mmol) in ethanol (5 mL) was added water (15 mL) and conc hydrochloric acid (0.335 mL). The mixture was heated under reflux for 36 hours. The reaction was cooled and a brown solid precipitated. This was filtered, dried and

triturated under cold acetonitrile and then dried *in vacuo* to give the product as a pale brown solid (420 mg), 48%)

^{1}H NMR (400.13 MHz, DMSO-d_6) δ1.15 (6H, s), 1.55 - 1.90 (8H, m), 3.19 (3H, s), 3.53 (2H, s), 3.95 (3H, s), 5.07 - 5.16 (1H, m), 7.59 - 7.61 (2H, m), 8.11 (1H, s), 8.13 (1H, d), 9.53 (1H, s); MS m/z 440 $[M+H]^+$.

Example 243:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-3-piperidyl)benzamide

A solution of HATU (126 mg, 0.33 mmol) in DMA (5 mL) was added to a mixture of the 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid acid (Example 242 132 mg, 0.3 mmol), DIPEA (261 uL, 1.5 mmol) and 3-amino N-methylpiperidine dihydrochloride (71 mg, 0.375 mmol) in DMA (5 mL). The resulting mixture was stirred at room temperature for 2 hours, then partially purified by SCX. The compound was eluted from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave the title compound as a pale yellow amorphous solid (65 mg, 41%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ1.03 (6H, s), 1.34 - 1.87 (12H, m), 2.17 (5H, s), 2.41 (2H, s), 3.13 (3H, s), 3.20 (2H, s), 3.82 (3H, s), 4.19 (1H, s), 5.10 - 5.20 (1H, m), 7.09 (1H, s), 7.20 (1H, s), 7.34 (1H, s), 7.43 (1H, s), 7.68 (1H, s), 8.31 (1H, d); MS m/z 536 $[M+H]^+$.

Example 244:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[1-(2-methoxyethyl)-4-piperidyl]benzamide

A solution of HATU (126 mg, 0.33 mmol) in DMA (5 mL) was added to a mixture of 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid acid (Example 242 132 mg, 0.3 mmol), DIPEA (261 uL, 1.5 mmol) and 4-amino N-(2-methoxyethyl)piperidine (60 mg, 0.375) in DMA (5 mL). The resulting mixture was stirred at room temperature for 2 hours, then partially purified by SCX.

The compound was retrieved from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave a pale yellow amorphous solid. (55 mg, 32%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ1.13 (6H, s), 1.43 - 1.56 (2H, m), 1.58 - 1.74 (4H, m), 1.87 - 1.97 (4H, m), 2.04 (2H, d), 2.44 (2H, t), 2.76 (2H, t), 3.10 - 3.12 (2H, m), 3.23 (3H, s), 3.29 - 3.30 (2H, m), 3.30 (3H, s), 3.59 - 3.62 (2H, m), 3.90 (2H, s), 4.03 - 4.07 (1H, m), 5.20 - 5.28 (1H, m), 6.04 (1H, d), 7.17 - 7.20 (2H, m), 7.34 (1H, d), 7.55 (1H, s), 7.79 (1H, s), 8.42 (1H, d). MS m/z 580 $[M+H]^+$.

Example 245:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

A solution of HATU (126 mg, 0.33 mmol) in DMA (5 mL) was added to a mixture of 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzoic acid , (Intermediate 129; 123 mg, 0.3 mmol) DIPEA (261 uL, 1.5 mmol) and 4-amino N-methylpiperidine (43 mg, 0.375) in DMA (5 mL). The resulting mixture was stirred at room temperature for 2 hours, then partially purified by SCX. The compound was eluted from the SCX column using 7N ammonia in methanol, then concentrated *in vacuo*, and further purified by column chromatography, eluting with 0-10% ammonia (7N in methanol) in DCM. The pure material was recovered as an orange oil, which foamed and solidified under high vacuum. Trituration under ether gave a pale yellow amorphous solid. (100 mg, 66%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ1.13 (6H, s), 1.43 - 1.53 (2H, m), 1.60 - 1.73 (4H, m), 1.83 - 1.95 (4H, m), 2.01 - 2.09 (2H, m), 2.37 - 2.42 (2H, m), 2.44 (3H, s), 3.06 (2H, d), 3.22 (3H, s), 3.30 (2H, s), 4.01 - 4.07 (1H, m), 5.16 - 5.25 (1H, m), 6.07 (1H, d), 6.99 (1H, s), 7.58 (2H, d), 7.65 (2H, d), 7.77 (1H, s); MS m/z 506 $[M+H]^+$.

Example 246:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-methylpiperidin-4-yl)-3-methoxybenzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 153 mg, 0.5 mmol) 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 158 mg, 0.6 mmol) were combined with p-toluenesulphonic acid monohydrate (190 mg, 1.0 mmol) in 4-methyl-2-pentanol (4 mL) mixed and heated by microwave irradiation at 160°C for 1 hour, cleaned up partially by SCX, then purified by column chromatography, eluting with 0-6% methanolic ammonia in DCM, to give the product as a clear oil, which solidified on trituration with ether to give the title compound as a white solid (160 mg, 60%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.61 - 0.64 (2H, m), 1.09 - 1.12 (2H, m), 1.42 - 1.52 (2H, m), 1.61 - 1.76 (6H, m), 1.98 - 2.11 (4H, m), 2.23 (2H, t), 2.35 (3H, s), 2.89 (2H, d), 3.30 (3H, s), 3.47 (2H, s), 3.99 (3H, s), 3.99 - 4.10 (1H, m), 4.93 - 4.99 (1H, m), 5.99 (1H, d), 7.26 (1H, dd), 7.43 (1H, d), 7.65 (1H, s), 7.87 (1H, s), 8.53 (1H, d)MS m/z 534 $[M+H]^+$.

Example 247:

3-chloro-N-(2-morpholin-4-ylethyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 104; 104mg, 0.36mmol), 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 52; 100 mg, 0.36 mmol) and p-toluenesulphonic acid monohydrate (174 mg, 0.91mmol) were heated at 140°C in 4-methyl-2-pentanol (2.5ml) for 4.5 hrs. The reaction mixture was cooled and absorbed onto an SCX column, washed with methanol and eluted with ammonia in methanol. After concentration of the product containing fractions methanol was added to the residue and the suspension filtered to give the title compound as an off-white coloured solid (42 mg, 22%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 2.41 - 2.47 (6H, m), 2.89 (2H, m), 3.36 (2H, t), 3.59 (4H, m), 4.01 - 4.03 (2H, m), 7.19 - 7.22 (1H, m), 7.36 - 7.43 (3H, m), 7.51 - 7.55 (3H, m), 7.69 (1H, s), 7.83 (1H, d), 7.97 (1H, s), 8.27 (1H, t), 9.66 (1H, s); MS m/z 522 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 255 utilising 4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide Intermediate 55 to give the title compound as a white solid (31 mg, 17%)

Example 248:

3-chloro-N-(1-methyl-4-piperidyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.54 - 1.58 (2H, m), 1.74 (2H, d), 1.91 - 1.97 (2H, m), 2.17 (3H, s), 2.74 - 2.79 (2H, m), 2.89 (2H, m), 3.64 – 3.74 (1H, m), 4.00 - 4.03 (2H, m), 7.20 - 7.23 (1H, m), 7.35 - 7.41 (3H, m), 7.53 (3H, d), 7.68 (1H, s), 7.87 (1H, d), 7.96 (1H, s), 8.10 (1H, d), 9.65 (1H, s); MS m/z 506 $[M+H]^+$.

Example 249:

N-(2-morpholin-4-ylethyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl)amino]benzamide

4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark; 188mg, 0.75mmol) and 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 160mg, 0.63mmol) were heated together in EtOH:water (8ml, 1:3) in the prescence of concentrated hydrochloric acid (126ul) for 24 hours. The mixture was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and the solvent evaporated to give product as a brown gum, which was purified by base, modified reverse phase HPLC to yield the title compound as a white solid. (35 mg , 13%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 2.43 (m, 4H), 2.88 (m, 3H), 3.34 (m, 2H), 3.59 (m, 4H), 3.99 (m, 3H), 7.18 (d, 2H), 7.38 (m, 5H), 7.53 (t, 2H), 7.93 (s, 1H), 8.00 (m, 1H), 9.28 (s, 1H), 9.57 (s, 1H); MS m/z 488 $[M+H]^+$.

Example 250:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(2-morpholin-4-ylethyl)benzamide

4-amino-3-methoxy-N-(2-morpholin-4-ylethyl)benzamide (Intermediate 135 176 mg, 0.75 mmol) and 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2 168 mg, 0.63mmol) were heated together in EtOH:water (8ml, 1:3) in the prescence of concentrated hydrochloric acid (126ul) for 24 hours. The mixture was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and the solvent evaporated to give product as a brown gum, which was purified by base, modified reverse phase HPLC to yield the title compound as a white solid. (154 mg, 54%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.73 (m, 8H), 2.45 (m, 6H), 2.62 (m, 2H), 3.39 (m, 4H), 3.58 (m, 6H), 3.94 (s, 3H), 5.09 (m, 1H), 7.46 (m, 2H), 7.60 (s, 1H), 7.80 (s, 1H), 8.25 (t, 1H), 8.38 (d, 1H), 9.41 (s, 1H); MS m/z 510 $[M+H]^+$.

Example 251:

3-methoxy-N-(1-methyl-4-piperidyl)-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 173 mg, 0.66 mmol) and 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 150mg, 0.55mmol) were heated together in EtOH:water (8 mL, 1:3) in the presence of concentrated hydrochloric acid (110 ul) for 24 hours. p-toluenesulphonic acid monohydrate (105 mg, 0.55 mmol) was added and the mixture heated at 150 deg for 3h by microwave irradiation. The mixture was cooled to ambient temperature and loaded onto an SCX-2 (5 g) column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and solvent evaporated to give a brown gum which was purified by base modified reverse phase HPLC to yield the title compound as a white solid (73 mg, 27%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.57 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.84 (m, 4H), 3.70 (m, 1H), 3.87 (s, 3H), 4.01 (m, 2H), 6.91 (d, 1H), 7.39 (m, 6H), 7.53 (m, 2H), 7.93 (s, 1H), 7.95 (s, 1H), 9.60 (s, 1H); MS m/z 502 $[M+H]^+$.

Example 252:

N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-[(3-oxo-6-phenyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]benzamide

4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 183mg, 0.66mmol) and 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 150 mg, 0.55 mmol) were heated together in EtOH:water (8 mL, 1:3) in the presence of concentrated hydrochloric acid (110ul) for 24 hours. IPA/DMA was added to aid solution followed by p-toluenesulphonic acid monohydrate (52mg, 0.27mmol) and the mixture heated by microwave irradiation for 1 hour at 150^{0}C. The mixture was cooled to ambient temperature and loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and the solvent evaporated to give product as a brown gum which was purified by base modified reverse phase HPLC to yield the title compound as a gum (13 mg, 5%)

ES+518 (M+H), ES- 516 (M-H) Retention Time 2.18 minutes

Example 253:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide (Intermediate 136; 113mg, 0.45mmol) and10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 120mg, 0.45mmol) were heated together in EtOH:water (8ml, 1:3) in the presence of 4-toluenesulphonic acid (214mg, 1.13mmol) for 23 hours. The reaction mixture was heated by microwave irradiation at 150^{0}C for 20 minutes cooled to ambient temperature and loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and the solvent evaporated to give product as a gum, which was purified by base modified reverse phase HPLC to yield the title compound as a white solid. (77 mg, 36%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.88 (s, 6H), 1.61 (m, 4H), 1.74 (m, 2H), 1.90 (m, 2H), 2.19 (s, 2H), 2.27 (s, 6H), 2.61 (m, 2H), 3.18 (d, 2H), 3.57 (m, 2H), 5.14 (m, 1H), 7.69 (d, 2H), 7.78 (d, 2H), 7.79 (s, 1H), 8.30 (t, 1H), 9.31 (s, 1H), 9.38 (s, 1H); MS m/z 480 $[M+H]^+$.

Example 254:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

4-amino-N-(1-methyl-4-piperidyl)benzamide (Intermediate 4; 131mg, 0.56mmol) and 10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 150mg, 0.56mmol) were heated together in 4-methyl-2-pentanol (4ml) in the presence of p-toluenesulphonic acid (266mg, 1.40mmol) for 24 hours. The mixture was cooled to ambient temperature and then loaded onto an SCX-2 (5g) column pre-wet with methanol. The product was eluted with 2M NH3/MeOH and the solvent evaporated to give crude product, which was purified by base modified reverse phase HPLC to yield the title compound as a white solid. (56 mg, 22%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 (m, 6H), 1.75 (m, 4H), 1.92 (m, 4H), 2.17 (s, 3H), 2.61 (m, 2H), 2.77 (m, 2H), 3.57 (m, 2H), 3.72 (m, 1H), 5.14 (m, 1H), 7.75 (m, 4H), 7.79 (s, 1H), 7.95 (d, 1H), 9.29 (s, 1H), 9.38 (s, 1H); MS m/z 464 $[M+H]^+$.

Example 255:

3-chloro-4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide (Intermediate 107; 118mg, 0.37mmol), 10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 100mg, 0.37mmol) and p-toluenesulphonic acid monohydrate (179mg, 0.94mmol) were heated at 140°C in 4-methyl-2-pentanol for 2h. LC-MS indicated the reaction had not gone to completion with ~50% of product in the mixture. An SCX-3 column was washed with methanol then the solution was loaded onto it. The column was washed with methanol and eluted with 7N ammonia/methanol to give the crude product. The mixture was concentrated the resultant material purified by base modified reverse phase HPLC to yield the title compound as an odd-white solid (24mg, 12.6%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.89 (6H, s), 1.56 (4H, m), 1.71 (2H, s), 1.83 - 1.85 (2H, m), 2.18 (2H, s), 2.27 (6H, s), 2.62 (2H, t), 3.18 - 3.20 (2H, s), 3.57 (2H, t), 5.03 (1H, m), 7.73 - 7.76 (1H, m), 7.80 (1H, s), 7.94 (1H, d), 8.03 (1H, s), 8.28 (1H, d), 8.46 (1H, s), 9.44 (1H, s); MS m/z 514 $[M+H]^+$.

Example 256:

4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

10-chloro-2-cyclopentyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 2; 150mg, 0.56mmol), 4-amino-N-(2-morpholin-4-ylethyl)benzamide (Buttpark ; 141mg, 0.56mmol) and p-toluenesulphonic acid monohydrate (268mg, 1.41mmol) were heated in 4-methyl-2-pentanol (4 mL) for 2 hours at 140°C.The reaction mixture was loaded onto an SCX-3 column pre-wet with methanol. The column was washed with methanol and 7N ammonia/methanol to elute the crude product. Product containing fractions were evaporated, dissolved in DMF and purified by base modified reverse phase HPLC to yield the title compound as a white solid (77 mg, 28.5%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.62 (2H, m), 1.67 (2H, m), 1.76 (2H, m), 1.91 (2H, m), 2.43 - 2.46 (6H, m), 2.62 (2H, t), 3.38 (2H, q), 3.58 (6H, t), 5.12 - 5.16 (1H, m), 7.74 - 7.77 (3H, m), 7.77 (2H, d), 8.15 (1H, t), 9.33 (1H, s), 9.40 (1H, s); MS m/z 481 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 256 utilising 4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide Intermediate 50 to give the title compound as a yellow solid (44 mg, 15%)

Example 257:

3-chloro-4-[(6-cyclopentyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.57 (4H, d), 1.68 - 1.72 (2H, m), 1.85 (2H, s), 2.43 (6H, m), 2.62 (2H, t), 3.39 (2H, q), 3.58 (6H, t), 5.03 (1H, m), 7.78 (2H, t), 7.95 (1H, d), 8.00 (1H, s), 8.30 (1H, d), 8.39 (1H, t), 9.44 (1H, s); MS m/z 515 $[M+H]^+$.

Example 258:

3-methoxy-4-[[6-(1-methoxypropan-2-yl)-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-9-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-(1-methoxypropan-2-yl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 137; 35 mg, 0.13 mmol)), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 34 mg, 0.13 mmol) and *p*-toluenesulphonic acid monohydrate (61 mg, 0.32 mmol) were dissolved in 4-methyl-2-pentanol (2 mL) and heated at 100 °C for 18 hrs. The reaction mixture was cooled to room temperature dissolved in MeOH and added to a 2g SCX-2 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated and the resultant material purified by base modified reverse phase HPLC to yield the title compound as a cream coloured solid (13 mg, 20%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.29 (d, 3H), 1.61 (m, 2H), 2.06 (m, 2H), 2.18 (m, 2H), 2.31 (s, 3H), 2.77 (m, 2H), 2.84 (m, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.68 (m, 2H), 3.97 (s, 3H), 4.00 (m, 1H), 5.27 (m, 1H), 5.90 (d, 1H), 6.94 (s, 1H), 7.23 (m, 1H), 7.42 (d, 1H), 7.60 (s, 1H), 7.70 (s, 1H), 8.43 (d, 1H); MS m/z 498 $[M+H]^+$.

Example 259:

4-[(6-cyclopentyl-2-ethyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclopentyl-6-ethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 139; 221 mg, 0.75 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 198 mg, 0.75 mmol) and p-toluenesulphonic acid (357 mg, 1.88 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 18 hours. The reaction mixture was allowed to cool to room temperature and loaded onto a 10 g SCX-2 cartridge, washing with methanol (10 mL), water (10 mL) and methanol (10 mL) before the product was eluted off with 7 N methanolic ammonia to provide a brown oil upon evaporation of product containing fractions. The resultant material was purified by flash silica chromatography, 0-10% methanolic ammonia/DCM to give a pale yellow glass which was purified by base modified reverse phase HPLC to yield the title compound as a white solid (192 mg, 0.36 mmol, 49%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.00 (t, 3H), 1.55 - 1.82 (m, 12H), 1.91 - 1.98 (m, 4H), 2.18 (s, 3H), 2.79 (d, 2H), 3.60 - 3.63 (m, 2H), 3.69 - 3.79 (m, 3H), 3.96 (s, 3H), 4.74

(quintet, 1H), 7.48 - 7.51 (m, 2H), 7.77 (s, 1H), 8.08 (d, 1H), 8.13 (s, 1H), 8.39 (d, 1H); MS m/z 523 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 259 utilising 10-chloro-2-cyclopentyl-6-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 142 to give the title compound as a white solid (77 mg, 14%)

Example 260:

4-[(6-cyclopentyl-3-oxo-2-propan-2-yl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

^1H NMR (399.902 MHz, DMSO-d_6) δ 1.14 (d, 6H), 1.54 - 1.81 (m, 12H), 1.92 - 1.98 (m, 4H), 2.18 (s, 3H), 2.79 (br d, 2H), 3.56 - 3.59 (m, 2H), 3.70 - 3.80 (m, 1H), 3.96 (s, 3H), 4.40 (septet, 1H), 4.63 (quintet, 1H), 7.48 - 7.51 (m, 2H), 7.80 (s, 1H), 8.03 (s, 1H), 8.08 (d, 1H), 8.40 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 261:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-thiazole-4-carboxamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 150 mg, 0.53 mmol), 2-amino-N-(1-methyl-4-piperidyl)-1,3-thiazole-4-carboxamide (Intermediate 145; 123 mg, 0.48 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (26 mg, 0.04 mmol) were dissolved in 1,4-dioxane (4.5 mL) Caesium carbonate (315 mg, 0.97 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (27mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled three times with nitrogen and then heated at 100°C overnight. The mixture was cooled, filtered and the filtrate absorbed onto an SCX column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by reverse phase preparative chromatography to give the title compound as a pale brown solid (80 mg, 34%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.49 - 1.83 (10H, m), 1.99 - 2.05 (4H, m), 2.18 (3H, s), 2.61 (2H, t), 2.67 - 2.75 (2H, m), 3.19 (3H, s), 3.64 - 3.72 (3H, m), 5.00 (1H, m), 7.48 (1H, d), 7.66 (1H, s), 8.14 (1H, s), 11.28 (1H, s); MS m/z 485 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 261 utilising 2-amino-4-methyl-N-(1-methyl-4-piperidyl)-1,3-thiazole-5-carboxamide Intermediate 146. A solid that precipitated from the basic fractions of the SCX column was filtered off. The filtrate was concentrated and methanol added to the residue giving further precipitated material, which was filtered and combined with the original precipitate to give the title compound as a white solid (95mg, 40%)

Example 262:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-4-methyl-N-(1-methyl-4-piperidyl)1,3-thiazole-5-carboxamide

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.50 - 1.76 (10H, m), 1.90 – 2.03 (4H, m), 2.16 (3H, s), 2.43 (3H, s), 2.61 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.60 - 3.67 (3H, m), 5.07 (1H, m), 7.60 (1H, d), 8.13 (1H, s), 11.33 (1H, s);

1H NMR (399.9 MHz, DMSO-d6) +d4 AcOH δ1.63 - 1.90 (10H, m), 1.86 - 1.92 (2H, m), 2.01 (2H, s), 2.44 (3H, s), 2.46 (3H, s), 2.61 (2H, t), 3.08 (2H, m), 3.18 (3H, s), 3.65 (2H, m), 3.78 - 3.85 (1H, m), 5.05 (1H, d), 8.12 (1H, s); MS m/z 499 $[M+H]^+$.

Example 263:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-thiazole-5-carboxamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 148 mg, 0.53 mmol), 2-amino-N-(1-methyl-4-piperidyl)-1,3-thiazole-5-carboxamide (Intermediate 147; 115 mg, 0.48 mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (25 mg, 0.04 mmol) were dissolved in 1,4-dioxane (5 mL) Caesium carbonate (312 mg, 0.96 mmol) was added and the mixture purged with a stream of

nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (27mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled three times with nitrogen and then heated at 100°C overnight. The mixture was cooled, filtered and the filtrate absorbed onto an SCX column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by normal phase chromatography (5% ammonia in methanol/DCM) to give a yellow solid which was suspended in DCM, filtered and dried on the filter to give the title compound as a white solid (48mg, 21%). ^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.50 – 1.79 (10H, m), 1.90 – 2.04 (4H, m), 2.17 (3H, s), 2.62 (2H, t), 2.77 (2H, d), 3.19 (3H, s), 3.65 - 3.71 (3H, m), 5.09 (1H, m), 8.03 (1H, s), 8.07 (1H, d), 8.15 (1H, s), 11.45 (1H, s) ; MS m/z 485 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 263 utilising 2-amino-N-(1-methyl-4-piperidyl)-1,3-oxazole-5-carboxamide Intermediate 148 the final product being purified by base modified reverse phase HPLC to give the title compound as a pale brown solid (25 mg, 41%)

Example 264:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-oxazole-5-carboxamide

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.48 – 1.76 (10H, m), 1.85 – 1.97 (4H, m), 2.17 (3H, s), 2.56 - 2.61 (2H, m), 2.76 (2H, d), 3.18 (3H, s), 3.59 - 3.68 (3H, m), 4.79 (1H, m), 7.63 (1H, s), 8.03 (1H, d), 8.07 (1H, s), 10.64 (1H, s); MS m/z 469 $[M+H]^+$.

Example 265:

2-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)1,3-oxazole-4-carboxamide

2-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-1,3-oxazole-4-carboxylic acid (Intermediate 150; 85 mg, 0.23 mmol), HATU (131 mg, 0.34 mmol) and 4-amino-1-methylpiperidine (40 mg, 0.34 mmol) were stirred in DMF (5 mL) and DIPEA (120 µL, 0.68 mmol) added. The mixture was stirred overnight, absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product

containing fractions were concentrated and purified by normal phase chromatography (5% ammonia in methanol/DCM) to give the title compound as a white solid (66 mg, 61%)
^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.50 - 1.74 (10H, m), 1.88 - 1.98 (4H, m), 2.16 (3H, s), 2.58 (2H, t), 2.82 (2H, d), 3.18 (3H, s), 3.60 - 3.63 (2H, m), 3.66 - 3.75 (1H, m), 4.71 - 4.80 (1H, m), 7.54 (1H, d), 8.06 (1H, s), 8.26 (1H, s), 10.46 (1H, s); MS m/z 469 $[M+H]^+$.

Example 266:

9-[(6-chloropyridin-3-yl)amino]-6-cyclopentyl-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 157 mg, 0.56 mmol), 5-amino-2-chloropyridine (65 mg, 0.51mmol) and 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (27 mg, 0.05 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (330 mg, 1.01 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (28 mg, 0.03 mmol) was added and the apparatus was evacuated and backfilled three times with nitrogen and then heated at 100°C for 8h. The mixture was cooled, filtered and the filtrate absorbed onto an SCX column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by preparative reverse phase chromatography to give the title compound as a white solid (14mg, 7%)
^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.56 – 1.74 (6H, m), 1.93 - 1.98 (2H, m), 2.57 - 2.60 (2H, m), 3.18 (3H, s), 3.61 - 3.64 (2H, m), 4.79 (1H, m), 7.40 (1H, d), 8.09 (1H, s), 8.18 - 8.20 (1H, m), 8.75 (1H, d), 9.51 (1H, s); MS m/z 373 $[M+H]^+$.

Utilising the appropriate commercially available anilines, the following examples were prepared by an analogous process to that used in the preparation of Example 266.

Example 267:

6-cyclopentyl-9-[(6-methoxypyridin-3-yl)amino]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.52 - 1.73 (6H, m), 1.89 - 2.08 (2H, m), 2.53 - 2.58 (2H, m), 3.16 (3H, s), 3.58 - 3.61 (2H, m), 3.81 (3H, s), 4.69 - 4.77 (1H, m), 6.75 (1H, d), 7.98 - 8.04 (2H, m), 8.39 - 8.40 (1H, m), 9.04 (1H, s); MS m/z 369 $[M+H]^+$.

Example 268:

6-cyclopentyl-2-methyl-9-(pyridin-4-ylamino)-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.61 - 1.78 (6H, m), 1.97 - 2.08 (2H, m), 2.59 - 2.62 (2H, m), 3.19 (3H, s), 3.63 - 3.66 (2H, m), 4.81 - 4.89 (1H, m), 7.76 - 7.78 (2H, m), 8.13 (1H, s), 8.34 (2H, d), 9.81 (1H, s) MS m/z 339 $[M+H]^+$.

Example 269:

6-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)pyridine-3-carboxamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 100 mg, 0.36 mmol), 6-amino-N-(1-methyl-4-piperidyl)pyridine-3-carboxamide (Intermediate 152; 76 mg, 0.32 mmol) and caesium carbonate (211 mg, 0.65 mmol) were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (18 mg, 0.02 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene(17 mg , 0.03mmol) were added and the mixture heated at 100 °C overnight. The reaction mixture was cooled to room temperature filtered and the filter cake washed with DCM. The filtrate added to a 5g SCX-2 column pre wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated to give a brown gum which was purified by base modified reverse phase HPLC to give the title compound as a white solid (117 mg, 75%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.54 - 1.80 (m, 8H), 2.03 (m, 4H), 2.17 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.70 (m, 2H), 4.00 (m, 1H), 4.84 (m, 1H), 5.85 (d, 1H), 7.94 (s, 1H), 7.99 (s, 1H), 8.05 (m, 1H), 8.40 (d, 1H), 8.63 (m, 1H); MS m/z 479 $[M+H]^+$.

The following example was prepared by an analogous process to that used in the preparation of Example 269 utilising 5-amino-N-(1-methyl-4-piperidyl)pyridine-2-carboxamide (Intermediate 153), to give the title compound as a yellow solid (104 mg, 61%)

Example 270:

5-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-N-(1-methyl-4-piperidyl)pyridine-2-carboxamide

^{1}H NMR (399.902 MHz, CDC_{13}) δ1.68 (m, 8H), 2.02 (m, 4H), 2.18 (m, 2H), 2.31 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.69 (m, 2H), 3.98 (m, 1H), 4.85 (m, 1H), 7.11 (s, 1H), 7.78 (d, 1H), 7.94 (s, 1H), 8.13 (d, 1H), 8.31 (m, 1H), 8.59 (d, 1H); MS m/z 479 $[M+H]^+$.

Example 271:

3-methoxy-4-[(6-methyl-5-oxo-2-prop-2-ynyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

9-chloro-2-methyl-6-prop-2-ynyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-3-one (Intermediate 154; 53 mg, 0.21 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 66 mg, 0.25 mmol) p-toluenesulphonic acid monohydrate acid (80 mg, 0.42 mmol) and isopropanol (4 mL) were combined in a 10 mL microwave reactor tube and heated in by microwave irradiation at 150 ^{0}C for 80 minutes. The sample was transferred to an SCX (10 g) cartridge pre-wet with methanol, washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as an off white gum (4 mg, 3%).

MS m/z 478 $[M+H]^+$. Retention Time 1.03 minutes Monitor Acid

Example 272:

3-methoxy-4-[[6-methyl-2-[(4-methylpentan-2-yloxycarbonimidoyl)methyl]-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

2-(10-chloro-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-2-

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yl)acetonitrile (Intermediate 155; 97 mg, 0.39 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 124mg,0.47mmol) and p-toluenesulphonic acid monohydrate (148 mg, 0.78 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 100 ^{0}C for 24 hours. The reaction mixture was diluted with water and methanol and the solution loaded onto an SCX-2 (5 g) column pre-wet with methanol. The column was washed with methanol (x2) and eluted with 2M NH3/MeOH. Fractions containing product identified as the addition product of the solvent and nitrile group were combined and evaporated. To the residue was added 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220 62 mg, 0.24 mmol) and p-toluenesulphonic acid monohydrate (74 mg, 0.39 mmol) and the mixture heated by microwave irradiation in isopropanol (4 mL) for 20 minutes at 150 ^{0}C. The cooled mixture was loaded onto an SCX-2 (5 g) column pre-wet with MeOH. The column was washed with MeOH and eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a light brown solid (21 mg, 9%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.75 (m, 2H), 0.81 (d, 3H), 1.13 (d, 3H), 1.24 (m, 1H), 1.52 (m, 5H), 1.76 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.46 (m, 2H), 2.75 (m, 4H), 3.22 (s, 3H), 3.75 (m, 3H), 3.95 (s, 3H), 4.22 (s, 1H), 4.91 (m, 1H), 7.48 (m, 2H), 7.59 (s, 1H), 7.80 (s, 1H), 8.04 (d, 1H), 8.43 (d, 1H); MS m/z 582 $[M+H]^+$.

Example 273:

4-[[2-[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

9-chloro-6-[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-3-one (Intermediate 156; 81 mg, 0.25 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 80 mg, 0.30 mmol) p-toluenesulphonic acid monohydrate acid (96 mg, 0.5 mmol) and isopropanol (4 mL) were combined in a 10 mL microwave reactor tube and heated in by microwave irradiation at 150

^{0}C for 80 minutes. The sample was transferred to an SCX (20 g) cartridge pre-wet with methanol, washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as an off white gum (61 mg, 45%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 (2H, m), 1.76 (2H, m), 1.94 (2H, m), 2.08 (3H, s), 2.17 (3H, s), 2.36 (3H, s), 2.61 (2H, m), 2.78 (2H, m), 3.17 (3H, s), 3.53 (2H, m), 3.73 (1H, m), 3.95 (3H, s), 4.61 (2H, s), 7.49 (2H, m), 7.83 (1H, s), 8.05 (1H, d), 8.19 (1H, s), 8.35 (1H, d).

Example 274:

4-[[2-(2-fluoroethyl)-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-(2-fluoroethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 157; 86 mg, 0.33 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 104 mg,0.40 mmol) and p-toluenesulphonic acid monohydrate (126 mg, 0.66 mmol) were heated together in 4-methyl-2-pentanol (4 mL) at 100 ^{0}C for 24 hours. The reaction mixture was diluted with water and methanol and the solution loaded onto an SCX-2 (5 g) column pre-wet with methanol. The column was washed with methanol (x2) and the product eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a yellow solid (60 mg, 37%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.59 (m, 2H), 1.75 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.73 (m, 4H), 3.13 (s, 3H), 3.57 (m, 2H), 3.72 (s, 3H), 3.72 (m, 1H), 3.83 (t, 2H), 4.05 (t, 2H), 6.91 (d, 1H), 7.32 (m, 2H), 7.89 (s, 1H), 7.91 (d, 1H); MS m/z 466 $[M+H]^+$-HF.

Example 275:

N-cyclohexyl-4-[[2-(2-dimethylaminoethyl)-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-3-methoxy-benzamide

10-chloro-2-(2-dimethylaminoethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 158; 84 mg, 0.30 mmol), 4-amino-3-methoxy-N-(1-methyl-4-

piperidyl)benzamide (WO06/018220; 90 mg, 0.36 mmol) and p-toluenesulphonic acid monohydrate (113 mg, 0.60 mmol) were heated together in IPA (4 mL) by microwave irradiation at 150 ^{0}C for 20 minutes. The reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with methanol; the column was washed with methanol and the product eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (59 mg, 40%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.24 (m, 5H), 1.72 (m, 6H), 2.19 (s, 6H), 2.54 (t, 2H), 2.62 (m, 2H), 3.17 (s, 3H), 3.70 (t, 3H), 3.75 (m, 2H), 3.95 (s, 3H), 7.48 (m, 2H), 7.70 (s, 1H), 8.01 (d, 1H), 8.07 (s, 1H), 8.35 (d, 1H); MS m/z 496 $[M+H]^+$.

Example 276:

N-cyclohexyl-3-methoxy-4-[[6-methyl-5-oxo-2-[2-(1-piperidyl)ethyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]benzamide

10-chloro-6-methyl-2-[2-(1-piperidyl)ethyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 159; 90 mg, 0.28 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 83 mg, 0.34 mmol) and p-toluenesulphonic acid monohydrate (107 mg, 0.56 mmol) were heated together in IPA (4 mL) by microwave irradiation at 150 ^{0}C for 20 minutes. The reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with methanol; the column was washed with methanol and the product eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (40 mg, 27%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.15 (m, 1H), 1.34 (m, 6H), 1.47 (m, 4H), 1.72 (m, 6H), 2.35 (m, 4H), 2.54 (t, 2H), 2.62 (m, 2H), 3.17 (s, 3H), 3.69 (t, 2H), 3.74 (m, 2H), 3.94 (s, 3H), 7.49 (m, 2H), 7.69 (s, 1H), 8.01 (d, 1H), 8.06 (s, 1H), 8.33 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 277:

N-cyclohexyl-3-methoxy-4-[[6-methyl-2-(2-morpholin-4-ylethyl)-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]benzamide

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10-chloro-6-methyl-2-(2-morpholin-4-ylethyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 160; 95 mg, 0.29 mmol), -amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 86 mg, 0.35 mmol) and p-toluenesulphonic acid monohydrate (110 mg, 0.58 mmol) were heated together in IPA (4 mL) by microwave irradiation at 150 ^{0}C for 20 minutes. The reaction mixture was loaded onto an SCX-2 (5g) column pre-wet with methanol; the column was washed with methanol and the product eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated. The resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (56 mg, 36%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.15 (m, 1H), 1.32 (m, 4H), 1.72 (m, 6H), 2.39 (m, 4H), 2.60 (m, 4H), 3.17 (s, 3H), 3.55 (t, 4H), 3.73 (m, 4H), 3.94 (s, 3H), 7.48 (m, 2H), 7.72 (s, 1H), 8.01 (d, 1H), 8.06 (s, 1H), 8.30 (d, H); MS m/z 538 $[M+H]^+$.

Example 278:

4-[(2-cyclopentyl-4,4-dimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 127; 62 mg, 0.21 mmol) and 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 161; 63 mg, 0.21 mmol) were taken up in 4-methyl-2-pentanol (2 mL) and p-toluenesulphonic acid monohydrate (81 mg, 0.42 mmol) added. The reaction mixture was heated at 160 °C by microwave irradiation for 60 minutes. The cooled reaction mixture was treated with a mixture of methanol & water (5:2 v/v, 7 mL) . The resultant solution was loaded onto an SCX-3 cartridge (5 g) pre-wet with methanol. The cartridge was washed through with Methanol (~40 mL). Products were then eluted with 2M ammonia in methanol (~30 mL). The ammoniacal solution was evaporated and the resultant material was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (64 mg, 54%).

1H NMR (400.132 MHz, DMSO-d6) δ 0.90 - 0.95 (2H, m), 1.14 (6H, s), 1.41 - 1.50 (3H, m), 1.54 - 1.68 (4H, m), 1.71 - 1.78 (2H, m), 1.83 - 1.96 (4H, m), 2.01 - 2.10 (1H, m), 2.15 - 2.23 (2H, m), 2.42 (3H, s), 2.95 - 3.01 (2H, m), 3.27 - 3.28 (2H, m), 3.95 (3H, s), 4.28 - 4.39 (1H,

m), 5.23 (1H, quintet), 7.45 - 7.49 (2H, m), 7.59 (1H, s), 7.88 - 7.90 (2H, m), 8.35 (1H, d), 9.45 (1H, s); MS m/z 562 $[M+H]^+$.

Example 279:

4-(9'-cyclopentyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5'H)-one (Intermediate 131; 256 mg, 0.875 mmol) and 4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 162; 255 mg, 0.875 mmol) and the p-toluenesulphonic acid monohydrate (416 mg, 2.19 mmol) and 4-Methyl-2-pentanol (5 mL) were heated by microwave irradiation for 30 minutes at 160 °C. The cooled reaction mixture was dissolved up in methanol (50 mL) and loaded onto a SCX-2 cartridge (20 g) pre-wet with methanol. The cartridge was washed through with methanol (3 x 35 mL) and the product eluted with 7 *N* methanolic ammonia (~100 mL). The ammoniacal solution was evaporated and the resultant material purified on a silica column loaded as a solution in DCM (20 mL) and eluted with a linear gradient of 0 to 10% 7N NH_3/MeOH in DCM. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid after trituration under diethyl ether (104 mg, 22%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.77 - 0.80 (2H, m), 0.93 - 1.00 (2H, m), 1.17 - 1.30 (4H, m), 1.34 - 1.37 (2H, m), 1.47 (1H, s), 1.62 - 1.68 (4H, m), 1.88 - 1.93 (5H, m), 2.43 (3H, s), 2.40 - 2.49 (2H, m), 3.02 (2H, d), 3.27 (2H, s), 4.37 - 4.49 (1H, m), 4.98 - 5.07 (1H, m), 5.67 (1H, d), 7.11 (1H, d), 7.20 (1H, s), 7.41 - 7.44 (1H, m), 7.45 - 7.48 (1H, m), 7.63 (1H, s), 8.46 (1H, t); MS m/z 548 $[M+H]^+$.

Example 280:

4-(9'-cyclopentyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5'H)-one (Intermediate 131; 293 mg, 1.0 mmol) and 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 161; 303 mg, 1.0 mmol) and the p-toluenesulphonic acid monohydrate (476 mg, 2.5 mmol) and 4-Methyl-2-pentanol (10 mL) were combined and heated with stirring at 120 °C overnight. The cooled reaction mixture was dissolved up in methanol (60 mL) and loaded onto a SCX-2 cartridge (20 g) pre-wet with methanol. The cartridge was washed through with methanol (3 x 35 mL) and the product eluted with 7 *N* methanolic ammonia (~100 mL). The ammoniacal solution was evaporated and the resultant material purified on a silica column loaded as a solution in DCM (17 mL) and eluted with a linear gradient of 0 to 10% 2N NH_3/MeOH in DCM. Product containing fractions were combined and evaporated and the resultant material triturated under diethyl ether. The resultant filtered solid was treated with warm DMF (3 mL) and acetonitrile (8 mL) upon cooling in an ice/water bath a solid precipitate formed which was filtered and dried to yield the title compound as a white solid (251 mg, 45%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.77 - 0.79 (2H, m), 0.96 (2H, d), 1.19 - 1.33 (4H, m), 1.35 - 1.37 (2H, m), 1.44 - 1.48 (1H, m), 1.60 - 1.68 (4H, m), 1.85 - 1.98 (5H, m), 2.41 - 2.50 (2H, m), 2.43 (3H, s), 3.02 (2H, d), 3.25 (2H, s), 3.90 (3H, s), 4.41 - 4.46 (1H, m), 5.00 - 5.09 (1H, m), 5.75 (1H, d), 7.16 (1H, dd), 7.36 (1H, d), 7.55 (1H, s), 7.67 (1H, s), 7.75 (1H, s), 8.39 (1H, d); MS m/z 560 $[M+H]^+$.

Example 281:

3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

To a stirred solution of 3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzoic acid (Intermediate 163; 80 mg, 0.20 mmol), HATU (115 mg, 0.30 mmol) and 4-amino-1-methylpiperidine (Fluorochem; 35 mg, 0.30 mmol) in DMF (5 mL) was added diisopropylethylamine (105 µl, 0.60 mmol). The mixture was stirred for 2 hours at room temperature and then absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (5% ammonia in methanol/DCM) to yield the title compound as a white foam (87 mg, 88%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.26 (6H, d), 1.44 (3H, t), 1.55 - 1.65 (2H, m), 1.77 (2H, d), 1.92 - 1.98 (2H, m), 2.18 (3H, s), 2.60 (2H, m), 2.79 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.70 - 3.78 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.49 - 7.53 (2H, m), 7.67 (1H, s), 8.05 (2H, m), 8.41 (1H, d); MS m/z 496 $[M+H]^+$.

Example 282:

3-ethoxy-N-(1-ethyl-4-piperidyl)-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of **Example 281**, on a 0.2 mmol scale, utilising 4-amino-1-ethylpiperidine (Fluorochem; 39 mg, 0.3 mmol), as a white foam (67 mg, 66%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.01 (3H, t), 1.26 (6H, d), 1.44 (3H, t), 1.52 - 1.62 (2H, m), 1.77 - 1.80 (2H, m), 1.94 (2H, m), 2.34 (2H, q), 2.60 (2H, m), 2.89 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.72 - 3.80 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.48 - 7.52 (2H, m), 7.67 (1H, s), 8.05 (2H, m), 8.41 (1H, d); MS m/z 510 $[M+H]^+$.

Example 283:

3-ethoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 281, on a 0.2 mmol scale, utilising Endo-9-methyl-9-azabicyclo[3,3,1]nonane-3-one (Chempacific; 47 mg, 0.3 mmol), as a white foam (71 mg, 66%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.94 (2H, d), 1.27 (6H, d), 1.41 – 1.49 (6H, m), 1.89 - 1.96 (2H, m), 2.06 (1H, m), 2.15 - 2.23 (2H, m), 2.42 (3H, s), 2.61 (2H, m), 2.99 (2H, d), 3.18 (3H, s), 3.63 (2H, m), 4.22 (2H, q), 4.30 - 4.38 (1H, m), 4.78 - 4.85 (1H, m), 7.49 - 7.53 (2H, m), 7.67 (1H, s), 7.90 (1H, d), 8.07 (1H, s), 8.42 (1H, d); MS m/z 536 $[M+H]^+$.

Example 284:

3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

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10-Chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 10; 100 mg, 0.39mmol), 4-amino-3-ethoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 166; 104 mg, 0.39 mmol) and 4-toluenesulphonic acid monohydrate (187 mg, 0.98 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The cooled reaction mixture was absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified preparative reverse phase HPLC to yield the title compound as a white solid (114 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.26 (6H, d), 1.44 (3H, t), 1.73 - 1.81 (1H, m), 2.12 - 2.20 (1H, m), 2.27 (3H, s), 2.37 - 2.46 (2H, m), 2.57 - 2.70 (4H, m), 3.18 (3H, s), 3.62 (2H, m), 4.21 (2H, q), 4.38 - 4.44 (1H, m), 4.78 - 4.85 (1H, m), 7.51 - 7.55 (2H, m), 7.67 (1H, s), 8.07 (1H, s), 8.28 (1H, d), 8.41 (1H, d); MS m/z 482 $[M+H]^+$.

Example 285:

N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.26 mmol scale, utilising 4-amino-N-((1s,4s)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide (Intermediate 167; 66 mg, 0.36 mmol), as a white solid (39 mg, 29%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.26 (6H, d), 1.42 - 1.54 (7H, m), 1.72 - 1.80 (2H, m), 1.86 - 1.90 (2H, m), 2.99 – 2.03 (1H, m), 2.19 (6H, s), 2.60 (2H, m), 3.18 (3H, s), 3.62 (2H, m), 3.89 - 3.93 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.51 - 7.56 (2H, m), 7.66 (1H, s), 8.00 (1H, d), 8.07 (1H, s), 8.41 (1H, d); MS m/z 525 $[M+H]^+$.

Example 286:

N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.26 mmol scale, utilising 4-amino-N-((1r,4r)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide (Intermediate 168; 66 mg, 0.26 mmol), as a white solid (80 mg, 59%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.23 - 1.39 (10H, m), 1.44 (3H, t), 1.83 - 1.91 (4H, m), 2.11 - 2.19 (7H, m), 2.60 (2H, m), 3.18 (3H, s), 3.62 (2H, m), 3.71 - 3.75 (1H, m), 4.21 (2H, q), 4.78 - 4.85 (1H, m), 7.48 - 7.52 (2H, m), 7.67 (1H, s), 8.01 (1H, d), 8.07 (1H, s), 8.41 (1H, d); MS m/z 525 $[M+H]^+$.

Example 287:

5-ethoxy-2-fluoro-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.39 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 169; 116mg, 0.39 mmol), heating at 140 °C for 2 hours, as a white solid (73 mg, 37%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.27 (6H, d), 1.42 (3H, t), 1.52 - 1.62 (2H, m), 1.78 (2H, d), 1.99 (2H, t), 2.17 (3H, s), 2.62 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.64 (2H, m), 3.69 – 3.79 (1H, m), 4.18 (2H, q), 4.77 - 4.84 (1H, m), 7.20 (1H, d), 7.74 (1H, d), 7.79 - 7.82 (1H, m), 8.10 (1H, s), 8.35 (1H, d); MS m/z 515 $[M+H]^+$.

Example 288:

5-ethoxy-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.39 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 170; 132mg, 0.39 mmol), heating at 140 °C for 2 hours, as a white solid (92 mg, 43%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.92 (2H, d), 1.28 (6H, d), 1.39 – 1.46 (6H, m), 1.87 - 1.94 (2H, m), 1.99 - 2.10 (1H, m), 2.17 – 2.25 (2H, m), 2.42 (3H, s), 2.62 (2H, m), 2.98 (2H, d), 3.19 (3H, s), 3.64 (2H, m), 4.18 (2H, q), 4.26 - 4.34 (1H, m), 4.78 - 4.85 (1H, m), 7.22 (1H, d), 7.65 - 7.68 (1H, m), 7.75 (1H, d), 8.11 (1H, s), 8.36 (1H, d); MS m/z 555 $[M+H]^+$.

Example 289:

5-chloro-2-fluoro-N-(1-methyl-4-piperidyl)-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

4-amino-5-chloro-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 173; 91 mg, 0.32 mmol), 10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 178; 100 mg, 0.35 mmol) and XANTPHOS (17 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (225 mg, 0.64 mmol) was added and the system purged with a stream of nitrogen for 15 minutes before tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, which was washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (2.5% 3.5N ammonia in methanol/DCM) to yield the title compound as a white solid (96mg, 56%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.12 (6H, s), 1.21 (6H, d), 1.50 - 1.60 (2H, m), 1.77 - 1.80 (2H, m), 1.93 – 2.00 (2H, m), 2.17 (3H, s), 2.74 (2H, d), 3.21 (3H, s), 3.38 (2H, s), 3.67 - 3.72 (1H, m), 5.07 - 5.14 (1H, m), 7.67 (1H, d), 8.03 – 8.08 (3H, m), 8.31 - 8.36 (1H, m); MS m/z 532 $[M+H]^+$.

Example 290:

5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 289, on a 0.39 mmol scale, utilising 4-amino-5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide (Intermediate 174; 96 mg, 0.32 mmol), as a white solid (67 mg, 38%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.00 (3H, t), 1.12 (6H, s), 1.21 (6H, d), 1.48 - 1.58 (2H, m), 1.80 (2H, d), 1.96 (2H, t), 2.32 (2H, q), 2.84 (2H, d), 3.21 (3H, s), 3.38 (2H, s), 3.68 - 3.76 (1H, m), 5.07 - 5.14 (1H, m), 7.67 (1H, d), 8.03 – 8.07 (3H, m), 8.32 - 8.36 (1H, m); MS m/z 546 $[M+H]^+$.

Example 291:

5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 289, on a 0.39 mmol scale, utilising 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 175; 100 mg, 0.32 mmol), as a white solid (109 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.12 (6H, s), 1.17 - 1.37 (8H, m), 1.46 – 1.58 (2H, m), 1.68 – 1.94 (4H, m), 2.13 - 2.18 (7H, m), 3.20 (3H, s), 3.38 (2H, s), 3.64 – 3.71 and 3.91 - 4.95 (each 0.5H, m), 5.08 – 5.15 (1H, m), 7.62 - 7.67 (1H, m), 7.98 – 8.04 (3H, m), 8.29 - 8.34 (1H, m); MS m/z 560 $[M+H]^+$.

Example 292:

2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 178; 100 mg, 0.35mmol), 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 95 mg, 0.35 mmol) and p-toluenesulphonic acid monohydrate (169 mg, 0.88 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX column, which was washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified preparative reverse phase HPLC to yield the title compound as a white solid (60 mg, 33%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.12 (6H, s), 1.23 (6H, d), 1.68 - 1.76 (1H, m), 2.13 - 2.22 (1H, m), 2.27 (3H, s), 2.36 - 2.45 (2H, m), 2.59 - 2.64 (1H, m), 2.67 - 2.71 (1H, m), 3.20 (3H, s), 3.39 (2H, s), 3.93 (3H, s), 4.35 – 4.43 (1H, m), 5.09 - 5.16 (1H, m), 7.22 (1H, d), 7.75 (1H, d), 7.96 - 7.99 (1H, m), 8.03 (1H, s), 8.34 (1H, d); MS m/z 516 $[M+H]^+$.

Example 293:

3-ethoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.35 mmol scale, utilising 4-amino-3-ethoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 166; 94 mg, 0.35 mmol), as a white solid (106 mg, 59%). ^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.11 (6H, s), 1.23 (6H, d), 1.44 (3H, t), 1.74 - 1.80 (1H, m), 2.15 - 2.19 (1H, m), 2.27 (3H, s), 2.38 - 2.47 (2H, m), 2.61 - 2.71 (2H, m), 3.20 (3H, s), 3.38 (2H, s), 4.21 (2H, q), 4.39 - 4.43 (1H, m), 5.09 - 5.16 (1H, m), 7.51 - 7.54 (2H, m), 7.63 (1H, s), 7.98 (1H, s), 8.28 (1H, d), 8.38 (1H, d); MS m/z 511 $[M+H]^+$.

Example 294:

N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.26 mmol scale, utilising 4-amino-N-((1s,4s)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide (Intermediate 167; 80 mg, 0.26 mmol), as a white solid (91 mg, 59%). ^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.11 (6H, s), 1.23 (6H, d), 1.40 - 1.55 (7H, m), 1.72 – 1.81 (2H, m), 1.86 - 1.90 (2H, m), 2.01 – 2.05 (1H, m), 2.19 (6H, s), 3.20 (3H, s), 3.38 (2H, s), 3.88 - 3.95 (1H, m), 4.21 (2H, q), 5.09 - 5.16 (1H, m), 7.51 - 7.55 (2H, m), 7.62 (1H, s), 7.97 - 8.01 (2H, m), 8.37 (1H, d); MS m/z 553 $[M+H]^+$.

Example 295:

N-(4-dimethylaminocyclohexyl)-3-ethoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.26 mmol scale, utilising 4-amino-N-((1r,4r)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide (Intermediate 168; 80 mg, 0.26 mmol), as a white solid (77 mg, 54%). ^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.11 (6H, s), 1.23 (6H, d), 1.27 - 1.39 (4H, m), 1.44 (3H, t), 1.83 - 1.92 (4H, m), 2.15 – 2.21 (7H, m), 3.20 (3H, s), 3.38 (2H, s), 3.71 - 3.75 (1H, m),

4.21 (2H, q), 5.09 - 5.15 (1H, m), 7.48 - 7.51 (2H, m), 7.63 (1H, s), 7.98 – 8.02 (2H, m), 8.37 (1H, d); MS m/z 553 $[M+H]^+$.

Example 296:

5-ethoxy-2-fluoro-N-(1-methyl-4-piperidyl)-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.39 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 169; 116 mg, 0.39 mmol), as a white solid (92 mg, 48%). ^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.12 (6H, s), 1.21 - 1.24 (6H, d), 1.42 (3H, t), 1.52 - 1.62 (2H, m), 1.77 - 1.80 (2H, m), 1.94 - 2.00 (2H, m), 2.17 (3H, s), 2.69 - 2.75 (2H, m), 3.20 (3H, s), 3.39 (2H, s), 3.69 - 3.76 (1H, m), 4.18 (2H, q), 5.07 - 5.14 (1H, m), 7.20 (1H, d), 7.71 (1H, d), 7.77 - 7.80 (1H, m), 8.02 (1H, s), 8.31 (1H, d); MS m/z 543 $[M+H]^+$.

Example 297:

5-ethoxy-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 292, on a 0.32 mmol scale, utilising 4-amino-5-ethoxy-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 186; 90 mg, 0.32 mmol), as a white foam (61 mg, 36%). ^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.12 (6H, s), 1.24 (6H, d), 1.42 (3H, t), 1.67 - 1.75 (1H, m), 2.13 - 2.22 (1H, m), 2.26 (3H, s), 2.34 - 2.47 (2H, m), 2.58 - 2.63 (1H, m), 2.66 - 2.70 (1H, m), 3.20 (3H, s), 3.39 (2H, s), 4.18 (2H, q), 4.34 - 4.43 (1H, m), 5.07 - 5.14 (1H, m), 7.21 (1H, d), 7.71 (1H, s), 7.95 - 7.98 (1H, m), 8.02 (1H, s), 8.31 (1H, d); MS m/z 529 $[M+H]^+$.

Example 298:

3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]benzamide

10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 178; 43 mg, 0.15 mmol) and 4-amino-3-fluoro-N-(9-methyl-9-

azabicyclo[3.3.1]non-7-yl)benzamide (Intermediate 162; 44 mg, 0.15 mmol) were combined with p-toluenesulphonic acid monohydrate (72 mg, 0.38 mmol) in 4-methyl-2-pentanol (1 mL) and heated by microwave irradiation for 50 minutes at 160 °C The cooled reaction mixture was diluted with methanol (5 mL) and loaded onto an SCX-3 cartridge (2 g) pre-wet with Methanol. The cartridge was washed with methanol (2 x 3 mL) and product eluted with 7 *N* methanolic ammonia (10 mL). The basic fraction was evaporated to give a yellow gum which was purified by base modified reverse phase HPLC to give the title compound as a white solid (46 mg, 57 %).

^{1}H NMR (400 MHz, DMSO-d6) δ 0.9 (2H, d), 1.1 (6H, s), 1.15 (6H, d), 1.45 (4H, t), 1.9 (2H, m), 2.05 (1H, m), 2.2 (3H, m), 2.4 (3H, s), 2.95 (2H, d), 3.20 (3H, s), 3.3 (2H, s), 4.3 (1H, m), 5.1 (1H, m), 7.65 (2H, m), 7.95 (2H, m), 8.15 (2H, m), 8.15 (1H, t), 8.55 (1H, s); MS m/z 539 $[M+H]^+$.

Example 299:

3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 178; 75 mg, 0.27 mmol), 4-amino-3-methoxy-N-(1-methylpyrrolidin-3-yl)benzamide (Intermediate 187; 67 mg, 0.27 mmol) and p-toluenesulphonic acid monohydrate (127 mg, 0.66 mmol) were heated at 140 °C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction mixture was loaded onto an SCX-3 column pre-wet with methanol. The column was washed with methanol and eluted with 2% 7N ammonia/methanol to. Product containing fractions were evaporated and the residue dissolved in DMF and purified by base modified reverse phase HPLC to give the title compound as a white solid (23 mg, 17.5%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.08 (6H, s), 1.22 (6H, d), 1.78 (1H, m), 2.18 (1H, m), 2.23 (3H, s), 2.38 (1H, m), 2.41 (1H, m), 2.61 (1H, m), 2.64 (1H, m), 3.18 (3H, s), 3.37 (2H, s), 3.95 (3H, s), 4.41 (1H, m), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 496 $[M+H]^+$.

Example 300:

N-(1-ethyl-4-piperidyl)-3-methoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299, on a 0.27 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 74 mg, 0.27 mmol), as a white solid (31 mg, 22%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.00 (3H, t), 1.10 (6H. s), 1.22 (6H. d), 1.55 (2H, q), 1.78 (2H, d), 1.95 (2H, t), 2.31 (2H, q), 2.89 (2H, d), 3.17 (3H, s), 3.37 (2H, s), 3.75 (1H, m), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 524 $[M+H]^+$.

Example 301:

3-methoxy-N-(2-pyrrolidin-1-ylethyl)-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299, on a 0.27 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 192; 70 mg, 0.27 mmol), as a white solid (52 mg, 38%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.10 (6H, s), 1.22 (6H, d), 1.68 (4H, m), 2.49 (4H, m), 2.60 (2H, t), 3.18 (3H, s), 3.38 (2H, s), 3.40 (2H, m), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 510 $[M+H]^+$.

Example 302:

N-(2-dimethylaminoethyl)-3-methoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299, on a 0.27 mmol scale, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide (Intermediate 194; 63 mg, 0.27 mmol), as a white solid (38 mg, 30%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.10 (6H, s), 1.22 (6H, d), 2.18 (6H, s), 2.39 (2H, t), 3.18 (3H, s), 3.35 (2H, t), 3.37 (2H, s), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 510 $[M+H]^+$.

Example 303:

N-(3-dimethylaminopropyl)-3-methoxy-4-[(4,4,6-trimethyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzamide

The title compound was prepared by an analogous method to the preparation of Example 299, on a 0.27 mmol scale, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide (Intermediate 196; 67 mg, 0.27 mmol), as a white solid (8 mg, 6%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.10 (6H, s), 1.22 (6H, d), 1.68 (2H, m), 2.18 (3H, s), 2.28 (2H, t), 3.17 (3H, s), 3.29 (2H, t), 3.37 (2H, s), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 498 $[M+H]^+$.

Example 304:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

10-chloro-4,4-diethyl-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 198; 100 mg, 0.322 mmol), p-toluene sulphonic acid monohydrate (153 mg, 0.81 mmol) and 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 84 mg, 0.322 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The reaction mixture was loaded on to an SCX column (10 g), pre-wet with methanol, washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound, after drying under vacuum at 70 °C, as a white solid (97 mg, 56%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.25 (d, 6H), 1.63 - 1.49 (m, 4H), 1.70 (sextet, 2H), 2.07 - 2.04 (m, 2H), 2.19 - 2.13 (m, 2H), 2.30 (s, 3H), 2.84 - 2.81 (m, 2H), 3.28 (s, 3H), 3.40 (s, 2H), 4.04 - 3.92 (m, 4H), 5.32 (sextet, 1H), 5.93 (d, 1H), 7.24 (dd, 1H), 7.43 (d, 1H), 7.59 (s, 1H), 7.83 (s, 1H), 8.48 (d, 1H); MS m/z 538 $[M+H]^+$.

Example 305:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 89 mg, 0.322 mmol), as a white solid (89 mg, 30%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.10 (t, 3H), 1.25 (d, 6H), 1.63 - 1.49 (m, 4H), 1.75 - 1.66 (m, 2H), 2.17 - 2.06 (m, 4H), 2.44 (q, 2H), 2.93 - 2.90 (m, 2H), 3.28 (s, 3H), 3.40 (s, 2H), 4.05 - 3.97 (m, 4H), 5.32 (septet, 1H), 5.91 (d, 1H), 7.23 (dd, 1H), 7.43 (d, 1H), 7.59 (s, 1H), 7.83 (s, 1H), 8.47 (d, 1H); MS m/z 552 $[M+H]^+$.

Example 306:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 97 mg, 0.322 mmol), as a white solid (83 mg, 45%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.78 (t, 6H), 1.22 (d, 6H), 1.60 - 1.40 (m, 6H), 1.89 - 1.77 (m, 2H), 2.16 - 2.03 (m, 2H), 2.42 - 2.33 (m, 2H), 3.18 (s, 3H), 3.29 (s, 4H), 3.41 (s, 2H), 3.69 - 3.57 (m, 2H), 3.97 (s, 3H), 4.70 - 4.52 (m, 1H), 5.24 - 5.18 (m, 1H), 7.53 - 7.51 (m, 2H), 7.67 (s, 1H), 7.98 (s, 1H), 8.31 - 8.22 (m, 1H), 8.41 (d, 1H), 9.27 - 9.18 (m, 1H); MS m/z 578 $[M+H]^+$.

Example 307:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-

azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 204; 103 mg, 0.322 mmol), as a white solid (100 mg, 52%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.85 (t, 6H), 1.05 - 1.03 (m, 2H), 1.34 - 1.26 (m, 8H), 1.59 - 1.49 (m, 3H), 1.70 (sextet, 2H), 2.02 - 1.91 (m, 3H), 2.57 - 2.50 (m, 5H), 3.10 - 3.07 (m, 2H), 3.29 (s, 3H), 3.42 (s, 2H), 3.95 (s, 3H), 4.57 - 4.46 (m, 1H), 5.30 (septet, 1H), 6.55 (dd, 1H), 7.57 (d, 1H), 7.64 (s, 1H), 7.85 (s, 1H), 8.38 (d, 1H); MS m/z 596 $[M+H]^+$.

Example 308:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.322 mmol scale, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 95 mg, 0.322 mmol), as a white solid (87 mg, 48%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.85 (t, 6H), 1.10 (t, 3H), 1.27 (d, 6H), 1.75 - 1.49 (m, 6H), 2.08 - 2.06 (m, 2H), 2.20 - 2.14 (m, 2H), 2.44 (q, 2H), 2.88 - 2.85 (m, 2H), 3.29 (s, 3H), 3.42 (s, 2H), 3.95 (s, 3H), 4.10 - 4.00 (m, 1H), 5.33 - 5.26 (m, 1H), 6.68 (dd, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 7.85 (s, 1H), 8.38 (d, 1H); MS m/z 570 $[M+H]^+$.

Example 309:

4-[(4,4-diethyl-6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 304, on a 0.33 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol), as a white solid (76 mg, 40%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.01 (s, 6H), 1.24 (d, 6H), 1.53 (sextet, 2H), 1.71 (sextet, 2H), 1.86 - 1.81 (m, 4H), 2.57 (s, 2H), 2.72 - 2.68 (m, 4H), 3.28 (s, 3H), 3.40 - 3.39 (m, 4H), 3.97 (s, 3H), 5.34 (septet, 1H), 7.20 (dd, 1H), 7.58 (d, 1H), 7.62 (s, 1H), 7.84 (s, 1H), 8.44 (d, 1H), 9.28 (s, 1H); MS m/z 5780 $[M+H]^+$.

Example 310:

(R)-5-chloro-2-fluoro-4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-methylpyrrolidin-3-yl)benzamide

2'-chloro-9'-isopropyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 208; 88 mg, 0.32mmol), 4-amino-5-chloro-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 207; 101 mg, 0.36 mmol) and XANTPHOS (17 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (229 mg, 0.65 mmol) was added and the system purged with a stream of nitrogen for 15 minutes before tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, which was washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (2.5% 7N ammonia in MeOH/DCM) to yield the title compound as a pale yellow foam (148 mg, 90%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.70 - 0.73 (2H, m), 0.94 - 0.96 (2H, m), 1.15 (6H, d), 1.67 - 1.75 (1H, m), 2.12 - 2.21 (1H, m), 2.26 (3H, s), 2.33 - 2.43 (2H, m), 2.56 - 2.62 (1H, m), 2.67 - 2.71 (1H, m), 3.19 (3H, s), 3.49 (2H, s), 4.31 - 4.40 (1H, m), 4.79 - 4.86 (1H, m), 7.69 (1H, d), 8.04 (2H, m), 8.23 - 8.25 (1H, m), 8.36 - 8.41 (1H, m); MS m/z 516 $[M+H]^+$.

Example 311:

5-chloro-N-(1-ethylpiperidin-4-yl)-2-fluoro-4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)benzamide

The title compound was prepared by an analogous method to the preparation of Example 310, on a 0.29 mmol scale, utilising 4-amino-5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide (Intermediate 174; 87 mg, 0.29 mmol), after purification by base modified reverse phase preparative HPLC, as a white solid (98 mg, 62%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.72 (2H, m), 0.94 (2H, m), 1.00 (3H, t), 1.17 (6H, d), 1.51 - 1.57 (2H, m), 1.80 (2H, d), 1.96 (2H, t), 2.32 (2H, q), 2.84 (2H, d), 3.18 (3H, s), 3.49 (2H, s), 3.67 – 3.78 (1H, m), 4.79 – 4.86 (1H, m), 7.67 (1H, d), 8.02 - 8.07 (3H, m), 8.38 (1H, d); MS m/z 544 $[M+H]^+$.

Example 312:

4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(2-(pyrrolidin-1-yl)ethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 284, on a 0.36 mmol scale, utilising 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 94 mg, 0.36 mmol), heating at 140 °C for 2 hours, as a white solid (65 mg, 36%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.69 (2H, t). 0.93 (2H, t), 1.19 (6H, d), 1.69 – 1.72 (4H, s), 2.71 (4H, s), 2.80 (2H, s), 3.17 (3H, s), 3.39 – 3.41 (2H, t), 3.48 (2H, s), 3.95 (3H, s), 4.82 – 4.86 (1H, m), 7.49 (1H, d), 7.50 (1H, s), 7.63 (1H, s), 7.99 (1H, s), 8.32 (1H, t), 8.43 (1H, d); MS m/z 509 $[M+H]^+$.

Example 313:

N-(3-(dimethylamino)-2,2-dimethylpropyl)-4-(9'-isopropyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxybenzamide

The title compound was prepared by an analogous method to the preparation of **Example 284**, on a 0.36 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide (Intermediate 206; 100 mg, 0.36 mmol), heating at 140 °C for 2 hours, as a white solid (78 mg, 42%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.69 (2H, t), 0.89 (6H, s), 0.93 (2H, t), 1.18 (6H, d), 2.21 (2H, s), 2.25 (6H, s), 3.17 (3H, s), 3.21 (2H, d), 3.48 (2H, s), 3.95 (3H, s), 4.82 – 4.86 (1H, m), 7.49 (1H, d), 7.50 (1H, s), 7.63 (1H, s), 7.99 (1H, s), 8.32 (1H, t), 8.43 (1H, d); MS m/z 525 $[M+H]^+$.

Example 314:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-propyl-4-piperidyl)benzamide

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Example 111; 231 mg, 0.56 mmol), DIPEA (0.3 mL, 1.68 mmol) and HATU (283 mg, 0.75 mmol) were stirred together in DMA (4 mL) at ambient temperature for 10 minutes. 4-amino-1-propylpiperidine (Fluorochem; 100 mg, 0.70 mmol) was added and the mixture stirred at room temperature for 4 hours. The reaction mixture was loaded onto an SCX-2 (10g) column pre-wet with MeOH. The column was washed with MeOH (x2) and the product eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC. Product containing fractions were combined and evaporated to yield the title compound as a gum (194 mg, 65%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.86 (t, 3H), 1.44 (m, 2H), 1.66 (m, 10H), 1.94 (m, 4H), 2.24 (t, 2H), 2.59 (m, 2H), 2.87 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.76 (m, 1H), 3.95 (s, 3H), 4.82 (m, 1H), 7.48 (m, 2H), 7.72 (s, 1H), 8.05 (d, 1H), 8.08 (s, 1H), 8.38 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 315:

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-dimethylaminoethyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 80 mg, 0.285 mmol) and 4-amino-3-chloro-N-(2-dimethylaminoethyl)benzamide (Intermediate 213; 69 mg, 0.285 mmol), p-toluenesulphonic acid monohydrate (136 mg, 0.713 mmol) were combined in 4-Methyl-2-pentanol (2 mL) and heated at 100 °C overnight. Methanol was added to the cooled reaction mixture and the solution loaded onto an SCX-3 column (5 g) pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were evaporated and the residue dissolved in DCM with a little MeOH. The resultant solution was purified on a silica column, eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (21 mg, 15%).

^{1}H NMR (399.902 MHz, CDCl3) δ1.56 - 1.79 (m, 6H), 2.02 (m, 2H), 2.29 (s, 6H), 2.53 (m, 2H), 2.68 (m, 2H), 3.30 (s, 3H), 3.51 (m, 2H), 3.70 (m, 2H), 4.87 (m, 1H), 6.71 (s, 1H), 7.53 (s, 1H), 7.68 (m, 1H), 7.83 (m, 1H), 7.95 (s, 1H), 8.63 (d, 1H); MS m/z 486 $[M+H]^+$.

Example 316:

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 80 mg, 0.285 mmol) and 4-amino-3-chloro-N-(1-ethyl-4-piperidyl)benzamide (Intermediate 212; 76 mg, 0.285 mmol), p-toluenesulphonic acid monohydrate (136 mg, 0.713 mmol) were combined in 4-Methyl-2-pentanol (2 mL) and heated at 100 °C overnight. Methanol was added to the cooled reaction mixture and the solution loaded onto an SCX-3 column (5 g) pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were evaporated and the residue dissolved in DCM with a little MeOH. The resultant solution was purified on a silica column, eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 10% 2M ammonia in MeOH / DCM. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (22 mg, 15%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.11 (t, 3H), 1.54 - 1.79 (m, 8H), 2.08 (m, 6H), 2.44 (q, 2H), 2.68 (m, 2H), 2.92 (m, 2H), 3.30 (s, 3H), 3.70 (m, 2H), 3.99 (m, 1H), 4.87 (m, 1H), 5.84 (d, 1H), 7.54 (s, 1H), 7.62 (m, 1H), 7.80 (m, 1H), 7.96 (s, 1H), 8.64 (d, 1H); MS m/z 526 $[M+H]^+$.

Example 317:

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.356 mmol scale, utilising 4-amino-3-chloro-N-(3-dimethylaminopropyl)benzamide (Intermediate 214; 91 mg, 0.356 mmol), as a white solid (31 mg, 17%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.55 - 1.80 (m, 8H), 2.03 (m, 2H), 2.33 (s, 6H), 2.53 (m, 2H), 2.68 (m, 2H), 3.30 (s, 3H), 3.56 (m, 2H), 3.70 (m, 2H), 4.88 (m, 1H), 7.54 (s, 1H), 7.65 (d, 1H), 7.84 (s, 1H), 7.96 (s, 1H), 8.57 (s, 1H), 8.63 (d, 1H); MS m/z 500 $[M+H]^+$.

Example 318:

3-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.356 mmol scale, utilising 4-amino-3-chloro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 215; 95 mg, 0.356 mmol), as a white solid (39 mg, 21%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.56 - 1.82 (m, 10H), 2.02 (m, 2H), 2.58 (m, 4H), 2.70 (m, 4H), 3.30 (s, 3H), 3.55 (m, 2H), 3.70 (m, 2H), 4.87 (m, 1H), 6.74 (s, 1H), 7.53 (s, 1H), 7.67 (m, 1H), 7.84 (m, 1H), 7.95 (s, 1H), 8.63 (d, 1H); MS m/z 512 $[M+H]^+$.

Example 319:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[1-(cyclopropylmethyl)-4-piperidyl]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 314, on a 0.24 mmol scale, utilising 1-(cyclopropylmethyl)-4-piperidinamine di hydrochloride (Aldrich; 95 mg, 0.356 mmol) and DIPEA (210 µL, 1.3 mmol) and stirring at ambient temperature for 24 hours, as a white solid (85 mg, 64%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.00 (m, 2H), 0.38 (m, 2H), 0.75 (m, 1H), 1.60 (m, 10H), 1.90 (m, 4H), 2.11 (d, 2H), 2.51 (m, 2H), 2.91 (m, 2H), 3.10 (s, 3H), 3.55 (m, 2H), 3.68 (m, 1H), 3.87 (s, 3H), 4.74 (m, 1H), 7.40 (m, 2H), 7.64 (s, 1H), 7.98 (d, 1H), 8.00 (s, 1H), 8.30 (d, 1H); MS m/z 548 $[M+H]^+$.

Example 320:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-methoxy-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.285 mmol scale, utilising 4-amino-2-chloro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide (Intermediate 216; 85 mg, 0.285 mmol), as a white solid (108 mg, 70%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.61 (m, 4H), 1.76 (m, 4H), 2.09 (m, 4H), 2.20 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.78 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.03 (m, 1H), 4.97 (m, 1H), 6.56 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.62 (s, 1H); MS m/z 542 $[M+H]^+$.

Example 321:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-[(3R)-pyrrolidin-3-yl]benzamide

tert-butyl (3R)-3-[[5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoyl]amino]pyrrolidine-1-carboxylate (Example 324; 175 mg, 0.29 mmol) was dissolved in 1,4-dioxane (5 mL) and 4M $HCl_{(aq)}$ in 1,4-dioxane (10 mL) added. The mixture was stirred at room temperature for 2 hours. TFA (2 mL) was added an the reaction stirred for a further 1 hour. The reaction was concentrated, dissolved in DCM (10 mL) and TFA (3 mL) added. The reaction was stirred at room temperature for 1 hour, concentrated and the residue dissolved in methanol, absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the residue purified by column chromatography (7.5% ammonia in methanol/DCM) to yield the title compound as a white foam (112 mg, 77%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.58 - 1.77 (8H, m), 1.92 - 2.02 (3H, m), 2.60 - 2.77 (5H, m), 2.87 - 3.01 (2H, m), 3.19 (3H, s), 3.65 (2H, m), 4.23 - 4.31 (1H, m), 4.76 - 4.84 (1H, m), 7.70 (1H, d), 8.07 - 8.17 (3H, m), 8.33 (1H, d); MS m/z 502 $[M+H]^+$.

Example 322:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoic acid (Intermediate 219; 100 mg, 0.23 mmol), 4-amino-1-methylpiperidine (Fluorochem; 40 mg, 0.35 mmol) and HATU (132 mg, 0.35 mmol) were stirred in DMF (3 mL). *N,N*-diisopropylethylamine (121 µl, 0.69 mmol) was added and the mixture heated at 50 °C for 2 hours. The mixture was cooled and absorbed on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and the residue purified by base modified reverse phase preparative chromatography to yield the title compound as a white solid (58 mg, 48%)

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.50 - 1.80 (10H, m), 1.92 - 1.99 (4H, m), 2.17 (3H, s), 2.61 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.63 - 3.74 (3H, m), 4.76 - 4.84 (1H, m), 7.67 (1H, d), 8.07 (1H, d) 8.14 (1H, m), 8.31 - 8.36 (1H, m); MS m/z 530 $M+H]^+$.

Example 323:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 322, on a 0.23 mmol scale, utilising 4-amino-1-ethylpiperidine (Fluorochem; 45 mg, 0.35 mmol), as a white solid (60 mg, 48%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.00 (3H, t), 1.59 (8H, d), 1.80 (2H, d), 1.93 - 1.98 (4H, m), 2.32 (2H, q), 2.61 (2H, m), 2.84 (2H, d), 3.19 (3H, s), 3.63 - 3.76 (3H, m), 4.76 - 4.84 (1H, m), 7.67 (1H, d), 8.08 (1H, d), 8.14 (2H, d), 8.31 - 8.36 (1H, m); MS m/z 544 $[M+H]^+$.

Example 324:

tert-butyl (3R)-3-[[5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoyl]amino]pyrrolidine-1-carboxylate

The title compound was prepared by an analogous method to the preparation of Example 322, on a 0.46 mmol scale, utilising boc-R-(3R)-aminopyrrolidine (Aldrich; 130 mg, 0.75 mmol)

and purification by normal phase chromatography (5% MeOH/DCM), as a white foam (179 mg, 65%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.42 (9H, s), 1.56 – 1.74 (7H, m), 1.87 – 1.97 (3H, m), 2.09 – 2.13 (1H, m), 2.60 – 2.64 (2H, m), 3.19 (4H, m), 3.37 - 3.44 (1H, m), 3.49 – 3.57 (1H, m), 3.63 – 3.67 (2H, m), 4.38 (1H, m), 4.80 (1H, m), 7.70 (1H, d), 8.09 - 8.25 (2H, m), 8.32 - 8.37 (1H, m), 8.44 (1H, d); MS m/z 602 $[M+H]^+$.

Example 325:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-[(3R)-pyrrolidin-3-yl]benzamide (Example 321; 95 mg, 0.19 mmol) was dissolved in 37% aqueous formaldehyde solution (1.1 mL) and acetic acid (120 µl, 1.89 mmol). Sodium acetate (156 mg, 1.89 mmol) was added and the mixture cooled in an ice/water bath. Sodium cyanoborohydride (12 mg, 0.19 mmol) was added and the mixture allowed to warm to room temperature. After stirring for 1 hour, the mixture was absorbed on to an SCX column, and subsequently washed with methanol and eluted with ammonia in methanol. The product containing fractions were concentrated and purified by column chromatography (2% 7N ammonia in methanol/DCM) to yield the title compound as a white foam (69mg, 70%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.58 - 1.73 (7H, m), 1.90 – 1.96 (2H, m), 2.12 – 2.21 (1H, m), 2.26 (3H, s), 2.38 - 2.43 (3H, m), 2.56 – 2.64 (3H, m), 2.67 - 2.71 (1H, m), 3.19 (3H, s), 3.63 – 3.67 (2H, m), 4.34 - 4.36 (1H, m), 4.80 (1H, m), 7.69 (1H, d), 8.14 (2H, m), 8.27 (1H, d), 8.33 (1H, d); MS m/z 516 $[M+H]^+$.

Example 326:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-methoxy-N-[(3R)-pyrrolidin-3-yl]benzamide (Example 55; 100 mg, 0.21 mmol) in DMF (3 mL) was added triethylamine (59 ul, 0.42 mmol) and ethyl bromide (Acros; 24 ul,

0.31 mmol). The reaction mixture was heated to 90 °C by microwave irradiation for 1 hour. The cooled reaction mixture was poured onto an SCX-3 cartridge (5 g) and the cartridge washed through with methanol (40 mL) and then eluted with 2M ammonia in methanol. Ammoniacal fractions were combined and evaporated. The residue was purified by base modified reverse phase preparative HPLC and product containing fractions combined and evaporated to yield the title compound as a white solid (27 mg, 25%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.97 (t, 3H), 1.51 - 1.75 (m, 7H), 1.87 (m, 2H), 2.08 (m, 1H), 2.32 - 2.68 (m, 8H), 3.10 (s, 3H), 3.56 (m, 2H), 3.88 (s, 3H), 4.32 (m, 1H), 4.75 (m, 1H), 7.44 (m, 2H), 7.65 (s, 1H), 8.01 (s, 1H), 8.22 (d, 1H), 8.31 (d, 1H); MS m/z 508 $[M+H]^+$.

Example 327:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(3R)-1-propylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 326, on a 0.21 mmol scale, utilising n-propyl bromide (Aldrich; 29 µL, 0.31 mmol) and heating for 45 minutes at 90 °C , as an off-white gum (63 mg, 58%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.88 (t, 3H), 1.45 (m, 2H), 1.56 - 1.82 (m, 7H), 1.95 (m, 2H), 2.14 (m, 1H), 2.35 (m, 2H), 2.44 (m, 2H), 2.61 (m, 3H), 2.74 (m, 1H), 3.17 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.39 (m, 1H), 4.82 (m, 1H), 7.50 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.27 (d, 1H), 8.38 (d, 1H); MS m/z 522 $[M+H]^+$.

Example 328:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(3R)-1-(2-methoxyethyl)pyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 326, on a 0.21 mmol scale, utilising 2-bromoethyl methylether (Aldrich; 30 µL, 0.31 mmol) and heating for 45 minutes at 90 °C , as an off-white gum (57 mg, 50%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.57 - 1.82 (m, 7H), 1.95 (m, 2H), 2.13 (m, 1H), 2.52 (d, 2H)[obscured by DMSO], 2.59 (m, 4H), 2.69 (m, 1H), 2.79 (m, 1H), 3.17 (s, 3H), 3.24 (s, 3H), 3.43 (t, 2H), 3.63 (m, 2H), 3.95 (s, 3H), 4.39 (m, 1H), 4.82 (m, 1H), 7.51 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.29 (d, 1H), 8.38 (d, 1H); MS m/z 538 $[M+H]^+$.

Example 329:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide

4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 162; 1.0 g, 3.43 mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 0.96 g, 3.43 mmol) and p-toluenesulphonic acid monohydrate (1.63 g, 8.56 mmol) were stirred and heated together at 110 ^{0}C in 4-methyl-2-pentanol (30 mL) for 18 hours. The cooled reaction mixture was diluted with water and methanol and the solution loaded onto an SCX-2 (20g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and the product eluted with 2M NH3/MeOH (2 column volumes). Product containing fractions were combined and evaporated and the residue purified by chromatography on a silica column eluting with a 0-100% gradient of 10% 2M NH_3-MeOH in DCM. Product containing fractions were combined and evaporated to give a foam which on trituration with ethyl acetate yielded, on filtration, the title compound as a white solid (473 mg, 26%) 536 (M+H), ES- 534 (M-H)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.94 (m, 2H), 1.55 (m, 9H), 1.90 (m, 4H), 2.03 (m, 1H), 2.19 (m, 3H), 2.42 (s, 3H), 2.58 (m, 2H), 2.98 (m, 2H), 3.17 (s, 3H), 3.60 (m, 2H), 4.32 (m, 1H), 4.74 (m, 1H), 7.69 (m, 2H), 8.00 (d, 1H), 8.06 (s, 1H), 8.12 (m, 1H), 8.72 (s, 1H); MS m/z 536 [M+H]+.

Example 330:

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoic acid (Intermediate 221; 85 mg, 0.18 mmol), HATU (104 mg, 0.27 mmol) and 4-amino-1-methylpiperidine (32 mg, 0.27m mol) were stirred in DMF (3 mL) and diisopropylethylamine (95 µl, 0.54 mmol) added. The mixture was stirred for 2 hours and absorbed on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the residue purified by column chromatography (4% ammonia in methanol/DCM) to yield the title compound as a white solid (67 mg, 66%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.26 - 1.65 (10H, m), 1.79 (2H, d), 1.98 (2H, t), 2.17 (3H, s), 2.55 (2H + DMSO, m), 2.73 (2H, d), 3.15 (3H, s), 3.53 - 3.55 (2H, m), 3.67 - 3.74 (1H, m), 4.37 (1H, t), 7.65 (1H, d), 7.96 (1H, s), 8.43 (1H, d), 9.01 (1H, s); MS m/z 564 [M+H]+.

Example 331:

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 330, on a 0.21 mmol scale, utilising utilising 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 30 μL, 0.31 mmol) and separation of the cis-isomer by column chromatography, as a white solid (21 mg, 19%).

^{1}H NMR (500.13 MHz, DMSO-d_6) δ1.38 - 1.92 (16H, m), 2.04 – 2.08 (1H, m), 2.18 (6H, s), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.53 – 3.55 (2H, m), 3.9 1 –3.95 (1H, m), 4.39 (1H, m), 7.63 (1H, d), 7.95 (1H, s), 8.39 (1H, d), 9.00 (1H, s); MS m/z 592 [M+H]+.

Example 332:

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 330, on a 0.21 mmol scale, utilising utilising 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 30 μL, 0.31 mmol) and separation of the trans-isomer by column chromatography, as a white solid (42 mg, 39%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.22 – 1.68 (12H, m), 1.80 – 1.85 (2H, m), 1.90 – 1.95 (2H, m), 2.10 - 2.14 (1H, m), 2.18 (6H, s), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.53 - 3.56 (2H, m), 3.63 – 3.71 (1H, m), 4.33 – 4.42 (1H, m), 7.64 (1H, d), 7.95 (1H, s), 8.39 (1H, d), 9.01 (1H, s); MS m/z 592 [M+H]+.

Example 333:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 80 mg, 0.285 mmol), 4-amino-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 228; 80 mg, 0.285 mmol), p-toluenesulphonic acid monohydrate (136 mg, 0.732 mmol) and 4-Methyl-2-pentanol (3 mL) were combined and heated at 100 °C overnight. The cooled reaction mixture was added to an SCX-2 column (5 g), pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC and product containing fractions combined and evaporated to yield the title compound as a cream solid (94 mg, 36%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.63 (m, 2H), 1.77 (m, 8H), 2.06 (m, 2H), 2.58 (m, 4H), 2.68 (m, 2H), 2.72 (m, 2H), 3.30 (s, 3H), 3.60 (m, 2H), 3.71 (m, 2H), 3.95 (s, 3H), 4.91 (m, 1H), 7.31 (m, 1H), 7.57 (d, 1H), 7.72 (s, 1H), 7.95 (s, 1H), 8.40 (d, 1H); MS m/z 526 [M+H]+.

Example 334:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 100 mg, 0.356 mmol), 4-amino-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 229; 83 mg, 0.324 mmol) and caesium carbonate (211 mg, 0.648 mmol) was added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone) palladium (II) (11 mg, 0.019 mmol) and XANTPHOS (17 mg, 0.029 mmol) were added and the mixture heated to 100 °C overnight. The cooled reaction mixture was filtered and the filter cake washed with DCM and the filtrate evaporated. The residue was dissolved in DCM and purified on a silica column eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM over 30 column volumes. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a yellow solid (91 mg, 56%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.64 (m, 2H), 1.75 (m, 5H), 2.05 (m, 2H), 2.30 (m, 1H), 2.41 (m, 4H), 2.67 (m, 4H), 2.89 (m, 1H), 3.30 (s, 3H), 3.71 (m, 2H), 4.65 (m, 1H), 4.88 (m,

1H), 6.95 (m, 1H), 7.30 (m, 1H), 7.81 (m, 1H), 7.96 (s, 1H), 8.45 (m, 1H); MS m/z 500 [M+H]+.

Example 335:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 334, on a 0.324 mmol scale, utilising 4-amino-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 230; 87 mg, 0.324 mmol), as a white solid (117 mg, 70%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.63 (m, 2H), 1.77 (m, 8H), 2.05 (m, 2H), 2.57 (m, 4H), 2.70 (m, 4H), 3.30 (s, 3H), 3.58 (m, 2H), 3.71 (m, 2H), 4.88 (m, 1H), 7.28 (m, 2H), 7.82 (m, 1H), 7.96 (s, 1H), 8.46 (m, 1H); MS m/z 514 [M+H]+.

Example 336:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-methoxy-benzoic acid (Intermediate 231; 100mg, 0.224 mmol), (3R)-1-methylpyrrolidin-3-amine di Hydrochloride (Intermediate 184; 40 mg, 0.235 mmol), HATU (94 mg, 0.246 mmol) and DIPEA (195 µL, 1.12 mmol) were combined in DMF (3 mL) and stirred at room temperature overnight. The reaction mixture was added to an SCX-2 column (5 g) pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (76 mg, 64%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.62 (m, 2H), 1.78 (m, 5H), 2.11 (m, 2H), 2.31 (m, 1H), 2.42 (m, 4H), 2.69 (m, 4H), 2.90 (m, 1H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.68 (m, 1H), 4.97 (m, 1H), 6.97 (m, 1H), 7.38 (s, 1H), 7.63 (s, 1H), 7.93 (s, 1H), 8.61 (s, 1H); MS m/z 528 [M+H]+.

Example 337:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 336, on a 0.224 mmol scale, utilising 4-amino-1-ethyl piperidine (Fluorochem; 32 mg, 0.246 mmol), as a white solid (97 mg, 79%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.11 (t, 3H), 1.60 (m, 4H), 1.75 (m, 4H), 2.09 (m, 4H), 2.19 (m, 2H), 2.44 (m, 2H), 2.68 (m, 2H), 2.88 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.06 (m, 1H), 4.97 (m, 1H), 6.58 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.61 (s, 1H); MS m/z 556 [M+H]+.

Example 338:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 336, on a 0.224 mmol scale, utilising 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 35 mg, 0.246 mmol), as a white solid (84 mg, 66%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.26 - 1.76 (m, 11H), 1.94 (m, 2H), 2.10 (m, 2H), 2.21 (m, 2H), 2.30 (m, 6H), 2.68 (m, 2H), 3.29 (m, 3H), 3.71 (m, 2H), 3.94 (m, 3.5H), 4.25 (m, 0.5H), 4.97 (m, 1H), 6.46 (d, 0.5H), 6.85 (d, 0.5H), 7.39 (s, 0.5H), 7.45 (s, 0.5H), 7.63 (m, 1H), 7.94 (m, 1H), 8.62 (m, 1H); MS m/z 570 [M+H]+.

Example 339:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 336, on a 0.224 mmol scale, utilising Endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 38 mg, 0.246 mmol), as a white solid (84 mg, 64%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.05 (m, 2H), 1.30 (m, 2H), 1.52 - 1.66 (m, 4H), 1.76 (m, 4H), 1.97 (m, 2H), 2.11 (m, 2H), 2.55 (m, 5H), 2.68 (m, 2H), 3.10 (m, 2H), 3.29 (s, 3H), 3.71

(m, 2H), 3.94 (s, 3H), 4.52 (m, 1H), 4.98 (m, 1H), 6.42 (d, 1H), 7.41 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.61 (s, 1H); MS m/z 582 [M+H]+.

Example 340:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[1-(2-methylpropyl)-4-piperidyl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 316, on a 0.49 mmol scale, utilising 1-isobutylpiperidin-4-amine hydrochloride (Ambinter; 96 mg, 0.61 mmol) and DIPEA (340 µL, 1.6 mmol) and stirring at ambient temperature for 24 hours, as a white solid (159 mg, 59%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.87 (d, 6H), 1.68 (m, 11H), 1.94 (m, 4H), 2.04 (d, 2H), 2.59 (m, 2H), 2.84 (m, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.77 (m, 1H), 3.95 (s, 3H), 4.81 (m, 1H), 7.47 (s, 1H), 7.50 (s, 1H), 7.72 (s, 1H), 8.04 (d, 2H), 8.08 (s, 1H), 8.38 (d, 1H); MS m/z 550 [M+H]+.

Example 341:

7-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-methyl-4-piperidyl)benzo[1,3]dioxole-4-carboxamide

7-amino-N-(1-methyl-4-piperidyl)benzo[1,3]dioxole-4-carboxamide (Intermediate 223; 60mg, 0.21mmol), 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 60 mg, 0.21 mmol) and p-toluenesulphonic acid monohydrate (102 mg, 0.53 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 2 hours. The cooled reaction mixture was absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were evaporated and the residue purified by normal phase chromatography (2.5% 7N NH3 in methanol/DCM) and then base modified reverse phase preparative HPLC to yield the title compound as a white solid (35 mg, 32%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.48 – 1.60 (6H, m), 1.63 – 1.69 (2H, m), 1.79 – 1.83 (4H, m), 2.00 - 2.05 (2H, m), 2.17 (3H, s), 2.55 - 2.58 (2H, m), 2.67 - 2.70 (2H, m), 3.17 (3H, s), 3.59 (2H, m), 3.74 - 3.78 (1H, m), 4.69 – 1.77 (1H, m), 6.14 (2H, s), 7.23 (1H, d), 7.27 (1H, d), 7.48 - 7.51 (1H, m), 8.04 (1H, s), 8.60 (1H, s); MS m/z 522 $[M+H]^+$.

Example 342:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-yl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 314, on a 0.49 mmol scale, utilising 1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-amine (CBI Building Blocks; 103 mg, 0.61 mmol) and DIPEA (260 µL, 1.47 mmol) and stirring at ambient temperature for 2 hours, as a single isomer of unspecified stereochemistry, as a white solid (52 mg, 19%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (6H, m), 1.66 (11H, m), 1.94 (2H, m), 2.07 (2H, m), 2.16 (3H, s), 2.59 (2H, m), 2.81 (1H, m), 3.18 (3H, s), 3.63 (3H, m), 3.95 (3H, s), 4.81 (1H, m), 7.49 (2H, m), 7.73 (1H, s), 7.97 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 562 $[M+H]^+$.

Example 343:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-yl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 314, on a 0.49 mmol scale, utilising 1-methyl-3,4,4a,5,6,7,8,8a-octahydro-2H-quinolin-4-amine (CBI Building Blocks; 103 mg, 0.61 mmol) and DIPEA (260 µL, 1.47 mmol) and stirring at ambient temperature for 2 hours, as a single isomer of unspecified stereochemistry, as a white solid (102 mg, 37%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.94 (1H, m), 1.21 (3H, m), 1.44 (2H, m), 1.66 (10H, m), 1.88 (3H, m), 2.10 (2H, m), 2.19 (3H, s), 2.59 (2H, m), 3.18 (3H, s), 3.63 (2H, m), 3.96 (3H, s), 4.17 (1H, m), 4.81 (1H, m), 7.40 (1H, s), 7.45 (2H, d), 7.56 (1H, d), 7.75 (1H, s), 8.08 (1H, s), 8.37 (1H, d); MS m/z 562 $[M+H]^+$.

Example 344:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

4-amino-2-fluoro-5-methoxy-N-(9-methyl-9-azabicyclo[3.3.1]non-7-yl)benzamide (Intermediate 204; 50 mg, 0.16 mmol), 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 1; 45 mg, 0.16 mmol) and p-toluenesulphonic acid monohydrate (76 mg, 0.40 mmol) were stirred and heated together in 4-methyl-2-pentanol (3 mL) at 110 ^{0}C for 18 hours.

A further portion of 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 1; 20 mg, 0.07 mmol) was added and the mixture heated by microwave irradiation at 150 ^{0}C for 1hour and 30 minutes.

The cooled reaction mixture was loaded onto an SCX-3 (5 g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and eluted with 2M NH3/MeOH. Product containing fractions were evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (48 mg, 53%). ^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 (m, 2H), 1.42 (m, 3H), 1.69 (m, 6H), 1.96 (m, 5H), 2.21 (m, 2H), 2.41 (s, 3H), 2.61 (m, 2H), 2.97 (m, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 3.93 (s, 3H), 4.30 (m, 1H), 4.84 (m, 1H), 7.22 (d, 1H), 7.67 (m, 1H), 7.81 (s, 1H), 8.12 (s, 1H), 8.34 (d, 1H); MS m/z 566 [M+H]+.

Example 345:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-fluoro-benzamide

10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 1; 212 mg, 0.75 mmol), 4-amino-N-(1-ethylpiperidin-4-yl)-3-fluorobenzamide (Intermediate 225; 200 mg, 0.75 mmol) and p-toluenesulphonic acid monohydrate (0.335 mL, 1.88 mmol) were suspended in 4-Methyl-2-pentanol (5 mL) and sealed in a microwave tube. The reaction was heated to 160 °C for 30 minutes in the microwave reactor and allowed to cool to room temperature.

The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were

evaporated to dryness to afford the crude product as an orange oil which was purified by base modified reverse phase preparative HPLC. Fractions containing the desired compound were evaporated to dryness to afford the title compound as a white solid (35 mg, 9%).

^{1}H NMR DMSO-d6 δ 0.65 (t, 2H), 0.9 (t, 2H), 1.0 (t. 3H), 1.5 (m, 7H), 1.6 (m, 2H), 1.9 (t, 2H), 2.3 (q, 2H), 2.9 (d, 2H), 3.2 (s, 3H), 3.4 (s, 2H), 3.6 (m, 1H), 4.75 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.6 (s, 1H); MS m/z 510 [M+H]+.

Example 346:

N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

To a solution of 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 1; 70 mg, 0.17 mmol) in DMF (3 mL) was added a solution of 4-(azetidin-1-yl)cyclohexan-1-amine (Intermediate 226; 39 mg, 0.25 mmol) in DMF (1 mL). DIPEA (90 uL, 0.51 mmol) was added, followed by HATU (98 mg, 0.26 mmol). The resultant mixture was stirred at ambient temperature for 4 hours.

The reaction mixture was evaporated and the residue partitioned between DCM (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was separated by gravity elution through a PTFE filter cup and evaporated to an amber gum which was purified by base modified reverse phase preparative HPLC to yield the title compound as an white solid (29 mg, 31%) assigned as the trans isomer.

The cis isomer (Example 347) was isolated as a tan coloured solid (32 mg, 34%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.92 - 1.00 (2H, m), 1.29 - 1.38 (2H, m), 1.57 - 1.99 (15H, m), 2.58 - 2.60 (2H, m), 3.07 (4H, t), 3.17 (3H, s), 3.61 - 3.65 (2H, m), 3.66 - 3.76 (1H, m), 3.95 (3H, s), 4.82 (1H, quintet), 7.45 - 7.48 (2H, m), 7.72 (1H, s), 8.01 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 548 $[M+H]^+$.

Example 347:

N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

The title compound was isolated from the reaction above to produce Example 346 as a tan coloured solid (32 mg, 34%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.30 - 1.40 (2H, m), 1.43 - 1.50 (2H, m), 1.56 - 1.77 (10H, m), 1.86 - 1.98 (4H, m), 2.18 - 2.23 (1H, m), 2.58 - 2.60 (2H, m), 3.07 (4H, t), 3.18 (3H, s), 3.62 - 3.65 (2H, m), 3.77 - 3.87 (1H, m), 3.95 (3H, s), 4.82 (1H, quintet), 7.50 - 7.54 (2H, m), 7.71 (1H, s), 8.04 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 548 $[M+H]^+$.

Example 348:

tert-butyl 3-[[4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoyl]amino]azepane-1-carboxylate

The title compound was prepared by an analogous method to the preparation of Example 314, on a 0.30 mmol scale, utilising tert-butyl 3-aminoazepane-1-carboxylate (Anichem; 78 mg, 0.36 mmol) and DIPEA (151 µL, 0.91 mmol) and stirring at ambient temperature for 19 hours, as an amber gum (153 mg, 83%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.24 - 1.46 (11H, m), 1.50 - 2.00 (14H, m), 2.57 - 2.61 (2H, m), 3.06 - 3.19 & 3.30 - 3.37 (1H, m), 3.18 (3H, s), 3.54 - 3.70 (3H, m), 3.95 (3H, s), 4.08 - 4.22 (1H, m), 4.75 - 4.87 (1H, m), 7.36 - 7.49 (2H, m), 7.74 (1H, s), 8.01 & 8.16 (2 x d, 1H), 8.09 (1H, s), 8.39 (1H, d); MS m/z 608 $(M+H)^+$

Example 349:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(4-piperidyl)benzamide

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 50 mg, 0.16 mmol) and tert-butyl 4-[(4-amino-3-methoxy-benzoyl)amino]piperidine-1-carboxylate (Intermediate 234; 85 mg, 0.24 mmol) were dissolved in 4-methyl-2-pentanol (1 mL) and p-toluenesulphonic acid monohydrate (44 mg, 0.32 mmol) added. The reaction mixture was heated at 90°C by microwave irradiation for 20 minutes and then at 150°C for a further 45 minutes.

The reaction mixture was diluted with water (3 mL) and methanol (3 mL) and the solution poured directly onto an SCX-3 (2 g) cartridge. The cartridge was washed with methanol (30 mL) and then eluted with 2M ammonia in methanol. Evaporation to dryness of the

ammoniacal fractions afforded an amber gum, which was purified by base modified reverse phase, preparative HPLC to yield the title compound as a white solid (32 mg, 38%).
^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.10 (s, 6H), 1.43 (m, 2H), 1.55 - 1.79 (m, 10H), 1.89 (m, 2H), 2.96 (m, 2H), 3.19 (s, 3H), 3.38 (s, 2H), 3.83 (m, 1H), 3.95 (s, 3H), 5.19 (m, 1H), 7.48 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.05 (d, 1H), 8.36 (d, 1H); MS m/z 522 $[M+H]^+$.

Example 350:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 115 mg, 0.37 mmol) and 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 104 mg, 0.37 mmol) were dissolved 4-methyl-2-pentanol (3 mL). p-Toluenesulphonic acid monohydrate (142 mg, 0.74 mmol) was added and mixture heated by microwave irradiation at 160 °C for 1 hour.

After cooling, the reaction mixture was diluted with MeOH (5 mL) and poured directly onto an SCX-3 (5 g) cartridge. The cartridge was washed with methanol (40 mL) and eluted with 2M ammonia in methanol (40 mL). Evaporation to dryness of the ammoniacal fractions afforded a yellow gum which was purified by base modified reverse phase, preparative HPLC to yield the title compound as a white solid (125 mg, 61%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.01 (t, 3H), 1.11 (s, 6H), 1.53 - 1.97 (m, 14H), 2.34 (q, 2H), 2.90 (m, 2H), 3.20 (s, 3H), 3.39 (s, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 5.20 (m, 1H), 7.48 (m, 2H), 7.68 (s, 1H), 8.00 (s, 1H), 8.07 (d, 1H), 8.37 (d, 1H); MS m/z 550 $[M+H]^+$.

Example 351:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.24 mmol scale, utilising 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 68 mg, 0.24 mmol), as a white foam (47 mg, 53%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.90 (s, 6H), 1.11 (s, 6H), 1.62 (m, 4H), 1.75 (m, 2H), 1.90 (m, 2H), 2.21 (s, 2H), 2.29 (s, 6H), 3.21 (m, 5H), 3.40 (s, 2H), 3.96 (s, 3H), 5.20 (m, 1H), 7.42 (m, 1H), 7.47 (d, 1H), 7.70 (s, 1H), 8.00 (s, 1H), 8.39 (d, 1H), 8.44 (t, 1H); MS m/z 552 $[M+H]^+$.

Example 352:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of **Example 350**, on a 0.31 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (**Intermediate 204**; 96 mg, 0.31 mmol) heating by microwave irradiation at 150 ^{0}C for 1 hour, as a white foam (47 mg, 53%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.16 - 1.23 (8H, m), 1.52 - 1.65 (4H, m), 1.73 - 1.83 (5H, m), 1.97 - 2.11 (5H, m), 2.54 - 2.65 (5H, m), 3.17 - 3.26 (2H, m), 3.31 (3H, s), 3.40 (2H, s), 3.96(3H, s), 4.51 - 4.62 (1H, m), 5.29 (1H, quintet), 6.60 - 6.74 (1H, m), 7.57 (1H, d), 7.70 (1H, s), 7.88 (1H, s), 8.39 (1H, d); MS m/z 594 $[M+H]^+$.

Example 353:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.34 mmol scale, utilising 4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide **(Intermediate 162;** 100 mg, 0.34 mmol) heating by microwave irradiation at 150 ^{0}C for 40 minutes, as a white foam (52 mg, 27%).

^{1}H NMR (399.902 MHz, DMSO-d6) δ 0.9 (2H, d), 1.1 (6H, s), 1.45 (3H, m), 1.55 (4H, m), 1.7 (2H, m), 1.8 (2H, m), 1.9 (2H, m), 2.05 (1H, m) 2.2 (2H, m), 2.40 (2H, s), 3.0 (2H, d), 3.2 (3H, s), 3.35 (2H, s) 4.3 (1H, m), 5.2 (1H, m), 7.65 (1H, d), 7.70 (1H, d), 8.0 (2H, m), 8.15 (1H, t), 8.65 (1H, s); MS m/z 564 $[M+H]^+$.

Example 354:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 99 mg, 0.32 mmol) heating thermally at 140 ^{0}C for 2 hours, as a white solid (104 mg, 56%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.94 (2H, d), 1.10 (6H, s), 1.42 - 1.49 (3H, m), 1.63 (4H, s), 1.75 (2H, s), 1.89 - 1.96 (3H, m), 1.92 - 1.95 (2H, m), 2.16 - 2.21 (2H, m), 2.42 (3H, s), 2.99 (2H, d), 3.20 (3H, s), 3.39 (2H, s), 3.96 (3H, s), 4.32 - 4.38 (1H, m), 5.21 (1H, m), 7.47 (1H,d), 7.50 (1H, s), 7.68 (1H, s), 7.92 (1H, d), 8.00 (1H, s), 8.38 (1H, d); MS m/z 576 $[M+H]^+$.

Example 355:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 100mg, 0.32mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 101 mg, 0.36 mmol) and caesium carbonate (22 mg, 0.65 mmol) added to dioxane (5 mL) and the suspension bubbled with nitrogen for 10 minutes. tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) and XANTPHOS (17 mg, 0.03 mmol) were added and the mixture heated at 110 °C overnight. The mixture was filtered and the filtrate loaded onto an SCX (10 g) cartridge pre-wet with methanol, washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white crystalline solid (97mg, 54%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.00 (3H, t), 1.11 (6H, s), 1.48 - 1.55 (2H, m), 1.60 (4H, d), 1.73 (2H, s), 1.77 - 1.82 (2H, m), 1.88 (2H, d), 1.93 - 1.99 (2H, m), 2.32 (2H, q), 2.83 (2H, d), 3.20 (3H, s), 3.39 (2H, s), 3.70 - 3.74 (1H, m), 5.21 (1H, m), 7.40 - 7.45 (1H, m), 7.95 - 7.98 (1H, m), 8.02 (1H, s), 8.20 - 8.25 (1H, m), 8.88 (1H, s); MS m/z 556 $[M+H]^+$.

Example 356:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.32 mmol scale, utilising 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 96 mg, 0.32 mmol), as a white solid (38 mg, 22%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.11 (6H, s), 1.54 - 1.58 (2H, m), 1.59 (3H, s), 1.74 (3H, d), 1.79 (2H, s), 1.87 (2H, s), 1.95 (1H, d), 1.99 (1H, s), 2.17 (3H, s), 2.75 (2H, d), 3.20 (3H, s), 3.37 (2H, s), 3.70 (1H, m), 5.22 (1H, m), 7.40 - 7.45 (1H, m), 7.95 - 7.98 (1H, m), 8.02 (1H, s), 8.20 - 8.25 (1H, m), 8.88 (1H, s); MS m/z 540 $[M+H]^+$.

Example 357:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-N-(3-dimethylaminopropyl)-3-methoxy-benzamide (Intermediate 196; 82 mg, 0.32 mmol) heating thermally at 140 ^{0}C for 2 hours, as a white solid (84 mg, 50%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.11 (6H, s), 1.63 (2H, m), 1.65 - 1.71 (4H, m), 1.75 (2H, s), 1.86 - 1.89 (2H, t), 2.16 (6H, s), 2.28 - 2.34 (2H, t), 3.15 - 3.20 (3H, s), 3.28 – 3.31 (2H, m), 3.36 - 3.39 (2H, s), 3.95 (3H, s), 5.18 – 5.22 (1H, m), 7.47 - 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.37 (1H, s), 8.39 (1H, t); MS m/z 524 $[M+H]^+$.

Example 358:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 86 mg, 0.32 mmol) heating thermally at 140 ^{0}C for 2 hours, as a white solid (56 mg, 32%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.11 (6H, s), 1.63 (3H, m), 1.68 - 1.71 (3H, m), 1.74 (3H, d), 1.86 - 1.89 (3H, m), 2.48 (4H, m), 2.58 (2H, t), 3.18 (3H, s), 3.39 (4H, t), 3.92 - 3.98 (3H, s), 5.18 (1H, m), 7.47 - 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.29 (1H, 4), 8.39 (1H, d); MS m/z 536 $[M+H]^+$.

Example 359:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide (Intermediate 194; 77 mg, 0.32 mmol) heating thermally at 140 ^{0}C for 2 hours, as a white solid (37 mg, 22%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 1.11 (6H, s), 1.63 - 1.68 (4H, m), 1.75 (2H, m), 1.92 (2H, m), 2.15 (6H, s), 2.40 (2H, t), 3.19 (3H, s), 3.33 – 3.37 (4H, m), 3.95 (3H, s), 5.18 (1H, m), 7.47 - 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.29 (1H, 4), 8.39 (1H, d); MS m/z 510 $[M+H]^+$.

Example 360:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(4-pyrrolidin-1-ylcyclohexyl)benzamide

To a solution of 4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid (Intermediate 236; 83 mg, 0.19 mmol) in DMF (3 mL) was added a solution of 4-pyrrolidin-1-ylcyclohexan-1-amine (Intermediate 237; 78 mg, 0.46 mmol). DIPEA (100 uL, 0.57 mmol) was added, followed by HATU (107 mg, 0.28 mmol). The resultant mixture was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated to a gum, which was partitioned between DCM (20 mL) and saturated aqueous sodium bicarbonate solution (20

mL). The organic phase was separated by gravity elution through a PTFE filter cup and evaporated to an amber gum which was purified by base modified reverse phase preparative HPLC to yield the title compound as an off white solid (34 mg, 30%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.29 (m, 2H), 1.41 - 1.83 (m, 12H), 1.95 - 2.20 (m, 7H), 2.60 (m, 4H), 3.30 (s, 3H), 3.37 (s, 2H), 3.94 (m, 1H), 3.97 (s, 3H), 5.31 (m, 1H), 5.83 (d, 1H), 7.20 (m, 1H), 7.42 (d, 1H), 7.60 (s, 1H), 7.85 (s, 1H), 8.47 (d, 1H); MS m/z 590 $[M+H]^+$.

Example 361:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.49 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide (Intermediate 27; 144 mg, 0.51 mmol), as a white foam (66 mg, 24%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.11 (s, 6H), 1.52 - 1.68 (m, 6H), 1.76 (m, 4H), 1.95 (m, 4H), 2.16 (s, 3H), 2.73 (m, 2H), 3.20 (s, 3H), 3.40 (s, 2H), 3.73 (m, 1H), 3.92 (s, 3H), 5.19 (m, 1H), 7.19 (d, 1H), 7.79 (m, 2H), 8.02 (s, 1H), 8.31 (d, 1H); MS m/z 554 $[M+H]^+$.

Example 362:

3-chloro-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.34 mmol scale, utilising 4-amino-3-chloro-N-(3-dimethylaminopropyl)benzamide (Intermediate 214; 98 mg, 0.38 mmol), as an off-white solid (27 mg, 15%).

^{1}H NMR (400.132 MHz, DMSO-d6) d 1.10 (s, 6H), 1.50 - 1.74 (m, 8H), 1.83 (m, 2H), 2.15 (s, 6H), 2.27 (t, 2H), 3.19 (s, 3H), 3.28 (m, 2H), 3.37 (s, 2H), 5.11 (m, 1H), 7.77 (m, 1H), 7.96 (d, 1H), 7.99 (s, 1H), 8.11 (s, 1H), 8.27 (d, 1H), 8.48 (t, 1H); MS m/z 528 $[M+H]^+$.

Example 363:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.49 mmol scale, utilising 4-amino-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide (Intermediate 239; 144 mg, 0.51 mmol), as a white foam (39 mg, 14%).

^{1}H NMR (400.132 MHz, DMSO-d6) d 1.10 (s, 6H), 1.21 - 2.04 (m, 16H), 2.10 - 2.21 (m, 7H), 3.19 (s, 3H), 3.38 (s, 2H), 3.72 & 3.92 (m, 1H), 3.95 (s, 3H), 5.19 (m, 1H), 7.49 (m, 2H), 7.66 (d, 1H), 7.99 (s, 1H), 8.01 (d, 1H), 8.36 (d, 1H); MS m/z 564 [M+H]+.

Example 364:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.32 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 77 mg, 0.32 mmol) heating thermally at 140 ^{0}C for 3 hours, as a white solid (84 mg, 49%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.11 (6H, s), 1.64 - 1.76 (7H, m), 1.87 – 1.94 (2H, m), 2.13 - 2.22 (1H, m), 2.26 (3H, s), 2.34 - 2.45 (2H, m), 2.58 - 2.64 (1H, m), 2.66 - 2.71 (1H, m), 3.20 (3H, s), 3.41 (2H, s), 3.93 (3H, s), 4.36 - 4.41 (1H, m), 5.15 – 5.24 (1H, m), 7.22 (1H, d), 7.78 (1H, d), 7.97 - 8.00 (1H, m), 8.03 (1H, s), 8.32 (1H, d); MS m/z 540 [M+H]+.

Example 365:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.32 mmol scale, utilising 4-amino-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 241; 93 mg, 0.34 mmol), as an off-white solid (113 mg, 62%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.91 (2H, d), 1.11 (6H, s), 1.38 (1H, m), 1.42 (2H, m), 1.61 (2H, s), 1.64 (2H, t), 1.75 (1H, s), 1.84 (2H, m), 1.89 (2H, m), 2.03 (1H, m), 2.20 (2H, m), 2.39 (3H, s), 2.98 (2H, d), 3.17 (3H, s), 3.40 (2H, s), 4.28 (1H, m), 5.23 (1H, m), 7.38 (1H, d), 7.52 (1H, t), 7.64 (1H, m), 7.89 (1H, d), 8.01 (1H, s), 9.62 (1h, s); MS m/z 565 $[M+H]^+$.

Example 366:

5-chloro-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.29 mmol scale, utilising 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 175; 92 mg, 0.29 mmol) heating at 110 ^{0}C for 3 hours, as an off-white solid (55 mg, 32%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.11 (6H, s), 1.25 - 1.37 (3H, m), 1.47 - 2.01 (13.5H, m), 2.13 (6.5H, d), 3.20 (3H, s), 3.40 (2H, s), 3.62 – 3.71 and 3.88 – 3.95 (each 0.5H, m), 5.12 – 5.20 (1H, m), 7.65 - 7.68 (1H, m), 7.99 - 8.04 (2H, m), 8.10 (1H, d), 8.30 - 8.35 (1H, m); MS m/z 587 $[M+H]^+$.

Example 367:

3-chloro-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 355, on a 0.34 mmol scale, utilising 4-amino-3-chloro-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)benzamide (Intermediate 244; 123 mg, 0.39 mmol) heating at 110 ^{0}C for 3 hours, as an off-white solid (35 mg, 18%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 (s, 6H), 1.10 (s, 6H), 1.49 - 1.85 (m, 12H), 2.42 (s, 2H), 2.60 (m, 4H), 3.19 (s, 3H), 3.21 (d, 2H), 3.36 (s, 2H), 5.09 (m, 1H), 7.73 (m, 1H), 7.88 (d, 1H), 7.98 (s, 1H), 8.15 (s, 1H), 8.25 (d, 1H), 8.69 (t, 1H); MS m/z 582 [M+H]+.

Example 368:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.33 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-

methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol) heating thermally at 120 ^{0}C for 3 days, as a white solid (55 mg, 29%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.20 (s, 3H), 1.54 – 160 (m, 8H), 1.80 - 1.63 (m, 8H), 2.03 - 1.95 (m, 2H), 2.56 (s, 2H), 2.72 - 2.65 (m, 4H), 3.29 (s, 3H), 3.37 (s, 2H), 3.39 (d, 2H), 3.98 (s, 3H), 5.34 (quintet, 1H), 7.20 (d, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.86 (s, 1H), 8.43 (d, 1H), 9.16 - 9.10 (m, 1H); MS m/z 578 $[M+H]^+$.

Example 369:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.22 mmol scale, utilising 4-amino-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide (Intermediate 245; 70 mg, 0.26 mmol) heating by microwave irradiation at 160 ^{0}C for 1 hour, as a white solid (50 mg, 42%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.04 (t, 3H), 1.10 (s, 6H), 1.55 - 1.93 (m, 9H), 2.15 (m, 1H), 2.43 (m, 4H), 2.65 (m, 1H), 2.73 (m, 1H), 3.19 (s, 3H), 3.38 (s, 2H), 3.95 (s, 3H), 4.40 (m, 1H), 5.19 (m, 1H), 7.51 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.28 (d, 1H), 8.37 (d, 1H); MS m/z 536 [M+H]+.

Example 370:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 127; 52 mg, 0.17 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 50 mg, 0.17mmol) and p-toluenesulphonic acid monohydrate (81 mg, 0.43 mmol) were stirred and heated together in 4-methyl-2-pentanol (2 mL) by microwave irradiation at 150 ^{0}C for 1 hour. A further portion of 10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (10mg) was added and reaction continued for a further 1 hour. The cooled solution was loaded onto an SCX-3 (5g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and eluted with 2M NH3/MeOH. Product containing fractions were combined and

evaporated and the residue purified by base modified reverse phase preparative HPL to yield the title compound as a white solid (49 mg, 51%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.00 (t, 3H), 1.11 (s, 6H), 1.74 (m, 12H), 2.32 (q, 2H), 2.83 (m, 2H), 3.17 (s, 3H), 3.40 (s, 2H), 3.73 (m, 1H), 3.92 (s, 3H), 5.19 (m, 1H), 7.19 (d, 1H), 7.77 (s, 1H), 7.80 (m, 1H), 8.02 (s, 1H), 8.31 (d, 1H); MS m/z 568 [M+H]+.

Example 371:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.45 mmol scale, utilising 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 65; 114 mg, 0.45 mmol) heating by microwave irradiation at 160 ^{0}C for 30 minutes, as a white solid (96 mg, 41%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.1 (s, 6H), 1.55 (m, 6H), 1.7 – 1.85 (m, 6H), 1.95 (t, 2H), 2.8 (d, 2H), 3.2 (s, 3H), 3.35 (s, 2H), 3.75 (m, 1H), 5.15 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.85 (s, 1H); MS m/z 525 $[M+H]^+$.

Example 372:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.16 mmol scale, utilising 4-amino-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide (single undefined isomer) (Intermediate 248; 50 mg, 0.16 mmol) heating by microwave irradiation at 150 ^{0}C for 1 hour, as a white solid (30 mg, 32%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, s), 1.63 (14H, m), 1.90 (2H, m), 2.07 (1H, m), 2.17 (6H, s), 3.20 (3H, s), 3.40 (2H, s), 3.92 (3H, s), 3.94 (1H, m), 5.19 (1H, m), 7.19 (1H, d), 7.71 (1H, m), 7.77 (1H, s), 8.02 (1H, s), 8.31 (1H, d); MS m/z 582 $[M+H]^+$.

Example 373:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, on a 0.16 mmol scale, utilising 4-amino-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide (single undefined isomer) (Intermediate 249; 50 mg, 0.16 mmol) heating by microwave irradiation at 150 ^{0}C for 1 hour, as a white solid (50 mg, 54%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, s), 1.30 (4H, m), 1.75 (12H,m), 2.12 (1H, m), 2.18 (6H, s), 3.20 (3H, s), 3.40 (2H, s), 3.69 (1H, m), 3.92 (3H, s), 5.18 (1H, m), 7.19 (1H, d), 7.73 (1H, m), 7.76 (1H, s), 8.02 (1H, s), 8.30 (1H, d); MS m/z 582 $[M+H]^+$.

Example 374:

N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 346, utilising 10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 75 mg, 0.17 mmol) and 4-(azetidin-1-yl)cyclohexan-1-amine (Intermediate 226; 39 mg, 0.25 mmol) as an off white solid (35 mg, 36%) assigned as the trans isomer.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.92 - 1.00 (2H, m), 1.10 (6H, s), 1.29 - 1.39 (2H, m), 1.58 - 1.94 (15H, m), 3.07 (4H, t), 3.19 (3H, s), 3.38 (2H, s), 3.67 - 3.76 (1H, m), 3.94 (3H, s), 5.19 (1H, quintet), 7.45 - 7.48 (2H, m), 7.67 (1H, s), 7.99 (1H, s), 8.00 (1H, d), 8.36 (1H, d); MS m/z 576 $[M+H]^+$.

Example 375:

N-[4-(azetidin-1-yl)cyclohexyl]-4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

The title compound was isolated from the reaction above to produce Example 374, as an off white solid (35 mg, 36%) assigned as the cis isomer.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.03 (6H, s), 1.24 - 1.31 (2H, m), 1.37 - 1.42 (2H, m), 1.50 - 1.70 (10H, m), 1.78 - 1.86 (4H, m), 2.12 - 2.16 (1H, m), 2.96 - 3.04 (4H, m), 3.12 (3H,

s), 3.31 (2H, s), 3.69 - 3.79 (1H, m), 3.87 (3H, s), 5.12 (1H, quintet), 7.42 - 7.46 (2H, m), 7.58 (1H, s), 7.91 (1H, s), 7.96 (1H, d), 8.28 (1H, d); MS m/z 576 $[M+H]^+$.

Example 376:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

10-chloro-2-cyclopentyl-4,4-diethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 250; 111 mg, 0.33 mmol), p-toluenesulphonic acid monohydrate (155 mg, 0.81 mmol) and 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The sample was transferred to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (55 mg, 27%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.01 (s, 6H), 1.80 - 1.48 (m, 14H), 2.02 - 1.94 (m, 2H), 2.56 (s, 2H), 2.69 (s, 4H), 3.28 (s, 3H), 3.39 (d, 2H), 3.42 (s, 2H), 3.98 (s, 3H), 5.42 (quintet, 1H), 7.20 (d, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.84 (s, 1H), 8.43 (d, 1H), 9.14 (s, 1H); MS m/z 606 $[M+H]^+$.

Example 377:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

10-chloro-2-cyclopentyl-4,4-diethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 250; 100 mg, 0.30 mmol), p-toluenesulphonic acid monohydrate (142 mg, 0.75 mmol) and 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-

3-yl]benzamide (Intermediate 202; 91 mg, 0.30 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The sample was transferred to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (80 mg, 44%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.09 - 1.07 (m, 2H), 1.44 - 1.38 (m, 2H), 1.63 - 1.48 (m, 6H), 1.80 - 1.66 (m, 6H), 2.03 - 1.94 (m, 3H), 2.56 - 2.49 (m, 4H), 3.14 - 3.11 (m, 2H), 3.28 (s, 3H), 3.42 (s, 2H), 3.97 (s, 3H), 4.58 - 4.47 (m, 1H), 5.42 - 5.32 (m, 1H), 5.94 (d, 1H), 7.25 (dd, 1H), 7.25 (d, 1H), 7.25 (d, 1H), 7.44 (d, 1H), 7.60 (s, 1H), 7.83 (s, 1H), 8.47 (d, 1H); MS m/z 604 $[M+H]^+$.

Example 378:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 204; 96 mg, 0.30 mmol), as a white solid (25 mg, 13%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.84 (t, 6H), 1.07 - 1.04 (m, 2H), 1.36 - 1.30 (m, 2H), 1.63 - 1.49 (m, 6H), 1.82 - 1.66 (m, 7H), 2.04 - 1.91 (m, 4H), 2.57 - 2.51 (m, 4H), 3.11 - 3.08 (m, 2H), 3.29 (s, 3H), 3.44 (s, 2H), 3.95 (s, 3H), 4.58 - 4.46 (m, 1H), 5.36 (quintet, 1H), 6.55 (dd, 1H), 7.57 (d, 1H), 7.67 (s, 1H), 7.85 (s, 1H), 8.37 (d, 1H); MS m/z 622 $[M+H]^+$.

Example 379:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 89 mg, 0.30 mmol), as a white solid (35 mg, 20%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.10 (t, 3H), 1.62 - 1.49 (m, 6H), 1.81 - 1.65 (m, 6H), 2.08 - 1.98 (m, 4H), 2.19 - 2.13 (m, 2H), 2.43 (q, 2H), 2.89 - 2.86 (m, 2H), 3.29 (s, 3H), 3.44 (s, 2H), 3.95 (s, 3H), 4.09 - 3.99 (m, 1H), 5.34 (quintet, 1H), 6.68 (dd, 1H), 7.55 (d, 1H), 7.67 (s, 1H), 7.84 (s, 1H), 8.37 (d, 1H); MS m/z 596 $[M+H]^+$.

Example 380:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 79 mg, 0.30 mmol), as a white solid (30 mg, 18%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.64 - 1.48 (m, 6H), 1.80 - 1.66 (m, 6H), 2.00 - 1.92 (m, 2H), 2.07 - 2.05 (m, 2H), 2.20 - 2.14 (m, 2H), 2.31 (s, 3H), 2.84 - 2.81 (m, 2H), 3.28 (s, 3H), 3.42 (s, 2H), 4.03 - 3.92 (m, 4H), 5.38 (quintet, 1H), 5.89 (d, 1H), 7.22 (dd, 1H), 7.41 (d, 1H), 7.59 (s, 1H), 7.84 (s, 1H), 8.48 (d, 1H); MS m/z 564 $[M+H]^+$.

Example 381:

4-[(2-cyclopentyl-4,4-diethyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 377, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 83 mg, 0.30 mmol), as a white solid (90 mg, 52%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.77 (t, 6H), 1.03 (t, 3H), 1.56 - 1.41 (m, 6H), 1.73 - 1.59 (m, 6H), 1.95 - 1.87 (m, 2H), 2.10 - 1.98 (m, 4H), 2.37 (q, 2H), 2.86 - 2.83 (m, 2H), 3.22 (s, 3H), 3.35 (s, 2H), 3.98 - 3.91 (m, 4H), 5.31 (quintet, 1H), 5.82 (d, 1H), 7.15 (dd, 1H), 7.34 (d, 1H), 7.52 (s, 1H), 7.77 (s, 1H), 8.41 (d, 1H); MS m/z 578 $[M+H]^+$.

Example 382:

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethylpiperidin-4-yl)benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 108 mg, 0.35 mmol) 4-amino-3-chloro-N-(1-ethyl-4-piperidyl)benzamide (Intermediate 212; 118 mg, 0.42 mmol), and p-toluenesulphonic acid monohydrate (133 mg, 0.7 mmol) were combined in 4-methyl-2-pentanol (4 mL) and heated by microwave irradiation at 160 °C for 1 hour. The reaction mixture was loaded onto to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (38 mg, 20%).

^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.66 - 0.69 (2H, m), 0.90 - 0.93 (2H, m), 1.00 (3H, t), 1.41 - 1.70 (8H, m), 1.77 - 1.85 (4H, m), 1.90 - 1.96 (2H, m), 2.32 (2H, q), 2.88 (2H, d), 3.18 (3H, s), 3.47 (2H, s), 3.72 - 3.76 (1H, m), 4.74 - 4.82 (1H, m), 7.79 (1H, dd), 7.98 - 8.00 (2H, m), 8.08 (1H, s), 8.20 (1H, d), 8.30 - 8.34 (1H, m)

MS m/z 552 $[M+H]^+$.

Example 383:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.33 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 91 mg, 0.33 mmol) and p-toluenesulphonic acid monohydrate (156 mg, 0.81 mmol) were heated at 140 °C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction mixture was loaded onto to an SCX-3 cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with 2% 7N ammonia/methanol. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (89 mg, 50%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.67 - 0.69 (2H, t), 0.90 - 0.93 (2H, t), 1.01 (3H, t), 1.51 - 1.51 (1H, m), 1.52 (1H, d), 1.56 - 1.62 (4H, m), 1.68 (1H, s), 1.70 (1H, d), 1.78 (1H, d), 1.81 (1H, s), 1.93 (4H, d), 2.33 (2H, q), 2.90 (2H, d), 3.19 (3H, s), 3.49 (2H, s), 3.61 – 3.65 (1H,

m), 3.96 (3H, s), 4.86 (1H, m), 7.47 (1H, t), 7.50 (1H, d), 7.68 (1H, s), 8.00 (1H, s), 8.07 (1H, d), 8.40 (1H, d); MS m/z 549 $[M+H]^+$.

Example 384:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 86 mg, 0.30 mmol), as a white solid (20 mg, 11%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.67 - 0.69 (2H, t), 0.90 - 0.93 (2H, t), 1.52 (2H, d), 1.61 (2H, t), 1.65 - 1.71 (7H, m), 1.89 - 1.92 (3H, m), 2.58 (2H, t), 3.18 (3H, s), 3.20 (2H, t) – found under water, 3.39 (2H, q), 3.49 (2H, s), 3.95 (3H, s), 4.86 (1H, s), 7.46 (1H, d), 7.48 - 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, s), 8.31 (1H, t), 8.40 - 8.42 (1H, m); MS m/z 535 $[M+H]^+$.

Example 385:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 99 mg, 0.30 mmol), as a white solid (114 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.67 - 0.70 (2H, t), 0.90 - 0.93 (2H, t), 0.95 (2H, s), 1.42 - 1.48 (2H, m), 1.43 - 1.49 (2H, m), 1.54 (2H, t), 1.60 - 1.63 (1H, m), 1.68 (1H, s), 1.70 (1H, d), 1.89 - 1.97 (4H, m), 2.08 (1H, d), 2.16 - 2.24 (2H, m), 2.42 (3H, s), 2.98 - 3.01 (2H, d), 3.18 (3H, s), 3.49 (2H, s), 3.97 (3H, s), 4.34 (1H, m), 4.87 (1H, m), 7.47 (1H, d), 7.50 (1H, t), 7.68 (1H, s), 7.92 (1H, d), 8.00 (1H, s), 8.40 (1H, d); MS m/z 575 $[M+H]^+$.

Example 386:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 92 mg, 0.30 mmol), as a white solid (89 mg, 50%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.67 - 0.69 (2H, m), 0.89 (6H, s), 0.90 - 0.93 (2H, t), 1.51 (1H, d), 1.54 (1H, s), 1.58 (1H, d), 1.61 - 1.62 (1H, m), 1.69 (2H, d), 1.90 (2H, d), 2.21 (2H, s), 2.29 (6H, s), 3.19 (3H, s), 3.21 (2H, d), 3.48 (2H, s), 3.96 (3H, s), 4.86 (1H, m), 7.41 - 7.43 (1H, m), 7.47 (1H, d), 7.70 (1H, s), 7.99 (1H, s), 8.41 (1H, d), 8.44 (1H, t); MS m/z 551 $[M+H]^+$.

Example 387:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 383, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide (Intermediate 194; 78 mg, 0.30 mmol), as a white solid (82 mg, 50%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.67 - 0.70 (2H, t), 0.92 (2H, t), 1.51 (1H, d), 1.55 (1H, d), 1.60 - 1.63 (2H, m), 1.70 (2H, t), 1.90 (2H, s), 2.19 (6H, s), 2.41 (2H, t), 3.18 (3H, s), 3.37 (2H, q), 3.49 (2H, s), 3.95 (3H, s), 4.86 (1H, m), 7.46 (1H, d), 7.48 - 7.51 (1H, d), 7.69 (1H, s), 7.99 (1H, d), 8.27 (1H, t), 8.39 - 8.42 (1H, m); MS m/z 509 $[M+H]^+$.

Example 388:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 108 mg, 0.35 mmol) and 4-amino-3-fluoro-N-(9-methyl-9-azabicyclo[3.3.1]non-7-yl)benzamide (Intermediate 162; 102 mg, 0.35 mmol) were combined with p-toluenesulphonic acid monohydrate (167 mg, 0.88 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 25 minutes at 160 °C The cooled reaction mixture was diluted with methanol (10 mL) and loaded onto an SCX-3 cartridge (5 g) pre-wet with methanol. The cartridge was washed with methanol (2 x 5 mL) and eluted with 7 N methanolic ammonia (10 mL). Product containing fractions were evaporated and the resultant material purified by base modified reverse phase preparative HPLC to give the title compound as a white solid (54 mg, 28 %).

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.65 (t, 2H), 0.9 (m, 4H), 1.5 (m. 7H), 1.65 (m, 2H), 1.85 (m, 4H), 2.05 (m, 1H), 2.2 (m, 2H), 2.4 (s, 3H), 3.0 (d, 2H), 3.2 (s, 3H), 3.45 (s, 2H), 4.3 (m, 1H), 4.8 (m, 1H) 7.65 (m, 1H), 7.75 (m, 1H), 7.95 (m, 2H), 8.15 (t, 1H), 8.65 (s, 1H); MS m/z 562 $[M+H]^+$.

Example 389:

5-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 85 mg, 0.30 mmol), 4-amino-5-chloro-2-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 173; 101 mg, 0.33 mmol) and XANTPHOS (16 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (210 mg, 0.59 mmol) was added and the system purged with a stream of nitrogen for 15 minutes before tris(dibenzylideneacetone) palladium (II) (17 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (100 mg, 60%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.69 - 0.71 (2H, m), 0.92 - 0.95 (2H, m), 1.51 - 1.64 (6H, m), 1.66 – 1.71 (2H, m), 1.77 - 1.80 (2H, m), 1.85 – 1.99 (4H, m), 2.17 (3H, s), 2.74 (2H, d), 3.19 (3H, s), 3.50 (2H, s), 3.66 - 3.73 (1H, m), 4.80 – 4.88 (1H, m), 7.68 (1H, d), 8.04 – 8.09 (3H, m), 8.35 - 8.39 (1H, m); MS m/z 556 $[M+H]^+$.

Example 390:

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2-dimethylaminoethyl)benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.33 mmol) and 4-amino-3-chloro-N-(2-dimethylaminoethyl)benzamide (Intermediate 213; 89 mg, 0.37 mmol) were dissolved in 1,4 dioxane (4 mL) and caesium carbonate (234 mg, 0.72 mmol) was added. The reaction mixture was sparged with nitrogen for 15 minutes prior to addition of tris-dibenzylideneacetonedipalladium (II) (19 mg, 0.02 mmol) followed by XANTPHOS (19 mg, 0.03 mmol). The reaction mixture was heated at 100 °C overnight, cooled to room temperature and diluted with DCM (20 mL). The resultant mixture was filtered and the filtrate loaded onto an SCX-3 (5 g) cartridge. The cartridge was washed through with methanol (50 mL) and then eluted with 2M ammonia in methanol (50 mL). Evaporation of the ammoniacal fraction afforded an amber gum which was purified by acid modified reverse phase preparative HPLC. The resultant material was dissolved in MeOH/Water and poured onto an SCX-3 cartridge (2 g) and cartridge which was then washed with methanol and eluted with 2M ammonia in methanol, and the ammoniacal solution evaporated to yield the title compound as a solid (7 mg, 3%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.67 (m, 2H), 0.91 (m, 2H), 1.41 - 1.69 (m, 6H), 1.83 (m, 2H), 2.19 (s, 6H), 2.41 (t, 2H), 3.18 (s, 3H), 3.35 (m, 2H), 3.47 (s, 2H), 4.78 (m, 1H), 7.78 (m, 1H), 7.97 (d, 1H), 7.99 (s, 1H), 8.10 (s, 1H), 8.32 (d, 1H), 8.37 (t, 1H); MS m/z 512 $[M+H]^+$.

Example 391:

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 390, utilising 4-amino-3-chloro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 215; 97 mg, 0.36 mmol), as a white solid (7 mg, 3%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.67 (m, 2H), 0.91 (m, 2H), 1.50 (m, 4H), 1.67 (m, 6H), 1.83 (m, 2H), 2.58 (t, 2H), 3.18 (s, 3H), 3.38 (m, 2H), 3.47 (s, 2H), 4.78 (m, 1H), 7.79 (m, 1H), 7.97 (d, 1H), 7.99 (s, 1H), 8.10 (s, 1H), 8.32 (d, 1H), 8.42 (t, 1H); MS m/z 538 $[M+H]^+$.

Example 392:

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 390, utilising 4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide (Intermediate 107; 103 mg, 0.36 mmol), as a white solid (4 mg, 2%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.67 (m, 2H), 0.88 (s, 6H), 0.91 (m, 2H), 1.41 - 1.70 (m, 6H), 1.83 (m, 2H), 2.18 (s, 2H), 2.27 (s, 6H), 3.19 (m, 5H), 3.46 (s, 2H), 4.77 (m, 1H), 7.75 (m, 1H), 7.94 (d, 1H), 7.99 (s, 1H), 8.13 (s, 1H), 8.29 (d, 1H), 8.46 (t, 1H); MS m/z 554 $[M+H]^+$.

Example 393:

5-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 389, utilising 4-amino-5-chloro-N-(1-ethyl-4-piperidyl)-2-fluoro-benzamide (Intermediate 174; 90 mg, 0.30 mmol), as a white solid (102mg, 60%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.69 - 0.71 (2H, m), 0.92 - 0.95 (2H, m), 1.00 (3H, t), 1.49 – 2.01 (14H, m), 2.32 (2H, q), 2.84 (2H, d), 3.19 (3H, s), 3.50 (2H, s), 3.68 - 3.74 (1H,

m), 4.82 – 4.88 (1H, m), 7.68 (1H, d), 8.04 – 8.08 (3H, m), 8.35 - 8.39 (1H, m); MS m/z 570 $[M+H]^+$.

Example 394:

5-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 389, utilising 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 175; 94 mg, 0.30 mmol), as a white solid (65 mg, 37%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.69 - 0.71 (2H, m), 0.92 - 0.95 (2H, m), 1.340 – 1.35(2H, m), 1.49 – 1.94 (14H, m), 2.25 - 2.30 (7H, m), 3.19 (3H, s), 3.50 (2H, s), 3.67 – 3.71 and 3.91 – 3.97 (each 0.5H. m), 4.80 – 4.88 (1H, m), 7.65 - 7.68 (1H, m), 8.01 - 8.04 (2H, m), 8.08 (1H, d), 8.34 - 8.38 (1H, m); MS m/z 584 $[M+H]^+$.

Example 395:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.33 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 102 mg, 0.36 mmol) and caesium carbonate (213 mg, 0.65 mmol) added to dioxane (5 mL) and the suspension bubbled with nitrogen for 10 minutes. tris-dibenzylideneacetonedipalladium (II) (18 mg, 0.02 mmol) and XANTPHOS (17 mg, 0.03 mmol)were added and the mixture heated at 110 °C overnight. The mixture was filtered, and the filtrate loaded onto to an SCX-3 cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a light orange gum (99 mg, 55%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.69 (2H, t), 0.93 (2H, t), 1.05 (3H, t), 1.52 – 1.58 (4H, m), 1.61 (2H, m), 1.65 – 1.67 (2h, m), 1.80 (2H, d), 1.85 (2H, d), 2.10 – 2.12 (2H, t), 2.41 (2h, q), 2.91 (2H, d), 3.17 (3H, s), 3.45 (2H, s), 3.75 (1H, m), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 554 $[M+H]^+$.

Example 396:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 395, utilising 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 97 mg, 0.36 mmol), as an off-white solid (122 mg, 69%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.69 (2H, t), 0.93 (2H, t), 1.05 (3H, t), 1.52 – 1.58 (4H, m), 1.61 (2H, m), 1.65 – 1.67 (2h, m), 1.80 (2H, d), 1.85 (2H, d), 2.10 – 2.12 (2H, t), 2.22 (3H, s), 2.91 (2H, d), 3.17 (3H, s), 3.45 (2H, s), 3.75 (1H, m), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 540 $[M+H]^+$.

Example 397:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 395, utilising 4-amino-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 230; 97 mg, 0.36 mmol), as a pale yellow gum (121 mg, 69%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.69 (2H, t), 0.93 (2H, t), 1.48 – 1.55 (4H, m), 1.58 – 1.64 (6H, m), 1.85 – 1.92 (2H, m), 2.57 (4H, m), 2.68 (2H, t), 3.17 (3H, s), 3.40 (2H, m), 3.45 (2H, s), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 540 $[M+H]^+$.

Example 398:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 80 mg, 0.26 mmol), 4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 192; 73 mg, 0.26 mmol) and p-toluenesulphonic acid monohydrate (124 mg, 0.65 mmol) were combined in 4-methyl-2-pentanol (3 mL) and heated at 100 °C for 18 hours. The cooled reaction mixture was loaded on to an SCX-2 column (5 g) pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) then eluted with 2M ammonia in MeOH. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (85 mg, 59%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ0.62 (m, 2H), 1.11 (m, 2H), 1.46 (m, 2H), 1.72 (m, 4H), 1.79 (m, 4H), 2.03 (m, 2H), 2.58 (m, 4H), 2.72 (m, 2H), 3.29 (s, 3H), 3.47 (s, 2H), 3.60 (m, 2H), 3.95 (s, 3H), 4.96 (m, 1H), 7.31 (m, 1H), 7.56 (d, 1H), 7.70 (s, 1H), 7.87 (s, 1H), 8.41 (d, 1H); MS m/z 552 $[M+H]^+$.

Example 399:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 100 mg, 0.32 mmol), 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 87 mg, 0.32 mmol) and 4-toluenesulphonic acid monohydrate (154 mg, 0.81 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (80 mg, 46%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.67 – 0.72 (2H, m), 0.91 – 0.96 (2H, m), 1.53 - 1.75 (7H, m), 1.87 – 1.96 (2H, m), 2.13 - 2.22 (1H, m), 2.26 (3H, s), 2.34 - 2.45 (2H, m), 2.57 –

2.64 (1H, m), 2.66 - 2.70 (1H, m), 3.18 (3H, s), 3.50 (2H, s), 3.93 (3H, s), 4.35 – 4.43 (1H, m), 4.83 – 4.92 (1H, m), 7.22 (1H, d), 7.77 (1H, s), 7.98 - 8.00 (1H, m), 8.03 (1H, s), 8.35 (1H, d); MS m/z 539 $[M+H]^+$.

Example 400:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 109 mg, 0.36 mmol), aniline (Intermediate **229**; 83 mg, 0.324 mmol), and caesium carbonate (211 mg, 0.648 mmol) added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris-dibenzylideneacetonedipalladium (II) (11 mg, 0.02 mmol) and XANTPHOS (17 mg, 0.03 mmol) were added and the mixture heated to 100 °C for 16 hours. The reaction mixture was cooled to room temperature filtered, and the filter cake washed with DCM and the filtrate evaporated. The residue was dissolved in DCM and purified on a silica column eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM over 30 column volumes. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (95 mg, 56%). ^{1}H NMR (399.902 MHz, $CDCl_3$) δ0.64 (m, 2H), 1.12 (m, 2H), 1.46 (m, 2H), 1.74 (m, 5H), 2.02 (m, 2H), 2.29 (m, 1H), 2.42 (m, 4H), 2.67 (m, 2H), 2.90 (m, 1H), 3.29 (s, 3H), 3.48 (s, 2H), 4.65 (m, 1H), 4.93 (m, 1H), 6.96 (m, 1H), 7.28 (m, 1H), 7.80 (m, 1H), 7.88 (s, 1H), 8.46 (m, 1H); MS m/z 526 $[M+H]^+$.

Example 401:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 101 mg, 0.33 mmol), p-toluenesulphonic acid monohydrate (155 mg, 0.81 mmol) and 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-

3-methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol) were added to 4-methyl-2-pentanol (7 mL). The reaction was heated at 120 °C over the weekend. The sample was transferred to an SCX cartridge (10 g) pre-wet with methanol, then washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (34 mg, 18%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.63 - 0.60 (m, 2H), 1.01 (s, 6H), 1.10 - 1.07 (m, 2H), 1.51 - 1.43 (m, 2H), 1.74 - 1.61 (m, 4H), 1.83 - 1.76 (m, 4H), 2.05 - 1.98 (m, 2H), 2.56 (s, 2H), 2.72 - 2.65 (m, 4H), 3.28 (s, 3H), 3.39 (d, 2H), 3.46 (s, 2H), 3.98 (s, 3H), 4.98 (quintet, 1H), 7.20 (dd, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 7.87 (s, 1H), 8.46 (d, 1H), 9.15 (s, 1H); MS m/z 576 $[M+H]^+$.

Example 402:

3-chloro-4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-chloro-benzoic acid (Intermediate 253; 52 mg, 0.12 mmol) was suspended in DMF (4 mL). DIPEA (62 ul, 0.35 mmol) was added to give a straw coloured solution. Endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 26 mg, 0.16 mmol) was added, followed by HATU (67 mg, 0.17 mmol) and the resultant mixture was stirred at ambient temperature overnight.

The reaction mixture was evaporated to an amber gum, which was partitioned between DCM (5 mL) and saturated aqueous sodium bicarbonate solution (5 mL). The organic phase was separated by gravity elution through a PTFE filter cup and the filtrate evaporated to dryness to afford an amber oil which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (46 mg, 56%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.68 (m, 2H), 0.92 (m, 4H), 1.39 - 1.70 (m, 9H), 1.80 - 2.08 (m, 5H), 2.19 (m, 2H), 2.41 (s, 3H), 2.98 (m, 2H), 3.18 (s, 3H), 3.47 (s, 2H), 4.31 (m, 1H), 4.78 (m, 1H), 7.80 (m, 1H), 7.99 (s, 1H), 8.00 (d, 1H), 8.05 (d, 1H), 8.08 (s, 1H), 8.32 (d, 1H); MS m/z 578 $[M+H]^+$.

Example 403:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 350, utilising, 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 75 mg, 0.24 mmol), and 4-amino-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide (Intermediate 245; 70 mg, 0.26 mmol) heating by microwave irradiation at 160 ^{0}C for 1 hour, as an off-white foam (50 mg, 39%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.04 (t, 3H), 1.10 (s, 6H), 1.55 - 1.93 (m, 9H), 2.15 (m, 1H), 2.43 (m, 4H), 2.65 (m, 1H), 2.73 (m, 1H), 3.19 (s, 3H), 3.38 (s, 2H), 3.95 (s, 3H), 4.40 (m, 1H), 5.19 (m, 1H), 7.51 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.28 (d, 1H), 8.37 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 404:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 55 mg, 0.17 mmol), 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 204; 53 mg, 0.17 mmol) and p-toluenesulphonic acid monohydrate (82 mg, 0.43 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 2 hours. The reaction mixture was cooled and absorbed on to an SCX column, which was then washed with methanol and eluted with ammonia in methanol. Product containing fractions were evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (35mg, 35%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.68 - 0.71 (2H, m), 0.91 - 0.94 (4H, m), 1.40 - 1.46 (3H, m), 1.51 – 1.73 (6H, m), 1.86 - 1.94 (4H, m), 1.99 – 2.09 (1H, m), 2.18 - 2.25 (2H, m), 2.42

(3H, s), 2.98 (2H, d), 3.19 (3H, s), 3.51 (2H, s), 3.94 (3H, s), 4.27 - 4.35 (1H, m), 4.84 - 4.92 (1H, m), 7.22 (1H, d), 7.66 - 7.69 (1H, m), 7.77 (1H, s), 8.03 (1H, s), 8.35 (1H, d); MS m/z 592 $[M+H]^+$.

Example 405:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 70 mg, 0.23 mmol), 4-amino-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide (Intermediate 254; 70 mg, 0.22 mmol), and p-toluenesulphonic acid monohydrate (136 mg, 0.71 mmol) were stirred and heated together in 4-methyl-2-pentanol (3 mL) at 110 ^{0}C for 18 hours.

The cooled reaction solution was loaded onto an SCX-3 (5g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and the product eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (38 mg, 29%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.34 (2H, m), 0.50 (2H, m), 0.69 (2H, m), 0.92 (2H, m), 1.61 (12H, m), 1.92 (2H, m), 2.44 (2H, s), 2.50 (2H, s), 3.18 (3H, s), 3.36 (2H, d), 3.51 (2H, s), 3.93 (3H, s), 4.89 (1H, m), 7.37 (1H, d), 7.80 (1H, s), 8.03 (1H, s), 8.37 (2H, d), 8.41 (1H, m); MS m/z 592 $[M+H]^+$.

Example 406:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-3-fluoro-benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 231 mg, 0.75 mmol), 4-amino-N-(1-ethylpiperidin-4-yl)-3-fluorobenzamide (200 mg, 0.75 mmol) and p-toluenesulfonic acid monohydrate (335 mg, 1.88 mmol) were suspended in 4-Methyl-2-pentanol (5 mL) and sealed into a microwave tube. The reaction was heated to 160 °C for 30 minutes in the microwave

reactor and allowed to cool to room temperature.

The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford an orange / brown oil which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield the title compound as a white solid (48 mg, 12%).

^{1}H NMR (400 MHz, DMSO-d6) δ 0.65 (t, 2H), 0.9 (t, 2H), 1.0 (t. 3H), 1.5 (m, 7H), 1.6 (m, 2H), 1.9 (t, 2H), 2.3 (q, 2H), 2.9 (d, 2H), 3.2 (s,3H), 3.4 (s, 2H), 3.6 (m, 1H), 4.75 9m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.6 (s, 1H); MS m/z 537 $[M+H]^+$.

Example 407:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 121 mg, 0.39 mmol) and 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 116 mg, 0.39 mmol) were taken up in 4-methyl-2-pentanol (4 mL) and p-toluenesulphonic acid monohydrate (150 mg, 0.79 mmol) added. The reaction mixture was heated at 160 ^{0}C by microwave irradiation for 1 hour. The cooled reaction mixture was poured into a mixture of methanol & water (5:2 v/v, 7 mL) and the resultant solution loaded onto an SCX-3 cartridge (5 g), which had been pre-wet with methanol. The cartridge was washed through with methanol (40 mL) and eluted with 2M ammonia in methanol (30 mL). The ammoniacal solution was evaporated to give an amber gum afforded which was purified by base modified reverse phase preparative HPLC which was re-purified by flash chromatography on a silica column eluting with 2.5-10% ammonia/methanol in DCM. Product containing fractions were combined and evaporated and the residue triturated with diethyl ether and resultant solid dried under vacuum, at 60 ^{0}C, for 3 hours to yield the title compound as a flocculent white solid (86 mg, 39%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.67 - 0.70 (2H, m), 0.91 - 0.94 (2H, m), 1.00 (3H, t), 1.48 - 1.99 (14H, m), 2.32 (2H, q), 2.82 - 2.85 (2H, m), 3.18 (3H, s), 3.50 (2H, s), 3.69 - 3.79

(1H, m), 3.93 (3H, s), 4.82 - 4.91 (1H, m), 7.20 (1H, d), 7.76 (1H, s), 7.79 - 7.82 (1H, m), 8.02 (1H, s), 8.34 (1H, d); MS m/z 566 $[M+H]^+$.

Example 408:

7-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-methyl-4-piperidyl)benzo[1,3]dioxole-4-carboxamide

To 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 108 mg, 0.35 mmol) and 7-amino-N-(1-methylpiperidin-4-yl)benzo[d][1,3]dioxole-4-carboxamide (Intermediate 223; 98 mg, 0.35 mmol) in 4-methyl-2-pentanol (3 mL) was added p-toluenesulphonic acid monohydrate (139 mg, 0.73 mmol) and the reaction mixture heated at 160 °C by microwave irradiation for 1 hour.

After cooling the reaction mixture was diluted with MeOH (5 mL) and water (2 mL). The mixture was then submitted to ion exchange chromatography, using an SCX-2 column (10 g). After eluting through with methanol (100 mL) the crude product was eluted from the column using 2M ammonia in methanol (50 mL) and evaporated to afford a brown residue, which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield the title compound as a grey solid (43 mg, 22 %).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.57 - 0.59 (2H, m), 0.81 - 0.83 (2H, m), 1.31 - 1.60 (8H, m), 1.69 - 1.78 (4H, m), 1.92 - 1.97 (2H, m), 2.09 (3H, s), 2.58 - 2.65 (2H, m), 3.09 (3H, s), 3.36 (2H, s), 3.63 - 3.73 (1H, m), 4.71 (1H, quintet), 6.07 (2H, s), 7.14 (1H, d), 7.22 (1H, d), 7.45 (1H, d), 7.87 (1H, s), 8.51 (1H, s); MS m/z 548 $[M+H]^+$.

Example 409:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopentane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(1-methylpiperidin-4-yl)benzamide

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclohexane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 255; 80 mg, 0.24 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 63mg, 0.24mmol) and p-toluenesulphonic acid monohydrate (114 mg, 0.60 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX column, which was then washed with methanol and eluted with ammonia in methanol. Product containing fractions were evaporated and the residue purified on a silica column (2% 7N ammonia in methanol/DCM) to give the title compound as a white solid. (70 mg, 52%)

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.31 - 1.37 (2H, m), 1.50 – 1.80 (14H, m), 1.89 - 2.06 (6H, m), 2.18 (3H, s), 2.79 (2H, d), 3.21 (3H, s), 3.43 (2H, s), 3.71 - 3.79 (1H, m), 3.96 (3H, s), 4.98 – 5.06 (1H, m), 7.47 – 7.51 (2H, m), 7.70 (1H, s), 8.02 (1H, s), 8.07 (1H, d), 8.38 (1H, d); MS m/z 562 $[M+H]^+$.

Example 410:

3-methoxy-4-[[6-methyl-5-oxo-2-(2-oxocyclopentyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl]amino]-N-(1-methyl-4-piperidyl)benzamide

10-chloro-6-methyl-2-(2-oxocyclopentyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 261; 58 mg, 0.19 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 53 mg, 0.20 mmol) and p-toluene sulphonic acid monohydrate (80 mg, 0.42 mmol) were dissolved in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation at 150 °C for 30 minutes. After cooling, the reaction mixture was dissolved in methanol (5 mL) and water (5 mL) and poured directly onto an SCX-3 cartridge (5 g). The cartridge was washed with methanol (50 mL), before elution of products with 2M ammonia in methanol (50 mL). The ammoniacal fraction was evaporated and the residue was purified by base modified reverse phase preparative HPLC to yield the title compound as a yellow solid (11 mg, 7%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.60 (m, 2H), 1.73 - 2.09 (m, 8H), 2.17 (s, 3H), 2.25 (m, 2H), 2.62 (m, 2H), 2.78 (m, 2H), 3.19 (s, 3H), 3.60 (m, 2H), 3.74 (m, 1H), 3.93 (s, 3H), 4.67 (m, 1H), 7.48 (m, 2H), 7.74 (s, 1H), 8.06 (d, 1H), 8.13 (s, 1H), 8.18 (d, 1H); MS m/z 522 $[M+H]^+$.

Example 411:

2-chloro-4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-fluoro-N-(1-methyl-4-piperidyl)benzamide

2-amino-9-cyclohexyl-5-methyl-8,9-dihydro-5H-pyrimido[5,4-b][1,4]diazepin-6(7H)-one (Intermediate 263; 100 mg, 0.36 mmol), 4-bromo-2-chloro-5-fluoro-N-(1-methylpiperidin-4-yl)benzamide (Intermediate 262; 133 mg, 0.38 mmol), xantphos (12.61 mg, 0.02 mmol), palladium(II) acetate (163 mg, 0.73 mmol) and caesium carbonate (14.20 mg, 0.04 mmol) were added to dioxane (10 mL) and heated at 103 °C overnight. The resulting solution was filtered and passed through a 5g SCX-3 column. The obtained yellow foam was triturated with hot ethyl acetate to afford a yellow solid.

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.16 - 1.08 (m, 1H), 1.43 - 1.35 (m, 2H), 1.63 - 1.48 (m, 5H), 1.80 - 1.71 (m, 6H), 2.08 - 1.99 (m, 2H), 2.19 (s, 3H), 2.59 - 2.56 (m, 2H), 2.78 - 2.75 (m, 2H), 3.17 (s, 3H), 3.71 - 3.60 (m, 3H), 4.41 - 4.36 (m, 1H), 7.30 (d, 1H), 8.06 (s, 1H), 8.16 (d, 1H), 8.26 (d, 1H), 8.78 (s, 1H); MS m/z 544 $[M+H]^+$.

Example 412:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 266; 33 mg, 0.113 mmol), 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 29 mg, 0.108 mmol) and caesium carbonate were added to dioxane (3 mL) and the suspension bubbled with nitrogen for 10 minutes. tris(dibenzylideneacetone) palladium (II) (4 mg, 0.006 mmol) and XANTPHOS (6 mg, 0.1 mmol) were added and the mixture heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature and filtered. The filter-cake was washed with DCM and the filtrate evaporated. The residue was dissolved in DCM and purified on a silica column eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM over 30 column volumes. Fractions containing product were combined and evaporated to a solid, which was triturated with isohexane then filtered and dried to yield the title compound as a pale yellow solid (46 mg, 81%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.18 (m, 1H), 1.57 (m, 6H), 1.78 (m, 1H), 1.91 (m, 4H), 2.06 (m, 2H), 2.17 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.80 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 4.01 (m, 1H), 4.48 (m, 1H), 6.58 (m, 1H), 7.29 (m, 1H), 7.82 (m, 1H), 7.94 (s, 1H), 8.38 (m, 1H); MS m/z 528 $[M+H]^+$.

Example 413:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2,5-difluoro-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide (Intermediate 269; 50 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (42 mg, 46%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ0.39 (m, 2H), 0.57 (m, 2H), 1.17 (m, 1H), 1.54 (m, 4H), 1.75 (m, 5H), 1.92 (m, 4H), 2.49 (s, 2H), 2.54 (m, 4H), 2.68 (m, 2H), 3.29 (s, 3H), 3.46 (m, 2H), 3.72 (m, 2H), 4.50 (m, 1H), 7.29 (m, 1H), 7.83 (m, 1H), 7.94 (s, 1H), 8.32 (m, 1H), 8.64 (m, 1H); MS m/z 569 $[M+H]^+$.

Example 414:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate **229**; 41 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (49 mg, 59%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.18 (m, 1H), 1.54 (m, 4H), 1.76 (m, 2H), 1.91 (m, 4H), 2.29 (m, 1H), 2.42 (m, 4H), 2.68 (m, 4H), 2.90 (m, 1H), 3.29 (s, 3H), 3.72 (m, 2H), 4.48 (m, 1H), 4.66 (m, 1H), 6.94 (m, 1H), 7.29 (m, 1H), 7.81 (m, 1H), 7.94 (s, 1H), 8.37 (m, 1H); MS m/z 514 $[M+H]^+$.

Example 415:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 46 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (60 mg, 69%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.10 (t, 3H), 1.18 (m, 1H), 1.55 (m, 6H), 1.78 (m, 1H), 1.91 (m, 4H), 2.11 (m, 4H), 2.43 (q, 2H), 2.68 (m, 2H), 2.89 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 4.04 (m, 1H), 4.48 (m, 1H), 6.59 (m, 1H), 7.28 (m, 1H), 7.82 (m, 1H), 7.94 (s, 1H), 8.38 (m, 1H); MS m/z 542 $[M+H]^+$.

Example 416:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 230; 43 mg, 0.161 mmol) triturating the final product with diethyl ether prior to filtration and drying, as a white solid (64 mg, 76%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.18 (m, 1H), 1.54 (m, 4H), 1.77 (m, 5H), 1.90 (m, 4H), 2.57 (m, 4H), 2.70 (m, 4H), 3.29 (s, 3H), 3.58 (m, 2H), 3.71 (m, 2H), 4.49 (m, 1H), 7.29 (m, 2H), 7.82 (m, 1H), 7.94 (s, 1H), 8.39 (m, 1H); MS m/z 526 $[M+H]^+$.

Example 417:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 162; 150 mg, 0.515 mmol), the final product being taken up in methanol (1 mL) diluted with water and freeze dried, as a cream coloured solid (201 mg, 71%).

^{1}H NMR (399.902 MHz, $CDCl_3$) d1.06 (m, 2H), 1.18 (m, 1H), 1.33 (m, 2H), 1.52 (m, 4H), 1.77 (m, 1H), 1.95 (m, 8H), 2.52 (m, 5H), 2.67 (m, 2H), 3.11 (m, 2H), 3.29 (s, 3H), 3.70 (m,

2H), 4.49 (m, 2H), 5.75 (d, 1H), 7.24 (m, 1H), 7.52 (m, 2H), 7.92 (s, 1H), 8.56 (m, 1H); MS m/z 550 $[M+H]^+$.

Example 418:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 154 mg, 0.509 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (137 mg, 48%).

^{1}H NMR (399.902 MHz, $CDCl_3$) d1.04 (m, 2H), 1.19 (m, 1H), 1.31 (m, 2H), 1.53 (m, 6H), 1.79 (m, 1H), 1.96 (m, 6H), 2.54 (m, 5H), 2.67 (m, 2H), 3.10 (m, 2H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.50 (m, 2H), 5.77 (d, 1H), 7.25 (m, 1H), 7.40 (d, 1H), 7.69 (s, 1H), 7.91 (s, 1H), 8.49 (d, 1H); MS m/z 562 $[M+H]^+$.

Example 419:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide (Intermediate 254; 65 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (4 mg, 3%).

MS m/z 580 $[M+H]^+$. Retention time 3.69 minutes

Example 420:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 55 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (20 mg, 19%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.20 (m, 1H), 1.56 (m, 4H), 1.78 (m, 2H), 1.92 (m, 4H), 2.32 (m, 1H), 2.43 (m, 4H), 2.68 (m, 4H), 2.89 (m, 1H), 3.28 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.52 (m, 1H), 4.67 (m, 1H), 7.00 (m, 1H), 7.56 (m, 1H), 7.76 (s, 1H), 7.92 (s, 1H), 8.31 (d, 1H); MS m/z 526 $[M+H]^+$.

Example 421:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-3-methoxy-N-(1-methylpyrrolidin-3-yl)benzamide (Intermediate 187; 51 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (37 mg, 36%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.22 (m, 1H), 1.52 (m, 4H), 1.77 (m, 2H), 1.94 (m, 4H), 2.23 (m, 1H), 2.44 (m, 4H), 2.56 (m, 1H), 2.67 (m, 2H), 2.81 (m, 1H), 2.98 (m, 1H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 4.70 (m, 1H), 6.48 (d, 1H), 7.31 (m, 1H), 7.41 (m, 1H), 7.70 (s, 1H), 7.91 (s, 1H), 8.49 (d, 1H); MS m/z 508 $[M+H]^+$.

Example 422:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 60 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (27 mg, 24%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.10 (t, 3H), 1.21 (m, 1H), 1.55 (m, 6H), 1.78 (m, 1H), 1.92 (m, 4H), 2.12 (m, 4H), 2.43 (q, 2H), 2.68 (m, 2H), 2.89 (m, 2H), 3.28 (s, 3H), 3.71 (m,

2H), 3.95 (s, 3H), 4.05 (m, 1H), 4.52 (m, 1H), 6.67 (m, 1H), 7.56 (d, 1H), 7.74 (s, 1H), 7.92 (s, 1H), 8.32 (d, 1H); MS m/z 554 $[M+H]^+$.

Example 423:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 57 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (61 mg, 56%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.11 (t, 3H), 1.21 (m, 1H), 1.54 (m, 6H), 1.78 (m, 1H), 1.94 (m, 4H), 2.12 (m, 4H), 2.44 (q, 2H), 2.67 (m, 2H), 2.92 (m, 2H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.03 (m, 1H), 4.50 (m, 1H), 5.88 (d, 1H), 7.23 (m, 1H), 7.39 (m, 1H), 7.68 (s, 1H), 7.91 (s, 1H), 8.50 (d, 1H); MS m/z 536 $[M+H]^+$.

Example 424:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(3-dimethylaminopropyl)-3-methoxy-benzamide (Intermediate 196; 51 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (50 mg, 48%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.22 (m, 1H), 1.54 (m, 4H), 1.76 (m, 3H), 1.95 (m, 4H), 2.30 (s, 6H), 2.51 (m, 2H), 2.67 (m, 2H), 3.28 (s, 3H), 3.58 (m, 2H), 3.70 (m, 2H), 3.97 (s, 3H), 4.53 (m, 1H), 7.27 (m, 1H), 7.48 (m, 1H), 7.72 (s, 1H), 7.91 (s, 1H), 8.38 (m, 1H), 8.50 (d, 1H); MS m/z 510 $[M+H]^+$.

Example 425:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 228; 57 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (19 mg, 17%).

^{1}H NMR (399.902 MHz, CDCl3) δ1.20 (m, 1H), 1.56 (m, 4H), 1.77 (m, 5H), 1.91 (m, 4H), 2.58 (m, 4H), 2.70 (m, 4H), 3.28 (s, 3H), 3.60 (m, 2H), 3.71 (m, 2H), 3.95 (s, 3H), 4.53 (m, 1H), 7.32 (m, 1H), 7.57 (d, 1H), 7.73 (s, 1H), 7.92 (s, 1H), 8.33 (d, 1H); MS m/z 540 $[M+H]^+$.

Example 426:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide (Intermediate 194; 48 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (31 mg, 31%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.22 (m, 1H), 1.54 (m, 4H), 1.76 (m, 1H), 1.94 (m, 4H), 2.29 (s, 6H), 2.54 (m, 2H), 2.67 (m, 2H), 3.28 (s, 3H), 3.53 (m, 2H), 3.70 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 6.74 (m, 1H), 7.32 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.91 (s, 1H), 8.50 (d, 1H); MS m/z 496 $[M+H]^+$.

Example 427:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-5-methoxy-N-[(1R,5S)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 411, utilising 4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 204; 65 mg, 0.204 mmol), the final product being purified by base modified reverse phase preparative HPLC, as a white solid (52 mg, 44%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.04 (m, 2H), 1.21 (m, 1H), 1.32 (m, 2H), 1.56 (m, 6H), 1.79 (m, 1H), 1.95 (m, 6H), 2.54 (m, 5H), 2.68 (m, 2H), 3.09 (m, 2H), 3.28 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.53 (m, 2H), 6.53 (m, 1H), 7.59 (d, 1H), 7.75 (s, 1H), 7.93 (s, 1H), 8.31 (d, 1H); MS m/z 580 $[M+H]^+$.

Example 428:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 267; 89 mg, 0.3 mmol) and 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 61; 76 mg, 0.3 mmol) were combined with p-toluenesulphonic acid monohydrate (143 mg, 0.75 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 30 minutes at 160 °C. The cooled reaction mixture was diluted with methanol (10 mL) and filtered and the filtrate loaded onto an SCX-3 cartridge (5 g) pre-wet with methanol. The cartridge was washed with methanol (2 x 10 mL) and eluted with 7 *N* methanolic ammonia (20 mL). The basic fraction was evaporated to give a yellow solid, which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (55 mg, 37%).

^{1}H NMR (400 MHz, DMSO-d6) δ1.15 (m, 2H), 1.45 (m, 3H), 1.6 (m, 4H), 1.7 (m, 1H), 1.8 (m, 6H), 1.95 (t, 2H), 2.15 (s, 3H), 2.6 (m, 2H), 2.7 (m, 2H), 3.15 (s, 3H), 3.65 (m, 2H), 3.7 (m, 1H), 4.4 (t, 1H), 7.5 (m, 2H), 7.7 (m, 2H), 8.1 (s, 1H), 9.6 (s, 1H); MS m/z 511 $[M+H]^+$.

Example 429:

4-[(2-cyclohexyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-fluoro-N-(1-methyl-4-piperidyl)benzamide

10-chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 267; 89 mg, 0.3 mmol) and 4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 65; 76 mg, 0.3 mmol) were combined with p-toluenesulphonic acid monohydrate (143 mg, 0.75 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 30 minutes at 160 °C The cooled reaction mixture was

diluted with methanol (10 mL) and filtered and the filtrate loaded onto an SCX-3 cartridge (5 g) pre-wet with methanol. The cartridge was washed with methanol (2 x 10 mL) and eluted with 7 *N* methanolic ammonia (20 mL). The basic fraction was evaporated to give a yellow gum, which was purified by base modified reverse phase preparative HPLC to give the title compound as a white solid (56 mg, 37 %).

^{1}H NMR (400 MHz, DMSO-d6) δ1.1 (m, 1H), 1.3 (q, 2H), 1.55 (m, 5H), 1.75 (m, 6H), 1.95 (t, 2H), 2.2 (s, 3H), 2.6 (m, 2H), 2.75 (d, 2H), 3.2 (s, 3H), 2.6 (m, 2H), 2.75 (d, 2H), 3.2 (s, 3H), 3.6 (m, 2H), 3.7 (m, 1H), 4.3 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 8.0 (s, 1H), 8.1 (m, 2H), 8.7 (s, 1H); MS m/z 511 $[M+H]^+$.

Example 430:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-(1-methyl-4-piperidyl)benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 100 mg, 0.31 mmol), 4-amino-3-methoxy-N-(1-methyl-4-piperidyl)benzamide (WO06/018220; 83 mg, 0.31 mmol) and p-toluenesulphonic acid monohydrate (149 mg, 0.78 mmol) were heated at 140 °C in 4-methyl-2-pentanol (4 mL) for 2 hours. The reaction mixture was loaded onto an SCX-3 column was pre-wet with methanol and the column washed with methanol and eluted with 2% 7N ammonia/methanol. The ammoniacal fraction was evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (97 mg, 57%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.68 - 0.71 (2H, t), 0.92 - 0.95 (2H, t), 1.40 - 1.50 (4H, m), 1.59 - 1.63 (2H, m), 1.65 - 1.68 (1H, m), 1.77 (2H, s), 1.79 (4H, t), 1.86 (1H, s), 1.93 - 1.98 (2H, m), 2.18 (3H, s), 2.80 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.70 – 3.76 (1H, m), 3.96 (3H, s), 4.45 (1H, m), 7.46 (1H, m), 7.48 - 7.51 (1H, d), 7.67 (1H, s), 7.96 (1H, s), 8.09 (1H, d), 8.39 (1H, d); MS m/z 547 $[M+H]^+$.

Example 431:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 430, utilising 4-amino-N-(3-dimethylaminopropyl)-3-methoxy-benzamide (Intermediate 196; 79 mg, 0.31 mmol), , as a white solid (96 mg, 58%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.68 - 0.71 (2H, t), 0.92 - 0.95 (2H, t), 1.47 - 1.51 (2H, m), 1.68 (4H, q), 1.76 - 1.78 (4H, m), 1.85 (2H, d), 2.15 (6H, s), 2.28 (2H, t), 3.17 (3H, s), 3.25 (2H, t), 3.51 (2H, s), 3.96 (3H, s), 4.45 (1H, m), 7.45 - 7.47 (1H, m), 7.51 (1H, d), 7.67 (1H, s), 7.96 (1H, s), 8.40 (1H, d), 8.41 (1H, d); MS m/z 537 $[M+H]^+$.

Example 432:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 430, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 202; 95 mg, 0.31 mmol), , as a white solid (111 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.68 - 0.71 (2H, m), 0.93 (2H, d), 0.93 (2H, d), 1.42 (2H, d), 1.45 - 1.47 (3H, m), 1.49 (2H, d), 1.77 (4H, d), 1.85 (4H, d), 1.93 (2H, t), 2.21 (1H, d), 2.42 (3H, s), 2.99 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.98 (3H, s), 4.29 – 4.34 (1H, m), 4.45 (1H, m), 7.47 (1H, d), 7.48 - 7.52 (1H, s), 7.67 (1H, s), 7.92 (1H, d), 7.97 (1H, s), 8.39 - 8.41 (1H, d); MS m/z 589 $[M+H]^+$.

Example 433:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 430, utilising 4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide (Intermediate 190; 87 mg, 0.31 mmol), , as a white solid (122 mg, 70%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.68 - 0.71 (2H, t), 0.92 - 0.95 (2H, t), 1.01 (3H, t), 1.45 (3H, t), 1.57 - 1.61 (2H, m), 1.77 (4H, d), 1.82 - 1.86 (3H, m), 1.88 (2H, t), 1.93 (2H, d), 2.33 (2H, q), 2.90 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.74 – 3.78 (1H, m), 3.96 (3H, s), 4.41 – 4.45 (1H, m), 7.46 (1H, d), 7.48 - 7.51 (1H, m), 7.67 (1H, s), 7.96 (1H, s), 8.09 (1H, d), 8.39 - 8.41 (1H, m); MS m/z 563 $[M+H]^+$.

Example 434:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 100 mg, 0.31 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide (Intermediate 235; 98 mg, 0.34 mmol) and caesium carbonate (204 mg, 0.62 mmol) added to dioxane (5 mL) and the suspension bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone) palladium (II) (18 mg, 0.02 mmol) and XANTPHOS (17 mg, 0.03 mmol) added and the mixture heated at 110 °C overnight. The mixture was filtered and the filtrate loaded onto an SCX-3 column was pre-wet with methanol and the column washed with methanol and eluted with 2% 7N ammonia/methanol. The ammoniacal fraction was evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white crystalline solid (19 mg, 11%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.69 - 0.72 (2H, t), 0.93 - 0.96 (2H, t), 1.00 (3H, t), 1.42 (2H, t), 1.48 (2H, d), 1.49 - 1.54 (2H, m), 1.63 (2H, d), 1.70 (2H, d), 1.78 (4H, s), 1.95 (2H, d), 2.30 - 2.35 (2H, m), 2.84 (2H, d), 3.17 (3H, s), 3.50 (2H, s), 3.75 (1H, m), 4.46 (1H, m), 7.41 - 7.45 (1H, m), 7.98 (1H, d), 7.99 (1H, s), 8.13 - 8.18 (1H, m), 8.79 (1H, s); MS m/z 589 $[M+H]^+$.

Example 435:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 97 mg, 0.3 mmol) and 4-amino-3-fluoro-N-(9-methyl-9-azabicyclo[3.3.1]non-7-yl)benzamide (Intermediate 162; 88 mg, 0.3 mmol) were combined with p-toluenesulphonic acid monohydrate (143 mg, 0.75 mmol) in 4-methyl-2-pentanol (2 mL) and heated by microwave irradiation for 30 minutes at 160 °C. The cooled reaction mixture was diluted with methanol (5 mL) and loaded onto an SCX-3 (5 g) cartridge pre-wet with methanol. The cartridge was washed with methanol (2 x 10 mL) and product eluted with 7 *N* methanolic ammonia (20 mL). Product containing fractions were evaporated and the resultant material purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (82 mg, 48%).

^{1}H NMR (400 MHz, DMSO-d6) δ0.7 (m, 2H), 0.95 (m, 4H), 1.15 (m, 1H), 1.35 (m, 2H), 1.45 (m, 4H), 1.7 (m, 4H), 1.8 (d, 2H), 1.95 (m, 2H), 2.05 (m, 1H), 2.15 (m, 2H), 2.9 (s, 3H), 2.95 (d, 2H), 3.15 (s, 3H), 3.45 (s, 2H), 4.35 (m, 2H), 7.65 (m, 1H), 7.7 (m, 1H), 7.9 (s, 1H), 7.95 (m, 1H), 8.2 (t, 1H), 8.55 (s, 1H); MS m/z 576 $[M+H]^+$.

Example 436:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 434, utilising 4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide (Intermediate 59; 93 mg, 0.34 mmol), as a white solid (76 mg, 44%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.69 - 0.72 (2H, t), 0.93 - 0.96 (2H, t), 1.44 (4H, m), 1.54 - 1.61 (2H, m), 1.71 (2H, d), 1.78 (4H, d), 1.94 - 1.99 (2H, m), 2.17 (3H, s), 2.73 (2H, d), 3.17 (3H, s), 3.29 (2H, d), 3.50 (2H, s), 3.65 – 3.72 (1H,m), 4.46 (1H, m), 7.41 - 7.45 (1H, m), 7.96 (1H, d), 7.98 (1H, s), 8.13 - 8.18 (1H, m), 8.78 (1H, s); MS m/z 554 $[M+H]^+$.

Example 437:

5-chloro-4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 103 mg, 0.32 mmol), 4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 175; 92 mg, 0.29 mmol), and XANTPHOS (16 mg, 0.03 mmol) were dissolved in 1,4-dioxane (7.5 mL). Caesium carbonate (210 mg, 0.59 mmol) was added and the system purged with a stream of nitrogen for 15 minutes before tris(dibenzylideneacetone) palladium (II) (17 mg, 0.02 mmol) was added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, and the column then washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and the residue purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (49 mg, 28%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.71 (2H, m), 0.94 (2H, m), 1.10 (2H, m), 1.25 - 1.84 (16H, m), 2.09 - 2.19 (7H, m), 3.18 (3H, s), 3.52 (2H, s), 3.63 – 3.70 and 3.88 – 3.94 (each 0.5H, m), 4.43 (1H, m), 7.67 (1H, d), 8.00 - 8.04 (3H, m), 8.27 (1H, d); MS m/z 598 $[M+H]^+$.

Example 438:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 103 mg, 0.32 mmol), 4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide (Intermediate 182; 87 mg, 0.32 mmol) and p-toluenesulphonic acid monohydrate (154 mg, 0.81 mmol) were heated in 4-methyl-2-pentanol (3 mL) at 140 °C for 3 hours. The mixture was cooled and absorbed on to an SCX

column, which was then washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated and purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (70 mg, 40%). ^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.70 - 0.73 (2H, m), 0.93 - 0.96 (2H, m), 1.10 1.20 (1H, m), 1.40 - 1.54 (4H, m), 1.64 – 1.84 (6H, m), 2.13 - 2.22 (1H, m), 2.26 (3H, s), 2.33 - 2.47 (2H, m), 2.56 - 2.64 (1H, m), 2.66 - 2.71 (1H, m), 3.17 (3H, s), 3.53 (2H, s), 3.94 (3H, s), 4.34 – 4.41 (1H, m), 4.45 - 4.50 (1H, m), 7.22 (1H, d), 7.74 (1H, s), 7.99 (1H, s), 8.01 - 8.03 (1H, m), 8.26 (1H, d); MS m/z 554 $[M+H]^+$.

Example 439:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 86 mg, 0.27 mmol) and 4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide (Intermediate 22; 75 mg, 0.27 mmol) were taken up in 4-methyl-2-pentanol (3 mL) and p-toluenesulphonic acid monohydrate (102 mg, 0.54 mmol) added. The reaction mixture was heated at 160 °C for 1 hour by microwave irradiation. After cooling, the reaction mixture was diluted with methanol (5 mL) and water (5 mL) and the resultant solution loaded onto an SCX-3 (5 g) cartridge. The cartridge was wahsed with methanol (40 mL) and then eluted with 2M ammonia in methanol (25 mL). Evaporation of the ammoniacal solution gave an opaque cream coloured film which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white foam (83 mg, 55%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.69 (m, 2H), 0.90 (s, 6H), 0.93 (m, 2H), 1.16 (m, 1H), 1.44 (m, 4H), 1.62 - 1.88 (m, 5H), 2.22 (s, 2H), 2.28 (s, 6H), 3.17 (s, 3H), 3.21 (d, 2H), 3.50 (s, 2H), 3.96 (s, 3H), 4.45 (m, 1H), 7.40 (m, 1H), 7.47 (d, 1H), 7.68 (s, 1H), 7.96 (s, 1H), 8.40 (d, 1H), 8.50 (t, 1H); MS m/z 564 $[M+H]^+$.

Example 440:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 439, on a 0.33 mmol scale, utilising 4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide (Intermediate 206; 100 mg, 0.33 mmol) heating thermally at 120 ^{0}C over the weekend, as a white solid (46 mg, 24%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.57 - 0.54 (m, 2H), 0.93 (s, 6H), 1.12 - 1.02 (m, 4H), 1.46 - 1.25 (m, 4H), 1.74 - 1.64 (m, 4H), 1.82 (d, 4H), 2.48 (s, 2H), 2.64 - 2.58 (m, 4H), 3.20 (s, 3H), 3.33 (d, 2H), 3.39 (s, 2H), 3.90 (s, 3H), 4.53 - 4.47 (m, 1H), 7.19 - 7.17 (m, 1H), 7.43 (s, 1H), 7.58 (s, 1H), 7.77 (s, 1H), 8.38 (d, 1H), 8.92 - 8.88 (m, 1H); MS m/z 590 $[M+H]^+$.

Example 441:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Example 439, on a 0.24 mmol scale, utilising 4-amino-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide (Intermediate 245; 70 mg, 0.26 mmol), as a white solid (57 mg, 38%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.69 (m, 2H), 0.93 (m, 2H), 1.04 (t, 3H), 1.15 (m, 1H), 1.45 (m, 4H), 1.76 (m, 6H), 2.15 (m, 1H), 2.43 (m, 4H), 2.66 (m, 1H), 2.72 (m, 1H), 3.16 (s, 3H), 3.50 (s, 2H), 3.96 (s, 3H), 4.42 (m, 2H), 7.50 (m, 1H), 7.54 (d, 1H), 7.66 (s, 1H), 7.96 (s, 1H), 8.31 (d, 1H), 8.40 (d, 1H); MS m/z 548 $[M+H]^+$.

Example 442:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 439, on a 0.17 mmol scale, utilising 4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-

azabicyclo[3.3.1]non-3-yl]benzamide (Intermediate 204; 55 mg, 0.17 mmol), heating thermally at 140 ^{0}C for 2 hours, as a white solid (24 mg, 23%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.70 - 0.73 (2H, m), 0.90 – 0.96 (4H, m), 1.13 – 1.20 (1H, m), 1.40 – 1.55 (7H, m), 1.67 (1H, d), 1.75 - 1.95 (6H, m), 2.01 - 2.11 (1H, m), 2.18 - 2.26 (2H, m), 2.42 (3H, s), 2.98 (2H, d), 3.17 (3H, s), 3.53 (2H, s), 3.94 (3H, s), 4.27 - 4.34 (1H, m), 4.45 – 1.52 (1H, m), 7.22 (1H, d), 7.68 – 7.72 (1H, m), 7.74 (1H, s), 8.00 (1H, s), 8.26 (1H, d); MS m/z 606 $[M+H]^+$.

Example 443:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 54 mg, 0.17 mmol), 4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide (Intermediate 205; 50 mg, 0.17 mmol), and p-toluenesulphonic acid monohydrate (81 mg, 0.43 mmol) were stirred together in 4-methyl-2-pentanol (3 mL) and heated at 110 ^{0}C for 18 hours. The cooled reaction mixture was loaded onto an SCX-3 (5 g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and eluted with 2M NH3/MeOH. Solvent evaporation of the combined ammoniacal fractions gave a brown gum which was purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (48 mg, 49%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.70 (m, 2H), 0.94 (m, 2H), 1.00 (t, 3H), 1.14 (m, 2H), 1.61 (m, 12H), 1.96 (m, 2H), 2.32 (q, 3H), 2.83 (d, 2H), 3.17 (s, 3H), 3.52 (s, 2H), 3.72 (m, 1H), 3.93 (s, 3H), 4.47 (m, 1H), 7.19 (d, 1H), 7.73 (s, 1H), 7.82 (m, 1H), 7.99 (s, 1H), 8.26 (d , 1H); MS m/z 580 $[M+H]^+$.

Example 444:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 443, on a 0.18 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 228; 50 mg, 0.18 mmol), as a white solid (58 mg, 57%). ^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.71 (m, 2H), 0.94 (m, 2H), 1.15 (m, 2H), 1.61 (m, 12H), 2.50 (m, 4H), 2.58 (t, 3H), 3.16 (s, 3H), 3.39 (m, 2H), 3.52 (s, 2H), 3.93 (s, 3H), 4.48 (m, 1H), 7.30 (d, 1H), 7.76 (bs, 1H), 7.91 (m, 1H), 7.99 (s, 1H), 8.27 (d, 1H); MS m/z 566 $[M+H]^+$.

Example 445:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

The title compound was prepared by an analogous method to the preparation of Example 443, on a 0.16 mmol scale, utilising 4-amino-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide (Intermediate 254; 52 mg, 0.16 mmol), as a white solid (53 mg, 55%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.34 (2H, m), 0.51 (2H, m), 0.71 (2H, m), 0.94 (2H, m), 1.16 (1H, m), 1.47 (5H, m), 1.72 (10H, m), 2.44 (2H, s), 2.49 (2H, s), 3.17 (3H, s), 3.37 (2H, d), 3.53 (2H, s), 3.93 (3H, s), 4.48 (1H, m), 7.39 (1H, d), 7.78 (1H, s), 7.99 (1H, s), 8.26 (1H, d), 8.37 (1H, m); MS m/z 606 $[M+H]^+$.

Example 446:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-(1-methyl-4-piperidyl)benzamide

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 200 mg, 0.62 mmol), 4-amino-3-fluoro-N-(1-methylpiperidin-4-yl)benzamide (Intermediate 65; 157 mg, 0.62 mmol) and p-toluenesulfonic acid monohydrate (296 mg, 1.56 mmol) were suspended in 4-Methyl-2-pentanol (5 mL) and sealed into a microwave tube. The reaction was heated at 160 °C for 30 minutes in the microwave reactor and then allowed to cool to room temperature.

The reaction mixture was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M NH3/MeOH and pure fractions were evaporated to dryness to afford a cream coloured solid which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield the title compound as a white solid (125 mg, 37%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ0.65 (t, 2H), 0.95 (t, 2H), 1.1 (m, 1H), 1.35 (q, 2H), 1.45 (q, 2H), 1.5-1.7 (m, 5H), 1.8 (m, 4H), 1.95 (t, 2H), 2.15 (t, 2H), 2.2 (s, 3H), 2.8 (d, 2H), 3.2 (s, 3H), 3.45 (s, 2H), 3.7 (m, 1H), 4.4 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s 1H), 8.15 (m, 2H), 8.6 (s, 1H); MS m/z 536 $[M+H]^+$.

Example 447:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-tricn-10-yl)amino]-2,5-difluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

p-Toluenesulphonic acid monohydrate (338 mg, 1.78 mmol) was added to 4-amino-2,5-difluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 274; 220 mg, 0.71 mmol), and 2-chloro-9-cyclopentyl-5-methyl-8,9-dihydro-5H-pyrimido[5,4-b][1,4]diazepin-6(7H)-one (Intermediate 1; 200 mg, 0.71 mmol) in 4-methyl-2-pentanol (4 mL) at 25 °C. The resulting mixture was heated by microwave irradiation at 150 °C for 1 hour. The crude product was purified by ion exchange chromatography, using an SCX-3 (5g) column. The desired product was eluted from the column using 2M NH_3/MeOH and product-containing fractions were evaporated to dryness. The residue was further purified by base modified reverse phase preparative HPLC to yield the title compound as a white solid (91 mg, 23.%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 - 0.93 (2H, m), 1.37 - 1.44 (4H, m), 1.57 - 1.71 (6H, m), 1.86 - 2.04 (4H, m), 2.17 - 2.24 (2H, m), 2.41 (3H, s), 2.58 - 2.61 (2H, m), 2.96 - 2.99 (2H, m), 3.18 (3H, s), 3.62 - 3.64 (2H, m), 4.21 - 4.33 (1H, m), 4.78 - 4.86 (1H, m), 7.42 - 7.46 (1H, m), 7.81 (1H, d), 8.11 (1H, s), 8.20 - 8.25 (1H, m), 8.91 (1H, s); MS m/z 555 $[M+H]^+$.

Example 448:

4-(9'-cyclopentyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 446, on a 0.65 mmol scale, utilising 2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 200mg, 0.65 mmol), as a white solid (50 mg, 13%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.67 - 0.70 (2H, m), 0.90 - 0.93 (4H, m), 1.36 - 1.60 (7H, m), 1.64 - 1.71 (2H, m), 1.85 - 1.93 (4H, m), 1.97 - 2.04 (1H, m), 2.17 - 2.24 (2H, m), 2.40 (3H, s), 2.96 - 2.98 (2H, m), 3.18 (3H, s), 3.48 (2H, s), 4.21 - 4.32 (1H, m), 4.82 - 4.91 (1H, m), 7.42 - 7.46 (1H, m), 7.79 - 7.82 (1H, m), 8.02 (1H, s), 8.23 - 8.28 (1H, m), 8.85 (1H, s); MS m/z 581 $[M+H]^+$.

Example 449:

4-(9'-cyclohexyl-5'-methyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-2,5-difluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

The title compound was prepared by an analogous method to the preparation of Example 446, on a 0.62 mmol scale, utilising 2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 270; 200mg, 0.62 mmol), as a white solid (37 mg, 10%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.69 - 0.72 (2H, m), 0.90 - 0.95 (4H, m), 1.09 - 1.16 (1H, m), 1.33 - 1.50 (8H, m), 1.61 - 1.80 (4H, m), 1.86 - 1.92 (2H, m), 1.97 - 2.04 (1H, m), 2.16 - 2.24 (2H, m), 2.41 (3H, s), 2.96 - 2.98 (2H, m), 3.17 (3H, s), 3.50 (2H, s), 4.21 - 4.32 (1H, m), 4.43 - 4.49 (1H, m), 7.42 - 7.47 (1H, m), 7.81 - 7.84 (1H, m), 7.99 (1H, s), 8.13 - 8.18 (1H, m), 8.76 (1H, s); MS m/z 595 $[M+H]^+$.

Example 450:

4-(9'-cyclohexyl-6'-oxo-5',6',8',9'-tetrahydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepine]-2'-ylamino)-3-fluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide

2'-chloro-9'-cyclohexyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (100 mg, 0.33 mmol), 4-amino-3-fluoro-N-((1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]nonan-3-yl)benzamide (95 mg, 0.33 mmol) and p-Toluenesulfonic acid . H2O (155 mg, 0.81 mmol) were suspended in 4-Methyl-2-pentanol (2 mL) and sealed into a microwave tube. The reaction was heated to 160 °C for 25 minutes by microwave irradiation and then cooled to room temperature. The reaction mixture was filtered through a PTFE Filter cup to give an off white solid which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to yield the title compound as a white solid (27 mg, 15 %).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.8 (t, 2H), 0.9 (d, 2H), 1.1 (t, 2H), 1.2-1.5 (m, 8H), 1.6 (b, 3H), 1.75 (d, 2H), 1.9 (m,2H), 2.0 (m, 1H), 2.2 (m, 2H), 2.4 (s,3H), 2.95 (d, 2H), 3.4 (s, 2H), 4.3 (m, 1H), 4.5 (m, 1H), 7.55 (d, 1H), 7.6 (d, 1H), 7.85 (s, 1H), 7.95 (d, 1H), 8.15 (t, 1H), 8.5 (s, 1H), 9.5 (s, 1H); MS m/z 563 $[M+H]^+$.

Example 451:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-methoxy-N-[(1R,5S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]non-7-yl]benzamide

p-Toluenesulphonic acid monohydrate (143 mg, 0.83 mmol) was added to 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 93 mg, 0.33 mmol) and 4-amino-3-methoxy-N-[(1R,5S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]non-7-yl]benzamide (Intermediate 275; 100 mg, 0.33 mmol) in 4-methyl-2-pentanol (3 mL) at 25°C. The resulting suspension was stirred at 110 °C for 18 hours. The reaction mixture was cooled to ambient temperature and purified by ion exchange chromatography, using an SCX-2 (5g) column. The desired product was eluted from the

column using 2M NH3/MeOH and fractions were evaporated to dryness to afford the crude product as a gum which was purified by preparative HPLC using decreasingly polar mixtures of water (containing 1% NH3) and MeCN as eluent. Fractions containing the desired compound were combined and evaporated to dryness to afford the title compound as a white solid (15 mg, 8 %).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.36 - 1.40 (2H, m), 1.57 - 1.72 (6H, m), 1.89 - 1.95 (2H, m), 2.33 - 2.41 (2H, m), 2.45 (3H, s), 2.57 - 2.63 (4H, m), 3.17 (3H, s), 3.61 - 3.64 (2H, m), 3.71 - 3.74 (2H, m), 3.89 - 3.91 (2H, m), 3.93 (3H, s), 4.39 - 4.45 (1H, m), 4.74 - 4.82 (1H, m), 7.29 (1H, d), 7.38 (1H, s), 7.75 (1H, s), 8.07 (1H, s), 8.37 (1H, d), 8.83 (1H, d); MS m/z 551 $[M+H]^+$.

Example 452:

N-(azepan-3-yl)-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide

A solution of tert-butyl 3-[[4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoyl]amino]azepane-1-carboxylate (Example 348; 149 mg, 0.25 mmol) in DCM (2 mL) was treated with TFA (1 mL) The resulting solution was stirred at ambient temperature for 5 hours.

The reaction mixture was diluted with DCM (10 mL) and submitted to ion exchange chromatography, using an SCX-3 column. The column was eluted with DCM (50 mL) and methanol (50 mL) before the desired product was eluted from the column using 2M NH3/MeOH. The ammoniacal solution was evaporated to dryness to afford the title compound as an amber gum (95 mg, 76 %).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.41 - 1.92 (16H, m), 2.51 - 2.53 (2H, m), 2.60 - 2.67 (1H, m), 2.73 (1H, t), 2.92 (1H, dd), 3.10 (3H, s), 3.54 - 3.58 (2H, m), 3.88 (3H, s), 3.90 - 3.99 (1H, m), 4.70 - 4.79 (1H, m), 7.38 - 7.43 (2H, m), 7.66 (1H, s), 7.93 (1H, d), 8.01 (1H, s), 8.31 (1H, d); MS m/z 508 $(M+H)^+$

Example 453:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-N-(1-methylazepan-3-yl)benzamide

To a solution of N-(azepan-3-yl)-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzamide (Example 453; 88 mg, 0.17 mmol) in formaldehyde (1 mL, 13.35 mmol) and acetic acid (100 µL, 1.75 mmol), was added sodium acetate (142 mg, 1.73 mmol). The reaction mixture was cooled to 0 °C with stirring. Sodium cyanoborohydride (12 mg, 0.19 mmol) was added and the reaction mixture stirred at 0 °C for 5 minutes before removing the cooling bath. The reaction mixture was allowed to warm to ambient temperature and stirred for 2 hours and then submitted to ion exchange chromatography, using an SCX-3 column. The column was washed with methanol, before the crude products were eluted from the column using 2M NH3/MeOH. Evaporation of the ammoniacal solution afforded the crude product as an amber gum which was purified by flash silica chromatography, elution gradient 5 to 10% 2M ammonia/MeOH in DCM. Pure fractions were combined and evaporated to dryness to give 4-(9-cyclopentyl-5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrimido[5,4-b][1,4]diazepin-2-ylamino)-3-methoxy-N-(1-methylazepan-3-yl)benzamide as an amber glass (44 mg, 49 %)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.53 - 1.86 (12H, m), 1.91 - 1.96 (1H, m), 2.03 - 2.10 (2H, m), 2.45 (3H, s), 2.65 - 2.70 (3H, m), 2.79 - 2.86 (2H, m), 3.30 (3H, s), 3.68 - 3.72 (2H, m), 3.99 (3H, s), 4.25 - 4.33 (1H, m), 4.91 (1H, quintet), 7.18 - 7.25 (1H, m), 7.31 (1H, d), 7.48 (1H, d), 7.65 (1H, s), 7.95 (1H, s), 8.51 (1H, d); MS m/z 522 $(M+H)^+$

Preparation of Intermediates:

Intermediate 1:

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

To a cold (0 °C) solution of 9-chloro-6-cyclopentyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one (Intermediate 2; 241 mg, 0.90 mmol) in DMA (20 mL) was added MeI (62 uL, 0.99 mmol) followed by NaH (39 mg, 0.96 mmol) and the reaction mixture stirred at 0 °C for 30 mins then at ambient temperature for 1 hr. The solution was diluted with Ethyl Acetate (20 mL), washed with water (2 x 30 mL), brine (30 mL), dried ($MgSO_4$) and the volatiles were removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient: 2% MeOH in DCM) afforded the title compound (187 mg, 74%) as a solid.

^{1}H NMR (400 MHz, DMSO-D6) δ_H 1.52 - 1.66 (m, 4H), 1.66 - 1.75 (m, 2H), 1.85 - 1.96 (m, 2H), 2.63 - 2.67 (m, 2H), 3.18 (s, 3H), 3.64 - 3.68 (m, 2H), 4.71 - 4.79 (m, 1H), 8.15 (s, 1H); MS 281, 283 $[M+H]^+$.

Intermediate 2:

9-Chloro-6-cyclopentyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-3-one

To a solution of methyl 3-[(2-chloro-5-oxidoazonoyl-pyrimidin-4-yl)-cyclopentyl-amino]propanoate (Intermediate 3; 1.00 g, 3.04 mmol) in AcOH (50 mL) was added powdered Fe (1.00 g, 3.04 mmol) and the reaction stirred at 70 °C for 30 mins. The reaction mixture was filtered hot through a pad of celite, washed with AcOH (25 mL) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient: 0-100% Ethyl Acetate in hexane) gave the title compound (480 mg, 43%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.46 - 1.56 (m, 2H), 1.62 - 1.80 (m, 3H), 1.94 - 2.04 (m, 3H), 2.77 - 2.79 (m, 2H), 3.60 - 3.63 (m, 2H), 5.17 - 5.26 (m, 1H), 7.79 (s, 1H), 7.99 (s, 1H); MS m/z 267, 269 $[M+H]^+$.

Intermediate 3:

Methyl 3-[(2-chloro-5-oxidoazonoyl-pyrimidin-4-yl)-cyclopentyl-amino]propanoate

To a solution of methyl 3-(cyclopentylamino)propanoate (2.46 g, 14.37 mmol) in acetone (40 mL) was added K_2CO_3 (2.03 g, 14.65 mmol) and 2,4-dichloro-5-nitropyrimidine (3.07 g, 15.80 mmol) and the reaction mixture stirred at ambient temperature under an atmosphere of nitrogen for 18 hrs. The volatiles were removed under reduced pressure and the crude material was dissolved in Ethyl Acetate (50 mL), washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient: 0-10% Ethyl Acetate in hexane) afforded the title compound (2.23 g, 53%) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.44 - 1.54 (m, 2H), 1.62 - 1.78 (m, 4H), 1.86 - 1.96 (m, 2H), 2.69 (t, 2H), 3.61 (s, 3H), 3.66 (t, 2H), 3.71 - 3.80 (m, 1H), 8.84 (s, 1H); MS m/z 329, 331 $[M+H]^+$.

Intermediate 4:

4-Amino-*N*-(1-methyl-4-piperidyl)benzamide

p-Aminobenozoic acid (137 mg, 1 mmol), 4-amino-*N*-methylpiperidine (114 mg, 1 mmol) and DIPEA (522 uL, 3 mmol) were dissolved in DMA (5 mL). HATU (570 mg, 1.5 mmol) in DMA (5 mL) was added and the reaction stirred at ambient temperature for 2 h. The volatiles were removed under reduced pressure and $NaHCO_3$ (50 mL, sat. aq.) was added. The resulting precipitate was removed by filtration and the aqueous phase neutralised with HCL (2N). The reaction mixture was then loaded onto an SCX-2 cartridge washing with copious quantities of water. The crude product was the eluted from the SCX-2 cartridge with NH_3 (60 mL, 7M in MeOH). Purification by column chromatography (SiO_2, eluent: 10% NH_3 [7M in MeOH] in DCM) afforded the title compound (167 mg, 72%) as a solid.

^1H NMR (400 MHz, DMSO-d_6) δ_H 1.50 - 1.60 (2H, m), 1.69 - 1.73 (1H, m), 1.72 (1H, t), 1.89 - 1.96 (2H, m), 2.16 (3H, s), 2.75 (2H, d), 3.65 - 3.71 (1H, m), 5.52 - 5.54 (1H, m), 6.52 - 6.55 (2H, m), 7.56 - 7.59 (2H, m), 7.69 (1H, d); MS m/z 234 $[M+H]^+$.

Intermediate 5:

10-chloro-2-cyclopentyl-4,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

To a cold (-78 °C) solution of 10-chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (90 mg, 0.32 mmol) in dry THF (4 mL) was added LiHMDS (640 µL, 1M in THF, 0.64 mmol) dropwise over 10 mins. MeI (40 µL, 0.64 mmol) in THF (1 mL) was added and the reaction mixture was stirred at –78 °C for 20 mins and then at 0 °C for 1 hr. The reaction mixture was diluted with DCM (20 mL) and washed with water (2 x 20 mL), brine (40 mL), dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure to yield the title compound (106 mg, 100%) as a solid.

MS m/z 295, 297 $[M+H]^+$.

Intermediate 6:

4-[(9-Cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoic acid

Methyl 4-[(9-cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate (Intermediate 7; 250 mg, 0.61 mmol) and HCl (2 mL, concentrated aqueous) were suspended in water (4 mL) and heated at reflux for 24 h. The reaction mixture was then cooled to ambient temperature and the volatiles were removed under reduced pressure. The solid obtained was dissolved in MeOH:DCM (1:10, 40 mL) and washed with $NaHCO_3$ (saturated aqueous, 40 mL). The organic layer was then dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure to afford the title compound (240 mg, 99%) as a solid.

^1H NMR (400MHz, DMSO-d_6) δ_H 1.57 (m, 4H), 1.73 (m, 2H), 1.88 (m, 4H), 2.70 (s, 3H), 2.95 (t, 2H), 3.47 (m, 2H), 3.87 (s, 3H), 4.86 (quintet, 1H), 7.20 (s, 1H), 7.42 (d, 1H), 7.50 (s, 1H), 7.52 (s, 1H), 7.96 (s, 1H), 8.28 (d, 1H); MS m/z 398 $[M+H]^+$.

Intermediate 7:

Methyl 4-[(9-cyclopentyl-5-methyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate

$BH_3.SMe_2$ (1.36 mL, 5.0 M in Et_2O, 6.8 mmol) was added to solution of methyl 4-[(9-cyclopentyl-5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate (Intermediate 8; 290 mg, 0.68 mmol) in THF (4 mL) and stirred for 5 h at ambient temperature under an atmosphere of nitrogen. HCl (10 mL, concentrated aqueous) was added and the resulting solution was stirred at ambient temperature for 16 h. The HCl solution was then diluted with water (50 mL), and loaded onto an SCX-2 column. The SCX-2 column was then washed with water (50 mL) and MeOH (50 mL). The product was then eluted from the SCX-2 column with NH_3 (50 mL, 7M in MeOH). The volatiles were then removed under reduced pressure to afford the title compound (250 mg, 89%) as a solid.

^1H NMR (400 MHz, DMSO-d_6) δ_H 1.67 (m, 6H), 1.96 (m, 4H), 2.77 (s, 3H), 3.06 (t, 2H), 3.58 (m, 2H), 3.88 (s, 3H), 4.00 (s, 3H), 4.91 (quintet, 1H), 7.57 (m, 3H), 7.71 (s, 1H), 8.59 (d, 1H); MS m/z 412 $[M+H]^+$.

Intermediate 8:

Methyl 4-[(9-cyclopentyl-5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrimido[4,5-b][1,4]diazepin-2-yl)amino]-3-methoxybenzoate

2-Chloro-9-cyclopentyl-5-methyl-5,7,8,9-tetrahydro-6H-pyrimido[4,5-b][1,4]diazepin-6-one (Intermediate 1; 500 mg, 1.78 mmol), methyl 4-amino-3-methoxybenzoate (324 mg, 1.78 mmol) and p-toluenesulfonic acid (847 mg, 4.45 mmol) were suspended in (2R/S)-4-methyl-2-pentanol (10 mL) and heated at reflux for 5 h. The reaction mixture was cooled and loaded onto an SCX-2 column and washed with MeOH (20 mL). The crude product was then eluted from the SCX-2 column with NH_3 (40 mL, 7M in MeOH) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient 0-10% MeOH in DCM) afforded the title compound (290 mg, 38%) as a solid.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ_H 1.71 (m, 6H), 2.00 (m, 2H), 2.65 (m, 2H), 3.23 (s, 3H), 3.69 (m, 2H), 3.89 (s, 3H), 4.01 (s, 3H), 4.87 (m, 1H), 7.56 (d, 1H), 7.64 (d, 1H), 7.90 (s, 1H), 8.16 (s, 1H), 8.55 (d, 1H); MS m/z 426 $[M+H]^+$.

Intermediate 9:

10-Chloro-2,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-methyl-amino]-N-methyl-propanamide (Intermediate 15; 2.09 g, 6.20 mmol), tris(dibenzylideneacetone)dipalladium(0) (171 mg, 0.19 mmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (288 mg, 0.50 mmol) and Cs_2CO_3 (2930 mg, 8.99 mmol) in 1,4-dioxane (50 mL) were heated at reflux for 16 h under an atmosphere of nitrogen. The reaction mixture was evaporated then suspended in DCM (20 mL) and filtered through a layer of celite washing with DCM (40 mL). Purification by column chromatography (SiO_2, eluent gradient: 2-10% MeOH in DCM) afforded the title compound (190 mg, 19%) as a foam.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 2.67 (tr, 2H), 3.08 (s, 3H), 3.20 (s, 3H), 3.72 (tr, 2H), 8.19 (s, 1H); MS m/z 227 $[M+H]^+$.

Intermediate 10

10-Chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Intermediate 11:

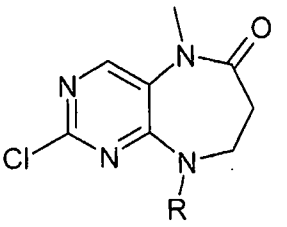
10-Chloro-6-methyl-2-(3-methylbutyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Intermediate 12:

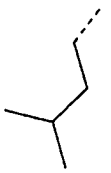
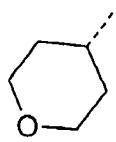
10-Chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Intermediate 13:

10-Chloro-6-methyl-2-(oxan-4-yl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one



Intermediates 10-13 were prepared, using the appropriate secondary amide (Intermediates 14, 16-18), by an analogous process to that used in the preparation of Intermediate 9.

Example	R	^{1}H NMR (400 MHz, DMSO-d_6)	MS m/z $[M+H]^+$
10		1.18 (d, 6H), 2.65 (tr, 2H), 3.19 (s, 3H), 3.61 (tr, 2H), 8.12 (s, 1H).	225
11		0.99 (d, 6H),1.57 (m, 3H), 2.71 (tr, 2H), 3.22 (s, 3H), 3.63 (tr, 2H), 3.78 (tr, 2H), 8.19 (s, 1H).	283
12		1.14 (m, 1H), 1.32 (m, 2H), 1.60 (m, 3H), 1.78 (m, 4H). 2.61 (tr, 2H), 3.18 (s, 3H), 3.65 (tr, 2H), 4.30 (m, 1H), 8.12 (s, 1H).	295
13		1.68 (m, 2H), 1.83 (m, 2H), 2.63 (tr, 2H), 3.41 (tr, 2H), 3.69 (m, 2H), 3.93 (m, 2H) 4.51 (m, 1H), 8.18 (s, 1H).	297

Intermediate 14:

3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-propan-2-yl-amino]-N-methyl-propanamide

5-Bromo-2,4-dichloropyrimidine (1.83 g, 8.00 mmol), N-methyl-3-(propan-2-ylamino)propanamide (Intermediate 14, 1.16 g, 8.00 mmol) and Et_3N (1.2 mL, 8.16 mmol) were combined in MeCN (50 mL) and shaken at ambient temperature for 3 days before the solvent was removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient 2-10% MeOH to DCM) to afford the title compound (2.08 g, 78%) as a gum. ^1H NMR (400 MHz, DMSO-d_6) δ_H 1.16 - 1.20 (6H, m), 2.31 (2H, t), 2.55 - 2.58 (3H, d), 3.65 (2H, t), 4.55 - 4.62 (1H, septet), 7.71 - 7.72 (1H, br s), 8.39 (1H, s); MS m/z 337 $[M+H]^+$.

Intermediate 15:

3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-methyl-amino]-N-methyl-propanamide

Intermediate 16

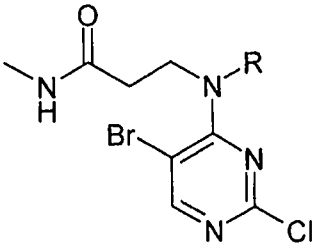
3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-(3-methylbutyl)amino]-N-methyl-propanamide

Intermediate 17:

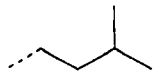
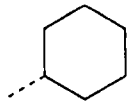
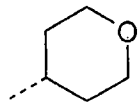
3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-cyclohexyl-amino]-N-methyl-propanamide

Intermediate 18:

3-[(5-Bromo-2-chloro-pyrimidin-4-yl)-(oxan-4-yl)amino]-N-methyl-propanamide



Intermediates 15-18 were prepared in an analogous manner to Intermediate 14 using 5-bromo-2,4-dichloropyrimidine as the electrophile and the appropriate known or described (Intermediates 19 – 21) β-aminoamides:

Example	R	^{1}H-NMR (400 MHz, DMSO-d_6)	MS m/z $[M+H]^+$
15	Me	2.46 (2H, t), 2.56 - 2.57 (3H, d), 3.19 (3H, s), 3.86 (2H, t), 7.86 (1H, br s), 8.33 (1H, s)	309
16		0.92 (6H, d), 1.48 - 1.52 (2H, m), 1.59 (1H, m), 2.45 (2H, t), 2.57 (3H, d), 3.63 (2H, m), 3.83 (2H, t), 7.84 (1H, br s), 8.32 (1H, s)	365
17		1.10 - 1.15 (1H, m), 1.27 (2H, q), 1.54 - 1.57 (1H, m), 1.59 (1H, d), 1.62 - 1.63 (1H, m), 1.69 - 1.72 (2H, m), 1.78 (2H, d), 2.31 (2H, t), 2.55 (3H, d), 3.67 (2H, t), 4.14 - 4.20 (1H, m), 7.70 (1H, br s), 8.38 (1H, s)	377
18		1.62 - 1.66 (2H, m), 1.82 - 1.89 (2H, m), 2.32 (2H, t), 2.56 (3H, d), 3.33 (2H, d), 3.69 (2H, t), 3.91 - 3.95 (2H, m), 4.34 - 4.40 (1H, m), 7.72 (1H, br s), 8.43 (1H, s)	379

Intermediate 19:

N-Methyl-3-(propan-2-ylamino)propanamide

N-Methylacrylamide (851 mg, 10.00 mmol) and isopropylamine (1.71 mL, 1.18 g, 20.00 mmol) in MeOH (10 mL) were irradiated to 140 °C for 30 mins in a microwave reaction vessel. The reaction mixture was cooled and loaded onto a SCX-2 column and washed with MeOH (100 mL). The crude product was then eluted from the SCX-2 column with NH_3 (100 mL, 7M in MeOH) and the volatiles removed under reduced pressure to afford the title compound (1.56 g, Quant.) as an oil, which was used without further purification.

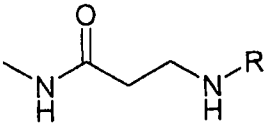
^{1}H NMR (400 MHz, DMSO-d_6) δ_H 0.96 (d, 6H), 2.18 (t, 2H), 2.57 (d, 3H), 2.65 - 2.71 (m, 3H), 7.81 (br s, 1H).

Intermediate 20:

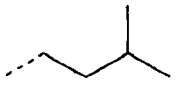
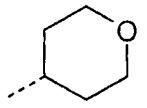
N-Methyl-3-(3-methylbutylamino)propanamide

Intermediate 21:

N-Methyl-3-(oxan-4-ylamino)propanamide

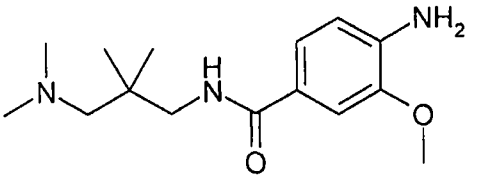


Intermediates 20 and 21 were prepared in an analogous manner to Intermediate 19 using the N-methylacrylamide as the α,β-unsaturated amide and the appropriate commercially available primary amine:

Example	R	^{1}H NMR (400 MHz, DMSO-d_6)
20		0.87 (d, 6H), 1.28 (dt, 2H), 1.60 (septet, 1H), 2.19 (t, 2H), 2.46 - 2.52 (m, 3H), 2.56 (d, 3H), 2.67 (t, 2H), 7.81 (br s, 1H)
21		1.14 - 1.27 (m, 2H), 1.64 (d, 1H), 1.73 (d, 2H), 2.19 (t, 2H), 2.57 (d, 3H), 2.72 (t, 2H), 3.23 - 3.31 (m, 3H), 3.78 - 3.84 (m, 2H), 7.80 (br s, 1H)

Intermediate 22:

4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-benzamide



A suspension of N-(3-dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-nitro-benzamide (Intermediate 23; 5.7 g, 18.40 mmol), 5% Pd on charcoal (569 mg) in EtOH (300 mL) was

stirred at 40 °C under a hydrogen atmosphere for 16 h. The reaction mixture was then filtered through celite, washed with copious MeOH and the volatiles removed under reduced pressure to afford the title compound (5.36 g, Quant.) as a foam.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.88 (m, 6H), 2.18 (s, 2H), 2.28 (s, 6H), 3.18 (m, 2H), 3.82 (s, 3H), 5.21 (m, 2H), 6.63 (d, 1H), 7.25 m, 2H), 8.11 (m, 1H); MS m/z 280 $[M+H]^+$.

Intermediate 23:

N-(3-Dimethylamino-2,2-dimethyl-propyl)-3-methoxy-4-nitro-benzamide

To a suspension of 4-nitro-3-methoxybenzoic acid (Aldrich; 5.0 g, 25.3 mmol), N,N-2-tetramethyl-1,3-propanediamine (Aldrich; 4.64 mL, 27.83 mmol) and DIPEA (8.8 mL, 50.60 mmol) in anhydrous DMA (100 mL) under nitrogen at ambient temperature was added HATU (10.6 g, 27.83 mmol) and the resulting reaction mixture was stirred at 50 °C for 3 h and ambient temperature for a further 12 h. Evaporation removed any volatiles and the residue was dissolved in DCM (100 mL) and washed with $NaHCO_3$ (100 mL), brine (100 mL), dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification by column chromatography (SiO_2, eluent gradient: 2-10% MeOH in DCM) afforded the title compound (5.7 g, 73%) as a solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.06 (s, 6H), 2.42 (s, 2H), 2.82 (s, 6H), 3.30 (s, 2H), 3.98 (s, 3H), 7.57 (dd, 1H), 7.71 (s, 1H), 8.93 (d, 1H); MS m/z 310 $[M+H]^+$.

Intermediate 24:

1-cyclopropylpiperidin-4-amine

N-benzyl-1-cyclopropyl-piperidin-4-amine (Intermediate 25; 2.3 g 10 mmol), 10% Palladium on Carbon (230 mg) and Methanol (230 mL) were combined and heated with stirring at 30°C under Hydrogen at 5 bar pressure for 16 hours.

The mixture was filtered and concentrated, taken up in DCM, dried ($MgSO_4$) and concentrated to give the title compound (1.29g, 64%) as a yellow liquid

^{1}H NMR (399.9 MHz, $CDCl_3$) δ0.36 – 0.46 (4H, m), 1.26 – 1.36 (4H, m), 1.52 – 1.58 (1H, m), 1.76 – 1.82 (2H, m), 2.18 – 2.25 (2H, m), 2.63 – 2.70 (1H, m), 2.94 – 2.99 (2H, m); MS m/z 161.90 $[M+H]^+$.

Intermediate 25:

N-benzyl-1-cyclopropyl-piperidin-4-amine

1-cyclopropylpiperidin-4-one Intermediate 26 (3g, 21.55mmol), benzylamine (4.7ml, 43.10mmol) and acetic acid (1.25ml) were stirred together and sodium triacetoxyborohydride (6.86g, 32.33mmol) added portion-wise. DCM (20ml) was added and the mixture stirred at room temperature overnight. The mixture was concentrated and partitioned between ethyl acetate and 2M potassium carbonate solution. The aqueous layer was re-extracted with ethyl acetate and the combined organics washed with brine, dried ($MgSO_4$) and concentrated. Column chromatography (2% 7N ammonia in methanol / DCM) gave a brown liquid which contained Benzylamine and thus was taken up in DCM and stirred with PS-benzaldehyde (NovaBiochem, ≈3.2mmol/g ; ≈1.5 equivalents compared to benzylamine) for 3h. The mixture was filtered and the combined filtrates concentrated to give the title compound (2.33g, 47%) as a brown oil.

^{1}H NMR (399.9 MHz, $CDCl_3$) δ0.38 - 0.43 (4H, m), 1.33 - 1.40 (2H, m), 1.46 (1H, s), 1.52 - 1.57 (1H, m), 1.86 - 1.90 (2H, m), 2.18 - 2.24 (2H, m), 2.51 - 2.56 (1H, m), 2.96 - 3.01 (2H, m), 3.82 (2H, s), 7.22 - 7.25 (1H, m), 7.29 - 7.33 (4H, m)

Intermediate 26:

1-cyclopropylpiperidin-4-one

1-Ethyl-1-methyl-4-oxopiperidinium iodide (Journal of the Chemical Society (1949), 708-15; 15 g, 55.74 mmol) was added to cyclopropylamine (Aldrich; 19.3 mL, 278.69 mmol) in toluene (150 mL). Sodium hydrogen carbonate (469 mg, 5.57 mmol) in water (21 mL) was added and the mixture heated at 78°C over night. The mixture was cooled and the layers separated. The aqueous layer was extracted (x2) with ethyl acetate and the combined organics washed with brine , dried ($MgSO_4$) and concentrated. Column chromatography of the residue (2% MeOH/DCM) gave the title compound (4.1g, 53%) as a pale brown liquid.

^{1}H NMR (399.9 MHz, $CDCl_3$) δ0.47 - 0.53 (4H, m), 1.74 (1H, d), 2.40 - 2.44 (4H, m), 2.92 (4H, t)

Intermediate 27:

4-amino-2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide

2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)-4-nitro-benzamide Intermediate 28; 1.3 g, 4.2 mmol) 10% Palladium on Carbon (100 mg) and Methanol (50 mL) were combined and stirred at 25^{0}C under Hydrogen at 1 bar pressure for 18 hours.

The reaction mixture was filtered through a plug of celite, washing with ethanol and concentrated under reduced pressure to give the title compound (1.16 g, 100%.) as a yellow solid.

^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.54 (qd, 2H), 1.72 - 1.80 (m, 2H), 1.97 (td, 2H), 2.16 (s, 3H), 2.70 (br d, 2H), 3.67 - 3.74 (m, 1H), 3.78 (s, 3H), 5.55 (s, 2H), 6.39 (d, 1H), 7.05 (d, 1H), 7.34 (t, 1H); MS m/z 282.27 $[M+H]^+$.

Intermediate 28:

2-fluoro-5-methoxy-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

To a stirred solution of 2-fluoro-5-methoxy-4-nitro-benzoic acid (Intermediate 29; 861 mg, 4.00 mmol) in DMA (20 mL) was added 4-amino-1-methylpiperidine (Fluorochem; 503 mg, 4.40 mmol) followed by DIPEA (1.4 mL, 8.00 mmol) and HATU (1.68 g, 4.40 mmol) and the resulting yellow solution stirred at room temperature for 1 hr.. The solvent was removed under reduced pressure and the residue taken up in methanol (approx 10 mL) and loaded onto a 20 g SCX-2 cartridge washing with methanol (50 mL) and eluting with 7 N methanolic ammonia (50 mL) to give a yellow solid, 1.47 g. This was purified by flash silica chromatography (Companion, 40 g, 0-5% ammonia in methanol /.DCM) to give the desired product as a pale yellow solid (1.25g, 4.00 mmol, 100%.)

^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.54 (qd, 2H), 1.77 - 1.85 (m, 2H), 1.98 (td, 2H), 2.17 (s, 3H), 2.74 (br d, 2H), 3.72 (m, 1H), 3.96 (s, 3H), 7.43 (d, 1H), 7.98 (d, 1H), 8.46 (d, 1H);); MS m/z 161.90 $[M+H]^+$.

Intermediate 29:

2-fluoro-5-methoxy-4-nitro-benzoic acid

2,5-Difluoro-4-nitrobenzoic acid (Fluorochem; 100 mg, 0.43 mmol) and caesium carbonate (708 mg, 2.17 mmol) were taken up in dry DMF (2 mL) and dry methanol (120 uL, 2.88 mmol) was added and the reaction stirred at room temperature for 2 hrs. The reaction mixture was diluted with Ethyl Acetate (50 mL) and water (50 mL) and acidified to pH1 with 2N HCl solution. The organics were removed and the aqueous further extracted with Ethyl Acetate (2 x 50 mL). The combined organics were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the title compound as a yellow solid (91 mg, 0.42 mmol, 98%).

^{1}H NMR (399.902 MHz, CDCl3) d 4.00 (s, 3H), 7.63 (d, 1H), 7.70 (d, 1H), 10.78 (br s, 1H); MS m/z 215.27 $[M+H]^+$.

Intermediate 30:

Benzyl (1R,5S)-6-amino-3-azabicyclo[3.1.0]hexane-3-carboxylate

Benzyl (1R,5S)-6-[(2-methylpropan-2-yl)oxycarbonylamino]-3-azabicyclo[3.1.0]hexane-3-carboxylate (Bioorganic & Medicinal Chemistry Letters (2004), 14(11), 2773-2776, Compound 9; 6.74g, 20.3mmol) was stirred and dissolved in DCM (90 mL) at ambient temperature and TFA (10ml) was added. The solution was stirred at room temperature for 2 hours. Sat. bicarbonate (100ml) was added followed by potassium carbonate solid until neutral. The DCM layer was separated and washed once more with water. The DCM solution was dried (MgSO4), filtered and evaporated to a gum.

Yield = 4.05g (86%)

^{1}H NMR (400.132 MHz, CDCl3) δ 1.48 (s, 2H), 2.00 (s, 1H), 3.43 (m, 4H), 5.02 (s, 2H), 7.25 (m, 7H).

Intermediate 31:

Methyl (1S,3R)-3-aminocyclopentane-1-carboxylate Hydrochloride Salt

(1S,3R)-3-aminocyclopentane-1-carboxylic acid (Acros; 952 mg, 7.37 mmol) was suspended in MeOH (15 ml) and cooled in an acetone / ice bath. Thionyl chloride (1.1 mL, 14.74 mmol) was added dropwise and the resulting pale yellow solution stirred in the acetone / ice bath for

30 minutes and then allowed to warm to room temperature, stirred at room temperature for 1 hr then heated at reflux for 1 hr. Solvents were evaporated to give the title compound as a cream solid after drying under high vacuum. (1.32g 100%)

^{1}H NMR (399.902 MHz, DMSO-D6) δ1.65 (m, 1H), 1.76 (m, 1H), 1.93 (m, 3H), 2.27 (m, 1H), 2.87 (m, 1H), 3.49 (m, 1H), 3.64 (s, 3H), 8.09 (s, 3H)

Intermediate 32:

[(2R)-1-(cyclopropylmethyl)pyrrolidin-2-yl]methanamine

Preparation contained in WO98/39295

Intermediate 33:

[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methanamine

To a solution of 1-(pyrrolidine-1-carbonyl)cyclopropane-1-carboxamide (Intermediate 34; 5.0 g, 27.5 mmol) in anhydrous THF (150 mL) was slowly added a 1 M anhydrous THF solution of Lithium Aluminium Hydride (138 mL, 138 mmol) controlling the reaction temperature at 40^{0}C with an ice / water bath.

The resultant clear solution was stirred overnight at room temperature under an inert gas flow to give a cloudy suspension.

Water (5.24 mL) was carefully added to the reaction mixture maintaining the reaction temperature at < 30^{0}C with an ice / water bath to give thick white slurry. 15% w/v aqueous Soium Hydroxide solution (5.24 mL) was carefully added followed by water (15.71 mL). The reaction was filtered and the filtrate evaporated to dryness to give the title compound (3.26 g, 77%)

Intermediate 34:

1-(pyrrolidine-1-carbonyl)cyclopropane-1-carboxamide

To 1-(aminocarbonyl)-1-cyclopropane carboxylic acid (Aldrich; 25 g, 193.6 mmol) in DCM (625 mL) was added HATU (73.61 g, 193.6 mmol) and the suspension stirred for 30 minutes. Pyrrolidine (Aldrich; 24.25 mL) and Hunig's base (67 mL) was added and the reaction stirred at room temperature over the weekend.

The reaction was evaporated to dryness, DCM added and extracted with water (3x 150 mL).

The aqueous extracts were evaporated to dryness and the resultant material triturated with Ethyl acetate to give the title compound as a white solid 11.14 g, 32%)

Intermediate 35:

2-methoxy-N'-(2-pyrrolidin-1-ylethyl)benzene-1,4-diamine

To a stirred solution of 4-fluoro-2-methoxy-1-nitro-benzene (Fluorochem; 2.57 g; 15 mmol) in DMA was 2-pyrrolidin-1-ylethanamine (Aldrich; 1.88 g, 16.5 mmol) followed by DIPEA (2.97 mL, 18 mmol). The mixture was heated at 80°C for 20 hours, then cooled to room temp. The mixture was concentrated *in vacuo*, dissolved in DCM and purified by SCX (50 g SCX 2 column). The product was eluted from the column with 7*N* ammonia in methanol, concentrated *in vacuo* to give the title compound (53 mg) which was dissolved in Methanol as a 0.05 mmol solution and reduced using an H-cube hydrogenator. 10% Pd/C catalyst, 1 bar hydrogen (full hydrogen setting), 3 mL / min flow- rate at 50°C. The resultant solution was concentrated *in vacuo*, and the resultant material purified by column chromatography, eluting with 0-10% ammonia/methanol in DCM, to give the title compound as a solid.
MS m/z 236 $[M+H]^+$, Retention Time 1.50 minutes.

In a similar manner intermediates 36-42 were prepared from the specified amines

Intermediate 36:

2-methoxy-N'-methyl-N'-(1-methyl-4-piperidyl)benzene-1,4-diamine

Intermediate 37:

2-methoxy-4-[4-(2-methoxyethyl)piperazin-1-yl]aniline

Intermediate 38:

2-methoxy-4-[4-(1-piperidyl)-1-piperidyl]aniline

Intermediate 39:

N'-(2-dimethylaminoethyl)-2-methoxy-benzene-1,4-diamine

Intermediate 40:

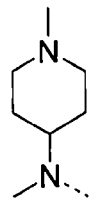
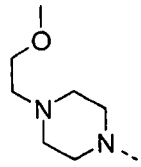
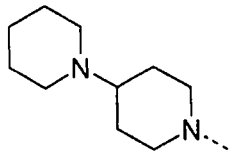
4-(4-cyclohexylpiperazin-1-yl)-2-methoxy-aniline

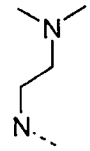
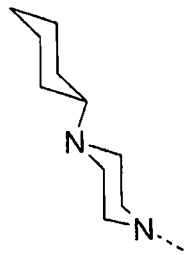
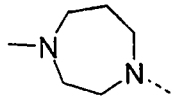
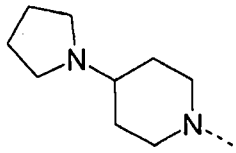
Intermediate 41:

2-methoxy-4-(4-methyl-1,4-diazepan-1-yl)aniline

Intermediate 42:

2-methoxy-4-(4-pyrrolidin-1-yl-1-piperidyl)aniline

Intermediate	R	Source	MS m/z [M+H]+	Retention time
36		Aldrich	250	1.39
37		Fluorochem	266	1.45
38		Aldrich	290	1.84

Intermediate	R	Source	MS m/z [M+H]+	Retention time
39		Aldrich	210	1.26
40		Bulletin of the Chemical Society of Japan (1961), 34 655-9	290	2.02
41		Aldrich	236	1.48
42		Fluorochem	279	1.79

Intermediate 43:

2-methoxy-4-[(1-methyl-4-piperidyl)oxy]aniline

To a stirred solution of 4-(3-methoxy-4-nitro-phenoxy)-1-methyl-piperidine (Intermediate 44; 12.86 g, 48.34 mmol) in ethanol (250 mL) under nitrogen was added in one portion the Pd/C catalyst (10%, 1.29 g). The resulting mixture was evacuated and backfilled with nitrogen 4 x before hydrogen gas was introduced via a balloon. The reaction mixture was stirred at room temperature for 18 hrs. The catalyst was removed by filtration through celite and the filtrate concentrated under reduced pressure to give a light red oil (11.1 g, 47.0 mmol, 97%).

^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.52 - 1.63 (m, 2H), 1.82 - 1.90 (m, 2H), 2.06 - 2.15 (m, 2H), 2.17 (s, 3H), 2.56 - 2.65 (m, 2H), 3.73 (s, 3H), 4.10 (septet, 1H), 4.28 (s, 2H), 6.32 (dd, 1H), 6.45 (d, 1H), 6.53 (d, 1H); MS m/z 237.21 $[M+H]^+$.

Intermediate 44:

4-(3-methoxy-4-nitro-phenoxy)-1-methyl-piperidine

To a solution of 4-Fluoro-2-methoxy-1-nitrobenzene (Apollo Scientific; 10.3 g, 60 mmol) in toluene (50 mL) and 25% KOH aq. (50 mL) , were added at room temperature, 4-hydroxy-1-methylpiperidine (13.8 g, 120 mmol) and tetra-n-butylammonium bromide (3.87 g, 12 mmol). The mixture was heated at 60 °C for 18 hrs. The reaction mixture was cooled to room temperature, poured onto ice-water (300 mL) and extracted with Ethyl Acetate (3 x 150 mL). The organic layer was extracted with dil HCl (2 M HCl, 300 mL)

The acidic aqueous layer was taken to pH 4/5 with 2 M NaOH solution and split between 2 x 50 g SCX-2 cartridges, washing with water and eluting with 7 N methanolic ammonia to give the title compound as a yellow oil, which slowly solidified over time (12.86 g, 80%)

^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.64 - 1.72 (m, 2H), 1.93 - 2.00 (m, 2H), 2.17 - 2.24 (m, 5H), 2.59 - 2.64 (m, 2H), 3.92 (s, 3H), 4.60 (septet, 1H), 6.71 (dd, 1H), 6.78 (d, 1H), 7.94 (d, 1H); MS m/z 267.24 $[M+H]^+$.

Intermediate 45:

2-methoxy-4-(1-methylpyrrolidin-3-yl)oxy-aniline

To a stirred solution of 3-(3-methoxy-4-nitro-phenoxy)-1-methyl-pyrrolidine (Intermediate 46; 5.50 g, 20.68 mmol) in ethanol (125 mL) under nitrogen was added in one portion the Pd/C catalyst (10%, 500 mg). The resulting mixture was evacuated and backfilled with nitrogen (x 4) before hydrogen gas was introduced via a balloon. The reaction mixture was stirred at room temperature for 18 hrs. The catalyst was removed by filtration through celite and the filtrate concentrated under reduced pressure to give a the title compound as a light red oil (4.74 g, 100%)

^{1}H NMR (399.902 MHz, CDCl3) δ 1.94 - 2.02 (m, 1H), 2.22 - 2.30 (m, 1H), 2.36 - 2.45 (m, 1H), 2.38 (s, 3H), 2.73 - 2.83 (m, 3H), 3.50 (s, 2H), 3.81 (s, 3H), 4.74 (octet, 1H), 6.26 (dd, 1H), 6.45 (d, 1H), 6.61 (d, 1H); MS m/z 223.22 $[M+H]^+$.

Intermediate 46:

3-(3-methoxy-4-nitro-phenoxy)-1-methyl-pyrrolidine

To a solution of 4-Fluoro-2-methoxy-1-nitrobenzene (Apollo Scientific; 4.28 g, 25 mmol) in toluene (20 mL) and 25% KOH aq. (20 mL), were added at room temperature, 1-methyl-3-pyrrolidiniol (5.0 g, 50 mmol) and tetra-n-butylammonium bromide (1.66 g, 5 mmol). The mixture was heated at 60 °C for 18 hrs. The reaction mixture was cooled to room temperature, poured onto ice-water (200 mL) and extracted with Ethyl Acetate (3 x 100 mL). The organic layer was washed with 2 M HCl (250 ml) and then loaded onto a 50 g SCX-2 cartridge, washing with water and eluting with 7 N methanolic ammonia to give the title compound as a yellow oil, which solidified on standing (5.50 g, 87%).

^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.73 - 1.84 (m, 1H), 2.27 (s, 3H), 2.31 - 2.37 (m, 2H), 2.65 (dd, 1H), 2.68 - 2.73 (m, 1H), 2.77 (dd, 1H), 3.92 (s, 3H), 5.02 - 5.07 (m, 1H), 6.62 (dd, 1H), 6.73 (d, 1H), 7.95 (d, 1H); MS m/z 253.23 $[M+H]^+$.

Intermediate 47:

2-methoxy-4-(2-morpholin-4-ylethoxy)aniline

To 4-[2-(3-methoxy-4-nitro-phenoxy)ethyl]morpholine (Intermediate 48; 16.97 g, 60 mmol, 1eq) in ethanol (120 mL) was added 10% palladium on charcoal (850mg, 5%wt). The reaction was stirred at room temperature for 19hours. After filtering off the palladium residues the solvent was evaporated under reduced pressure. The product was dissolved in ethyl acetate (100ml) and extracted twice with 2M HCl. The aqueous layers were combined, washed with ethyl acetate then basified by the addition of 2N NaOH. The basic layer was re-acidified and captured onto mp-TsOH resin. After washing several times with methanol the product was released using 10% ammonia in methanol. After evaporation *in vacuo* the title compound was obtained as a dark brown oil. (14.5 g, 89%)

^{1}H NMR (300.132 MHz, DMSO-D6) δ2.49 - 2.51 (4H, m),2.69 (2H, t),3.60 (4H, t),3.74 (3H, s),3.98 (2H, t),4.62 (2H, s),6.30 (1H, dd),6.46 (1H, d),6.54 (1H, d); MS m/z 253 $[M+H]^+$.

Intermediate 48:

4-[2-(3-methoxy-4-nitro-phenoxy)ethyl]morpholine

To a solution of 4-fluoro-2-methoxy-1-nitro-benzene (Apollo Scientific; 10.27 g, 60 mmol) in toluene (50 mL) and 25% KOH (aq) (50 mL), was added 4-(2-hydroxyethyl)morpholine (Aldrich; 15.75 g, 120 mmol) and tetra-n-butylammonium bromide (3.87 g, 12 mmol) at room temperature. The mixture was heated at 60^{0}C for 22 hours. The reaction mixture was cooled to room temperature, poured into water and extracted three times with ethyl acetate. The organic layers were combined and washed twice with 2M sodium hydroxide then brine. Dried with magnesium sulphate, filtered and evaporated under reduced pressure to yield the title compound as a yellow oil (16.97 g, 100%)

^{1}H NMR (300.132 MHz, DMSO-D6) δ2.48 (4H, t),2.72 (2H, t),3.58 (4H, t),3.93 (3H, s),4.23 (2H, t),6.68 (1H, dd),6.81 (1H, d),7.94 (1H, d); MS m/z 283 $[M+H]^+$.

Intermediate 49:

N-[(4-aminophenyl)methyl]pyridine-2-carboxamide

Pyridine-2-carboxylate (Aldrich; 0.35 g, 2.84 mmol), 4-aminobenzylamine (Aldrich; 0.51 g, 4.26 mmol) and HATU (1.65g, 4.26mmol) were dissolved in DMF (7.5ml). *N,N*-Diisopropylethylamine (1.5ml, 8.53mmol) was added and the mixture stirred at room temperature for 2h. The mixture was absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and the residue purified by normal phase chromatography (2% MeOH/DCM) to give a yellow solid (440mg). which was suspended in DCM/Et_2O and filtered to give the title compound as a pale yellow solid (235mg, 36%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ4.33 (2H, d), 4.94 (2H, s), 6.50 - 6.53 (2H, m), 7.00 - 7.03 (2H, m), 7.58 - 7.62 (1H, m), 7.98 - 8.07 (2H, m), 8.62 - 8.64 (1H, m), 8.98 (1H, t); MS m/z 228.03 $[M+H]^+$.

Intermediate 50:

1-(3-amino-4-methoxy-phenyl)-N,N-dimethyl-pyrrolidin-3-amine

4-methoxy-N-(1-methyl-4-piperidyl)-3-nitro-benzamide (Intermediate 51; 400 mg, 1.4 mmol) 10% Palladium on Carbon (40 mg) and Methanol (50 mL) were combined and stirred at 25^{0}C under Hydrogen at 5 bar pressure for 2 hours.

The reaction mixture was filtered and evaporated to dryness. The residue was purified by column chromatography using 5% 7N ammonia in MeOH/DCM as the solvent system. Product containing fractions were combined and evaporated to give the title compound as a white solid (305mg, 85%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.55 - 1.61 (2H, m), 1.70 - 1.74 (2H, d), 1.89 - 1.96 (2H, t), 2.16 (3H, s), 2.74 - 2.77 (2H, d), 3.68 (1H, m), 3.81 (3H, s), 4.79 (2H, s), 6.81 (1H, d), 7.06 - 7.09 (1H, m), 7.14 (1H, d), 7.86 (1H, d); MS m/z 264.28 $[M+H]^+$.

Intermediate 51:

4-methoxy-N-(1-methyl-4-piperidyl)-3-nitro-benzamide

3-Nitro-4-methoxybenzoic acid (Aldrich; 300mg, 1.52mmol), 1-methyl-4-aminopiperidine (Fluorochem; 174mg, 1.52mmol), HATU (868mg, 2.28mmol) and DIPEA (796uL, 4.56mmol) were stirred in DMF (6mL) at room temperature for 2 hours. The reaction mixture was loaded onto an SCX-3 column pre-washed with methanol . The column was washed with methanol and then eluted with 2% 7N ammonia/methanol. Product containing fractions were combined and evaporated to give the title compound as an orange solid (341mg, 76.4%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.55 - 1.59 (2H, m), 1.75 (2H, d), 1.91 - 1.95 (2H, m), 2.17 (3H, s), 2.70 - 2.79 (2H, d), 3.68 – 3.78 (1H, m), 3.99 (3H, s), 7.46 (1H, d), 8.16 - 8.19 (1H, m), 8.41 (2H, d); MS m/z 294.31 $[M+H]^+$.

Intermediate 52:

4-amino-3-chloro-N-(2-morpholin-4-ylethyl)benzamide

3-chloro-N-(2-morpholin-4-ylethyl)-4-nitro-benzamide (Intermediate 53; 1.2 g, 3.82 mmol), iron powder (1.29 g, 22.95 mmol) and ammonium chloride (144 mg, 2.68 mmol) were heated in ethanol (27 mL) and water (9 mlL at reflux for 1h. A few drops of acetic acid were added and heating continued for a further 1h. The reaction mixture was cooled, filtered and the

filtrate concentrated. The residue was partitioned between DCM and sat $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Column chromatography of the residue gave the title compound as a white crystalline solid. (650mg, 60%)

^1H NMR (399.9 MHz, DMSO-d_6 + D_2O) δ2.38 – 2.46 (6H, m), 3.30 – 3.36 (2H, m), 3.55 – 3.59 (4H, m), 5.83 (1H, partially exchanged NH_2), 6.79 (1H, d), 7.53 - 7.55 (1H, m), 7.73 (1H, d), 8.10 (1H, s); MS m/z 284.08 $[M+H]^+$.

Intermediate 53:

3-chloro-N-(2-morpholin-4-ylethyl)-4-nitro-benzamide

3-chloro-4-nitro-benzoyl chloride (Intermediate 54; 1.1 g, 5.00 mmol) was dissolved in DCM (10 mL) and N,N-diisopropylethylamine (1.05 mL, 6.00 mmol) added. The mixture was cooled in an ice/water bath and 4-(2-aminoethyl)morpholine (Aldrich; 0.66 mL, 5.00 mmol) in DCM (5 mL) added dropwise. The mixture was allowed to warm to room temperature and stirred for 0.5 hr. The reaction mixture was washed with brine, 2N NaOH, dried ($MgSO_4$) and concentrated. Column chromatography of the residue (2% MeoH/DCM) gave the title compound as a yellow solid. (1.2 g, 76%)

^1H NMR (399.9 MHz, DMSO-d_6) δ2.43 (4H, t), 2.48 (2H, t), 3.39 - 3.44 (2H, m), 3.58 (4H, m), 7.98 - 8.01 (1H, m), 8.16 (1H, m), 8.19 (1H, d), 8.78 (1H, t); MS m/z 314.16 $[M+H]^+$.

Intermediate 54:

3-chloro-4-nitro-benzoyl chloride

3-Chloro-4-nitrobenzoic acid (Apin; 1g, 4.96 mmol) was suspended in toluene (10 mL) and thionyl chloride (1.1 mL, 14.88 mmol) added. The mixture was heated to 85°C for 45min Further thionyl chloride (1.1 mL) was added and the mixture heated at reflux. 0.5 hr. The reaction mixture was allowed to cool and stand overnight. The mixture was concentrated to give the title compound as a yellow liquid (1.15g, 100%).

^1H NMR (399.9 MHz, $CDCl_3$) δ7.87 (1H, s), 8.07 - 8.10 (1H, m), 8.23 (1H, d); MS m/z 198.92 $[M+H]^+$.

Intermediate 55:

4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 56; 1.8 g, 6 mmol) hydrogenated over 2 hours with agitation at 298K and pressure of 5 bar using a 5% Pt/C catalyst and EtOH (50 mL) solvent. The catalyst was filtered and the filtrate concentrated to give a yellow crystalline solid which was dissolved in DCM and purified by column chromatography (5% MeOH/DCM) to give the title compound as a pale yellow crystalline solid (1.62 g, 100%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.53 - 1.60 (2H, m), 1.71 - 1.74 (2H, m), 1.90 - 1.95 (2H, m), 2.16 (3H, s), 2.33 - 2.35 (1H, m), 2.67 - 2.69 (1H, m), 2.76 (2H, d), 3.66 - 3.70 (1H, m), 5.82 (2H, d), 6.78 (1H, d), 7.56 - 7.58 (1H, m), 7.76 (1H, d), 7.89 (1H, d); MS m/z 268.14 $[M+H]^+$.

Intermediate 56:

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

3-chloro-4-nitro-benzoyl chloride (Intermediate 54; 2.2 g, 10.00 mmol) was dissolved in DCM (20 mL) and N,N-diisopropylethylamine (2.095 mL, 12.00 mmol) added. The mixture was cooled in an ice/water bath and 4-amino-1-methylpiperidine (Fluorochem; 1.14 g, 10.00 mmol) in DCM (10 mL) added dropwise. The mixture was allowed to warm to room temperature and stirred for 0.5 hr. A white precipitate resulted. The reaction mixture was washed with 2N NaOH, filtered and the filter cake washed with water and dried on a sinter over the weekend to give the title compound as a white solid (1.80g, 60%) as a white solid.

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.53 - 1.63 (2H, m), 1.79 (2H, t), 1.92 - 1.99 (2H, m), 2.17 (3H, s), 2.78 (2H, d), 3.70 - 3.77 (1H, m), 7.99 - 8.02 (1H, m), 8.18 (2H, t), 8.60 (1H, d); MS m/z 298.2 $[M+H]^+$.

Intermediate 57:

10-amino-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 250 mg; 0.89 mmol), Diphenylmethanimine (Fluka; 178 mg, 0.979 mmol) and caesium carbonate (580 mg, 1.78 mmol) were added to dioxane (3 mlL and the suspension bubbled with nitrogen for 10 minutes. Tris(Dibenzylideneacetone)Dipalladium(0) (49 mg; 0.053 mmol) and XANTPHOS (46 mg, 0.080 mmol) were added and the mixture heated to 100 °C for 16 hrs. The reaction mixture was cooled to room temperature filtered and the filter cake washed with DCM. The filtrate was evaporated and the resultant material taken up in DCM and purified on silica (the column was made neutral prior to purification. by wetting with iso-hexane, running a solution of 5% triethylamine in iso-hexane through followed by iso-hexane, material was then added) eluting with a gradient of 40 – 60% Ethyl Acetate / iso-hexane then 60% Ethyl Acetate / iso-hexane. Fractions containing the imine intermediate were combined and evaporated to a yellow solid (162 mg, 43%), which was dissolved in THF (10 ml). 2M aq HCl (3 mL) was added and the solution stirred at room temperature for 20 minutes. The reaction mixture was added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and the a product eluted with 2M ammonia in MeOH. Solvents were evaporated to give the title compound as a white solid (80 mg, 80% from imine)

^{1}H NMR (399.902 MHz, DMSO-D6) ?1.46 (m, 4H), 1.59 (m, 2H), 1.83 (m, 2H), 3.03 (s, 3H), 3.46 (m, 2H), 4.60 (m, 1H), 5.99 (s, 2H), 7.75 (s, 1H);); MS m/z 262 $[M+H]^+$.

Intermediate 58:

4-bromo-2,6-difluoro-N-(1-methyl-4-piperidyl)benzamide

4-bromo-difluorobenzoic acid (Fluorochem; 3.0 g, 12.66 mol) and HBTU (5.3 g, 13.92 mol) were added to DMF (80 mL), to this was added the required 4-amino-1-methylpiperidine (Fluorochem; 1.59 g, 13.93 mol) and DIPEA (5.0 mL, 27.85 mol), the reaction was stirred for 48 hours, after which the solvent was removed in vacuo to yield a brown gum. The gum was treated with 2.0 M NaOH (50 mL) and extracted with DCM (3 x 200 ml). Combined extracts were dried and solvent removed *in vacuo* to yield a dark orange gum which was recrystallised from hot acetonitrile to give the title compound as a white solid (1.9 g, 45%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 8.64 (d, 1H), 7.55 (d, 2H), 3.74 - 3.64 (m, 1H), 2.74 - 2.65 (m, 2H), 2.15 (s, 3H), 1.98 (t, 2H), 1.82 - 1.74 (m, 2H), 1.52 - 1.42 (m, 2H); MS m/z 334 $[M+H]^+$.

Intermediate 59:

4-amino-2,5-difluoro-N-(1-methyl-4-piperidyl)benzamide

2,5-difluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 60; 633 mg 2.1 mmol), 10% Palladium on Carbon (70 mg) and Methanol (50 mL) were combined and stirred at 25)C under Hydrogen at 3 bar pressure for 16 hours..

The catalyst was filtered off and the filtrate evaporated to give the title compound as a yellow solid. (554 mg, 97%)

^{1}H NMR (400.132 MHz, CDCl3) δ1.58 (m, 2H), 2.03 (m, 2H), 2.18 (m, 2H), 2.30 (s, 3H), 2.78 (m, 2H), 3.99 (m, 1H), 4.14 (s, 2H), 6.47 (m, 2H), 7.71 (m, 1H); MS m/z 334 $[M+H]^+$.

Intermediate 60:

2,5-difluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

1,5-Difluoro-4-nitrobenzoic acid (Fluorochem; 1 g, 4.92 mmol), 4-Amino-1-methylpiperidine (Fluorochem; 620 mg, 5.41 mmol), HAT (2.05 g, 5.41 mmol), DIPEA (2.57 mL, 14.76 mmol) and DMF (10 mL) were combined and stirred at room temperature for 18 hrs. Solvents were evaporated and the resultant material partitioned between DCM and water. Both phases were acidified with 2M aq HCl and added to a 50g SCX-2 column pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and the crude product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated *in vacuo* and the resultant material taken up in DCM and purified on silica eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 5% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to give the title compound as a yellow solid. (635 mg, 43%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.53 (m, 2H), 1.80 (m, 2H), 1.98 (m, 2H), 2.16 (s, 3H), 2.73 (m, 2H), 3.70 (m, 1H), 7.79 (m, 1H), 8.21 (m, 1H), 8.59 (d, 1H); MS m/z 300 $[M+H]^+$.

Intermediate 61:

4-amino-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

2-fluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 62; 1.62 g, 5.8 mmol), 10% Palladium on Carbon (160 mg) and Methanol (50 mL) were combined and stirred at 25)C under Hydrogen at 5 bar pressure for 16 hours..

The catalyst was filtered off and the filtrate evaporated to give a brown solid which was triturated with 5% MeOH / DCM . The precipitate was collected by filtration and dried under vacuum to yield the title compound as a beige solid (560 mg, 39%).

^{1}H NMR (400.132 MHz, DMSO-D6) δ1.74 (m, 2H), 1.99 (m, 2H), 2.76 (s, 3H), 3.09 (m, 2H), 3.42 (m, 2H), 3.97 (m, 1H), 5.89 (s, 2H), 6.30 (m, 1H), 6.39 (m, 1H), 7.37 (m, 1H), 7.67 (s, 1H), 9.11 (s, 1H);); MS m/z 252 $[M+H]^+$.

Intermediate 62:

2-fluoro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

2-Fluoro-4-nitrobenzoic acid (Aldrich; 3 g, 16.21 mmol), 4-Amino-1-methylpiperidine (Fluorochem; 2.03 g, 17.83 mmol), HATU (6.77 g, 17.83 mmol), DIPEA (8.5 mL, 48.63 mmol) and DMF (3 0 mL) were combined and stirred at ambient temperature for 18 hrs. Solvents evaporated and partitioned between DCM (200 ml) and water (100 ml). The aqueous phase was re-extracted with DCM (100 ml). The combined organic phases were dried (MgSO4) and evaporated. The resultant material was taken up in DCM and purified on silica eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 5% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to give the title compound as a yellow solid (2.67 g, 59%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ1.53 (m, 2H), 1.80 (m, 2H), 2.26 (m, 5H), 2.85 (m, 2H), 3.74 (m, 1H), 7.72 (m, 1H), 8.06 (m, 1H), 8.12 (m, 1H), 8.54 (d, 1H); MS m/z 282 $[M+H]^+$.

Intermediate 63:

4-amino-3-methyl-N-(1-methyl-4- piperidyl)benzamide

3-methyl-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 64: 3.34 g) 10% Palladium on Carbon (350 mg) and Methanol (50 mL) were combined and stirred at 25)C under Hydrogen at 5 bar pressure for 16 hours..

The catalyst was filtered off and washed with EtOH. The filtrate was evaporated to yield a cream solid., which was triturated with DCM filtered and dried under vacuum to give the title compound as a white solid (1.2 g)

^{1}H NMR (400.132 MHz, DMSO-D6) δ1.75 (m, 2H), 1.96 (m, 2H), 2.08 (s, 3H), 2.74 (s, 3H), 3.04 (m, 2H), 3.38 (m, 2H), 3.96 (m, 1H), 5.36 (s, 2H), 6.58 (d, 1H), 7.47 (m, 2H), 7.86 (d, 1H), 9.13 (s, 1H); MS m/z 248 $[M+H]^+$.

The following intermediate was prepared in a manner analogous to Intermediate 62 utilising 3-Methyl-4-nitrobenzoic acid, available form Aldrich, as the starting Nitro acid.

Intermediate 64:

3-methyl-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

3-methyl-N-(1-methyl-4-piperidyl)-4-nitro-benzamide was prepared in a manner analogous to Intermediate 62 utilising 3-Methyl-4-nitrobenzoic acid, available form Aldrich, as the starting Nitro acid.

^{1}H NMR (400.132 MHz, DMSO-D6) δ1.71 (m, 2H), 1.92 (m, 2H), 3.16 (m, 2H), 3.91 (m, 1H), 7.86 (m, 1H), 7.92 (s, 1H), 8.06 (d, 1H), 8.56 (d, 1H); MS m/z 278 $[M+H]^+$.

Intermediate 65:

4-amino-3-fluoro-N-(1-methyl-4-piperidyl)benzamide

4-Amino-3-Fluorobenzoic acid (Fluorochem; 1 g, 6.44 mmol), 4-Amino-1-methylpiperidine (Fluorochem; 811 mg, 7.09 mmol), HATU (2.70 g, 7.09 mmol), DIPEA (3.4 mL, 19.32 mmol) and DMF (15 mL) were combined and stirred for 18 hrs at room temperature. The solvent was evaporated and the resultant material dissolved in DCM (with a little MeOH to aid solubility) and chromatographed on silica eluting with a gradient of 0 – 10% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to give an

orange solid which was dissolved in MeOH and added to a 50g SCX-2 column pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated to yield the title compound as a beige solid. (1.72 g, 100%)

^{1}H NMR (399.902 MHz, CDCl3) ?1.55 (m, 2H), 2.03 (m, 2H), 2.14 (m, 2H), 2.29 (s, 3H), 2.81 (m, 2H), 3.95 (m, 1H), 4.01 (s, 2H), 5.77 (d, 1H), 6.75 (m, 1H), 7.34 (m, 1H), 7.45 (m, 1H); MS m/z 252 $[M+H]^+$.

Intermediate 66:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-(2-methoxyethoxy)benzoic acid

To a stirred solution of Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-(2-methoxyethoxy)benzoate (Intermediate 67; 164 mg, 0.35 mmol) in ethanol (3 mL) was added a solution of lithium hydroxide (22 mg, 0.92 mmol) in water (1 ml). The reaction was stirred at ambient temperature overnight. A further addition of lithium hydroxide (20 mg) as a solution in water (1 ml) was added and stirring continued for 2.5 hrs and then heated to 50°C for 4 hrs. The reaction mixture was evaporated and the residue diluted with water (5 mL). The resultant opaque solution was treated with a few drops of 2M HCl (aq.) to adjust the pH to 2-3. A precipitate formed which was collected by suction filtration, washing through with more water and dried under vacuum, at 55°C, for 3 hours to afford the title compound as an off white solid (113 mg, 71%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.65 (m, 6H), 1.91 (m, 2H), 2.67 (m, 2H), 3.18 (s, 3H), 3.70 (m, 2H), 3.75 (m, 2H), 4.27 (m, 2H), 4.84 (m, 1H), 7.57 - 7.63 (m, 2H), 8.13 (s, 1H), 8.27 (d, 1H), 8.72 (m, 1H); MS m/z 456.4 $[M+H]^+$.

Intermediate 67:

Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-

trien-9-yl)amino]-3-(2-methoxyethoxy)benzoate

To 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]u ndeca-8,10,12-trien-5-one (Intermediate 1, 222 mg, 0.79 mmol) was added a solution of Methyl 4-amino-3-(2-methoxyethoxy)benzoate (Intermediate 68; 203 mg, 0.90 mmol) in ethanol (4 mL). Water (12 mL) was added followed by concentrated hydrochloric acid (36%; 160 µl). The reaction was heated to 80°C and stirred overnight. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~50 mL with water and the solution basified to pH 9 by addition of a few drops of aq. Ammonia. The resultant emulsion was treated with a little brine and extracted with DCM (2 x 50 mL). Combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to give an amber gum which was purified by flash chromatography on silica (40g Si cartridge; ISCO companion), eluting first with a rising gradient of 25-75% ethyl acetate in iso-hexane and then a rising gradient of 0-10% methanol in DCM. Product containing fractions were combined and evaporated to give a yellow oil which crystallised on standing overnight. This solid was triturated with diethyl ether, solid collected by suction filtration and dried to afford the title compound as a cream solid (173 mg, 47 %)

^{1}H NMR (400.132 MHz, $CDCl_3$) ? 1.59 - 1.81 (m, 6H), 2.04 (m, 2H), 2.67 (m, 2H), 3.29 (s, 3H), 3.48 (s, 3H), 3.70 (m, 2H), 3.81 (m, 2H), 3.90 (s, 3H), 4.27 (m, 2H), 4.89 (m, 1H), 7.58 (m, 1H), 7.69 (m, 1H), 7.87 (s, 1H), 7.95 (s, 1H), 8.56 (d, 1H);); MS m/z 470 $[M+H]^+$.

Intermediate 68:

Methyl 4-amino-3-(2-methoxyethoxy)benzoate

To a solution of Methyl 3-hydroxy-4-aminobenzoate (ABCR: 97 mg, 0.58 mmol) in acetone (3 mL), in a microwave tube, was added Methoxyethyl bromide (Aldrich; 85 µl, 0.90 mmol) and powdered potassium carbonate (120 mg, 0.87 mmol). The reaction was heated in a microwave (150W, CEM explorer) to 100°C and held for 30 minutes.

A further addition of Methoxyethyl bromide (40 µl, 0.43 mmol) was made and the reaction heated to 120°C for a further 30 minutes.

The reaction was repeated in two batches as follows. To a solution of Methyl 3-hydroxy-4-aminobenzoate (135 mg, 0.81 mmol) in acetone (4 ml), in a microwave tube. Was added

Potassium Carbonate (185 mg, 1.34 mmol) and Methoxyethyl bromide (115 µl, 1.22 mmol) The reaction was heated to 120°C in a microwave and held for 1 hour. The reactions was cooled, treated with a further aliquot of methoxyethyl bromide (58 µl, 0.62 mmol) and re-heated to 120°C holding for a further hour.

All three batches were combined and evaporated to dryness. The residue was partitioned between DCM (25 mL) and water (25 mL). The organic phase was separated and the aqueous phase re-extracted with DCM (20 mL). Combined organic phases were washed with brine, dried over magnesium sulphate and evaporated to give a brown oil which was purified by flash chromatography on silica (40g Cartridge) eluting with a rising gradient of 25-50% ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give the title compound as a dark orange oil (256 mg, 56%).

^{1}H NMR (400.132 MHz, DMSO-D6) δ 3.38 (s, 3H), 3.74 (m, 2H), 3.80 (s, 3H), 4.16 (m, 2H), 5.61 (s, 2H), 6.72 (d, 1H), 7.37 (m, 1H), 7.45 (m, 1H); MS m/z 226 $[M+H]^+$.

Intermediate 69:

4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoic acid

To a stirred solution of Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoate (Intermediate 70; 128 mg, 0.28 mmol) in Ethanol (3 mL) was added a solution of lithium hydroxide (26 mg, 0.92 mmol) in water (1.5 mL). The reaction was allowed to stir at 70°C for 4 hours, cooled, evaporated and the residue diluted with water (10 mL). The resultant solution was treated with a few drops of 2M HCl (aq.) until a precipitate persisted, pH ~ 3-4. The precipitate was collected by suction filtration, washing through with more water. Solid was dried under suction overnight to afford the title compound as a white solid (108 mg, 88 %)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.36 (d, 6H), 1.57 - 1.77 (m, 6H), 1.95 (m, 2H), 2.61 (m, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 4.69 - 4.85 (m, 2H), 7.52 - 7.56 (m, 2H), 7.83 (s, 1H), 8.10 (s, 1H), 8.46 (d, 1H), 12.62 (s, 1H); MS m/z 440 $[M+H]^+$.

Intermediate 70:

Methyl 4-[(6-cyclopentyl-2-methyl-3-oxo-2,6,8,10-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-9-yl)amino]-3-propan-2-yloxy-benzoate

To 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]u ndeca-8,10,12-trien-5-one (Intermediate 1, 190 mg, 0.68 mmol) was added a solution of Methyl 4-amino-3-propan-2-yloxy-benzoate (Intermediate 71, 145 mg, 0.69 mmol) in ethanol (4 mL), followed by water (12 mL). Concentrated hydrochloric acid (36%; 140 µl) was added and the reaction heated to 80°C, with stirring, overnight. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~40 mL with water and the solution basified to pH 9 by addition of a few drops of aq. ammonia, The resultant emulsion was treated with a little brine and extracted with DCM (2 x 30 mL). The biphasic mixture was poured into a PTFE cup and the organic phase allowed to drip through under gravity. Evaporation of the organic phase afforded an amber gum, which was purified by flash chromatography on silica (40g Si cartridge; ISCO companion), eluting with a rising gradient of 25-100% ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a colourless gum which was triturated with a small amount of diethyl ether and the resultant solid collected by suction filtration and dried to afford the title compound as a white solid (132 mg, 43 %)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.36 (d, 6H), 1.58 - 1.77 (m, 6H), 1.95 (m, 2H), 2.60 (m, 2H), 3.18 (s, 3H), 3.64 (m, 2H), 3.83 (s, 3H), 4.77 (m, 2H), 7.53 (m, 1H), 7.57 (m, 1H), 7.78 (s, 1H), 8.10 (s, 1H), 8.51 (d, 1H); MS m/z 452 $[M+H]^+$.

Intermediate 71:

Methyl 4-amino-3-propan-2-yloxy-benzoate

Methyl 3-hydroxy-4-aminobenzoate (ABCR: 100 mg, 0.60 mmol) & caesium carbonate (396 mg, 1.22 mmol) were taken up in acetone (4 mL) and 2-iodopropane (90 µl, 0.90 mmol) added and reaction heated in microwave (CEM discover; 150 W) to 120°C and held for 30 mins A further aliquot of 2-iodopropane (90 µl, 0.90 mmol) was added and reaction heated again to 120°C in microwave, holding for a further 30 mins

The reaction was repeated twice on a 0.89 mmol scale

Reaction mixtures were combined and evaporated to dryness and the residue partitioned between, ethyl acetate (40 ml) and water (50 ml). The organic phase was separated and the aqueous re-extracted with ethyl acetate (40 ml). Combined organic extracts were washed with brine, dried over magnesium sulphate and evaporated to give a brown oil which was purified by column chromatography, on silica (40 g cartridge; ISCO companion) eluting with a rising gradient of 5-50% ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to dryness to afford the product as a yellow oil (301 mg, 60%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.28 (d, 6H), 3.75 (s, 3H), 4.53 (m, 1H), 5.51 (s, 2H), 6.66 (d, 1H), 7.31 (m, 1H), 7.37 (m, 1H); MS m/z 209.4 $[M+H]^+$.

Intermediate 72:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-(2-dimethylaminoethoxy)benzoic acid

Methyl 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-hydroxy-benzoate (Intermediate 73; 63 mg, 0.15 mmol) was dissolved in DMA (2 mL) and treated sequentially with potassium carbonate powder (fine mesh; 106 mg, 0.79 mmol) and dimetylaminoethyl bromide hydrobromide (ASDI; 61 mg, 0.26 mmol). The reaction mixture was heated to 100°C, with stirring for 1 hour and allowed to cool overnight, before pouring into water (40 ml). The mixture was extracted with DCM (2 x 30 ml) and the organic extracts washed with brine, dried over magnesium sulphate, filtered and evaporated to give a brown liquid which was taken up in methanol and poured onto an SCX-3 cartridge (2 g). The cartridge was washed with methanol (~30 ml) before eluting products with 2M ammonia/methanol (~20 ml). The ammoniacal wash was evaporated to give the title compound as a brown gum (41 mg, 57%)

MS m/z 483.4 $[M+H]^+$, Retention Time 2.41 minutes.

Intermediate 73:

Methyl 4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-10-yl)amino]-3-hydroxy-benzoate

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 180 mg, 0.64 mmol) and Methyl 3-hydroxy-4-aminobenzoate (ABCR; 123 mg, 0.73 mmol) were taken up in ethanol (4 mL) and water (12 mL). Concentrated hydrochloric acid (36%; 130 µl) was added and the reaction heated to 80°C and stirred overnight. The reaction was allowed to stand and cool overnight, before evaporating ethanol. The aqueous residue was diluted to ~30 ml with water and the solution basified to pH 9 by addition of a few drops of aqueous Ammonia. The resultant mixture was extracted with DCM (2 x 50 ml). A solid persisted at the phase boundary. This solid was collected by suction filtration and dried to give the title compound as a purple/grey solid (64 mg, 24%)

The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to a pink/brown solid (153 mg) which was triturated with DCM (5 mL). The solid was then collected by suction filtration and dried to give the title compound as a dusky pink solid (79 mg, 30 %)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.57 - 1.75 (m, 6H), 1.95 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.80 (s, 3H), 4.82 (m, 1H), 7.44 (m, 2H), 7.84 (s, 1H), 8.09 (s, 1H), 8.36 (d, 1H); MS m/z 412.3 $[M+H]^+$.

Intermediate 74:

4-amino-N-(1-methyl-4-piperidyl)-3-(trifluoromethoxy)benzamide

To a solution of 4-amino-3-(trifluoromethoxy)benzoic acid (Maybridge ; 1.05 g, 4.75 mmol) in DMF (20 ml) was added 4-amino-1-methylpiperidine (Fluorochem; 604 mg, 5.29 mmol) followed by DIPEA (1.6 ml, 9.19 mmol) and HATU (2.06 g, 5.42 mmol). The reaction mixture was stirred at ambient temperature O/N. The reaction mixture was evaporated to dryness and the residue partitioned between DCM (75 mL) and saturated aqueous sodium bicarbonate solution (75 mL). The aqueous phase was re-extraced with DCM (50 ml) and the combined organic phases washed with brine, dried over magnesium sulphate, filtered and evaporated to give the title compound as an amber gum (1.17 g, 78%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.75 (m, 2H), 1.93 (m, 2H), 2.64 (s, 3H), 2.87 (m, 2H), 3.93 (m, 1H), 5.93 (s, 2H), 6.80 (d, 1H), 7.64 (m, 2H), 8.08 (d, 1H); MS m/z 316.4 $[M+H]^+$.

Intermediate 75:

4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-ethoxy-benzoic acid

To a solution of 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 280 mg, 1 mmol) and 4-amino-3-ethoxybenzoic acid (WO 2001077101; 205 mg, 1.13 mmol) in ethanol (5 mL) was added water (15 mL) and conc hydrochloric acid (0.17 mL, 2 mmol) . The mixture was heated under reflux for 36 hours. The reaction was cooled and a brown solid precipitated. This was filtered and dried, triturated under cold acetonitrile and then dried *in vacuo*. To yield the title compound as a brown solid (190 mg; 45%)

MS m/z 426 $[M+H]^+$. Retention Time 1.58 minutes

Intermediate 76:

10-chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-propan-2-yl-amino]-N-methyl-propanamide (Intermediate 77; 2.67 g, 7.9 6mmol) was dissolved in dioxane (80 mL) and tris(dibenzylideneacetone) palladium (II) (146mg, 0.16 mmol), XANTPHOS (277 mg, 0.48 mmol) and Caesium carbonate (3.76 g, 11.54 mmol) added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100°C for 24 hours. The mixture was filtered and concentrated and the residue purified by column chromatography (1% MeOH/DCM) to give the title compound as a viscous yellow oil (1.25g, 62%).

^{1}H NMR (399.9 MHz, $CDCl_3$) δ1.18 (6H, d), 2.59 - 2.61 (2H, m), 3.22 (3H, s), 3.59 - 3.62 (2H, m), 4.82 - 4.88 (1H, m), 7.87 (1H, s); MS m/z 255.16 $[M+H]^+$.

Intermediate 77:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-propan-2-yl-amino]-N-methyl-propanamide

N-methyl-3-(propan-2-ylamino)propanamide (Intermediate 78; 2 g, 13.87 mmol), 5-bromo-2,4-dichloropyrimidine (Aldrich; 3.8 g, 16.64 mmol) and triethylamine (2.3 mL, 16.64 mmol) were heated in acetonitrile (85 mL) at 100°C for 3h. The mixture was cooled and

concentrated. The residue was dissolved in DCM, washed with water, dried ($MgSO_4$) and concentrated. Column chromatography (0.5 – 1 – 2% 7N ammonia in methanol/DCM) gave: The the title compound as a pale yellow oil that crystallised on standing (2.67 g, 20%)
^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.20 (6H, d), 2.31 (2H, t), 2.55 (3H, d), 3.65 (2H, t), 4.55 - 4.62 (1H, m), 7.72 (1H, s), 8.39 (1H, s); MS m/z 337.05 $[M+H]^+$.

Intermediate 78:

N-methyl-3-(propan-2-ylamino)propanamide

Isopropylamine (Aldrich; 1.5ml, 17.62mmol) and methyl acrylamide (ABCR; 1.0g, 11.75mmol) were combined in methanol (10ml). The mixture was heated in a microwave at 140°C for 30min. The reaction was repeated and the combined reaction mixtures were concentrated to remove excess amine. The residue was re-dissolved in methanol and absorbed onto an SCX column (50g), washed with methanol and eluted with ammonia/methanol. Concentration of the product containing fractions gave the title compound as a colourless oil (3.2g, 94%) .
^{1}H NMR (399.9 MHz, $CDCl_3$) δ1.00 (6H, d), 2.27 (2H, t), 2.70 - 2.74 (4H, m), 2.76 - 2.80 (2H, m), 7.50 (1H, s)

Intermediate 79:

4-amino-3-chloro-N-(1-methyl-4-piperidyl)benzamide

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide (Intermediate 80; 270 mg, 1 mmol), 10% Palladium on Carbon (30 mg) and Methanol (50 mL) were combined and stirred at 25°C under Hydrogen at 5 bar pressure for 16 hours..
The catalyst was filtered off and solvents evaporated to give the title compound as a cream solid. (280 mg, 98%)
^{1}H NMR (400.132 MHz, CDCl3) δ1.49 (m, 2H), 1.95 (m, 2H), 2.09 (m, 2H), 2.24 (s, 3H), 2.75 (m, 2H), 3.89 (m, 1H), 4.27 (s, 2H), 5.69 (d, 1H), 6.68 (m, 1H), 7.41 (m, 1H), 7.62 (m, 1H); MS m/z 268 $[M+H]^+$.

Intermediate 80:

3-chloro-N-(1-methyl-4-piperidyl)-4-nitro-benzamide

Reagents combined and stirred at room temperature overnight. LCMS after 18 hrs shows complete reaction. Solvents evaporated and residues partitioned between DCM (25 ml) and water (25 ml) then gravity filtered through a PTFE cup. Taken up in DCM and purified on silica eluting with a gradient of 0 – 5% 2M ammonia in MeOH / DCM then 5% 2M ammonia in MeOH / DCM. The peak corresponding to the product (which was only 1 spot by tlc) was clearly split into 2 on the chromatography trace. The first peak (fractions 6 – 10) was labelled PH17082/048/1 and evaporated to a brown gum. The second peak (fractions 11 – 14) was labelled as PH17082/048/2 and evaporated to a white solid. Both products had identical LCMS traces and showed the mass ion for the desired product. NMR showed a difference in the aliphatic region and an additional small broad peak in the aromatic region of PH17082/048/1. It was concluded that PH17082/048/1 was a salt (possibly PF6 from HATU).

PH17082/048/1 was dissolved in MeOH and added to a 2g SCX-2 column pre-wet with MeOH (2 column volumes). The column was then flushed with MeOH (2 column volumes) and the product eluted with 2M ammonia in MeOH. This was then combined with the solid of PH17082/048/2 and evaporated to an off-white solid, 315mg.

^{1}H NMR (500.133 MHz, DMSO-D6) δ1.66 (m, 2H), 1.85 (m, 2H), 2.14 (m, 2H), 2.25 (s, 3H), 2.83 (m, 2H), 3.78 (m, 1H), 7.97 (m, 1H), 8.09 (m, 1H), 8.12 (m, 1H), 8.26 (d, 1H); MS m/z 298 $[M+H]^+$.

Intermediate 81:

10-chloro-2-ethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

Tris(dibenzylideneacetone)dipalladium(0) (52 mg, 0.06 mmol), XANTPHOS (98 mg, 0.17 mmol) and caesium carbonate (1.32 g, 4.06 mmol) were added to a stirred solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-ethyl-amino]-N-methyl-propanamide (Intermediate 82; 900 mg, 2.80 mmol) in 1,4-dioxane (28 mL). The apparatus was evacuated and backfilled with nitrogen twice and then heated to 100 °C for 18 hrs. The reaction mixture was filtered through a celite pad and dry loaded onto silica for purification by flash silica chromatography (companion, 40 g, 0-10% MeOH/DCM) to give the title compound as a yellow solid (638 mg, 2.65 mmol, 95%).

^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.17 (t, 3H), 2.66 - 2.69 (m, 2H), 3.19 (s, 3H), 3.57 (q, 2H), 3.72 - 3.74 (m, 2H), 8.13 (s, 1H); MS m/z 241.14 $[M+H]^+$.

Intermediate 82:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-ethyl-amino]-N-methyl-propanamide

5-Bromo-2,4-dichloropyrimidine (Aldrich; 1.14 g, 5.00 mmol), 3-ethylamino-N-methyl-propanamide (Intermediate 83; 0.642 g, 5.00 mmol) and triethylamine (0.71 mL, 5.10 mmol) were combined in acetonitrile (25 mL) and heated to 100 °C for 4 hrs. The solvent was removed under reduced pressure and the residue taken up in Ethyl Acetate, washed with water and purified by flash silica chromatography (companion, 40 g, 0-10% Methanol/DCM) to givethe title compound as a white solid (1.06 g, 3.3 mmol, 66%).

^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.18 (t, 3H), 2.46 (t, 2H), 2.58 (d, 3H), 3.67 (q, 2H), 3.81 (t, 2H), 7.85 (m, 1H), 8.31 (s, 1H); MS m/z 320.95 $[M+H]^+$.

Intermediate 83:

3-ethylamino-N-methyl-propanamide

N-methylacrylamide (ABCR: 851 mg, 10.00 mmol) and ethylamine (2 M in methanol, 10 mL, 20.00 mmol) were combined in a microwave reaction vessel, which was sealed and irradiated at 140 °C for 30 mins. The reaction mixture was allowed to cool and then loaded directly onto a 50 g SCX-2 cartridge, washing with methanol (100 mL) and eluting the desired product with 7 N methanolic ammonia (100 mL). Concentration under reduced pressure of product containing fractions gave the title compound as a clear oil (1.285 g; 99%) ^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.93 - 0.99 (3H, m), 2.19 (2H, t), 2.52 - 2.52 (2H, m), 2.54 - 2.59 (3H, d), 2.68 (2H, t), 7.80 (1H, br s)

Intermediate 84:

10-chloro-6-methyl-2-(2-methylpropyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methylpropyl)amino]-N-methyl-propanamide (Intermediate 85; 3.26 g, 9.32 mmol)) was suspended in dioxane (70 mL), Caesium Carbonate (6 g, 18,64 mmol) was added and the mixture bubbled with nitrogen for 10

minutes. Tris(dibenzylideneacetone)dipalladium(0) (512 mg, 0.56 mmol) and XANTPHOS (485 mg, 0.839 mmol) were added and the mixture heated at 100 °C for 24 hrs. The reaction mixture was cooled to room temperature, solvent evaporated and the residues partitioned between DCM (250 mL) and water (250 mL). The aqueous phase was re-extracted with DCM (200 mL) and the combined organic phases dried over MgSO4 and evaporated to a dark brown gum which was taken up in DCM and purified on silica, eluting with a gradient of 30 – 50% Ethyl Acetate / iso-hexane then 50% Ethyl Acetate / iso-hexane. Fractions containing product were combined and evaporated to a yellow solid, which was heated at reflux in iso-hexane (50 mL) for 15 minutes and allowed to cool to room temperature overnight. The resulting solid was filtered and dried to give the title compound as a pale yellow solid (1.02 g, 41%)

^{1}H NMR (400.132 MHz, CDCl3) δ0.85 (d, 6H), 2.03 (m, 1H), 2.65 (m, 2H), 3.23 (s, 3H), 3.45 (d, 2H), 3.69 (m, 2H), 7.89 (s, 1H); MS m/z 269 $[M+H]^+$.

Intermediate 85:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methylpropyl)amino]-N-methyl-propanamide

5-Bromo-2,4-dichloropyrimidine (Aldrich; 2.82 g, 12.37 mmol), N-methyl-3-(2-methylpropylamino)propanamide (Intermediate 86; 1.78 g; 11.25 mmol) , Triethylamine (1.65 mL, 11.81 mmol) and DCM (40 mL) were combined and stirred over the weekend at room temperature. The reaction mixture was washed saturated aqueous sodium bicarbonate solution and gravity filtered through a PTFE cup and solvent evaporated. The residue was dissolved in DCM and passed through a silica column eluting with a gradient of 30 – 50% Ethyl Acetate / iso-hexane over 10 column volumes then 50% Ethyl Acetate / iso-hexane. Fractions containing product combined and evaporated to give the title compound as a white solid. (3.26 g, 83%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ0.84 (d, 6H), 1.98 (m, 1H), 2.44 (m, 2H), 2.75 (d, 3H), 3.58 (m, 2H), 3.91 (m, 2H), 5.57 (s, 1H), 8.11 (s, 1H); MS m/z 351 $[M+H]^+$.

Intermediate 86:

N-methyl-3-(2-methylpropylamino)propanamide

N-methylacrylamide (ABCR; 1 g, 11.75 mmol) was dissolved in EtOH (5 mL). Isobutylamine (Aldrich; 2.33 mL, 23.5 mmol) was added and stirred at ambient temperature

in a stoppered flask over the weekend. The reaction was then transferred to a microwave reactor vessel and heated in a microwave for 10 minutes at 140 °C. Solvents were evaporated *in vacuo* to give the title compound as a colourless liquid. (1.78 g, 96%)

^{1}H NMR (400.132 MHz, CDCl3) δ0.93 (d, 6H), 1.74 (m, 1H), 2.35 (m, 2H), 2.43 (d, 2H), 2.78 (d, 3H), 2.85 (m, 2H), 7.88 (s, 1H)

Intermediate 87:

2-butan-2-yl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-butan-2-yl-amino]-N-methyl-propanamide (Intermediate 88; 559 mg, 1.60 mmol) in anhydrous 1,4-dioxane (15 mL) was added Caesium Carbonate (1.04 g, 3.19 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes, prior to addition of Tris(dibenzylideneacetone)dipalladium(0) (87 mg, 0.095 mmol) and XANTPHOS (88 mg, 0.152 mmol). The reaction was heated to 100°C and stiired under nitrogen mfor 18 hrs. The reaction mixture was cooled and diluted to ~40 ml with DCM. The reaction mixture was filtered to remove insoluble material, washing filter cake through with DCM. The filtrate was evaporated to give a brown gum which was purified by flash chromatography on silica (40g cartridge; ISCO companion) eluting with a 25-75% gradient of ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a waxy off white solid which was trituration with hot iso-hexane afforded, on cooling, and collection by suction filtration the title compound as a pale yellow solid (121 mg, 28%)

H NMR (400.132 MHz, DMSO-D6) δ 0.83 (t, 3H), 1.16 (d, 3H), 1.57 (m, 2H), 2.65 (m, 2H), 3.18 (s, 3H), 3.49 - 3.66 (m, 2H), 4.57 (m, 1H), 8.12 (s, 1H); MS m/z 269 $[M+H]^+$.

Intermediate 88:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-butan-2-yl-amino]-N-methyl-propanamide

To a solution of 3-(butan-2-ylamino)-N-methyl-propanamide (Intermediate 89; 563 mg, 3.56 mmol) in DCM (7 mL) was added triethylamine (550 µl, 3.94 mmol) and, as a solid, 5-bromo-2,4-dichloropyrimidine (Aldrich; 890 mg, 3.90 mmol). The reaction was stirred at ambient temperature overnight.

Saturated aqueous Sodium Bicarbonate solution (10 mL) was added and the mixture shaken. The organic phase was collected by gravity elution through a PTFE filter cup. The DCM solution was injected directly onto 40g Si cartridge and eluted with a 25-75% gradient of ethyl acetate in hexane. Product containing fractions were combined and evaporated to afford the title compound as a colourless crystalline solid (565 mg; 45%)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.83 (t, 3H), 1.28 (d, 3H), 1.58 (m, 1H), 1.72 (m, 1H), 2.44 (m, 2H), 2.83 (d, 3H), 3.64 (m, 1H), 3.85 (m, 1H), 4.58 (m, 1H), 5.78 (m, 1H), 8.23 (s, 1H); MS m/z 351 $[M+H]^+$.

Intermediate 89:

3-(butan-2-ylamino)-N-methyl-propanamide

A mixture of N-methylacrylamide (ABCR; 500 mg, 5.87 mmol), sec-butylamine (Aldrich; 530 mL, 5.22 mmol) and ethanol (4 mL) was heated in a microwave to 140°C for 45 minutes and then at 150°C for 30 minutes. The reaction mixture was cooled and poured onto an SCX-2 cartridge (5g) and cartridge washed through with methanol (~50 mL). Products were then eluted with 2M ammonia in methanol (~50 mL) and evaporated to afford the title compound as a straw coloured oil (563 mg; 61%)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.92 (t, 3H), 1.06 (d, 3H), 1.31 - 1.53 (m, 2H), 2.34 (m, 2H), 2.57 (m, 1H), 2.78 - 2.94 (m, 5H), 7.77 (s, 1H)

Intermediate 90:

10-chloro-2-cyclobutyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclobutyl-amino]-N-methyl-propanamide (Intermediate 91; 600 mg, 1.73 mmol) in anhydrous 1,4-dioxane (15 mL) was added Caesium Carbonate (1.1 g, 3.38 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes, prior to addition of Tris(dibenzylideneacetone)dipalladium(0) (99

mg, 0.11 mmol) and XANTPHOS (95 mg, 0.16 mmol). The reaction was heated to 100°C and stirred under nitrogen overnight

The reaction mixture was cooled and diluted to ~40 ml with DCM, filtered to remove insoluble material, washing filter cake through with DCM and evaporated to give a brown/green solid which was purified by flash chromatography on silica (120g cartridge; ISCO companion) eluting with a 25-100% gradient of ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a waxy off white solid which was trituration with warm iso-hexane which afforded, on cooling and collection by suction filtration the title compound as a pale yellow solid (216 mg, 47%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.68 (m, 2H), 2.09 (m, 2H), 2.21 (m, 2H), 2.63 (m, 2H), 3.19 (s, 3H), 3.69 (m, 2H), 4.43 (m, 1H), 8.19 (s, 1H); MS m/z 267.4 $[M+H]^+$.

Intermediate 91:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclobutyl-amino]-N-methyl-propanamide

Using 3-(cyclobutylamino)-N-methyl-propanamide - Intermediate 92 and analogous conditions to Intermediate 88 the title compound was obtained as a white solid (609 mg)

^{1}H NMR (400.132 MHz, CDCl3) δ 1.62 - 1.79 (m, 2H), 2.16 - 2.34 (m, 4H), 2.45 (m, 2H), 2.81 (d, 3H), 3.95 (m, 2H), 4.72 (m, 1H), 5.72 (m, 1H), 8.24 (s, 1H)

Intermediate 92:

3-(cyclobutylamino)-N-methyl-propanamide

Using cyclobutanamine - Aldrich and analogous conditions to Intermediate 89 the title compound was obtained as a pale yellow oil (541 mg)

^{1}H NMR (400.132 MHz, CDCl3) δ 1.64 - 1.75 (m, 4H), 2.23 (m, 2H), 2.33 (m, 2H), 2.77 - 2.81 (m, 5H), 3.26 (m, 1H), 7.32 (m, 1H)

Intermediate 93:

10-chloro-2-(cyclopropylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a partial solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(cyclopropylmethyl)amino]-N-methyl-propanamide (Intermediate 94; 426 mg, 1.18 mmol) in anhydrous 1,4-dioxane (15 mL) was added Caesium Carbonate (790 mg, 2.42 mmol). Nitrogen was bubbled through the reaction mixture for 10 minutes, prior to addition of Tris(dibenzylideneacetone)dipalladium(0) (69 mg, 0.075 mmol) and XANTPHOS (62 mg, 0.107 mmol). The reaction was heated to 100°C and stirred under nitrogenfor 18 hrs. The reaction mixture was cooled and diluted to ~40 ml with DCM, filtered to remove insoluble material, washing the filter cake through with DCM, and evaporated to give a brown gum which was purified by flash chromatography on silica (40g cartridge; ISCO companion) eluting with a 25-75% gradient of ethyl acetate in iso-hexane. Product containing fractions were combined and evaporated to give a crystalline yellow translucent solid. Trituration with hot iso-hexane afforded, on cooling, and collection by suction filtration the title compound as a pale yellow solid (165 mg, 50%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 0.00 (m, 2H), 0.33 (m, 2H), 0.59 (m, 1H), 1.44 (q, 2H), 2.60 (m, 2H), 3.11 (s, 3H), 3.55 (m, 2H), 3.68 (m, 2H), 8.05 (s, 1H)
MS m/z 281.4 $[M+H]^+$.

Intermediate 94:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(cyclopropylmethyl)amino]-N-methyl-propanamide

Using 3-(cyclopropylmethylamino)-N-methyl-propanamide- Intermediate 95 and analogous conditions to Intermediate 88 the title compound was obtained as a white solid (431 mg)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.35 (m, 2H), 0.60 (m, 2H), 1.14 (m, 1H), 2.57 (m, 2H), 2.84 (d, 3H), 3.66 (d, 2H), 4.03 (m, 2H), 5.79 (m, 1H), 8.21 (s, 1H); MS m/z 349.0 $[M+H]^+$.

Intermediate 95:

3-(cyclopropylmethylamino)-N-methyl-propanamide

Using 2-Cyclopropylethanamine- Aldrich and analogous conditions to Intermediate 89 the title compound was obtained as a pale yellow oil (590 mg)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.13 (m, 3H), 0.51 (m, 2H), 0.94 (m, 1H), 2.36 (m, 2H), 2.49 (d, 2H), 2.81 (d, 3H), 2.90 (m, 2H), 7.59 (s, 1H).

Intermediate 96:

10-chloro-2-[(2,4-dimethoxyphenyl)methyl]-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-[(3,5-dimethoxyphenyl)methyl]amino]-N-methyl-propanamide (Intermediate 97; 2.1 g, 4.73 mmol) in 1,4-dioxane (50 mL) was added Caesium Carbonate (3.4 g, 10.44 mmol) and the reaction mixture sparged with argon for 20 minutes.

Tris(dibenzylideneacetone)dipalladium(0) (260 mg, 0.28 mmol) and XANTPHOS (248 mg, 0.43 mmol) were added and reaction mixture heated to 100°C and left to stir under nitrogen overnight.

The reaction mixture was cooled and diluted to ~100 ml with DCM., filtered to remove insoluble material, washing filter cake through with DCM and evaporated to give a dark yellow oil with some solid which was taken up in DCM (~20 ml) and insoluble material removed by filtration. The filtrate was purified by flash chromatography on silica (120g cartridge) eluting with a rising gradient of 25-100% ethyl acetate in hexane. Product containing fractions were combined and evaporated to give the title compound as a pale yellow solid (690 mg)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 2.71 (m, 2H), 3.20 (s, 3H), 3.63 (m, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 4.68 (s, 2H), 6.48 (m, 1H), 6.59 (d, 1H), 7.06 (d, 1H), 8.17 (s, 1H); MS m/z 363.3 $[M+H]^+$.

Intermediate 97:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-[(3,5-dimethoxyphenyl)methyl]amino]-N-methyl-propanamide

3-[(3,5-dimethoxyphenyl)methylamino]-N-methyl-propanamide (Intermediate 98; 1 g, 3.96 mmol) was dissolved in DCM (10 mL) and triethylamine (0.68 mL, 4.36 mmol). 5-bromo-2,4-dichloropyrimidine (Aldrich; 993 mg, 4.36 mmol) was added and the mixture stirred at room temperature for 18 hours. The mixture was diluted with DCM and washed with water,

brine, dried ($MgSO_4$), filtered and evaporated to give a yellow gum which was purified on a 40g ISCO companion eluting with 50-70% ethyl acetate in iso-hexane to give the title compound as a white solid (461mg, 26%).

1H NMR (400.13MHz; DMSO-d_6) δ 2.5 (m, 2H) under DMSO, 2.55 (d, 3H), 3.72 (s, 6H), 3.8 (t, 2H), 4.85 (s, 2H), 6.41 (s, 3H), 7.84 (bm, 1H), 8.38 (s, 1H); MS m/z 443/445 $[M+H]^+$.

Intermediate 98:

3-[(3,5-dimethoxyphenyl)methylamino]-N-methyl-propanamide

N-methylacrylamide (ABCR; 500mg, 5.87 mmol) and 3.5-dimethoxybenzylamine (Aldrich; 0.98 mL, 6.46 mmol) were dissolved in ethanol (4 mL) and heated in a microwave at 140°C for 45 minutes. The mixture was poured onto a 20g SCX-2 column, washed with methanol and eluted with 3.5N NH_3 in methanol. The product fractions were evaporated to the title compound as a yellow oil (1.3 g, 88%).

1H NMR (CDCl3) 2.36 (t, 2H), 2.78 (d, 3H), 2.88 (t, 2H), 3.72 (s, 2H), 3.79 (s, 6H), 6.36 (m, 1H), 6.45 (m, 2H), 7.31 (bs, 1H); MS m/z 253 $[M+H]^+$.

Intermediate 99:

2-benzyl-10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a cooled (ice/water bath) suspension of sodium hydride (60% dispersion in mineral oil; 6.5 mg, 0.16 mmol) in DMA (0.5 mL) was added a solution of 10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 100; 32 mg, 0.15 mmol) in DMA (1.0 mL). The reaction mixture was allowed to stir, under nitrogen, in an ice bath for 15 minutes prior to addition of Benzyl bromide (Aldrich; 20 µl, 0.17 mmol). The reaction mixture was stirred on an ice bath for 15 minutes and then at ambient temperature for 3 hrs A further addition of Sodium hydride (2 mg) was made and stirring continued for 6 hrs. Saturated ammonium chloride (0.5 ml) was added and the reaction mixture poured directly onto an SCX-3 cartridge (2g). The cartridge was washed with methanol (~30 mL) before eluting products with 2M ammonia in methanol (~30 mL). Product containing fractions were evaporated to dryness to give a colourless gum, which was combined with the cartridge methanol pre-wash and this solution evaporated to dryness. The resultant material was

partitioned between DCM (10 mL) and water (10 mL). The organic phase was collected by gravity elution through a PTFE filter cup and evaporated to give the title compound as a pale yellow opaque gum (46 mg, 89%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 2.71 (m, 2H), 3.22 (s, 3H), 3.66 (m, 2H), 4.82 (s, 2H), 7.27 - 7.38 (m, 5H), 8.21 (s, 1H); MS m/z 303.3 $[M+H]^+$.

Intermediate 100:

10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-[(3,5-dimethoxyphenyl)methyl]amino]-N-methyl-propanamide (Intermediate 97; 83 mg, 0.23 mmol) was taken up in DCM (1 mL) and TFA (1 mL) and stirred for 30 minutes. A further addition of TFA (1 mL) was made and stirring continued overnight. The reaction mixture was diluted with DCM (25 m L) and poured directly onto a SCX-3 cartridge (2 g). The cartridge was washed through with methanol (~50 mL). Products were eluted with 2M ammonia in methanol and ammoniacal eluant evaporated to dryness to afford the title compound as an off white solid (34 mg, 70%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 2.66 (m, 2H), 3.21 (s, 3H), 3.52 (m, 2H), 8.14 (m, 1H), 8.28 (m, 1H); MS m/z 213.4 $[M+H]^+$.

Intermediate 101:

10-chloro-6-methyl-2-[(2-methyl-1,3-thiazol-4-yl)methyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a cooled (ice/water bath) suspension of sodium hydride (60% dispersion in mineral oil; 13 mg, 0.38 mmol) in DMA (0.5 mL) was added a solution of 10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 100; 63 mg, 0.30 mmol) in DMA (1 mL). The reaction mixture was allowed to stir, under nitrogen, in ice bath for 10 minutes prior to addition of 4-chlorometyl-2-methylthiazole (ASDI; 75 mg, 0.51 mmol). The reaction mixture was stirred in an ice bath for 20 minutes and then warmed to ambient temperature over 1 hour.

The reaction mixture was quenched by careful addition of saturated aqueous ammonium chloride (0.5 ml) and the reaction mixture was partitioned between DCM(10 mL) and water

(10 mL). The organic phase was separated by gravity filtration through a PTFE filter cup and evaporation to dryness to give the title compound as a straw coloured gum (61 mg; 63%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 2.64 (s, 3H), 2.74 (m, 2H), 3.21 (s, 3H), 3.78 (m, 2H), 4.82 (m, 2H), 7.31 (m, 1H), 8.20 (s, 1H); MS m/z 324.3 $[M+H]^+$.

Intermediate 102:

10-chloro-2-(cyclobutylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a cooled (ice/water bath) suspension of sodium hydride (60% dispersion in mineral oil; 13 mg, 0.38 mmol) in DMA (0.5 ml) was added a solution of (Intermediate 100; 63 mg, 0.30 mmol) in DMA (1 mL). The reaction mixture was allowed to stir, under nitrogen, on an ice bath for 10 minutes prior to addition of Bromomethyl cyclobutane (Aldrich; 40 µl, 0.36 mmol). The reaction mixture was stirred on an ice bath for 20 minutes and then warmed to ambient temperature over 1 hour.

A further addition of Sodium hydride (2 mg) and Bromomethyl cyclobutane (20 µl, 0.18 mmol was made and the reaction stirred for a further hour

The reaction mixture was quenched by careful addition of saturated aqueous ammonium chloride (0.5 ml) and the reaction mixture partitioned between DCM(10 mL) and water (10 mL). The organic phase was separated by gravity filtration through a PTFE filter cup and evaporation to dryness gave the title compound as a pale yellow gum (71 mg, 84%)

^{1}H NMR (400.132 MHz, DMSO-D6) δ 1.71 - 1.86 (m, 4H), 2.01 (m, 2H), 2.66 (m, 3H), 3.17 (s, 3H), 3.63 (d, 2H), 3.70 (m, 2H), 8.12 (s, 1H); MS m/z 281.3 $[M+H]^+$.

Intermediate 103:

10-chloro-6-methyl-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of 10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 104; 1.185 g, 4.31 mmol) in DMA (100 mL) at 0°C, was added methyl iodide (282 µL, 4.53 mmol) followed by sodium hydride (60% oil dispersion, 182 mg, 4.53 mmol) in one portion. The mixture was stirred at 0°C for 4hrs and ice was then added, resulting in a brown sticky precipitate, which was filtered and washed with water. A white solid precipitated from the filtrate, which was filtered off and triturated with diethylether to give the title compound (494mg).

The sticky brown precipitate was dissolved in DCM and suction columned in 2- 5% methanol/dichloromethane to give a yellow oil.

The aqueous filtrate was extracted with DCM and methanol, washed with saturated aqueous brine and evaporated to give a yellow oil which was purified by suction columned as above to give a yellow oil.

Both yellow oils were combined and triturated with diethylether to give the title compound as a white solid (401mg)

^{1}H NMR (399.9 MHz, DMSO-D6) : δ_H : 2.89 (m, 2H), 3.29 (s, 3H), 4.06 (m, 2H), 7.30 (m, 3H), 7.42 (m, 2H), 8.38 (s, 1H); MS m/z 289 $[M+H]^+$.

Intermediate 104:

10-chloro-2-phenyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Methyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-phenyl-amino]propanoate (Intermediate 105; 21.855 g, 64.9 mmol), iron powder (5.44 g, 97.35 mmol) and acetic acid (200 mL) were heated at 80°C for 2hrs and then stirred at room temperature overnight..

The reaction mixture was filtered through celite and the filter cake washed with dichloromethane. The solvent was evaporated and the resultant material was pre-absorbed onto silica with methanol/dichloromethane and then purified by vacuum filtration chromatography eluting with dichloromethane,. diethylether, . ethylacetate and finally. 20% methanol/dichloromethane. Product containing fractions were combined and evaporated To give a brown solid which was trituated with diethylether and then methanol and small % of dichloromethane to give the title compound as an off white solid (2.29 g)

The silica from the filtration column was suspended in 20% methanol/dichloromethane and filtered and washed with a further portion of 20% methanol/dichloromethane. Evaporation afforded a yellow solid which was triturated with methanol and small % of dichloromethane to give the title compound as an off white solid (1.35g)

^{1}H NMR (399.9 MHz, DMSO-D6) : δ_H : 2.89 (m, 2H), 3.98 (m, 2H), 7.32 (m, 3H), 7.42 (m, 2H), 8.01 (s, 1H), 9.90 (s, 1H); MS m/z 275 $[M+H]^+$.

Intermediate 105:

Methyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-phenyl-amino]propanoate

To a solution of; 3,4-dichloro-5-nitropyrimidine (Aldrich; 12.59 g, 64.9 mmol) in anhydrous THF (300 mL) at room temperature under a nitrogen atmosphere was added dropwise over 6hrs a solution of Methyl 3-anilinopropanoate (Intermediate 106; 12.795 g, 71.39 mmol) and Hunigs base (13.54 mL, 77.88 mmol) in anhydrous THF (300 mL) The reaction mixture was stirred over night at room temperature.

The solvent was evaporated at 40°C and the residue dissolved in DCM and washed with water and saturated brine. The resulting organic phase was dried over anhydrous sodium sulphate then pre-absorbed onto silica and purified by vacuum filtration chromatography eluting with dichloromethane. Evaporation of product containing fractions afforded the title compound as a dark red oil (24.25g, >100%)

MS m/z 275 $[M+H]^+$. Retention time 2.32mins

Intermediate 106:

Methyl 3-anilinopropanoate

Aniline (Acros; 59.89 mL, 657 mmol) , Methylacrylate (Acros; 62.54 mL, 690 mmol) and Glacial acetic acid (15 mL) an d were combined and heated at 79°C overnight

The reaction mixture was cooled to room temperature and added to ice water, a solid precipitated and was filtered off and dissolved in dichloromethane aliquot taken and pre-absorbed onto silica and purified by vacuum filtration chromatography eluting with DCM. Product containing fractions were combined and evaporated to give the title compound as a pale yellow sticky solid (14.33 g, 12%)

^1H NMR (399.9 MHz, DMSO-D6) : δ_H : 2.57 (tr, 2H), 3.29 (tr, 2H), 3.61 (s, 3H), 5.57 (tr, 1H), 6.55 (m, 3H), 7.08 (m, 1H); MS m/z 180 $[M+H]^+$.

Intermediate 107:

4-amino-3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)-4-nitro-benzamide (2.29 g, 7.67 mmol), iron powder (2.45 g, 43.79 mmol) and ammonium chloride (781 mg, 14.60 mmol) were heated in ethanol (50 mL) and water (18 mL) at reflux for one hour. A few drops of acetic acid were added and heating continued for a further hour. The reaction mixture was cooled,

filtered and the filtrate concentrated. This residue was partitioned between saturated $NaHCO_3$ (aq.) and DCM. The organic phase was washed with brine, dried with $MgSO_4$ and concentrated. Column chromatography gave the title compound as an orange crystalline solid. (850mg, 39%)

^1H NMR (399.9 MHz, DMSO-d_6) δ0.86 (6H, s), 2.16 (2H, s), 2.26 (6H, s), 3.14 (2H, d), 5.83 (2H, s), 6.80 (1H, d), 7.52 - 7.54 (1H, m), 7.72 (1H, d), 8.15 (1H, t); MS m/z 286.16 $[M+H]^+$.

Intermediate 108:

3-chloro-N-(3-dimethylamino-2,2-dimethyl-propyl)-4-nitro-benzamide

3-chloro-4-nitro-benzoyl chloride (Intermediate 54; 2.2 g, 10.00 mmol) was dissolved in DCM (20 mL) and N,N-diisopropylethylamine (2.095 mL, 12.00 mmol) added. The mixture was cooled in an ice/water bath and N,N,2,2-tetramethyl-1,3-propanediamine (3.652 mL, 10.00 mmol) in DCM (10 mL) added dropwise. The mixture was allowed to warm to room temperaturet and stirred for 0.5h. The mixture was washed with brine, 2N NaOH (aq.), dried ($MgSO_4$) and concentrated. Column chromatography of the residue (2% MeOH/DCM) gave the title compound as a yellow oil 17171/2/1 (2.29g, 77%).

^1H NMR (399.9 MHz, DMSO-d_6) δ0.89 (6H, s), 2.17 (2H, s), 2.26 (6H, s), 3.21 (2H, d), 7.96 - 7.98 (1H, m), 8.13 (1H, d), 8.18 (1H, d), 8.73 (1H, t); MS m/z 314.21 $[M+H]^+$.

Intermediate 109:

10-chloro-2-(2-methoxyethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methoxyethyl)amino]-N-methyl-propanamide (Intermediate 110; 1.12 g, 3.185 mmol) was suspended in dioxane (70 mL), Caesium Carbonate (2.08 g, 6.37 mmol) added and the mixture bubbled with nitrogen for 10 minutes. Tris(dibenzylideneacetone)dipalladium(0) (175 mg, 0.151 mmol) and XANTPHOS (166 mg, 0.287 mmol) were dded and the mixture heated to 100 °C for 20 hrs. A further 0.06 equivalent of Tris(dibenzylideneacetone)dipalladium(0) and 0.09 equvalent of XANTPHOS were added and heating continued for a further 2 hrs. The reaction mixture was cooled to room temperature filtered and the filter cake washed with DCM. The filtrate was evaporated and dissolved in DCM and purified on silica eluting with a gradient of 40 – 55% Ethyl Acetate /

iso-hexane then 55% Ethyl Acetate / iso-hexane and finally 70% Ethyl Acetate / iso-hexane. Fractions containing product were combined and evaporated to a yellow solid. Which was purified by base modified reverse phase HPLC to yield the title compound as a white solid (157 mg, 18%)

^{1}H NMR (399.902 MHz, CDCl3) δ2.73 (m, 2H), 3.29 (s, 3H), 3.35 (s, 3H), 3.68 (m, 2H), 3.84 (m, 2H), 3.90 (m, 2H), 7.95 (s, 1H); MS m/z 271 $[M+H]^+$.

Intermediate 110:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-(2-methoxyethyl)amino]-N-methyl-propanamide

3-(2-methoxyethylamino)-N-methyl-propanamide (Intermediate 111; 608 mg, 3.79 mmol) 5-Bromo-2,4-dichloropyrimidine (Aldrich; 950 mg, 4.17 mmol), Triethylamine (555 µL, 3.98 mmol), and DCM (5 mL) were combined and stirred over the weekend at room temperature. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution then gravity filtered through a PTFE cup and organic solvents evaporated. The residue was dissolved in DCM and passed through a silica column, eluting with 50% Ethyl Acetate / iso-hexane then 60% Ethyl Acetate / iso-hexane and finally 70% Ethyl Acetate / iso-hexane. Fractions containing product combined and evaporated to a colourless liquid which crystallised under high vacuum to give the title compound as a white solid (1.12 g, 84%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ2.57 (m, 2H), 2.82 (d, 3H), 3.35 (s, 3H), 3.63 (m, 2H), 3.95 (m, 2H), 4.01 (m, 2H), 5.80 (s, 1H), 8.20 (s, 1H); MS m/z 353 $[M+H]^+$.

Intermediate 111:

3-(2-methoxyethylamino)-N-methyl-propanamide

N-Methylacrylamide (ABCR; 500 mg, 5.87 mmol), 2-Methoxyethylamine (Aldrich; 441 mg, 5.87 mmol), and EtOH (2 mL) were combined and heated in a microwave at 140 °C for 40 minutes. The reaction mixture was cooled and added to a 5g SCX-2 column pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) then the product eluted with 2M ammonia in MeOH. Product containing fractions were evaporated *in vacuo* to give the the title compound as a clear oil (608 mg, 65%)

^{1}H NMR (399.902 MHz, CDCl3) δ2.35 (m, 2H), 2.79 (m, 5H), 2.88 (m, 2H), 3.37 (s, 3H), 3.49 (m, 2H), 7.55 (s, 1H)

Intermediate 112:

10-chloro-2-(1-methoxypropan-2-yl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 318 mg, 1.37 mmol), 2-Amino-1-methoxypropane (152 µl, 1.44 mmol), Triethylamine (382 µl, 2.74 mmol), Titanium Tetra-ethoxide (29 µl, 0.137 mmol) and DCM (5 mL) were combined and stirred at room temperature for 1hr, heated to 40 °C for 3hrs, cooled to room temperature, washed with water and gravity filtered through a PTFE . The organic solution was purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 10 – 50% Ethyl Acetate / iso-hexane. Product containing fractions were combined and evaporated to give the title compound as a clear gum (54 mg, 18%).

^{1}H NMR (399.902 MHz, CDCl3) δ1.25 (m, 3H), 2.69 (m, 2H), 3.29 (s, 3H), 3.34 (s, 3H), 3.53 (m, 2H), 3.75 (m, 2H), 4.99 (m, 1H), 7.94 (s, 1H); MS m/z 285 $[M+H]^+$.

Intermediate 113:

N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide

5-Methylamino-2,4-Dichloropyrimidine (800 mg, 4.5 mmol) was dissolved in THF (18 mL) and triethylamine (1.88 mL, 13.5 mmol) was added. A solution of 3-chloropropionyl chloride (644 µl, 6.55 mmol) in DCM (2 mL) was added dropwise giving an instantaneous precipitate The reaction was stirred at room temperature for 30 minutes. The precipitate was filtered off and the filtrate evaporated and the resultant material dissolved in DCM, washed with water, saturated aqueous sodium bicarbonate solution and then gravity filtered through a PTFE cup. The organic solvent was evaporated to give the crude product as a yellow gum which was dissolved in THF (18 mL). Triethylamine (1.8 mL) was added and a further portion of 3-chloropropionyl chloride (215 µl, 2.25 mmol). The reaction was stirred at room temp for 1 hr then worked up as previously to give the title compound as a brown gum (624 mg, 60%) MS m/z 232 $[M+H]^+$. Retention Time 1.39mins

Intermediate 114:

5-Methylamino-2,4-Dichloropyrimidine

To the methylamino-5-uracil (Intermediate 115; 6.81 g, 48.25 mmol) was added triethylamine (13.45 mL, 96.51 mmol) followed by phosphorus oxychloride (67.5 mL, 723 mmol) very slowly . The reaction was heated to reflux for 3 hrs cooled to room temperature and POCl3 evaporated and the residues azeotroped with toluene. The residue was diluted with toluene (100 mL) . Ice (200 mL) was added and the mixture stirred for 5 minutes. The mixture was then neutralised to pH8 with saturated aqueous sodium bicarbonate solution and extracted with toluene (300 mL). The aqueous phase was re-extracted with DCM (5 x 300 mL). The toluene solution was washed with water (100 mL), dried (MgSO4) and evaporated. The combined DCM solutions were also washed with water (300 mL), dried (MgSO4), combined with the toluene solution and evaporated to a brown gum which was dissolved in DCM with a little MeOH and chromatographed on silica eluting with a gradient of 0 – 10% Ethyl Acetate / iso-hexane followed by 10% Ethyl Acetate / iso-hexane then 15% Ethyl Acetate / iso-hexane. Fractions containing impure product were re-chromatographed eluting with 10% Ethyl Acetate / iso-hexane until the impurity had come off then 15% Ethyl Acetate / iso-hexane. Product containing fractions were evaporated to give the title compound as a cream solid (2.58 g, 30%)

^{1}H NMR (399.902 MHz, CDCl3) δ2.98 (d, 3H), 4.35 (s, 1H), 7.90 (s, 1H); MS m/z 175 $[M-H]^+$.

Intermediate 115:

Methylamino-5-uracil

5 Bromo Uracil (Aldrich; 49.66 g, 260 mmol) and 25% Methylamine in Ethanol (Aldrich; 200 mL) were combined and heated in an autoclave at 160 ^{0}C for 6 hours.

The solution was cooled and evaporated and the residue washed with water, acetone and diethylether to give the title compound as a white solid (28 g, 70%)

Intermediate 116:

10-chloro-2-(3-furylmethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one one

3-Furylmethylamine (Maybridge; 175 mg, 1.8 mmol), N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 347 mg, 1.5 mmol), Triethylamine (420 µL, 3 mmol), Titanium Tetra-ethoxide (157 µL, 0.75 mmol) and DCM (5 mL) were combined and stirred at room temp for 1hr, heated at 40 °C overnight then cooled to room temperature. The reaction mixture was washed with water then gravity filtered through a PTFE cup, the aqueous layer containing the titanium emulsion was washed with further DCM (3 x 10 mL) and the combined organic solutiuons gravity filtered through a PTFE cup and solvents evaporated. The residue was dissolved in DCM and purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 10 – 50% Ethyl Acetate / iso-hexane. Product containing fractions were combined and evaporated to give the title compound as a yellow gum (67 mg, 15%)

^{1}H NMR (399.902 MHz, CDCl3) δ2.63 (m, 2H), 3.31 (s, 3H), 3.75 (m, 2H), 4.60 (s, 2H), 6.49 (m, 1H), 7.41 (m, 1H), 7.50 (m, 1H), 8.00 (s, 1H); MS m/z 293 $[M+H]^+$.

Intermediate 117:

10-chloro-2-cyclopropyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Cyclopropylamine (Aldrich; 150 µL, 2.18 mmol), N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 337 mg, 1.45 mmol) Triethylamine (404 µL, 2.9 mmol), Titanium Tetra-ethoxide (152 µL, 0.725 mmol) and DCM (5 mL) were combined and stirred at room temp for 1hr, heated at 40 °C for 4 hrs then cooled to room temperature. The reaction mixture was washed with water then gravity filtered through a PTFE cup, the aqueous layer containing the titanium emulsion was washed with further DCM (3 x 10 mL) and the combined organic solutiuons gravity filtered through a PTFE cup and solvents evaporated. The residue was dissolved in DCM and purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 10 – 50% Ethyl Acetate / iso-hexane.

Product containing fractions were combined and evaporated to give the title compound as a cream solid (42 mg, 11%)

^{1}H NMR (399.902 MHz, CDCl3) δ0.58 (m, 2H), 0.91 (m, 2H), 2.68 (m, 2H), 2.85 (m, 1H), 3.28 (s, 3H), 3.84 (m, 2H), 8.02 (s, 1H); MS m/z 253 $[M+H]^+$.

Intermediate 118:

10-chloro-6-methyl-2-(1-methyl-4-piperidyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

4-Amino-1-methylpiperidine (Fluorochem; 200 mg, 1.74 mmol), N-(2,4-dichloropyrimidin-5-yl)-N-methyl-prop-2-enamide (Intermediate 113; 337 mg, 1.45 mmol) Triethylamine (404 µL, 2.9 mmol), Titanium Tetra-ethoxide (152 µL, 0.725 mmol) and DCM (5 mL) were combined and stirred at room temp for 1hr, heated at 40 °C for 3 hrs then cooled to room temperature. The reaction mixture was washed with water then gravity filtered through a PTFE cup, the aqueous layer containing the titanium emulsion was washed with further DCM (3 x 10 mL) and the combined organic solutions gravity filtered through a PTFE cup and solvents evaporated. The residue was dissolved in DCM and purified by chromatographic separation on silica eluting with a shallow gradient (25 column volumes) of 0 – 5% 2M ammonia in MeOH / DCM. Product containing fractions were combined and evaporated to give the title compound as a yellow solid (39 mg)

Intermediate 119:

4-amino-N-cyclohexyl-3-methoxy-benzamide

EDAC(7.46 g, 3.90 mmol) was added to a stirred solution of 4-amino-3-methoxy acid (Aldrich; 5 g, 2.9 mmol), cyclohexylamine (Aldrich; 5.13mL, 4.49 mmol) and DMAP (11 g, 9 mmol) in DCM (200 mL) and the reaction mixture was stirred for a 18hrs.under an atmosphere of nitrogen. The mixture was washed with 1M citric acid solution (x3), saturated sodium bicarbonate solution and dried. The solvent was evaporated off and the residue triturated with diethylether to give the title compound as a pink solid (5.3 g, 71%)
MS m/z 293 $[M+H]^+$.

Intermediate 120:

10-chloro-2-cyclopentyl-3,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one.

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclopentyl-amino]-N-methyl-butanamide (Intermediate 121; 196 mg, 0.52 mmol) was dissolved in 1,4-dioxane (5 mL) and Tris(dibenzylideneacetone)dipalladium(0) 10 mg, 0.02 mmol), XANTPHOS (20 mg, 0.02 mmol) and Caesium Carbonate (247 m, 0.76 mmol) were added to a microwave reaction vessel which was sealed and irradiated at 150 °C for 30 min. A further addition of Tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.02 mmol) and XANTPHOS (20 mg, 0.02 mmol) was made and the reaction mixture irradiated at 150 °C for 2 hrs.. The cooled reaction mixture was filtered through a pad of celite and the filtrate concentrated down onto silica and purified by flash silica chromatography (companion, 12 g, 0-5% methanol/DCM). Product containing fractions were combined and evaporated to give the title compound as a yellow solid (126 mg, 82%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.34 (d, 3H), 1.44 - 1.95 (m, 8H), 2.63 (dd, 1H), 2.77 (dd, 1H), 3.32 (s, 3H), 3.98 (ddq, 1H), 4.56 (quintet, 1H), 7.94 (s, 1H); MS m/z 295.2 $[M+H]^+$.

Intermediate 121:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclopentyl-amino]-N-methyl-butanamide

A stirred solution of 3-(cyclopentylamino)-N-methyl-butanamide (Intermediate 122; 887 mg, 4.80 mmol), 5-bromo-2,4-dichloropyrimidine (1.15 g, 5.04 mmol) and potassium carbonate (1.34 g, 9.60 mmol) in acetone (20 mL) were heated under reflux conditions to 65 °C for 3 days and then at 75 °C for a further 16 hrs.. The solvent was evaporated and the residue taken up in Ethyl Acetate (200 mL) and water (200 mL). The aqueous phase was separated and the organic phase further washed with water (200 mL) and brine (200 mL). The organic phase was evaporated and the residue purified by flash silica chromatography (companion, 40 g, 0-10% MeOH/DCM) followed by base modified preparative HPLC (30-50% gradient) to give the title compound as a yellow solid (117 mg, 6%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.29 (d, 3H), 1.36 - 1.51 (m, 2H), 1.65 - 1.93 (m, 6H), 4.03 (quintet, 1H), 4.48 (sextet, 1H), 7.69 (q, 1H), 8.26 (s, 1H), 5 protons obscured in DMSO signal. MS m/z 375.17 $[M+H]^+$.

Intermediate 122:

3-(cyclopentylamino)-N-methyl-butanamide

But-2-Enoic Acid Methylamide (Journal of Organic Chemistry (1981), 46(1), 27-34; 1 g, 10.0 mmol) and cyclopentlyamine (Aldrich; 1.49 mL, 15.0 mmol) were combined in methanol (6 mL) in a 10 mL microwave reaction vessel and the resultant solution heated to 140 °C for 60 minutes. The reaction mixture was concentrated under reduced pressure re-dissolved in methanol (6 mL) and reintroduced to a microwave reaction vessel with cyclopentylamine (1.49 mL, 15.0 mmol) and the sealed reaction vessel heated to 140 °C for a further 60 mins.

The process was repeated with cyclopentylamine (3.0 mL, 30 mmol) added and the sealed reaction vessel irradiated to 140 °C for 2 hrs. The solvent was removed under reduced pressure and the residue dissolved in methanol (approx 10 mL) and loaded directly onto a 50 g SCX-2 cartridge, washing with methanol (100 mL) and eluting the desired product with 7 N methanolic ammonia (100 mL). Product containing fractions were combined and evaporated to give the title compound as a brown oil (1.65 g, 90%)

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.96 (d, 3H), 1.17 - 1.81 (m, 8H), 1.99 (dd, 1H), 2.16 (dd, 1H), 2.56 (d, 3H), 2.93 (m, 1H), 3.09 (quintet, 1H), 3.31 (br s, 1H), 7.87 (br s, 1H)

Intermediate 123:

10-chloro-2-cyclopentyl-4-ethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5- one

To a solution of 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 1 g, 3.56 mmol) in anhydrous THF (50 mL) at 0°C was added dropwise a 2N solution of sodium bis (trimethylsilyl)amide in THF (1.96 mL, 3.92 mmol). The resulting solution was stirred at 0°C for 10 minutes. Ethyl iodide (314 µL, 3.92 mmol) was added dropwise via a syringe and the reaction stirred at 0°C for 2hrs and then at room temperature overnight.

The reaction mixture was evaporated, taken up in water and extracted with DCM. The organic phase was washed with saturated brine and dried over magnesium sulphate. Evaporation

afforded a gum, which was dissolved in DCM and purified by vacuum filtration chromatography, eluting with DCM and then 2. 2-5% Methanol / DCM.
Product containing fractions were evaporated to give the title compound as a white foam (483 mg, 44%)
^{1}H NMR (399.9 MHz, DMSO-D6) : δ_H : 0.81 (tr, 3H), 1.21-2.01 (m, 10H), 2.60 (m, 1H), 3.15 (s, 3H), 3.39 (m, 2H), 4.68 (m, 1H), 8.11 (s, 1H); MS m/z 309 $[M+H]^+$.

Intermediate 124:

10-chloro-2-cyclopentyl-6-methyl-4-propyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

To a solution of 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 1 g, 3.56 mmol) in anhydrous THF (50 mL) at 0°C was added dropwise a 2N solution of sodium bis (trimethylsilyl)amide in THF (1.96 mL, 3.92 mmol). The resulting solution was stirred at 0°C for 10 minutes. 1-Iodopropane (Aldrich; 382 µL, 3.92 mmol) was added dropwise via a syringe and the reaction stirred at 0°C for 2hrs and then at room temperature overnight.
The reaction mixture was evaporated, taken up in water and extracted with DCM. The organic phase was washed with saturated brine and dried over magnesium sulphate
Evaporation afforded a gum, which was dissolved in DCM and purified by vacuum filtration chromatography, eluting with DCM and then 2. 2-5% Methanol / DCM.
Product containing fractions were evaporated to give the title compound as a yellow foam (467 mg, 41%)
^{1}H NMR (399.9 MHz, DMSO-d_6) : δ_H : 0.81 (tr, 3H), 1.21-2.1 (m, 12H), 2.70 (m, 1H), 3.20 (s, 3H), 3.40 (m, 2H), 4.71 (m, 1H), 8.13 (s, 1H).; MS m/z 323 $[M+H]^+$.

Intermediate 125:

10-chloro-2-cyclopentyl-4,6-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

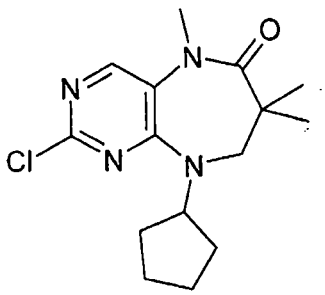
To a cold (-78°C) magnetically stirred solution of 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1 ; 801 mg, 2.85 mmol) in dry THF (15 mL) was added dropwise LHMDS (1 M in THF, 5.71 mL, 5.70 mmol).

After 10 minutes at this temperature a solution of methyl iodide (356 uL, 5.70 mmol) in THF (3 mL) was added. The reaction mixture was stirred at –78 °C for 20 minutes and then at 0 °C one hour. The reaction mixture was diluted with DCM and washed with water, followed by brine. The separated organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was dry-loaded onto silica and purified *via* column chromatography (0-50% Ethyl Acetate in hexane) to provide the title compound as a white solid. (613 mg, 73%)

MS m/z 323 $[M+H]^+$.

Intermediate 126:

10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one



To a stirred solution of 10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 9.67 g, 32.8 mmol) in DMA (710 mL) under nitrogen was added methyl iodide (2.25 mL, 36.08 mmol). The mixture was cooled in ice/water to 2.5°C. Sodium hydride (60% dispersion in mineral oil, 1.45 g, 36.08 mmol) was added in one portion. A small exotherm to 4°C was observed. The reaction mixture was stirred on an ice/water bath for 1 hour, and then stirred at room temperature overnight. Solvent was removed *in vacuo* and the light-brown liquid residue was treated with water. This afforded a solid, which was filtered off and washed with water. The solid material was dissolved in DCM (200 mL) and the solution dried using $MgSO_4$, filtered and evaporated to give an off white solid which was purified on a 330g Si column (Companion). loading as a solution in DCM (60 mL) The column having been equilibrated with 30% Ethyl Acetate in isohexane, and eluted with 30% Ethyl Acetate in isohexane for the first 5 minutes and then

with a linear gradient slowly rising to 100% Ethyl Acetate. Product containing fractions were combined and evaporated to dryness to give the title compound as a white solid (9.29 g, 92%) 1H NMR (400.13 MHz, $CDCl_3$) δ 1.20 (6H, s), 1.47 - 1.56 (2H, m), 1.64 - 1.80 (4H, m), 1.94 - 2.02 (2H, m), 3.29 (3H, s), 3.40 (2H, s), 5.25 - 5.34 (1H, m), 7.86 (1H, s); MS m/z 309 $[M+H]^+$.

Intermediate 127:

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

Ethyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclopentyl-amino]-2,2-dimethyl-propanoate (Intermediate 127; 23.73 g, 64 mmol) was dissolved in acetic acid (512 mL) by heating to 70-75°C under nitrogen in an oil bath. Iron powder (9.6 g) was added in portions over 10 minutes and the reaction stirred at 70°C for 3 hours. The reaction mixture was filtered whilst still hot through a bed of celite and the bed washed with DCM. The combined filtrate and washings was evaporated to dryness and the resulting residue azeotroped three times with toluene. The residue was taken up in DCM and celite added before filtering through a small bed of celite The volume of DCM was reduced and the solution purified in two batches by loading directly onto Biotage Flash 75 and a 400g Si cartridge pre-conditioned with 50% Ethyl Acetate in isohexane. The cartridge was eluted with ~500 ml of 50% Ethyl Acetate in isohexane followed by Ethyl Acetate. Product containg fractions were combined and evaporated and the resulting yellow solid triturated under isohexane. The solid material was collected by filtration, washed with isohexane and dried by desiccation under high vacuum at room temperature to constant weight to give the title compound as an off white solid (9.67 g , 51%)

1H NMR (400.13 MHz, DMSO-d_6) δ 1.14 (6H, s), 1.51 - 1.62 (4H, m), 1.69 - 1.74 (2H, m), 1.75 - 1.85 (2H, m), 3.32 (2H, s), 5.02 - 5.11 (1H, m), 7.93 (1H, s), 9.72 (1H, s); MS m/z 295.3 $[M+H]^+$.

Intermediate 128:

Ethyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclopentyl-amino]-2,2-dimethyl-propanoate

To a stirred clear colourless solution of Ethyl 3-(cyclopentylamino)-2,2-dimethyl-propanoate (US 2004/0176380 A1; 29.8 g, 139.7 mmol) in the acetone (700 mL) at room temperature was added potassium carbonate (21.3 g, 153.7 mmol) followed by 2,4-dichloro-5-nitropyrimidine (Aldrich; 29.81g, 153.7 mmol). The reaction mixture was stirred vigorously at room temperature overnight. Potassium carbonate (7.75 g, 56 mmol) was added stirring continued for a further 4 hours. The reaction mixture was concentrated *in vacuo* to low volume and partitioned between Ethyl Acetate (600 mL) and water (400 mL). Phases were separated and the aqueous phase re-extracted with Ethyl Acetate (1x200 ml, 1x100 ml). The combined organic extracts were dried using MgSO4 and evaporated to dryness The residue was dissolved in DCM (150 mL) and purified in two batches using a Biotage Flash 75 system with 400g Si column, conditioned with 10% Ethyl Acetate in isohexane and eluted with 10% Ethyl Acetate in isohexane. Product containing fractions were combined and evaporated giving the title compound as a yellow oil which solidified on standing in a freezer (27.90 g 54%)

1H NMR (399.9 MHz, $CDCl_3$) δ 1.22 (6H, s), 1.24 (3H, t), 1.50 - 1.62 (4H, m), 1.70 - 1.75 (2H, m), 1.89 - 1.95 (2H, m), 3.50 - 3.55 (1H, m), 3.82 (2H, s), 4.13 (2H, q), 8.74 (1H, s);); MS m/z 371 $[M+H]^+$.

Intermediate 129:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzoic acid

To a solution of 10-chloro-2-cyclopentyl-4,4,6-trimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 126; 308 mg, 1 mmol) and 4-amino-3-methoxybenzoic acid (Aldrich; 155 mg, 1.13 mmol) in ethanol (5 mL) was added water (15 mL) and concentrated hydrochloric acid (0.17 mL, 2 mmol). The mixture was heated under reflux for 36 hours. The reaction was cooled and a precipitate formed. This was filtered, dried and triturated under cold acetonitrile refiltered and dried *in vacuo*. To give the title compound as a brown solid (394 mg, 96%)

MS m/z 410 $[M+H]^+$.

Intermediate 130:

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one

To a stirred solution of 2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5'H)-one (Intermediate 131; 15 g, 51.24 mmol) in DMA (1 L) under nitrogen was added methyl iodide 3.51 mL, 56.36 mL). The mixture was cooled in ice/water to 4°C. Sodium hydride (60% mineral oil dispersion; 2.26 g, 56.36 mmol) was added in one portion. A small exotherm to 6°C was observed. The reaction mixture was stirred on an ice/water bath for 1 hour, the cooling bath was removed and the reaction stirred at room temperature overnight. Solvent was evaporated *in vacuo* and the residue treated with water. This afforded a solid, which was filtered off and washed with water to give an off white solid, which was crystallised from IPA (100 mL) with hot filtration through fluted paper to remove a small amount insoluble matter. The crystallised material was filtered, washed with chilled IPA, and dried by dessication under high vacuum at room temperature over the weekend to give the title compound as a white crystalline solid (12.78 g, 81%) ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.56 - 0.59 (2H, m), 1.04 - 1.07 (2H, m), 1.28 - 1.37 (2H, m), 1.57 - 1.63 (4H, m), 1.88 - 1.96 (2H, m), 3.20 (3H, s), 3.40 (2H, s), 4.82 - 4.91 (1H, m), 7.79 (1H, s); MS m/z 307.09 $[M+H]^+$.

Intermediate 131:

2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[4,5-b][1,4]diazepin]-6'(5'H)-one

Ethyl 1-[[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclopentyl-amino]methyl]cyclopropane-1-carboxylate (Intermediate 132; 35.92 g, 97.4 mmol) was dissolved in the acetic acid (750 mL) and the solution stirred and heated to 70 °C under nitrogen. Iron powder (14.61 g) was added in portions over 10 minutes. Over the next 10-15 minutes the resulting exotherm took the reaction mixture temperature up to a maximum of 92 °C. The temperature then slowly dropped back to 75 °C. The dark reaction mixture was then stirred at 75 °C for 3 hours. The reaction mixture was filtered whilst still hot through a bed of celite and the bed washed through with DCM. The acetic acid/DCM filtrate was evaporated to dryness and the resulting residue azeotroped three times with toluene.. The residue was left under high vacuum at

room temperature overnight, taken up in DCM and filtered through a small bed of celite. The celite was washed with DCM and the filtrate concentrated down to 250 mL and loaded onto a dry silica column pre-conditioned with DCM. The column was eluted with a 5-10% gradient of 7N NH_3/MeOH in DCM and product containing fractions were combined and evaporated. The resultant material was recrystallised from isopropanol. The solid precipitate was collected by filtration, washed with chilled isopropanol and dried by desiccation under high vacuum at room temperature to constant weight to yield the title compound as a grey solid (17.1 g. ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.79 - 0.84 (2H, m), 1.19 - 1.29 (2H, m), 1.36 - 1.41 (2H, m), 1.56 - 1.67 (4H, m), 1.85 - 1.95 (2H, m), 3.25 (2H, s), 4.95 - 5.04 (1H, m), 7.75 (1H, s), 8.56 (1H, s); MS m/z 292.97 $[M+H]^+$.

Intermediate 132:

Ethyl 1-[[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclopentyl-amino]methyl]cyclopropane-1-carboxylate

To a stirred solution of Ethyl 1-[(cyclopentylamino)methyl]cyclopropane-1-carboxylate in acetone (700 mL) at room temperature was added potassium carbonate (29.0 g, 209.6 mmol) followed by the 2,4-dichloro-5-nitropyrimidine (Frontier Scientific; 29.81 g, 153.7 mmol). The reaction mixture was stirred vigorously at room temperature overnight, concentrated *in vacuo* to low volume and the brown residue partitioned between Ethyl Acetate (600 mL) and water (400 mL). Phases were separated and the aqueous re-extracted with Ethyl Acetate (1 x 200 mL, 1x100 mL). The combined organic extracts were dried using $MgSO_4$ and evaporated to dryness giving a clear brown oil which solidified on standing. The resultant material was recrystallised from IPA. The solid was collected by filtration, washed with chilled IPA, sucked as dry as possible then dried to constant weight by desiccation under high vacuum at room temperature to yield the title compound as a light-brown solid (35.92 g, 70%) ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.88 - 0.91 (2H, m), 1.07 (3H, t), 1.26 - 1.29 (2H, m), 1.44 - 1.53 (2H, m), 1.71 - 1.88 (6H, m), 3.65 (2H, s), 3.65 - 3.71 (1H, m), 4.01 (2H, q), 8.65 (1H, s); MS m/z 369.03 $[M+H]^+$.

Intermediate 133:

Ethyl 1-[(cyclopentylamino)methyl]cyclopropane-1-carboxylate

To a stirred clear solution of Ethyl 1-(aminomethyl)cyclopropane-1-carboxylate (Intermediate 134; 74.15 g, 191.6 mmol) in DCM (900 mL) under nitrogen at room temperature was added cyclopentanone (Aldrich; 17.5 mL, 195.4 mmol). The reaction was stirred at room temperature for 1.25 hours. Sodium acetate (Aldrich; 16.03 g, 195.4 mmol) was added, followed by sodium triacetoxyborohydride (Aldrich; 60.93 g, 287.4 mmol). The resulting suspension was stirred at room temperature overnight.

The reaction mixture was treated with saturated aqueous sodium bicarbonate solution (1 L) followed by slow addition of 2M NaOH (aq.) to pH 8-9. The aqueous phase was separated re-extracted with DCM (3 x 250 mL). The combined organic solutions were combined, dried with $MgSO_4$ and evaporated. to give the title compound as a clear pale-yellow thin oil (39.39 g, 97%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.79 - 0.81 (2H, m), 1.23 (3H, t), 1.24 - 1.28 (2H, m), 1.30 - 1.33 (2H, m), 1.46 - 1.57 (2H, m), 1.63 - 1.73 (2H, m), 1.77 - 1.86 (2H, m), 1.91 (1H, s), 2.69 (2H, s), 3.03 - 3.10 (1H, m), 4.11 (2H, q)

Intermediate 134:

Ethyl 1-(aminomethyl)cyclopropane-1-carboxylate

Ethyl 1-cyanocyclopropane-1-carboxylate (Aldrich; 76.45 g, 550 mmol), Platinum Oxide (7.5 g) and Acetic acid (1 L) were combined then stirred at room temperature under hydrogen at 4 bar pressure for 8 hours. The reaction mixture was filtered and the filtrate concentrated *in vacuo* to give the title compound as a colourless oil containing 4.5 equivalents of acetic acid. (115 g, 51%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.81 - 0.84 (2H, m), 1.01 (3H, t), 1.12 - 1.15 (2H, m), 1.77 (13.5H, s - AcOH), 2.89 (2H, s), 3.92 (2H, q), 10.12 (6.5H, br s – AcOH + NH_2).

Intermediate 135:

4-amino-3-methoxy-N-(2-morpholin-4-ylethyl)benzamide

4-amino-3-methoxybenzoic acid (Aldrich; 5 g, 29.9 mmol) was stirred and dissolved in DMF (100 mL) at ambient temperature. 4-(2-aminoethyl)morpholine (Aldrich; 4.7 mL, 35.8 mmol)

was added followed by DIPEA (15.6 mL, 89.7 mmol) and HATU (13.7 g, 36.0 mmol) causing a slight exotherm. The brown solution was stirred for 24h and the solvent evaporated to a brown gum.

A sample (1.2g) was dissolved in methanol and purified by loading on an SCX-2 (20 g) column pre-wet with methanol and eluted with 2M NH3/MeOH. Product containing fractions were combined and evaporated to give the title compound as a gum (726 mg)

The remaining product was purified in the same manner on SCX-2 columns (5 g per 50 g column). To give the title compound as an orange solid (9.55 g)

^{1}H NMR (400.132 MHz, DMSO-D_6) δ 2.43 (4H, m), 3.18 (2H, m), 3.34 (2H, m), 3.57 (4H, m), 3.80 (3H, s), 5.20 (2H, s), 6.61 (1H, d), 7.27 (2H, m), 7.96 (1H, t); MS m/z 280 $[M+H]^+$.

Intermediate 136:

4-amino-N-(3-dimethylamino-2,2-dimethyl-propyl)benzamide

To a solution of 4-aminobenzoic acid (Aldrich; 4.0 g, 29.17 mmol) in DMF (100 mL) was added *N,N,2,2*-tetramethyl-*1,3*-diaminopropane (Aldrich; 5 mL, 31.38 mmol). An immediate solid precipitate formed. DIPEA (15 ml, 86.11 mmol) was added and the resultant suspension stirred HATU (13g, 34.18 mmol) was added portionwise at such a rate and time interval as to maintain internal reaction temp <30°C}. The resultant yellow solution was stirred at ambient temperature, overnight.

The solvent was removed *in vacuo*, and the residue partitioned between saturated aqueous sodium bicarbonate solution (250 mL) and DCM (250 mL). The organic phase was separated and the aqueous phase re-extracted with DCM (250 mL). Combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to a viscous orange syrup which was purified by flash chromatography on silica eluting with 0-10% 0.2M methanolic ammonia in DCM. Product containing fractions were combined and evaporated to give the title compound as a pale straw coloured gum (1.134 g, 15%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.90 (m, 6H), 2.07 - 2.40 (m, 6H), 2.67 - 2.95 (m, 2H), 3.15 - 3.20 (m, 2H), 5.57 (s, 2H), 6.56 (m, 2H), 7.55 (m, 2H), 7.97 - 8.17 (m, 1H); MS m/z 250.5 $[M+H]^+$.

Intermediate 137:

10-chloro-2-(1-methoxypropan-2-yl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of N-(2,4-dichloropyrimidin-5-yl)prop-2-enamide (Intermediate 138; 104 mg, 0.477 mmol) n THF (2 mL) was added triethylamine (73 µL, 0.525 mmol) followed by 2-amino-1-methoxypropane (Aldrich; 50 µL, 0.477 mmol) and the reaction stirred at room temperature for 90 minutes.

The reaction mixture was heated in a microwave at 150 °C for 30 minutes. And then at 160 °C for a further 90 minutes. The solvents were evaporated and the residue chromatographed on silica eluting with a gradient of 30 – 100% Ethyl Acetate / iso-hexane. Product containing fractions were combined and evaporated to give the title compound as an off white solid (35 mg, 29%)

MS m/z 250.5 $[M+H]^+$.

Intermediate 138:

N-(2,4-dichloropyrimidin-5-yl)prop-2-enamide

To a solution of 5-Amino-2,4-dichloropyrimidine (Chempacific; 100 mg, 0.610 mmol) in THF (2 mL) was added triethylamine (170 µL, 1.22 mmol) followed by 3-Chloropropionyl Chloride (Aldrich; 64 mL, 0.671 mmol) The reaction was stirred at room temperature for 18 hrs .

The reaction was filtered and the solvent evaporated. The residue was dissolved in DCM and washed with water then gravity filtered through a PTFE cup and the organic filtrate evaporated to give the title compound as a yellow gum (104 mg).

MS m/z 218 $[M+H]^+$.

Intermediate 139:

10-chloro-2-cyclopentyl-6-ethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

Tris(dibenzylideneacetone)dipalladium(0) (81 mg, 0.09 mmol), XANTPHOS (153 mg, 0.26 mmol) and Caesium Carbonate (2.08 g, 6.37 mmol) were added to a stirred solution of 3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclopentyl-amino]-N-ethyl-propanamide (Intermediate 140;

1.65 g, 4.39 mmol) in 1,4-dioxane (44 mL). The apparatus was evacuated and backfilled with nitrogen twice and then heated to 100 °C for 18 hrs. The reaction mixture was filtered through a celite pad and dry loaded onto silica for purification by flash silica chromatography (companion, 40 g, 0-10% MeOH/DCM) to give the title compound as a yellow gum (1.26 g, 4.27 mmol, 97%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.02 (t, 3H), 1.50 - 1.76 (m, 6H), 1.85 - 1.95 (m, 2H), 2.58 - 2.61 (m, 2H), 3.64 - 3.66 (m, 2H), 3.74 (q, 2H), 4.69 (quintet, 1H), 8.21 (s, 1H); MS m/z 295.15 $[M+H]^+$.

Intermediate 140:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclopentyl-amino]-N-ethyl-propanamide

5-Bromo-2,4-dichloropyrimidine (Aldrich; 1.825 g, 8.00 mmol), 3-(cyclopentylamino)-N-ethyl-propanamide (Intermediate 141; 1.48 g, 8.00 mmol) and triethylamine (1.2 mL, 8.16 mmol) were combined in acetonitrile (50 mL) and heated at 100 °C for 4 hours. The solvent was removed under reduced pressure and the residue taken up in Ethyl Acetate, washed with water and purified by flash silica chromatography (companion, 40 g, 0-10% Methanol/DCM) to give the title compound as a brown oil, (2.14 g, 71%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.99 (t, 3H), 1.45 - 1.58 (m, 2H), 1.60 - 1.77 (m, 4H), 1.78 - 1.90 (m, 2H), 2.33 (t, 2H), 3.03 (qd, 2H), 3.66 (t, 2H), 4.57 (quintet, 1H), 7.79 (t, 1H), 8.39 (s, 1H); MS m/z 376.78 $[M+H]^+$.

Intermediate 141:

3-(cyclopentylamino)-N-ethyl-propanamide

N-ethylacrylamide (ABCR: 1.045 g, 10.50 mmol) and cyclopentylamine (Aldrich; 987 uL, 10.00 mmol) in methanol (10 mL) were combined in a microwave reaction vessel, which was sealed and irradiated to 140 °C for 30 minutes. The reaction mixture was allowed to cool and loaded directly onto a 50 g SCX-2 cartridge, washing with methanol (100 mL) and eluting the desired product with 7 N methanolic ammonia (100 mL). Concentration under reduced pressure of combined product containing fractions afforded the title compound as a brown oil (1.48 g, 80%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.01 (3H, t), 1.27 - 1.32 (2H, m), 1.41 - 1.53 (2H, m), 1.55 - 1.64 (2H, m), 1.65 - 1.69 (2H, m), 2.18 (2H, t), 2.67 (2H, t), 2.94 - 3.01 (1H, m), 3.03 - 3.09 (2H, m), 7.89 (1H, br s)

Intermediate 142:

10-chloro-2-cyclopentyl-6-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

Tris(dibenzylideneacetone)dipalladium(0) (47 mg, 0.05 mmol), XANTPHOS (90 mg, 0.15 mmol) and Caesium carbonate (2.425 g, 7.44 mmol) were added to a stirred solution of PH17075-018 (purified reaction mixture, 2.00 g, 5.13 mmol) in 1,4-dioxane (50 mL). The apparatus was evacuated and backfilled with nitrogen twice and then heated to 100 °C for 1.5 hrs Tris(dibenzylideneacetone)dipalladium(0) (47 mg, 0.05 mmol) and XANTPHOS (90 mg, 0.15 mmol) were added and heating continued for a further 18 h. Tris(dibenzylideneacetone)dipalladium(0) (47 mg, 0.05 mmol) was added and the temperature increased to 120 °C for 18 hr. The reaction mixture was transferred to a microwave vessel and irradiated at 150 °C for 30 minutes.

The reaction mixture was filtered through a pad of celite, concentrated down onto silica and purified by flash silica chromatography (Companion, 40 g, 0-5% MeOH/DCM). Product containing fractiosn were combined and evaporated to give the title compound as a yellow oil (532 mg,, 33%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.24 (d, 6H), 1.50 - 1.80 (m, 6H), 1.97 - 2.07 (m, 2H), 2.57 - 2.60 (m, 2H), 3.66 - 3.69 (m, 2H), 4.52 (septet, 1H), 4.73 (quintet, 1H), 8.03 (s, 1H); MS m/z 309 [M+H]+.

Intermediate 143:

3-[(5-bromo-2-chloro-pyrimidin-4-yl)-cyclopentyl-amino]-N-propan-2-yl-propanamide

To a stirred solution of 3-(cyclopentylamino)-N-propan-2-yl-propanamide (Intermediate 144; 1.90 g, 9.58 mmol) and triethylamine (1.36 mL, 9.77 mmol) in acetonitrile (100 mL) was

added 5-bromo-2,4-dichloropryimidine (Aldrich; 2.30 g, 10.06 mmol) and the resulting solution heated at 100 °C for 18 hrs. The solvent was removed under reduced pressure and the residue was taken up in Ethyl Acetate (200 mL) and water (200 mL). The aqueous phase was removed and the organic phase washed with water (200 mL). The organic solution was loaded onto a 50 g SCX-2 cartridge, washing with methanol (50 mL), and Ethyl Acetate (50 mL), before eluting with 7 N methanolic ammonia. Product containing fractions were combined and evaporated and the residue purified by flash silica chromatography (companion, 120 g, 0-10% MeOH/DCM) to give clean the title compound a s a white solid (1.17 g, 31%)

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.06 (d, 6H), 1.53 - 1.62 (m, 2H), 1.66 - 1.80 (m, 4H), 1.84 - 1.94 (m, 2H), 2.35 (t, 2H), 3.69 (t, 2H), 3.84 (sextet, 1H), 4.60 (quintet, 1H), 7.71 (d, 1H), 8.44 (s, 1H); MS m/z 391 [M+H]+.

Intermediate 144:

3-(cyclopentylamino)-N-propan-2-yl-propanamide

N-Isopropylacrylamide (Aldrich; 1.19 g, 10.50 mmol) and cyclopentlyamine (Aldrich; 0.98 mL, 10.0 mmol) were combined in methanol (6 mL) in a 10 mL microwave reaction vessel and the resultant solution heated to 140 °C for 30 mins. The reaction mixture was loaded directly onto a 50 g SCX-2 cartridge, washing with methanol (100 mL) and eluting the desired product with 7 N methanolic ammonia (100 mL). The eluted product was concentrated under reduced pressure to give the title compound as a light brown oil (1.90 g,, 96%)

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.04 (d, 6H), 1.22 - 1.32 (m, 2H), 1.41 - 1.53 (m, 2H), 1.54 - 1.74 (m, 4H), 2.16 (t, 2H), 2.65 (t, 2H), 2.97 (quintet, 1H), 3.76 - 3.88 (m, 1H), 7.83 (br d, 1H); MS m/z 199 [M+H]+.

Intermediate 145:

2-amino-N-(1-methyl-4-piperidyl)-1,3-thiazole-4-carboxamide

2-Aminothiazole-4-carboxylate hydrobromide salt (Chempacific; 1.13 g, 5.02 mmol), HATU (2.87 g, 7.53 mmol) and 4-amino-1-methylpiperidine (0.86 g, 7.53 mmol) were stirred in DMF (5 mL) and DIPEA (5.2 mL, 30.12 mmol) added. The mixture was stirred at room temperature overnight. The reaction mixture was concentrated and the residue taken up in methanol, absorbed onto an SCX column , washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined, evaporated and the residue and further purified by column chromatography (5% 7N NH_3 in MeOH/DCM) Product containing fractions were combined and evaporated to give the title compound as a yellow solid (635mg, 53%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.49 - 1.59 (2H, m), 1.72 - 1.76 (2H, m), 1.98 (2H, t), 2.16 (3H, s), 2.67 - 2.70 (2H, m), 3.60 - 3.69 (1H, m), 7.09 (2H, s), 7.17 (1H, s), 7.38 - 7.40 (1H, m); MS m/z 241.44 $[M+H]^+$.

Intermediate 146:

2-amino-4-methyl-N-(1-methyl-4-piperidyl)-1,3-thiazole-5-carboxamide

Utilising 2-amino-4-methyl-1,3-thiazole-5-carboxylic acid – Buttpark and an analogous method to Intermediate 145 the title compound was obtained

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.49 - 1.59 (2H, m), 1.67 - 1.70 (2H, m), 1.88 - 1.94 (2H, m), 2.15 (3H, s), 2.31 (3H, s), 2.72 (2H, m), 3.56 - 3.62 (1H, m), 7.22 - 7.26 (3H, m); MS m/z 255.45 $[M+H]^+$.

Intermediate 147:

2-amino-N-(1-methyl-4-piperidyl)-1,3-thiazole-5-carboxamide

Utilising 2-amino-1,3-thiazole-5-carboxylic acid Journal of Medicinal Chemistry (1972), 15(12), 1310-12. Compound 1 and an analogous method to Intermediate 145 the title compound was obtained

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.47 - 1.57 (2H, m), 1.71 (2H, d), 1.94 (2H, t), 2.17 (3H, s), 2.75 (2H, d), 3.59 - 3.65 (1H, m), 7.08 (2H, s), 7.36 (1H, s), 7.68 (1H, d). MS m/z 241.06 $[M+H]^+$.

Intermediate 148:

2-amino-N-(1-methyl-4-piperidyl)-1,3-oxazole-5-carboxamide

Utilising 2-amino-1,3-oxazole-5-carboxylic acid – Intermediate 149 and an analogous method to Intermediate 145 the title compound was obtained

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.46 - 1.56 (2H, m), 1.70 - 1.74 (2H, m), 1.89 - 1.96 (2H, m), 2.16 (3H, s), 2.76 (2H, d), 3.59 - 3.63 (1H, m), 7.38 (2H, s), 7.63 (1H, s), 7.82 (1H, d)); MS m/z 225.14 $[M+H]^+$.

Intermediate 149:

2-amino-1,3-oxazole-5-carboxylic acid

Ethyl 2-aminooxazole-4-carboxylate (Apollo Scientific; 1.175 g, 7.50 mmol) was dissolved in THF (15 mL) and water (8 mL). Lithium hydroxide monohydrate (1.58 g, 37.52 mmol) was added and the mixture stirred overnight at room temperature. The mixture was neutralised with 2N $HCl_{(aqu)}$ and concentrated. The residue was suspended in water and filtered and the solid collected dissolved in 2N $NaOH_{(aqu)}$, filtered and then acidified with acetic acid to approximately pH4. The mixture was allowed to stand in an ice bath for 10 minutes and then filtered. The solid was dried on the filter and then in a dessicator overnight to give the title compound a s a yellow solid (194mg, 20%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ7.37 (2H, s), 7.45 (1H, s), 12.60 (1H, brS).

Intermediate 150:

2-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-1,3-oxazole-4-carboxylic acid

Ethyl 2-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-1,3-oxazole-4-carboxylate (Intermediate 151; 160 mg, 0.40 mmol) was dissolved in THF (1 mL) and water (0.5 mL). Lithium hydroxide monohydrate (84 mg, 2.0 mmol) was added and a few drops of methanol and the mixture stirred at room temperature overnight. The mixture was neutralised with 2N $HCl_{(aqu)}$ and concentrated. The residue was taken up in MeOH/Water and absorbed onto an SCX column, washed with methanol/water and eluted with ammonia in methanol. Product containing fractions were concentrated, the residue taken-up in DCM, dried ($MgSO_4$) and concentrated to give the title compound as a white solid (90mg, 60%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.54 - 1.66 (6H, m), 1.92 (2H, s), 2.57 - 2.60 (2H, m), 3.17 (3H, s), 3.61 (2H, t), 4.77 (1H, t), 7.96 (1H, s), 8.06 (1H, s); MS m/z 373.20 $[M+H]^+$.

Intermediate 151:

Ethyl 2-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-1,3-oxazole-4-carboxylate

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 248 mg, 0.88 mmol), ethyl 2-aminooxazole-4-carboxylate (Fluorochem; 125 mg, 0.80 mmol) and XANTPHOS (42 mg, 0.07 mmol) were dissolved in 1,4-dioxane (7.5 mlL). Caesium carbonate (522 mg, 1.60 mmol) was added and the mixture purged with a stream of nitrogen for 5 minutes. Tris(dibenzylideneacetone) palladium (II) (44 mg, 0.05 mmol) was added and the apparatus was evacuated and backfilled with nitrogen (x3) and the reaction heated at 100°C overnight. The mixture was cooled, filtered and the filtrate absorbed onto an SCX column, washed with methanol and the product eluted with ammonia in methanol. Product containing fractions were concentrated and purified by normal phase chromatography (5% methanol/DCM) to givethe title compound as a white solid (165mg, 51%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.29 (3H, t), 1.59 (6H, m), 1.95 (2H, m), 2.54 - 2.60 (2H, m), 3.18 (3H, s), 3.60 - 3.63 (2H, m), 4.27 (2H, q), 4.83 (1H, t), 8.08 (1H, s), 8.50 (1H, s), 10.65 (1H, s); MS m/z 401.24 $[M+H]^+$.

Intermediate 152:

6-amino-N-(1-methyl-4-piperidyl)pyridine-3-carboxamide

6-Aminonicotinic acid (Aldrich; 2 g, 14.48 mmol)and 4-amino-1-methylpiperdine (Fluorochem; 1.82 g, 15.92 g) were suspended in DMF (20 mL), DIPEA (7.5 mL, 43.44 mmol) and HATU (6.05 g, 15.92 mmol) were added and the reaction stirred at ambient temperature for 18 hrs. The solvent was evaporated and the residues stirred with water (50 mL for 1 hr filtered, acidified with 2M aq HCl and added to a 50g SCX-2 column pre-wet with MeOH (2 column volumes). Flushed with MeOH (2 column volumes) then the crude product eluted with 2M ammonia in MeOH and evaporated. The residue was dissolved in DCM with a little MeOH to help solubility and purified on silica eluting with a gradient of 10

– 20% 2M ammonia in MeOH / DCM. Fractions containing product combined and evaporated to give the title compound as a cream solid (1.75 g, 52%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ1.47 (m, 2H), 1.65 (m, 2H), 1.85 (m, 2H), 2.09 (s, 3H), 2.68 (m, 2H), 3.61 (m, 1H), 6.33 (m, 3H), 7.73 (m, 1H), 7.78 (d, 1H), 8.36 (m, 1H); MS m/z 235 $[M+H]^+$.

Intermediate 153:

5-amino-N-(1-methyl-4-piperidyl)pyridine-2-carboxamide

Utilising 5-aminopyridine-2-carboxylic acid – Chempacific and an analogous method to intermediate 152 the title compound was obtained as cream solid (1.29 g, 31%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ1.60 (m, 2H), 1.72 (m, 2H), 1.97 (m, 2H), 2.16 (s, 3H), 2.71 (m, 2H), 3.69 (m, 1H), 5.89 (s, 2H), 6.97 (m, 1H), 7.69 (d, 1H), 7.91 (m, 1H), 7.97 (d, 1H); MS m/z 235 $[M+H]^+$.

Intermediate 154:

9-chloro-2-methyl-6-prop-2-ynyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-3-one

To a cooled (ice/water bath) suspension of sodium hydride (60% dispersion in mineral oil; 15 mg, 0.38 mmol) in DMA (1 mL) was carefully added a solution of 10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 100; 65 mg, 0.31 mmol) in DMA (1.5 mL). The reaction mixture was allowed to stir, under nitrogen, on an ice bath for 1 hour prior to addition of propargyl chloride (34 mg, 0.47 mmol). The reaction mixture was left to stir at ambient temperature overnight and then quenched by addition of sataurated aqueous ammonium chloride solution (0.5 mL) and stirred for 15 minutes. The resultant mixture was partitioned between DCM (10 mL) and water (10 mL). The organic phase was separated by filtration through PTFE filter cup. The aqueous phase was re-extracted with DCM (5 mL) and the combined organic solutions evaporated to dryness to yield the title compound as a beige coloured solid (52 mg, 67%)

^{1}H NMR (400.132 MHz, DMSO) δ 2.70 (m, 2H), 3.20 (s, 3H), 3.26 (t, 1H), 3.80 (m, 2H), 4.33 (d, 2H), 8.25 (s, 1H); MS m/z 251 $[M+H]^+$.

Intermediate 155:

2-(10-chloro-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-2-yl)acetonitrile

The title compound was prepared by an analogous method to the preparation of Intermediate 154, on a 0.31 mmol scale, utilising bromoacetonitrile (Aldrich; 33 µL, 0.47 mmol), as an amber gum containing 0.6 equivalents of DMF (97 mg, 100%).

^{1}H NMR (400.132 MHz, DMSO) δ 2.74 (m, 2H), 3.21 (s, 3H), 3.81 (m, 2H), 4.53 (s, 2H), 8.36 (s, 1H); MS m/z 252 $[M+H]^+$.

Intermediate 156:

9-chloro-6-[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-2-methyl-2,6,8,10-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-3-one

To a stirred solution of 10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 100; 64 mg, 0.3 mmol) in DMF (2 mL) was added sodium hydride (60% mineral oil dispersion; 18 mg, 0.36 mmol) and the solution stirred at room temperature until effervescence had ceased. 3 choromethyl-2,4-dimethylisoxazole (Aldrich; 52 mg, 0.36 mmol) was added and the reaction heated at 50 ^{0}C with stirring overnight. The solvent was evaporated and residue dissolved in methanol, transferred to an SCX cartridge pre-wet with methanol, washed with methanol and eluted with methanolic ammonia. Product containing fractions were combined and evaporated to yield the title compound as an off white solid (82 mg, 85%)

Intermediate 157:

10-chloro-2-(2-fluoroethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

The title compound was prepared by an analogous method to the preparation of Intermediate 154, on a 0.31 mmol scale, utilising 1-bromo-2-fluoroethane (Apollo Scientific; 235 mg, 1.44 mmol), as a white crystalline solid containing 0.6 equivalents of DMF (86 mg, 100%).

1H NMR (400.132 MHz, DMSO) d 2.71 (m, 2H), 3.19 (s, 3H), 3.81 (m, 2H), 3.88 - 3.97 (m, 2H), 4.62 - 4.77 (m, 2H), 8.18 (s, 1H); MS m/z 259 $[M+H]^+$.

Intermediate 158:

10-chloro-2-(2-dimethylaminoethyl)-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

The title compound was prepared by an analogous method to the preparation of Intermediate 156, on a 0.3 mmol scale, utilising 2 chloroethyldimethylamine hydrochloride (Aldrich; 52 mg, 0.36 mmol) and Sodium Hydride (60% mineral oil dispersion; 36 mg, 0.75 mmol), as a solid (84 mg, 98%).

Intermediate 159:

10-chloro-6-methyl-2-[2-(1-piperidyl)ethyl]-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

The title compound was prepared by an analogous method to the preparation of Intermediate 156, on a 0.3 mmol scale, utilising 2-chloroethylpiperidine hydrochloride (Aldrich; 55 mg, 0.36 mmol) and Sodium Hydride (60% mineral oil dispersion; 36 mg, 0.75 mmol), as a solid (90 mg, 93%).

Intermediate 160:

10-chloro-6-methyl-2-(2-morpholin-4-ylethyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

The title compound was prepared by an analogous method to the preparation of Intermediate 156, on a 0.3 mmol scale, utilising N-(2-chloroethyl)morpholine hydrochloride (Aldrich; 67 mg, 0.36 mmol) and Sodium Hydride (60% mineral oil dispersion; 36 mg, 0.75 mmol), as a solid (95 mg, 97%).

Intermediate 161:

4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

A mixture of 4-Amino-3-Methoxybenzoic Acid (Aldrich; 5.015 g, 30 mmol) and Endo-9-methyl-9-azabicyclo[3,3,1]nonane-3-one (Chempacific; 5.095 g, 33 mol) were dissolved in DMF (150 mL), and to the solution was added DIPEA (10.4 mL, 60 mmol). The reaction was cooled on an ice-bath, and to the reaction was added, portionwise, HATU (12.55 g, 33 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The solvent was removed by evaporation, and the residue was partitioned between Ethyl Acetate (200 mL),

and saturated aqueous sodium carbonate solution (3 x 50 mL).,washed with brine (3 x 50 mL), dried over anhydrous magnesium sulphate, filtered, and the solvent removed by evaporation to give the crude product as an an oil (14g), which was purified on SCX-2 columns (4 x 50 g), developing and eluting with : 1) water; 2) MeOH ; and 3) 3.5M NH_3-MeOH. The solvent was removed by evaporation to give the product as a semi-solid, which was triturated with diethylether and filtered to yield the title compound as a tan coloured solid (4.84 g, 53%).

^{1}H NMR (400.1MHz ; DMSO-d_6) δ 0.88-0.96 (1H, d), 1.38-1.50 (3H, m), 1.86-1.96 (2H, m), 2.00-2.10 (1H, m), 2.10-2.20 (2H, m), 2.42 (3H, s), 2.92-3.00 (2H, d), 3.82 (3H, s), 4.22-4.38 (1H, m), 5.17 (2H, s), 6.58-6.62 (1H, d), 7.28 (1H, s), 7.30 (1H, s), 7.60-7.64 (1H, d). MS m/z 292 $[M+H]^+$.

Intermediate 162:

4-amino-3-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

4-amino-3-fluorobenzoic acid (Fluorochem; 5.0 g, 32.2 mmol), HATU (13.5 g, 35.4 mmol) and DIPEA (18.5 mL, 106 mmol) were stirred together in anhydrous DMA (100 mL) for 25 minutes. Endo-9-methyl-9-azabicyclo[3,3,1]nonane-3-one (Chempacific; 5.5 g, 35.4 mmol) was added and the solution stirred at ambient temperature overnight.

The solvent was evaporated and the residue dissolved in MeOH and loaded onto an SCX-2 column (50g x 4) pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and the product eluted with 2MNH3/MeOH (2 column volumes). The ammoniacal solution was evaporated and the resultant material purified on a silica column eluted with 0-10% 2NH3/MeOH/DCM. Product containing fractions were evaporated to yield the title compound as a white solid after trituration with ethyl acetate (5.7 g, 61%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.91 (m, 2H), 1.42 (m, 3H), 1.90 (m, 4H), 2.03 (m, 1H), 2.14 (m, 3H), 2.40 (s, 3H), 2.96 (m, 2H), 4.27 (m, 1H), 5.60 (bs, 2H), 6.74 (m, 1H), 7.46 (m, 1H), 7.53 (m, 1H), 7.70 (d, 1H); MS m/z 292 $[M+H]^+$.

Intermediate 163:

3-ethoxy-4-[(6-methyl-5-oxo-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]benzoic acid

10-Chloro-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 10; 625 mg, 2.45 mmol), 4-amino–3-ethoxybenzoic acid (Intermediate 164; 509 mg, 2.82 mmol) and 4-toluenesulphonic acid mono hydrate (1.17 g, 6.13 mmol) were heated at 140 °C in 4-methyl-2-pentanol (15 mL) for 1.5 hours. The mixture was cooled and filtered to yield the title compound as a white solid (135 mg, 14 %). The filtrate was absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (1% - 3% MeOH/DCM) to yield the title compound as a white solid (115 mg, 12%)

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.26 (6H, d), 1.44 (3H, t), 2.74 (2H, m), 3.18 (3H, s), 3.73 (2H, m), 4.22 (2H, q), 4.85 – 4.92 (1H, m), 7.57 (1H, d), 7.63 – 7.66 (1H, m), 8.20 (2H, m), 9.41 (1H, brs), 12.90 (1H, brs); MS m/z 400 [M+H]+.

Intermediate 164:

4-amino–3-ethoxybenzoic acid

A solution of 3-ethoxy-4-nitrobenzoic acid (Intermediate 165; 1.0 g, 4.74 mmol) ethanol:DMF (50 mL : 5 mL) over 5% Pd/C catalyst (100 mg) was hydrogenated with stirring at ambient temperature for 4 hours. The mixture was filtered and the catalyst washed with ethanol and the solvent evaporated and the residue that on trituration with diethyl ether yielded the title compound as an off white solid (688 mg, 81%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.36 (t, 3H), 4.04 (q, 2H), 5.45 (bs, 2H), 6.63 (d, 1H), 7.28 (s, 1H), 7.35 (d, 1H), 12.03 (bs, 1H).

Intermediate 165:

3-ethoxy-4-nitrobenzoic acid

3-fluoro-4-nitrobenzoic acid (Apollo Scientific; 15 g, 81 mmol) and potassium hydroxide (10.5 g, 186.3 mmol) were stirred together in ethanol (150 mL) at ambient temperature. The reaction mixture was slowly heating to reflux over 10 minutes. The reaction refluxed vigorously and a solid precipitate formed. The reaction was cooled, diluted with water (100

mL) and acidified with 2N HCl to give a precipitate which was filtered, washed with water and air dried to yield the title compound as a pale brown solid (16.88 g, 99%)
^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.35 (t, 3H), 4.29 (q, 2H), 7.63 (d, 1H), 7.75 (s, 1H), 7.95 (d, 1H), 13.58 (s, 1H); MS m/z 210 [M+H]+.

Intermediate 166:

4-amino-3-ethoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

4-amino–3-ethoxybenzoic acid (Intermediate 164; 400 mg, 2.21 mmol), HATU (1.26 g, 3.31 mmol) and (3R)-1-methylpyrrolidin-3-amine di Hydrochloride (Intermediate 184; 453 mg, 3.31 mmol) were stirred in DMF (5 mL) and diisopropylethylamine (1.7 ml, 9.95 mmol) added. The mixture was stirred for 2 hours and then absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (2.5% ammonia in methanol/DCM) to yield the title compound as a yellow foam (396 mg, 68%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.37 (3H, t), 1.70 - 1.78 (1H, m), 2.09 - 2.17 (1H, m), 2.25 (3H, s), 2.35 - 2.42 (2H, m), 2.56 - 2.62 (1H, m), 2.65 - 2.69 (1H, m), 4.05 (2H, q), 4.33 - 4.41 (1H, m), 5.16 (2H, s), 6.61 (1H, d), 7.30 - 7.54 (2H, m), 7.98 (1H, d); MS m/z 264 [M+H]+.

Intermediate 167:

4-amino-N-((1s,4s)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide

The title compound was prepared by an analogous method to the preparation of **Intermediate 166**, on a 2.21 mmol scale, utilising 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 472 mg, 3.31 mmol) and diisopropylethylamine 1.15 mL, 6.62 mmol), after separation of the cis isomer by column chromatography, as a yellow foam (162 mg, 24%).
^{1}H NMR (399.9 MHz, DMSO-d6) δ1.35 - 1.50 (7H, m), 1.68 – 1.78 (2H, m), 1.83 - 1.86 (2H, m), 2.00 (1H, m), 2.18 (6H, s), 3.87 (1H, m), 4.05 (2H, q), 5.13 (2H, s), 6.60 (1H, d), 7.31 (2H, m), 7.70 (1H, d); MS m/z 306 [M+H]+.

Intermediate 168:

4-amino-N-((1r,4r)-4-(dimethylamino)cyclohexyl)-3-ethoxybenzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 166, on a 2.21 mmol scale, utilising 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 472 mg, 3.31 mmol) and diisopropylethylamine 1.15 mL, 6.62 mmol), after separation of the trans isomer by column chromatography, as a white solid (164 mg, 24%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.20 - 1.39 (7H, m), 1.81 - 1.88 (4H, m), 2.12 (1H, t), 2.18 (6H, m), 3.64 - 3.70 (1H, m), 4.04 (2H, q), 5.14 (2H, s), 6.60 - 6.62 (1H, d), 7.28 (2H, m), 7.71 (1H, d) ; MS m/z 306 [M+H]+.

Intermediate 169:

4-amino-5-ethoxy-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

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4-amino-5-ethoxy-2-fluorobenzoic acid (Intermediate 171; 190 mg, 0.95 mmol), HATU (545 mg, 1.43 mmol) and 4-amino-1-methylpiperidine (Fluorochem; 164 mg, 1.43 mmol) were stirred in DMF (3 mL) and diisopropylethylamine (0.58 ml, 2.86 mmol) added. The mixture was stirred over night and then absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (3% ammonia in methanol/DCM) to yield the title compound as a white crystalline solid (245mg, 86%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.35 (3H, t), 1.50 - 1.55 (2H, m), 1.71 – 1.79 (2H, m), 1.94 - 1.99 (2H, m), 2.16 (3H, s), 2.68 - 2.71 (2H, m), 3.65 – 3.73 (1H, m), 4.00 (2H, q), 5.50 (2H, s), 6.40 (1H, d), 7.04 (1H, d), 7.33 (1H, t); MS m/z 296 [M+H]+.

Intermediate 170:

4-amino-5-ethoxy-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 169, on a 0.5 mmol scale, utilising Endo-9-methyl-9-azabicyclo[3,3,1]nonane-3-one (Chempacific; 111 mg, 0.75 mmol), as a white solid (171 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.91 (2H, d), 1.32 - 1.44 (6H, m), 1.86 - 1.92 (2H, m), 1.99 - 2.10 (1H, m), 2.14 - 2.22 (2H, m), 2.40 (3H, s), 2.96 (2H, d), 4.01 (2H, q), 4.21 - 4.30 (1H, m), 5.48 (2H, s), 6.40 (1H, d), 7.05 (1H, d), 7.24 (1H, t); MS m/z 336 [M+H]+.

Intermediate 171:

4-amino-5-ethoxy-2-fluorobenzoic acid

5-ethoxy-2-fluoro-4-nitrobenzoic acid (Intermediate 172; 1.24 g, 5.40 mmol) was stirred and dissolved in ethanol:DMF (50 mL : 5 mL) over 5% Pd/C (125mg) and hydrogenated at ambient temperature for 4 hours. The catalyst was filtered and washed with ethanol and the solvent evaporated. The resultant material was purified on a silica column, eluting with 0 – 5% MeOH/DCM. Product containing fractions were combined and evaporated to yield the title compound as a pale brown solid (433 mg, 40%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.33 (3H, t), 4.25 (2H, q), 7.66 (1H, d), 7.99 (1H, m), 13.99 (1H, s).

Intermediate 172:

5-ethoxy-2-fluoro-4-nitrobenzoic acid

2,5-difluoro-4-nitrobenzoic acid (Fluorochem; 1g, 4.92 mmol) was stirred and dissolved in DMF (10 mL) and caesium carbonate (4.8 g, 14.7 mmol) was added followed by ethanol (2.3 g, 49.9 mmol). The resulting white mixture was stirred at ambient temperature for 3 hours, diluted with water, acidified to pH1 with 2N HCl (aq), extracted with EtOAc (x3). Combined extracts were washed with water, dried (MgSO4), filtered and evaporated to yield the title compound as a yellow solid (1.24 g, 100%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.34 (3H, t), 4.00 (2H, q), 5.79 (2H, s), 6.38 (1H, d), 7.14 (1H, d), 12.32 (1H, s).

Intermediate 173:

4-amino-5-chloro-2-fluoro-N-(1-methyl-4-piperidyl)benzamide

4-amino-5-chloro-2-fluorobenzoic acid (Intermediate 176; 500 mg, 2.64 mmol), 4-amino-1-methylpiperidine (452 mg, 3.96 mmol) and diisopropylethylamine (1.38 ml, 7.91 mmol) were stirred in DMF (5 mL) and HATU (1.50 g, 3.96 mmol) added. The reaction mixture was stirred for 3 hours at room temperature. The mixture was absorbed on to an SCX column, which was washed with methanol and eluted with ammonia in methanol. Product containing

fractions were concentrated to give a crystalline solid that was suspended in diethyl ether and filtered to yield the title compound as a pale brown solid (572 mg, 76%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.47 – 1.58 (2H, m), 1.71 – 1.76 (2H, m), 1.95 (2H, t), 2.15 (3H, s), 2.69 - 2.72 (2H, m), 3.67 (1H, m), 6.09 (2H, s), 6.55 (1H, d), 7.49 (1H, d), 7.61 (1H, d); MS m/z 286 [M+H]+.

Intermediate 174:

4-amino-5-chloro-N-(1-cthyl-4-piperidyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 173, on a 2.64mol scale, utilising 4-amino-1-methylpiperidine (Fluorochem; 508 mg, 3.96 mmol) after purification on a silica column (gradient (3-4% ammonia in methanol/DCM), as a pale brown foam (647 mg, 82%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.99 (3H, t), 1.46 - 1.55 (2H, m), 1.75 - 1.78 (2H, m), 1.92 - 1.97 (2H, m), 2.31 (2H, q), 2.81 (2H, d), 3.67 - 3.71 (1H, m), 6.09 (2H, s), 6.53 - 6.57 (1H, m), 7.48 (1H, d), 7.59 - 7.62 (1H, m); MS m/z 300 [M+H]+.

Intermediate 175:

4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 173, on a 2.64mol scale, utilising 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 472 mg, 3.31 mmol) after purification on a silica column (gradient (3-4% ammonia in methanol/DCM), as a pale brown foam (716 mg, 86%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.19 - 1.35 (2H, m), 1.47 - 1.54 (2H, m), 1.62 – 1.91 (4H, m), 2.03 - 2.13 (1H, m), 2.17 (6H, s), 3.59 – 3.68 and 3.85 – 3.90 (both 0.5H, m), 6.08 (2H, s), 6.53 - 6.57 (1H, m), 7.47 - 7.49 (1H, m), 7.52 - 7.56 (1H, m); MS m/z 314 [M+H]+.

Intermediate 176:

4-amino-5-chloro-2-fluorobenzoic acid

4-Amino-5-chloro-2-fluorobenzoic acid *tert*-butyl ester (Intermediate 177; 3.0 g, 12.21 mmol) was dissolved in DCM (75 mL) and trifluoroacetic acid (25 mL) added. The mixture

was stirred for 1 hour at room temperature and then concentrated to yield the title compound as a pale yellow solid (2.45 g, 100%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ6.40 (2H, s), 6.53 - 6.56 (1H, m), 7.67 (1H, d), 12.56 (1H, s).

Intermediate 177:

4-Amino-5-chloro-2-fluorobenzoic acid *tert*-butyl ester

4-Amino-2-fluorobenzoic acid *tert*-butyl ester (ABChem Inc.; 1 g, 4.73 mmol) in DMF (15 mL) was added dropwise to N-chlorosuccinimide (633 mg, 4.73 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 72 hours. The reaction mixture was poured into water (130 mL) and extracted with ethyl acetate (2 x 50 mL). The combined extracts were washed with water, brine, dried ($MgSO_4$) and concentrated. Column chromatography (5% ethyl acetate/isohexane) yielded the title compound as a pale yellow, crystalline solid (321 mg, 27.5%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.50 (9H, s), 6.41 (2H, s), 6.54 (1H, d), 7.61 (1H, d)

Intermediate 178:

10-chloro-4,4,6-trimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

To a stirred solution of 10-Chloro-4,4-dimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 179; 2.96 g, 11.01 mmol) in DMA (240 mL), under nitrogen, was added methyl iodide (0.754 mL, 12.12 mmol). The mixture was cooled in an ice/water bath to 3 °C. Sodium hydride (60% mineral oil dispersion; 485 mg, 12.12 mmol) was added in one portion. The reaction mixture was stirred on an ice/water bath for 1 hour and then at room temperature overnight. The solvent was removed *in vacuo* and water was added to the resultant residue to afford a white solid, which was filtered off and washed well with water and dissolved in DCM (125 mL). The solution was dried using $MgSO_4$, filtered and evaporated and the resultant solid, dissolved in DCM (25 mL), purified on a Silica column, equilibrated with 30% EtOAc in isohexane, and eluted with 30% -100% EtOAc in isohexane gradient. Product containing fractions were combined and evaporated to yield the title compound as a white solid (2.7 g, 87%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.12 (6H, s), 1.13 (6H, d), 3.21 (3H, s), 3.29 (2H, s), 5.15 - 5.22 (1H, m), 7.78 (1H, s); MS m/z 283 [M+H]+.

Intermediate 179:

10-Chloro-4,4-dimethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one

4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide (Intermediate 180; 6.7 g, 19.43 mmol) was stirred and dissolved in the acetic acid (155 mL) by heating to 70 °C under nitrogen. Iron powder (2.92 g) was added in one portion and the reaction mixture stirred at 70°C for 2.5 hours. The reaction mixture was filtered whilst hot through a bed of celite and the bed washed with DCM. The filtrate was evaporated to dryness and the resulting residue azeotroped three times with toluene. The resultant residue was purified on a Silica column pre-conditioned the column with 50% EtOAc in isohexane, loading as a solution in DCM to which had been added celite and the resultant mixture filtered through a small bed of celite. The column was eluted with a 50% - 100% EtOAc in isohexane, gradient. Product containing fractions were combined and evaporated to yield the title compound as a white solid (2.96 g, 57%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.13 (6H, d), 1.19 (6H, s), 3.21 (2H, s), 5.23 - 5.30 (1H, m), 7.75 (1H, s), 8.39 (1H, s); MS m/z 269 [M+H]+.

Intermediate 180:

4-amino-5-chloro-N-(4-dimethylaminocyclohexyl)-2-fluoro-benzamide

To a stirred solution of the Name (Intermediate 181; 10 g; 53.4 mmol)) in acetone (250 mL) at room temperature was added potassium carbonate (11.07 g, 80.1 mmol) followed by the 2,4-dichloro-5-nitropyrimidine (Apollo Scientific; 10.35 g, 53.4 mmol). The resulting yellow suspension was stirred vigorously at room temperature over the weekend.

The reaction mixture was evaporated to dryness and the residue partitioned between EtOAc (250 mL) and water (150 mL). The phases were separated after filtration through a pad of celite, and the aqueous phase was re-extracted with EtOAc (2 x 100 mL, 1 x 75 mL). The combined organic extracts were dried using $MgSO_4$ and evaporated to dryness. The resultant brown oil was purified on a silica column pre-conditioned with 10% EtOAc in isohexane and

eluted with 10% EtOAc in isohexane. Product containing fractions were combined and evaporated to yield the title compound as a yellow crystalline solid (6.71 g, 36%)

MS m/z 350 [M+H]+. Retention time 2.72 minutes

Intermediate 181:

ethyl 2,2-dimethyl-3-(propan-2-ylamino)propanoate

To a stirred solution of ethyl, 3-amino-2,2-dimethylpropanoate (Macromolecules (1976), 9(2), 227-30; 30.85 g, 150.3 mmol) in DCM (500 mL) under nitrogen at room temperature was added acetone (13.25 mL, 180.36 mmol). After stirring at room temperature for 1 hour sodium acetate (12.57 g, 153.31 mmol) was added, followed by sodium triacetoxyborohydride (47.8 g, 225.45 mmol). The resulting suspension was stirred at room temperature overnight.

Acetone (7 mL, 90 mmol), sodium acetate (7 g, 75 mmol) and sodium triacetoxyborohydride (24 g, 112 mmol) were added and the reaction stirred again at room temperature overnight. This procedure of adding additional reagents was repeated.

A saturated aqueous sodium hydrogen carbonate (1.1 L) was cautiously added to the stirred reaction mixture followed by 2N sodium hydroxide to pH = 8. The phases were separated and the aqueous phased re-extracted with DCM (2x500,1x400 ml). The combined organic extracts were dried using $MgSO_4$ and then evaporated *at no less than 350 mbar!* This afforded the title compound as a clear almost-colourless liquid (27.50 g, 98%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.02 (6H, d), 1.18 (6H, s), 1.24 (3H, t), 2.65 (2H, s), 4.08 - 4.16 (2H, m).

Intermediate 182:

4-amino-2-fluoro-5-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

4-amino-2-fluoro-5-methoxybenzoic acid (Intermediate 183; 500 mg, 2.70 mmol), HATU (1.55 g, 4.05 mmol) and (3R)-1-methylpyrrolidin-3-amine di Hydrochloride (Intermediate 184; 631 mg, 3.31 mmol) were stirred in DMF (7.5 mL) and diisopropylethylamine (2.36 ml, 13.50 mmol) added. The reaction mixture was stirred for 2 hours and then absorbed on to an SCX column, which was then washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography

(2.5% ammonia in methanol/DCM) to yield the title compound as a viscous brown oil. (662 mg, 92%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.62 - 1.70 (1H, m), 2.11 – 2.20 (1H, m), 2.25 (3H, s), 2.32 - 2.46 (2H, m), 2.54 - 2.67 (2H, m), 3.78 (3H, s), 4.34 - 4.39 (1H, m), 5.57 (2H, s), 6.39 (1H, d), 7.07 (1H, d), 7.51 (1H, t); MS m/z 268 [M+H]+.

Intermediate 183:

4-amino-2-fluoro-5-methoxy-benzoic acid

2-fluoro-5-methoxy-4-nitrobenzoic acid (**Intermediate 12**; 7.76g, 36.1mmol) was stirred and dissolved in ethanol (200 mL) over 5% Pd/C (770mg) and hydrogenated at ambient temperature for 4 hours. During this time product precipitated in the reaction. DMF (20 mL) was added to give a solution. The catalyst was filtered off and washed with EtOH and the solvent evaporated. The residue was triturated with diethyl ether to yield the title compound as a dark brown solid (3.06 g, 46%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 3.78 (s, 3H), 5.84 (bs, 2H), 6.37 (d, 1H), 7.14 (d, 1H), 12.25 (bs, 1H).

Intermediate 184:

(3R)-1-methylpyrrolidin-3-amine di Hydrochloride

tert-butyl N-[(3R)-1-methylpyrrolidin-3-yl]carbamate (Intermediate 185; 1.18 g, 5.67 mmol) was dissolved in 1,4-dioxane (10 mL) and 4M HCl in dioxane (10 mL) added. The mixture was stirred at room temperature for 1 hour and then concentrated to yield the title compound as a white hygroscopic solid (810 mg, 100%).

^{1}H NMR (399.9 MHz, D_2O) 2.19 – 2.29 (1H, m), 2.60 – 2.71 (1H, m), 3.10 (3H, M), 3.48 – 3.67 (3H, m), 3.85 – 3.93 (1H, m), 4.18 – 4.26 (1H, m).

Intermediate 185

tert-butyl N-[(3R)-1-methylpyrrolidin-3-yl]carbamate

(3R)-3-(Bocamino)pyrrolidine (Fluorochem; 2.5 g, 13.42 mmol) was dissolved in 37% aqueous formaldehyde (78 mL) and acetic acid (8.5 mL, 134.23 mmol). Sodium acetate (11.0 g, 134.23 mmol) was added and the mixture cooled in an ice/water bath. Sodium

cyanoborohydride (844 mg, 13.42 mmol) was added and the mixture allowed to stir for 3 hours. Saturated aqueous sodium hydrogen carbonate was added until the mixture was basic. The mixture was extracted with DCM (x2) and the combined extracts dried ($MgSO_4$) and concentrated. Column chromatography (2.5 – 5% 7N ammonia in methanol) yielded the title compound as a colourless liquid that crystallised on standing (1.20 g, 45%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.38 (9H, s), 1.51 - 1.59 (1H, m), 1.97 - 2.06 (1H, m), 2.20 (4H, m), 2.34 - 2.47 (2H, m), 2.61 - 2.65 (1H, m), 3.89 (1H, m), 6.90 (1H, d).

Intermediate 186:

4-amino-5-ethoxy-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 169, on a 0.5 mmol scale, utilising (3R)-1-methylpyrrolidin-3-amine di hydrochloride (Intermediate 184; 129 mg, 0.75 mmol), as a white solid (95 mg, 68%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.35 (3H, t), 1.62 - 1.70 (1H, m), 2.13 - 2.18 (1H, m), 2.25 (3H, s), 2.32 - 2.46 (2H, m), 2.59 - 2.68 (2H, m), 4.00 (2H, q), 4.30 – 4.38 (1H, m), 5.53 (2H, s), 6.40 (1H, d), 7.06 (1H, d), 7.50 (1H, t); MS m/z 282 [M+H]+.

Intermediate 187:

4-amino-3-methoxy-N-(1-methylpyrrolidin-3-yl)benzamide

A solution of 3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-nitro-benzamide (Intermediate 188; 227 mg, 0.81 mmol) in methanol (25 mL) was hydrogenated using 10% Pd/C catalyst. Catalyst was filtered off and solvent evaporated to yield the title compound as a yellow gum (200 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.76 (1H, m), 2.12 (1H, m), 2.28 (3H, s), 2.41 (2H, m), 2.61 (1H, m), 2.69 (1H, m), 3.80 (3H, s), 4.36 (1H, m), 5.18 (2H, s), 6.60 (1H, d), 7.29 (1H, s), 7.31 (1H, s), 7.99 (1H, d); MS m/z 250 [M+H]+.

Intermediate 188:

3-methoxy-N-[(3R)-1-methylpyrrolidin-3-yl]-4-nitro-benzamide

3-methoxy-4-nitro-benzoyl chloride (Intermediate 189; 374 mg, 1.73 mmol) was dissolved in DCM (20 mL) and N,N-diisopropylethylamine (0.96 mL, 5.54 mmol) added. The mixture was cooled in an ice/water bath and (3R)-1-methylpyrrolidin-3-amine di hydrochloride (Intermediate 184; 300 mg, 1.73 mmol) in DCM (10 mL) added dropwise. The mixture was allowed to warm to room temperature and stirred for 0.5 hour. The mixture was washed with brine, 2N NaOH $_{(aq)}$, dried with $MgSO_4$ and evaporated to yield the title compound as a brown solid (227 mg, 46.9%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.78 (1H, m), 2.19 (2H, s), 2.26 (3H, s), 2.38 (1H, m), 2.65 (1H, m), 4.05 (3H, s), 4.41 (1H, m), 7.57 (1H, d), 7.72 (1H, s), 7.93 (1H, d), 8.70 (1H, d); MS m/z 280 [M+H]+.

Intermediate 189:

3-methoxy-4-nitro-benzoyl chloride

3-methoxy-4-nitrobenzoic acid (Aldrich; 9 g, 45.65 mmol) was suspended in toluene (90 mL) and thionyl chloride (9.99 mL, 136.95 mmol) added and the mixture heated to reflux for 1 hour. The reaction was evaporated to yield the title compound as a brown solid (9.84 g, 100%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ4.00 (3H, s), 7.64 - 7.67 (1H, m), 7.78 (1H, d), 7.97 (1H, m).

Intermediate 190:

4-amino-N-(1-ethyl-4-piperidyl)-3-methoxy-benzamide

The title compound was prepared in quantitative yield by an analogous method to the preparation of Intermediate 187, on a 2 g scale utilising N-(1-ethyl-4-piperidyl)-3-methoxy-4-nitro-benzamide (Intermediate 191).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.99 - 1.02 (3H, t), 1.49 - 1.59 (2H, m), 1.75 (2H, d), 1.92 (2H, t), 2.32 (2H, q), 2.87 (2H, d), 3.68 - 3.76 (1H, m), 3.81 (3H, s), 5.19 (2H, s), 6.59 - 6.62 (1H, m), 7.28 - 7.30 (2H, m), 7.77 (1H, d); MS m/z 280 [M+H]+.

Intermediate 191:

N-(1-ethyl-4-piperidyl)-3-methoxy-4-nitro-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 188, on a 9.28 mmol scale utilising 1-ethylpiperidin-4-amine (Fluorochem; 1.19 g, 9.28 mmol), as a brown solid (3.3 g, 100%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.01 (3H, t), 1.56 - 1.63 (2H, m), 1.82 (2H, m), 1.92 - 1.98 (2H, m), 2.34 (2H, q), 2.89 (2H, d), 3.75 - 3.79 (1H, m), 4.00 (3H, s), 7.54 - 7.57 (1H, m), 7.70 (1H, d), 7.96 (1H, d), 8.49 (1H, d); MS m/z 308 [M+H]+.

Intermediate 192:

4-amino-3-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared in quantitative yield by an analogous method to the preparation of Intermediate 187, on a 2 g scale utilising 3-methoxy-4-nitro-N-(2-pyrrolidin-1-ylethyl)benzamide (Intermediate 193).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.68 (4H, t), 2.49 (4H, s), 2.55 (2H, t), 3.36 (2H, d), 3.81 (3H, s), 5.20 (2H, s), 6.59 - 6.62 (1H, m), 7.26 - 7.29 (1H, m), 7.31 (1H, s), 8.00 (1H, s); MS m/z 280 [M+H]+.

Intermediate 193:

3-methoxy-4-nitro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of **Intermediate 188**, on a 9.28 mmol scale utilising 2-pyrrolidin-1-ylethanamine (Aldrich; 1.06 g, 9.28 mmol), as a brown solid (2.3 g, 85%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.67 - 1.72 (4H, m), 2.47 - 2.54 (4H, m), 2.60 (2H, t), 3.39 - 3.44 (2H, m), 3.99 (3H, s), 7.54 - 7.56 (1H, m), 7.72 (1H, d), 7.96 (1H, d), 8.71 (1H, t); MS m/z 294 [M+H]+.

Intermediate 194:

4-amino-N-(2-dimethylaminoethyl)-3-methoxy-benzamide

The title compound was prepared in quantitative yield by an analogous method to the preparation of Intermediate 187, on a 2 g scale utilising N-(2-dimethylaminoethyl)-3-methoxy-4-nitro-benzamide (Intermediate 195).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ2.19 (6H, s), 2.38 (2H, t), 3.38 (2H, m), 3.81 (3H, s), 5.20 (2H, s), 6.61 (1H, d), 7.25 - 7.28 (1H, m), 7.30 (1H, s), 7.96 (1H, t); MS m/z 238 [M+H]+.

Intermediate 195:

N-(2-dimethylaminoethyl)-3-methoxy-4-nitro-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 188, on a 9.28 mmol scale utilising N,N-dimethylethane-1,2-diamine (Aldrich; 818 mg, 9.28 mmol), as a brown solid (2.5 g, 100%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 2.24 (6H, s), 2.47 - 2.49 (2H, m), 3.37 - 3.41 (2H, m), 4.00 (3H, s), 7.55 - 7.57 (1H, m), 7.74 (1H, d), 7.96 (1H, d), 8.73 (1H, t); MS m/z 268 [M+H]+.

Intermediate 196:

4-amino-N-(3-dimethylaminopropyl)-3-methoxy-benzamide

The title compound was prepared in quantitative yield by an analogous method to the preparation of Intermediate 187, on a 2 g scale utilising N-(2-dimethylaminoethyl)-3-methoxy-4-nitro-benzamide (Intermediate 197).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.60 - 1.67 (2H, m), 2.14 (6H, s), 2.25 (2H, t), 3.21 - 3.26 (2H, m), 3.81 (3H, s), 5.19 (2H, s), 6.61 (1H, d), 7.25 - 7.30 (2H, m), 8.09 (1H, t); MS m/z 252 [M+H]+.

Intermediate 197:

N-(3-dimethylaminopropyl)-3-methoxy-4-nitro-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 188, on a 9.28 mmol scale utilising N,N-dimethylpropane-1,3-diamine (Aldrich; 948 mg, 9.28 mmol), as a brown solid (2.33 g, 90%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.65 - 1.72 (2H, m), 2.16 (6H, s), 2.29 (2H, t), 3.34 (2H, m), 4.00 (3H, s), 7.53 - 7.56 (1H, m), 7.72 (1H, d), 7.96 (1H, d), 8.77 (1H, t); MS m/z 282 [M+H]+.

Intermediate 198:

10-chloro-4,4-diethyl-6-methyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a stirred solution of 10-chloro-4,4-diethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 197; 2.7 g, 9.1 mmol) in DMA (50 mL) under nitrogen was added methyl iodide (0.627 mL, 10.0 mmol). The mixture was cooled on an ice/water bath to 3°C, and sodium hydride (60% mineral oil dispersion; 0.567 g, 11.8 mmol) added in one portion. The reaction was stirred overnight. The reaction was evaporated to dryness to afford a yellow solid, this was quenched with saturated $NH_4Cl_{(aq)}$ (50 mL), extracted with DCM (3 X 100 mL), dried ($MgSO_4$) and evaporated to yield a yellow solid. This was dissolved in a minimum amount of DCM, diethyl ether was added and the system was sonicated to afford an off white solid. (2.24 g, 80%)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.84 (t, 6H), 1.20 (d, 6H), 1.68 - 1.50 (m, 4H), 3.27 (s, 3H), 3.41 (s, 2H), 5.31 (septet, 1H), 7.83 (s, 1H); MS m/z 311 [M+H]+.

Intermediate 199:

10-chloro-4,4-diethyl-2-propan-2-yl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of 2,4-dichloro-5-nitropyrimidine (Aldrich; 5.1 g, 26.4 mmol) and K_2CO_3 (4.4 g, 31.6 mmol) in acetone (150 mL) was slowly added methyl 2-ethyl-2-[(propan-2-ylamino)methyl]butanoate (Intermediate 200; 5.3 g, 26.4 mmol) in acetone (30 mL). The mixture was stirred at room temperature for 18 hours. The reaction was filtered and the solvent evaporated. The residue and iron (4.4 g, 79.2 mmol) were added to acetic acid (175 mL) and heated at 80 °C overnight. The resulting solution was filtered and the solvent evaporated and the residue quenched with 2.0 N $NaOH_{(aq)}$ (75 mL), to the resultant emulsion, was added 10%MeOH/DCM (100 ml) and the suspension filtered through a pad of celite. The obtained filtrate was extracted with 10%MeOH/DCM (3 X 150 mlL, dried and the solvent

removed. The resultant material was dissolved in DCM and filtered. Acetonitrile was added to the DCM and the DCM was slowly removed *in vacuo* to give a precipitate, which was filtered and dried to yield the title compound as a white solid. (3.1 g, 33%)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.90 (t, 6H), 1.21 (d, 6H), 1.68 - 1.60 (m, 4H), 3.35 (s, 2H), 5.36 (septet, 1H), 7.83 (s, 1H), 8.65 (brs, 1H); MS m/z 297 [M+H]+.

Intermediate 200:

methyl 2-ethyl-2-[(propan-2-ylamino)methyl]butanoate

Methyl 2-(aminomethyl)-2-ethyl-butanoate (Intermediate 201; 8 g, 50 mmol) and acetone (4.35 g, 75 mmol) were added to methanol (230 mL) and stirred for 10 minutes before the rapid addition of sodium triacetoxyborohydride (15.9 g, 75 mmol). The reaction was stirred overnight before being evaporated to dryness. The residue was quenched with saturated $K_2CO_{3(aq)}$ (100 mL), extracted with DCM (3 x 150 mL), dried and solvent evaporated to yield a dark liquids. Purification was achieved via distillation (65oC @ 0.18 mbar) to yield the title compound as clear oil (5.3 g, 53%)

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.79 (t, 6H), 1.02 - 0.98 (m, 7H), 1.62 (q, 4H), 2.74 - 2.67 (m, 3H), 3.67 (s, 3H)

Intermediate 201:

methyl 2-(aminomethyl)-2-ethyl-butanoate

Methylcyanoacetate (Aldrich; 20 g, 0.201 mol) was dissolved in THF (250 mL), to this was added DBU (75 mL, 0.505 mol) and ethyl bromide (40 mL, 0.606 mol). The reaction was stirred at 50 °C for 2 hours before being cooled and quenched with sat $NH_4Cl_{(aq)}$. The organic layer was separated and the remaining aqueous was extracted with diethyl ether (2 x 100 mL), dried and solvent removed *in vacuo* to yield yellow oil. Purification was achieved via distillation at 70 °C at 0.5 mbar to afford methyl 2-cyano-2-ethyl-butanoate as a clear oil (20 g, 0.129 mol) which was reduced with hydrogen under pressure using Raney nickel catalyst (2 g). The reaction mixture was filtered and solvent evaporated to the title compound as a slightly dark oil. (16 g, 50%).

Intermediate 202:

4-amino-3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]benzamide

The title compound was prepared in quantitative yield by an analogous method to the preparation of Intermediate 187, on a 2 g scale utilising (Intermediate 203).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.92 (2H, d), 1.39 - 1.46 (3H, m), 1.88 - 1.95 (1H, m), 1.92 (1H, d), 2.06 (1H, s), 2.12 - 2.20 (2H, m), 2.41 (3H, s), 2.97 (2H, d), 3.82 (3H, s), 4.30 (1H, d), 5.18 (2H, s), 6.61 (1H, d), 7.29 - 7.31 (2H, m), 7.63 (1H, d); MS m/z 304 [M+H]+.

Intermediate 203:

3-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-4-nitro-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 188, on a 9.28 mmol scale utilising Endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 1.435 g, 9.28 mmol), as a brown solid (1.6 g, 52%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ0.93 (2H, d), 1.45 (3H, m), 1.89 - 1.95 (1H, m), 1.94 (1H, d), 2.03 (1H, t), 2.18 - 2.23 (2H, m), 2.42 (3H, s), 3.00 (2H, d), 4.00 (3H, d), 4.31 - 4.35 (1H, m), 7.56 - 7.59 (1H, m), 7.72 (1H, d), 7.96 (1H, d), 8.37 (1H, d); MS m/z 332 [M-H]+.

Intermediate 204:

4-amino-2-fluoro-5-methoxy-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

4-amino-2-fluoro-5-methoxybenzoic acid (Intermediate 183; 0.75 g, 4.07 mmol), HATU (1.70 g, 4.48 mmol) and DIPEA (2.1 mL, 12.21 mmol) were stirred together in DMF (10 mL) for 10 minutes. Endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 0.69 g, 4.48 mmol) in DMF (1 mL) was added and the brown solution stirred at ambient temperature for 2 hours. The solvent was evaporated and the residue dissolved in MeOH and loaded onto an SCX-2 (20 g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and the product eluted with 2M NH3/MeOH (2 column volumes). Product containing fractions were combined and evaporated and the resultant material purified on a silica column eluting with 0-10% 2MNH3/MeOH/DCM). Product containing fractions were combined and evaporated to yield the title compound as a dark brown gum (897 mg, 69%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.91 (m, 2H), 1.39 (m, 3H), 2.04 (m, 5H), 2.40 (s, 3H), 2.96 (m, 2H), 3.78 (s, 3H), 4.27 (m, 1H), 5.53 (s, 2H), 6.39 (d, 1H), 7.06 (d, 1H), 7.24 (m, 1H); MS m/z 322 [M+H]+.

Intermediate 205:

4-amino-N-(1-ethyl-4-piperidyl)-2-fluoro-5-methoxy-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 188, on a 5.43 mmol scale utilising 1-ethylpiperidin-4-amine (Fluorochem; 0.77 g, 5.97 mmol), as a gum (1.21 g, 76%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.99 (t, 3H), 1.52 (m, 2H), 1.78 (m, 2H), 1.97 (m, 2H), 2.31 (q, 2H), 2.80 (m, 2H), 3.72 (m, 1H), 3.77 (s, 3H), 5.54 (bs, 2H), 6.39 (d, 1H), 7.05 (d, 1H), 7.33 (m, 1H); MS m/z 296 [M+H]+.

Intermediate 206:

4-amino-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)-3-methoxy-benzamide

A mixture of the 4-amino-3-methoxy-benzoic acid (Aldrich; 2 g, 12 mmol) and 2,2-dimethyl-3-pyrrolidin-1-yl-propan-1-amine (WO 2004033419; 2.1 g, 13.2 mmol) were dissolved in DMF (50 mL), and to the solution was added DIPEA (3.1 g, 4.2 mL). The reaction was cooled with an ice-bath, and to it was added, portionwise, HATU (5.02 g, 13.2 mmol). The reaction mixture was stirred at ambient temperature for 18 hours. The solvent was evaporated, and the residue was partitioned between Ethyl Acetate (100 mL), and saturated aqueous sodium carbonate solution (3 x 40 mL), washed with brine (3 x 40 mL), dried over anhydrous Magnesium sulphate, filtered, and the solvent evaporated. The residue was purified by chromatography on a silica column pre-conditioned with Ethyl acetate and eluted with 10% MeOH-DCM +1% NH3. Those fractions containing the desired product were combined and the solvent was evaporated to yield the title compound as a pale brown gum, which crystallised on standing. (500mgs ; 14%).

^{1}H NMR (400.132 MHz, CDCl3) : δ 1.00 (6H,s), 1.75-1.85 (4H,m), 2.55 (2H,s), 2.63-2.75 (4H,m), 3.35-3.39 (2H,d), 3.90 (3H,s), 6.61-6.65 (1H,d), 7.06-7.11 (1H,d), 7.47 (1H,s), 9.05 (1H,bs). MS m/z 306 [M+H]+.

Intermediate 207:

4-amino-5-chloro-2-fluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

4-amino-5-chloro-2-fluorobenzoic acid (Intermediate 176; 300 mg, 1.58 mmol), HATU (903 mg, 2.37 mmol) and (3R)-1-methylpyrrolidin-3-amine di Hydrochloride (Intermediate 184; 325 mg, 2.37 mmol) were stirred in DMF (5 mL) and diisopropylethylamine (1.2 mL, 7.12 mmol) added. The mixture was stirred for 2 hours at room temperature and then absorbed on to an SCX column, washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and purified by column chromatography (5% ammonia in methanol/DCM) to yield the title compound as a pale orange solid (333 mg, 77%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.63 - 1.71 (1H, m), 2.09 - 2.18 (1H, m), 2.25 (3H, s), 2.33 - 2.41 (2H, m), 2.55 - 2.61 (1H, m), 2.64 - 2.69 (1H, m), 4.30 - 4.35 (1H, m), 6.10 (2H, s), 6.55 (1H, d), 7.50 (1H, d), 7.76 - 7.79 (1H, m)

Intermediate 208:

2'-chloro-9'-isopropyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one

To a solution of 2'-chloro-9'-isopropyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 209; 5.055 g, 19 mmol) in DMA (300 mL) was added methyl iodide (1.305 mL, 20.9 mmol), followed by sodium hydride (60% mineral oil dispersion; 814 mg, 20.33 mmol). The mixture was stirred at room temperature for 30 minutes. The DMA was removed *in vacuo*, then water (50 mL) was added. The product precipitated as a sticky gum, which turned into a solid on sonication. The solid was collected by filtration to give a brown powder. This material was dissolved in DCM and dried over sodium sulfate, then purified by column chromatography, eluting with 25% ethyl acetate in hexane, to yield the title compound as a white solid (3.73 g, 70%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.63 - 0.66 (2H, m), 1.11 - 1.16 (8H, m), 3.26 (3H, s), 3.44 (2H, s), 4.91 - 4.98 (1H, m), 7.84 (1H, s) ; MS m/z 281 [M+H]+.

Intermediate 209:

2'-chloro-9'-isopropyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one

Ethyl 1-[[(2-chloro-5-nitro-pyrimidin-4-yl)-propan-2-yl-amino]methyl]cyclopropane-1-carboxylate (Intermediate 208; 10.26 g, 30 mmol) was dissolved in acetic acid (500 mL) and heated to 70 °C. Iron powder (6 g) was added in portions over 10 minutes. The mixture was stirred at 70 °C for 3 hours. The reaction mixture was filtered hot through celite, and the pad washed with DCM. The filtrate was evaporated to dryness then sonicated in saturated aqueous sodium hydrogen carbonate solution to give a brown suspension. This was filtered, and the resulting solid washed with water. The solid was then sucked dry on a filter, and suspended in a small amount of methanol with sonication. The methanol suspension was then diluted with DCM (10 x excess), and filtered to give a yellow solution, which was dried over sodium sulphate, then concentrated *in vacuo* to give a yellow / green solid. The solid was triturated under cold methanol to yield the title compound as a white powder. (5 g, 63%)
MS m/z 267 [M-H]+. Retention time 1.81 minutes.

Intermediate 210:

ethyl 1-[[(2-chloro-5-nitro-pyrimidin-4-yl)-propan-2-yl-amino]methyl]cyclopropane-1-carboxylate

To a solution of ethyl 1-[(propan-2-ylamino)methyl]cyclopropane-1-carboxylate (Intermediate 211; 9.55 g, 50 mmol) in acetone (300 mL) was added potassium carbonate (7.05 g, 51 mmol) followed by 2,4-dichloro-5-nitropyrimidine (Aldrich; 10.675 g, 55 mmol). The mixture was stirred overnight at room temperature, concentrated *in vacuo* and partitioned between EtOAc and water. The EtOAc layer was separated, dried over sodium sulfate, then purified by column chromatography (EtOAc / isohexane 10:90), to yield the title compound as a yellow oil. (11 g, 64%)
^{1}H NMR (400.13 MHz, CDCl3) δ 0.75 - 0.78 (2H, m), 0.96 (3H, t), 1.10 - 1.14 (8H, m), 3.42 - 3.48 (1H, m), 3.59 (2H, s), 3.87 - 3.93 (2H, m), 8.48 (1H, s); MS m/z 343 [M+H]+.

Intermediate 211:

ethyl 1-[(propan-2-ylamino)methyl]cyclopropane-1-carboxylate

To a solution of ethyl 1-(aminomethyl)cyclopropane-1-carboxylate (Intermediate 114; 20.65 g, 250 mmol) in DCM (200 mL) was added acetone (3.74 mlL, 51 mmol). After stirring at room temperature for 15 minutes, sodium acetate (4.185 g, 51 mmol) was added, followed by sodium triacetoxyborohydride (15.905 g, 75 mmol). The suspension was stirred at room temperature for 2 days then partitioned between DCM and an aqueous solution of saturated sodium hydrogen carbonate. The organic layer was separated, then dried over sodium sulphate evaporated to yield the title compound as a clear oil (9.2 g, 100%).

^{1}H NMR (400.13 MHz, CDCl3) δ 0.60 - 0.63 (2H, m), 0.86 (6H, d), 1.02 - 1.09 (5H, m), 1.69 (1H, br s), 2.50 (2H, s), 2.58 - 2.64 (1H, m), 3.93 (2H, q).

Intermediate 212:

4-amino-3-chloro-N-(1-ethyl-4-piperidyl)benzamide

To a mixture of 4-amino-3-chloro-benzoic acid (Fluorochem; 2.575 g, 15 mmol) and 1-ethylpiperidin-4-amine (Fluorochem; 2.12 g, 16.5 mmol) in DMF (50 mL), was added DIPEA (5.2 mL, 30 mmol).The mixture was cooled with an ice-bath. HATU (6.27g), added and the reaction mixture stirred at ambient temperature for 18 hours. The solvent was evaporated and the residue partitioned between saturated aqueous sodium bicarbonate solution (100 mL), and Ethyl Acetate (4 x 50 mL). The organic extracts were washed with brine (2 x 75 ml), dried over anhydrous Magnesium sulphate, filtered, and the solvent evaporated to give the crude product as a gum, which was triturated with ether to yield the title compound as a tan solid (3.54 g, 84%).

^{1}H NMR ;400.1MHz (DMSO-d6) δ 1.20-1.26 (3H,t), 1.65-1.85 (2H,bm), 1.92-2.10 (2H,bm), 2.90-3.20 (4H,m), 3.30 (3H,s), 3.40-3.60 (2H,bm), 3.90-4.05 (1H,m), 5.98 (2H,s), 6.77-6.81 (1H,d), 7.554-7.60(1H,dd), 7.88 (1H,s), 8.10 (1H,bs); MS m/z 282 [M+H]+.

Intermediate 213:

4-amino-3-chloro-N-(2-dimethylaminoethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 212, on a 15 mmol scale utilising 2,2-Dimethyaminoethylamine (Aldrich; 1.455 g, 16.5 mmol), as a white solid (1.45 g, 40%).

^{1}H NMR ;400.1MHz (DMSO-d6) δ 2.83 (6H,s), 3.18-3.24 (2H,t), 3.50-3.58 (2H,quartet), 5.95 (2H,s), 6.80-6.83 (1H,d), 7.55-7.60 (1H,d), 7.76 (1H,s), 8.30-8.38 (1H,t); MS m/z 242 [M+H]+.

Intermediate 214:

4-amino-3-chloro-N-(3-dimethylaminopropyl)benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 212, on a 15 mmol scale utilising 3-Dimethylamino-1-propylamine (Aldrich; 1.685 g, 16.5 mmol), as a tan coloured solid (3.25 g, 85%).

^{1}H NMR 400.1MHz,(DMSO-d6) δ 1.80-1.90 (2H,m), 2.77 (6H,s), 3.00-3.08 (2H,m), 3.25-3.50 (2H,m), 5.88 (2H,s), 6.78-6.82 (1H,d), 7.53-7.59 (1H,dd), 7.75 (1H,s), 8.24-8.30 (1H,t); MS m/z 256 [M+H]+.

Intermediate 215:

4-amino-3-chloro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 212, on a 15 mmol scale utilising 2-pyrrolidin-1-ylethanamine (Aldrich; 1.885 g, 16.5 mmol), as a tan coloured solid (2.67 g, 66%).

^{1}H NMR ; 400.1MHz, (DMSO-d6) δ 1.80-2.05 (4H,m), 3.20-3.45 (6H,m), 3.48-3.58 (2H,q), 5.92 (2H,s), 6.78-6.82 (1H,d), 7.55-7.60 (1H,dd), 7.77 (1H,s), 8.30-8.40 (1H,t);); MS m/z 268 [M+H]+.

Intermediate 216:

4-amino-2-chloro-5-methoxy-N-(1-methyl-4-piperidyl)benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 212, on a 3.06 mmol scale utilising 4-amino-2-chloro-5-methoxy-benzoic acid (Intermediate 217; 617 mg, 3.06 mmol) and 1-methylpiperidin-4-amine (Fluorochem; 385 mg, 3.37 mmol), as an off-white solid (845 mg, 93%).

^{1}H NMR (399.902 MHz, CDCl3) δ1.61 (m, 2H), 2.05 (m, 2H), 2.20 (m, 2H), 2.30 (s, 3H), 2.76 (m, 2H), 3.88 (s, 3H), 4.03 (m, 3H), 6.57 (d, 1H), 6.63 (s, 1H), 7.34 (s, 1H); MS m/z 298 [M+H]+.

Intermediate 217:

4-amino-2-chloro-5-methoxy-benzoic acid

2-chloro-5-methoxy-4-nitro-benzoic acid (Intermediate 218; 762 mg, 3.8 mmol) was dissolved in EtOH (20 mL) and a catalytic amount of 5% Pt on carbon added under an inert atmosphere. The solution was de-gassed and stirred under an atmosphere of hydrogen at room temperature overnight. The catalyst was filtered off and washed with EtOH and solvent evaporated and the resultant material dried under vacuum to yield the title compound as an off-white solid. (617 mg, 98%)

^{1}H NMR (399.902 MHz, DMSO-d6) δ3.72 (s, 3H), 5.65 (br s, 2H), 6.59 (s, 1H), 7.21 (s, 1H), 12.30 (br s, 1H); MS m/z 201 [M+H]+.

Intermediate 218:

2-chloro-5-methoxy-4-nitro-benzoic acid

1-chloro-4-methoxy-2-methyl-5-nitro-benzene (APIN; 1 g, 4.96 mmol) was suspended in water (100 mL), potassium permanganate (3.14 g, 19.84 mmol) was added and the mixture diluted further with water (140 mL). The mixture was very slowed heated up to reflux over a 2 hour period and then stirred at reflux for 4 hours then allowed to cool to room temperature overnight with stirring. After 18 hours the mixture was reheated to 80 °C and filtered hot, the manganese filter cake was washed with boiling water (100 mL), then the aqueous filtrate was treated with a couple of drops of sodium metabisulfite solution and the permanganate colour was removed to give a yellow solution. The solution was acidified to pH 2 with concentrated hydrochloric acid and partially evaporated down to a volume of (200 mL) and extracted with EtOAc (2 x 100 mL). Combined organic extracts were washed with brine, dried (MgSO4) and evaporated to yield the title compound as a yellow solid. (752 mg, 65%).

^{1}H NMR (399.902 MHz, DMSO-d6) δ3.98 (s, 3H), 7.67 (s, 1H), 8.14 (s, 1H), 14.03 (br s, 1H); MS m/z 229 [M-H]+.

Intermediate 219:

5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoic acid

tert-butyl 5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoate (Intermediate 220; 220 mg, 0.45 mmol) was dissolved in DCM (7.5 mL) and trifluoroacetic acid (2.5 mL) added. The mixture was stirred at room temperature for 2 hours. The reraction mixture was evaporated, the residue dissolved in methanol/DCM and absorbed on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated to yield the title compound as a white solid (195 mg, 100%).
^{1}H NMR (399.9 MHz, DMSO-d6) δ1.54 – 1.73 (6H, m), 1.88 – 1.95 (2H, m), 2.58 – 2.63 (2H, m), 3.18 (3H, s), 3.61 – 3.65 (2H, m), 4.74 - 4.79 (1H, m), 7.70 (2H, brs), 7.70 (1H, d), 8.06 – 8.11 (2H, m); MS m/z 434 [M+H]+.

Intermediate 220:

tert-butyl 5-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoate

4-Amino-5-chloro-2-fluorobenzoic acid *tert*-butyl ester (Intermediate 177; 123 mg, 0.5 mmol) was dissolved in dioxane (7.5 mL). 10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 155 mg, 0.55 mmol), XANTPHOS (27 mg, 0.05 mmol) and caesium carbonate (327 mg, 1.0 mmol) were added. The system was purged with a stream of nitrogen for 15 minutes and then tris(dibenzylideneacetone) palladium (II) (28 mg, 0.03 mmol) added. The apparatus was evacuated and backfilled with nitrogen (x3) and then heated at 100 °C for 3 hours. The mixture was cooled, filtered and the filtrate absorbed on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were evaporated and the residue purified by column chromatography (2% MeOH/DCM) to yield the title compound as a pale yellow foam (225mg, 92%).
^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.53 – 1.74 (15H, m), 1.92 - 1.95 (2H, m), 2.62 (2H, t), 3.19 (3H, s), 3.65 (2H, t), 4.73 - 4.84 (1H, m), 7.85 (1H, d), 8.15 (1H, s), 8.24 (1H, s), 8.41 (1H, d); MS m/z 490 [M+H]+.

Intermediate 221:

3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoic acid

The title compound was prepared by an analogous method to the preparation of Intermediate 219, utilising tert-butyl 3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoate (Intermediate 222; 236 mg, 0.45mmol), as an off-white solid (180 mg, 87%).

^{1}H NMR (399.9 MHz, DMSO-d_6 + d_4 AcOH) δ1.30 – 1.63 (8H, m), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.51 - 3.54 (2H, m), 4.31 (1H, m), 7.75 (1H, d), 7.97 (1H, s); MS m/z 468 [M+H]+.

Intermediate 222:

tert-butyl 3,5-dichloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-2-fluoro-benzoate

The title compound was prepared by an analogous method to the preparation of Intermediate 220, utilising tert-butyl 4-amino-3,5-dichloro-2-fluoro-benzoate (Isolated as a by-product during the preparation of Intermediate 177; 236 mg, 0.45mmol), as an off-white solid (180 mg, 87%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.30 - 1.63 (17H, m), 2.55 (2H + DMSO-d6, m), 3.16 (3H, s), 3.52 - 3.54 (2H, m), 4.25 (1H, m), 7.89 (1H, d), 8.00 (1H, s), 9.18 (1H, s); MS m/z 524 [M+H]+.

Intermediate 223:

7-amino-N-(1-methyl-4-piperidyl)benzo[1,3]dioxole-4-carboxamide

N-(1-methyl-4-piperidyl)-7-nitro-benzo[1,3]dioxole-4-carboxamide (Intermediate 224; 290 mg, 0.94 mmol) was suspended in methanol (50 mL) and the system purged with nitrogen. 10% Pd/C (30 mg) was added and the mixture stirred under a hydrogen atmosphere for 2 hours. The catalyst was filtered off and the filtrate evaporated to give the title compound as a white solid (249mg, 96%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.43 – 1.53 (2H, m), 1.78 - 1.82 (2H, m), 1.98 – 2.05 (2H, m), 2.12 (3H, s), 2.67 (2H, d), 3.69 - 3.73 (1H, m), 5.48 (2H, d), 6.06 (2H, s), 6.32 (1H, d), 6.95 (1H, d), 7.11 (1H, d); MS m/z 278 [M+H]+.

Intermediate 224:

N-(1-methyl-4-piperidyl)-7-nitro-benzo[1,3]dioxole-4-carboxamide

4-Amino-1-methylpiperidine (Fluorochem; 325 mg, 2.84 mmol), HATU (1.09 g, 2.84 mmol) and 7-nitrobenzo[1,3]dioxole-4-carboxylic acid (WO 2003082827; 400 mg, 1.89m mol) were stirred in DMF (5 mL) and diisopropylethylamine (0.99 ml, 5.68 mmol) added. The mixture was stirred for 2 hours at room temperature. The reaction mixture was loaded on to an SCX column, which was subsequently washed with methanol and eluted with ammonia in methanol. Product containing fractions were concentrated and the solid suspended in methanol and filtered off to yield the title compound as a yellow solid (295mg, 51%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.50 - 1.60 (2H, m), 1.78 - 1.82 (2H, m), 1.96 - 2.03 (2H, m), 2.17 (3H, s), 2.72 (2H, d), 3.72 - 3.76 (1H, m), 6.42 (2H, s), 7.28 (1H, d), 7.62 (1H, d), 7.94 (1H, d); MS m/z 308 [M+H]+.

Intermediate 225:

4-amino-N-(1-ethyl-4-piperidyl)-3-fluoro-benzamide

4-amino-3-fluorobenzoic acid (2.115 g, 13.6 mmol), 4-Amino-1-Ethyl Piperidine (Fluorochem; 1.923 g, 15 mmol), HATU (5.7 g, 15 mmol) and DIPEA (7.1 mL, 40.8 mmol) were combined in DMA (60 mL) and the resulting yellow solution stirred at room temperature for 20 minutes. The reaction was left over the weekend at room temperature, solvent evaporated and the residue dissolved in methanol (10 mL) and loaded onto an SCX-2 column (50 g) which pre-wet with MeOH (40 mL), flushed with MeOH (4 x 30 ml) and eluted with 7N ammonia in MeOH (4 x 30 mL). Product containing, ammoniacal fractions were combined to yield the title compound as a brown solid (0.819 g, 22%)

MS m/z 266 [M+H]+. Retention time 1.5 minutes

Intermediate 226:

4-(azetidin-1-yl)cyclohexan-1-amine

tert-butyl N-[4-(azetidin-1-yl)cyclohexyl]carbamate (Intermediate 227; 260 mg, 1.01 mmol) was taken up in DCM (3 mL) and TFA (2 mL) and stirred at ambient temperature for 3 hours. The reaction mixture was poured directly onto an SCX-3 cartridge (5 g). The cartridge was washed through with DCM (30 mL), followed by methanol (30 mL) and then eluted with 2M ammonia in methanol (25 mL). Ammoniacal fractions were combined and evaporated to yield the title compound as a colourless oil (124 mg, 80%)

^{1}H NMR (400.132 MHz, CDCl3) δ 1.04 (m, 2H), 1.36 - 1.56 (m, 4H), 1.80 (m, 2H), 1.87 - 2.10 (m, 3H), 2.63 & 2.79 (2 x m, 1H), 3.16 (m, 4H).

Intermediate 227:

tert-butyl N-[4-(azetidin-1-yl)cyclohexyl]carbamate

To a stirred solution of N-4-boc-aminocyclohexanone (500 mg, 2.34 mmol) in DCM (7 mL) was added azetidine (220 ul, 3.26 mmol) and the mixture stirred for 15 minutes. Sodium acetate (193 mg, 2.34 mmol) was added, followed by careful addition of sodium triacetoxyborohydride (746 mg, 3.52 mmol) The reaction mixture was stirred, at ambient temperature, under nitrogen for 3 hours, diluted with DCM to 25 mL total volume and filtered. The filtrate was poured onto and SCX-2 (10 g) cartridge and the cartridge washed with methanol (75 mL) then eluted with 2M ammonia in methanol (75 mL). The ammoniacal solution was evaporated, to give a waxy off white solid (200 mg). The SCX cartridge wash was resubmitted to a second SCX-2 cartridge (10 g) and the cartridge again washed with methanol (75 mL) and eluted with 2M ammonia/methanol (75 mL). The ammoniacal solution was evaporated to a colourless gum. Solid products were combined and triturated with isohexane. The resultant crystalline solid was collected by suction filtration and dried to yield the title compound as a white solid (104 mg). A second crop crystallised from the filtrate. This was again collected and dried to give the title compound as fine white needles (260 mg). Total yield (364 mg, 61%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.80 - 0.90 (1H, m), 1.05 - 1.16 (1H, m), 1.21 - 1.30 (1H, m), 1.37 (9H, s), 1.41 - 2.09 (8H, m), 3.01 (4H, q), 3.06 - 3.26 (1H, m), 6.57 - 6.66 (1H, m).

Intermediate 228:

4-amino-2-fluoro-5-methoxy-N-(2-pyrrolidin-1-ylethyl)benzamide

4-amino-2-fluoro-5-methoxybenzoic acid (Intermediate 183; 0.75 g, 4.07 mmol), HATU (1.70 g, 4.48 mmol) and DIPEA (2.1 mL, 12.21 mmol) were stirred together in DMF (10 mL) for 25mins. N-(2-aminoethyl)pyrrolidine (Aldrich; 0.51 g, 4.48 mmol) in DMF (2 mL) was added and the solution stirred at ambient temp for 2 hours.

The solvent was evaporated and the residue dissolved in MeOH and loaded onto an SCX-2 (20 g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and eluted with 2MNH3/MeOH. Product containing fractions were combined and evaporated to a brown gum, which was purified on a silica column eluting with 0-10% 2MNH3/MeOH/DCM. Product containing fractions were combined and evaporated to yield the title compound as a pale brown solid (948 mg, 83%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.69 (m, 4H), 2.48 (m, 4H), 2.56 (t, 2H), 3.36 (m, 4H), 3.77 (s, 3H), 5.59 (s, 2H), 6.40 (d, 1H), 7.13 (d, 1H), 7.51 (m, 1H); MS m/z 282 [M+H]+.

Intermediate 229:

4-amino-2,5-difluoro-N-[(3R)-1-methylpyrrolidin-3-yl]benzamide

4-amino-2,5-difluoro-benzoic acid (Rare Chemicals GmbH; 450 mg, 2.6 mmol), (3R)-1-methylpyrrolidin-3-amine di Hydrochloride (Intermediate 184; 473 mg, 2.73 mmol), HATU (1.08 g2.86 mmol) and DIPEA (2.25 mL, 13 mmol) were combined in DMF (10 mL) and stirred at room temperature for 4 hours. The solvent was evaporated and the residue dissolved in MeOH and added to an SCX-2 column (20 g), pre-wet with MeOH (2 column volumes). The column was flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were combined and evaporated and the resultant material dissolved in DCM and purified on a silica column eluting with 5% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to a yellow gum. Diethylether was added and re-evaporated and dried under high vacuum to yield the title compound as a yellow gum, which slowly crystallised to a cream solid (550 mg, 83%)

^{1}H NMR (399.902 MHz, CDCl3) δ1.71 (m, 1H), 2.26 - 2.42 (m, 5H), 2.64 (m, 2H), 2.86 (m, 1H), 4.13 (s, 2H), 4.62 (m, 1H), 6.43 (m, 1H), 6.87 (m, 1H), 7.70 (m, 1H); MS m/z 256 [M+H]+.

Intermediate 230:

4-amino-2,5-difluoro-N-(2-pyrrolidin-1-ylethyl)benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 229, on a 5.77 mmol scale utilising 2-pyrrolidin-1-ylethanamine (Aldrich; 725 mg, 6.35 mmol), as a beige solid (648 mg, 42%)

^{1}H NMR (399.902 MHz, CDCl3) δ1.78 (m, 4H), 2.56 (m, 4H), 2.69 (m, 2H), 3.55 (m, 2H), 4.12 (s, 2H), 6.43 (m, 1H), 7.16 (m, 1H), 7.72 (m, 1H); MS m/z 270 [M+H]+.

Intermediate 231:

2-chloro-4-[(2-cyclopentyl-6-methyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-5-methoxy-benzoic acid

10-Chloro-2-cyclopentyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 1; 1 g, 3.56 mmol) and 2-Chloro-3-Methoxy-4-Amino-benzoic acid (Intermediate 223;) were suspended in a water / EtOH (3:1) mixture (40 mL). Concentrated hydrochloric acid (712 µL, 7.12 mmol) was added and the reaction heated at 80 °C overnight. The reaction mixture was cooled to room temperature and the resulting solid filtered and dried to give the title compound as a beige solid (951 mg, 60%)

^{1}H NMR (399.902 MHz, DMSO-d6) δ1.61 (m, 6H), 1.91 (m, 2H), 2.63 (m, 2H), 3.10 (s, 3H), 3.66 (m, 2H), 3.88 (s, 3H), 4.86 (m, 1H), 7.42 (s, 1H), 8.12 (s, 1H), 8.35 (s, 1H), 8.91 (br s, 1H), 13.10 (br s, 1H); MS m/z 446 [M+H]+.

Intermediate 232:

2-Chloro-3-Methoxy-4-Amino-benzoic acid

2-chloro-5-methoxy-4-nitro-benzoic acid (Intermediate 233; 5.87 g, 26.3 mmol) was dissolved in EtOH (100 mL) and a catalytic amount of 5% Pt on carbon added under an inert atmosphere. The solution was de-gassed and then stirred under an atmosphere of hydrogen at room temperature for 6 hours. The catalyst was filtered off and washed with EtOH and the

filtrate evaporated and the residue triturated with diethylether and the solid filtered and dried to yield the title compound as a yellow solid (4.53 g, 89%)

^{1}H NMR (399.902 MHz, DMSO-d6) δ3.80 (s, 3H), 5.73 (s, 2H), 6.67 (s, 1H), 7.29 (s, 1H), 12.42 (s, 1H); MS m/z 201 [M+H]+.

Intermediate 233:

2-chloro-5-methoxy-4-nitro-benzoic acid

1-chloro-4-methoxy-2-methyl-5-nitro-benzene (APIN Chemicals; 12.58 g, 62.4 mmol) was suspended in water (600 mL) and heated to 90 °C under nitrogen. Potassium permanganate (2 eq, 19.74 g, 125 mmol) in water (500 mL) was added over a period of 25 minutes and then the mixture was heated at reflux for 2 hours. A further addition of potassium permanganate (19.74 g, 125 mmol) in water (500 mL) was made over 15 minutes with the reaction temperature reduced to 91 °C and then heating continued at reflux for 3 hours and then cooled to room temperature and allowed to stand overnight.

The reaction was re-heated to reflux and further addition of potassium permanganate (9.86 g 62.5 mmol) in water (200 mL) made over 5 minutes and the reaction heated at reflux for 2 hours for a further 2 hours.

The reaction mixture was cooled to 80 °C and filtered hot through a pad of celite. The reactor vessel was washed with water (500 mL) and the Manganese filter cake was washed with boiling water (1200 mL). The combined aqueous washings were cooled to room temperature and any excess permanganate colour was removed by the addition of aqueous sodium metabisulfite solution. The resulting yellow solution was acidified to pH 1 with concentrated aqueous hydrochloric acid and the volume reduced from approximately 4000 mL to 3000 mL *in vacuo*. The aqueous layer was extracted with EtOAc (2 x 1000 mL) and the combined organic extracts washed with brine (500 mL), dried over $MgSO_4$ and evaporated to yield the title compound as a yellow solid. (8.45 g, 58%)

^{1}H NMR (399.902 MHz, DMSO-d6) δ 3.98 (s, 3H), 7.67 (s, 1H), 8.14 (s, 1H), 14.02 (br s, 1H); MS m/z 229 $[M-H]^+$.

Intermediate 234:

tert-butyl 4-[(4-amino-3-methoxy-benzoyl)amino]piperidine-1-carboxylate

To a solution of 4-amino-3-methoxybenzoic acid (Aldrich; 2.4 g, 14.36 mmol) in DMF (100 mL) was added 4-amino-1-bocpiperidine (Aldrich; 3.15 g, 15.72 mmol) and DIPEA (7.5 mL, 43.06 mmol). The resultant solution was carefully treated portionwise (2-3 portions) with HATU (6.88 g, 18.09 mmol) and the resultant mixture was stirred, under nitrogen, at ambient temperature overnight.

The solvent was removed *in vacuo* and the residue partitioned between saturated aqueous sodium bicarbonate solution (100 mL) and ethyl acetate (100 mL). The organic phase was separated and washed with water (150 mL) and brine (150 mL), dried over magnesium sulphate, filtered and evaporated. The residue was purified by flash chromatography on a silica cartridge eluting with a rising gradient of 0-10% Methanol in DCM. Product containing fractions were combined and evaporated to yield the title compound as a peach coloured foam (2.88 g, 57%)

1H NMR (400.132 MHz, DMSO) δ 1.35 - 1.47 (11H, m), 1.72 - 1.80 (2H, m), 2.76 - 2.90 (2H, m), 3.81 (3H, s), 3.91 - 4.00 (3H, m), 5.20 (2H, s), 6.61 (1H, d), 7.28 - 7.30 (2H, m), 7.80 (1H, d); MS m/z 348 $[M-H]^+$.

Intermediate 235:

4-amino-N-(1-ethyl-4-piperidyl)-2,5-difluoro-benzamide

The title compound was prepared by an analogous method to the preparation of Intermediate 229, on a 5.77 mmol scale utilising 4-amino-1-ethylpiperidine (Fluorochem; 815 mg, 6.35 mmol), as an orange solid (1.23 g, 75%)

^{1}H NMR (399.902 MHz, CDCl3) δ1.09 (t, 3H), 1.57 (m, 2H), 2.04 (m, 2H), 2.14 (m, 2H), 2.42 (q, 2H), 2.86 (m, 2H), 4.02 (m, 1H), 4.13 (s, 2H), 6.43 (m, 1H), 6.51 (m, 1H), 7.72 (m, 1H); MS m/z 284 $[M+H]^+$.

Intermediate 236:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-methoxy-benzoic acid

10-chloro-2-cyclopentyl-4,4-dimethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-8,10,12-trien-5-one (Intermediate 127; 200 mg, 0.65 mmol) and 4-amino-3methoxybenzoic acid (Aldrich; 130 mg, 0.78 mmol) were taken up in water/ethanol (3:1 v/v; 4 mL). Concentrated

hydrochloric acid (130 ul, 1.30 mmol) was added and reaction heated by microwave irradiation at 120°C for 30 minutes.

The reaction mixture was drowned into water (20 mL) and a precipitated solid collected by suction filtration and dried in vacuum oven, at 55°C for 90 minutes, to give a dark pink crystalline solid (180 mg).

The filtrate was evaporated to dryness to give further solid, which was combined with the first batch and triturated with an MeCN/Water mix gave a pink solid which was again collected by suction filtration (160 mg).

The filtrate was evaporated and combined with the solid purified by flash chromatography on a silica cartridge eluting with 0-5% MeOH in DCM. to give the title compound as an off white solid (85 mg, 30%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.16 (s, 6H), 1.56 - 1.93 (m, 8H), 3.20 (s, 3H), 3.52 (s, 2H), 3.96 (s, 3H), 5.14 (m, 1H), 7.60 (m, 2H), 8.08 (s, 1H), 8.19 (d, 1H), 9.18 (br s, 1H) OH just visible at 12.84 (br s, 1H); MS m/z 440 $[M+H]^+$.

Intermediate 237:

4-pyrrolidin-1-ylcyclohexan-1-amine

tert-butyl N-(4-pyrrolidin-1-ylcyclohexyl)carbamate (Intermediate 238; 222 mg, 0.83 mmol) was taken up in DCM (1.5 mL) and TFA (1 mL). The reaction mixture was stirred at ambient temperature for 3 hours, poured directly onto an SCX-3 cartridge (2 g), pre-wet with DCM. The cartridge was washed through with DCM (10 mL), followed by methanol (30 mL) and then eluted with 2M ammonia in Methanol (25 mL). Evaporation to dryness of the ammoniacal solution yielded the title compound as an amber coloured oil (103 mg, 74%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.94 - 1.20 (m, 4H), 1.63 (m, 4H), 1.73 (m, 2H), 1.87 (m, 3H), 2.45 (m, 4H), 3.29 (br m, 1H)

Intermediate 238:

tert-butyl N-(4-pyrrolidin-1-ylcyclohexyl)carbamate

The title compound was prepared by an analogous method to the preparation of Intermediate 227, on a 2.34 mmol scale utilising pyrrolidine (Aldrich; 250 µL, 3.04 mmol), as a white solid (175 mg, 44%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.15 (m, 4H), 1.38 (s, 9H), 1.64 (m, 4H), 1.75 (m, 2H), 1.88 (m, 3H), 2.45 (m, 4H), 3.15 (m, 1H), 6.64 (m, 1H).

Intermediate 239:

4-amino-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide

4-amino-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide (Intermediate 240; 500 mg, 1.56 mmol) was reduced with 10% Pd/C (60 mg) and hydrogen to yield the title compound (454 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.25 – 1.30 (2H, m), 1.40 – 1.44 (2H, m), 1.71 – 1.74 (1H, m), 1.80 (2H, m), 1.82 (2H, m), 2.19 (6H, d due to racemic mixture), 3.82 (3H, s), 3.65 and 3.85 (0.5H each due to racemic mixture), 5.16 (2H, s), 7.26 (1H, dd), 7.30 (1H, d), 7.71 (1H, t); MS m/z 292 $[M+H]^+$.

Intermediate 240:

4-amino-N-(4-dimethylaminocyclohexyl)-3-methoxy-benzamide

3-methoxy-4-nitro-benzoyl chloride (Intermediate 189; 1.0 g, 4.64 mmol) was dissolved in DCM (20 mL) and cooled on an ice bath. DIPEA (970 uL) was added dropwise. 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 660 mg, 4.64 mmol) was dissolved in DCM (10 mL) and added to the reaction solution. The reaction mixture was brought back to room temperature and stirred for 2 hours. The reaction mixture was washed with brine and $NaOH_{(aq)}$. The organic layer was extracted by filtering through a PTFE cup and evaporated to yield the title compound as an orange solid (1.54 g, 100%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ1.29 – 1.35 (2H, m), 1.45 – 1.48 (1H, m), 1.52 – 1.56 (1H, m), 1.75 (1H, m), 1.85 – 1.87 (2H, d), 1.95 (2H, d), 2.20 (6H, d due to N-dimethyl should be singlet but is doublet due to stereoisomers), 3.71 and 3.91 (two x 0.5H due to stereoisomers), 3.99 (3H, s), 7.51 (1H, t), 7.60 (1H, d), 7.92 (1H, t), 844 (1H, t); MS m/z 332 $[M+H]^+$.

Intermediate 241:

4-amino-2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]-4-nitro-benzamide (**Intermediate 242**; 500 mg, 1.56 mmol) was reduced using 10% Pd/C (50mg) and hydrogen

stirring at room temperature for 3 hours. The catalyst was removed by filtration and the filtrate evaporated to yield the title compound (454 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.90 (2H, d), 1.38 - 1.40 (3H, m), 1.85 – 1.95 (2H, m), 1.99 – 2.05 (1H, m), 2.14 - 2.22 (2H, m), 2.40 (3H, s), 2.96 (2H, d), 4.20 – 4.28 (1H, m), 5.81 – 5.85 (2H, s), 6.28 – 6.32 (1H, d), 6.38 – 6.43 (1H, m), 7.20 – 7.24 (1H, t), 7.38 – 7.41 (1H, t); MS m/z 292 $[M+H]^+$.

Intermediate 242:

2-fluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]-4-nitro-benzamide

2-fluoro-4-nitro-benzoyl chloride (Intermediate 243; 2.40 g, 11.79 mmol) was dissolved in DCM (20 mL) and cooled on an ice bath. DIPEA (2.46 mL, 14.15 mmol) was added dropwise followed by Endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 1.82 g, 11.79 mmol) dissolved in DCM (10 mL). The reaction mixture was allowed to return to room temperature and stirred for 2 hours and then washed with brine and NaOH $_{(aq)}$. The organic layer was evaporated to yield the title compound as an orange solid (3 g, 79%)

1H NMR (399.9 MHz, DMSO-d_6) δ 0.93 (2H, d), 1.34 - 1.41 (2H, m), 1.46 (1H, t), 1.90 (1H, t), 1.94 (2H, d), 2.21 - 2.29 (2H, m), 2.41 (3H, s), 2.98 - 3.00 (2H, m), 4.23 - 4.34 (1H, m), 7.79 - 7.83 (1H, m), 8.08 - 8.16 (1H, m), 8.18 - 8.24 (1H, m), 8.41 (1H, d); MS m/z 292 $[M+H]^+$.

Intermediate 243:

2-fluoro-4-nitro-benzoyl chloride

2-fluoro-4-nitrobenzoic acid (Fluorochem; 2.5 g, 13.51 mmol) was suspended in toluene (25 mL) and thionyl chloride (2.96 mL, 40.52 mmol) added. The reaction mixture was heated at reflux for 1.5 hours, allowed to cool and evaporated to give the title compound as a yellow liquid which gradually solidified on standing (2.74 g, 100%)

^{1}H NMR (399.9 MHz, DMSO-d_6) δ7.90 – 8.10 (3H, m).

Intermediate 244:

4-amino-3-chloro-N-(2,2-dimethyl-3-pyrrolidin-1-yl-propyl)benzamide

A mixture of the 4-amino-3-chloro-benzoic acid (Fluorochem; 2.49 g, 14.5 mmol) and 2,2-dimethyl-3-pyrrolidin-1-yl-propan-1-amine (Chemstep; 2.49 g, 15.95 mmol) were dissolved in DMF (50 mL), and to the solution was added DIPEA (5.1 mL, 29.0 mmol).The reaction mixture was cooled with an ice-bath, and HATU (6.06 g, 15.95 mmol) added, portionwise. The reaction mixture was stirred at ambient temperature for 18 hours. The solvent was evaporated and the residue partitioned between Ethyl Acetate (100 mL), and saturated aqueous sodium carbonate solution (3 x 40 mL), washed with brine (3 x 40 mL), dried over anhydrous Magnesium sulphate, filtered, and the solvent evaporated to give the crude product as an oily semi-solid, which was triturated with diethyl ether and filtered to yield the title compound as a pale yellow crystalline solid (850 mg, 19%) The mother-liquors from the trituration were purified on a silica column, pre-equilibrated ethyl acetate and eluting with 10% MeOH-DCM + 1%NH3. Product containing fractions were combined and evaporated to give the title compound as a viscous, yellow oil (1.72 g, 38%)

^{1}H NMR (400.1MHz , $CDCl_3$) δ 1.00 (6H,s), 1.82-1.88 (4H,m), 2.56 (2H,s), 2.65-2.72 (4H,bs), 3.33-3.36 (2H,d), 4.30 (2H,s), 6.73-6.77 (1H,d), 7.55-7.60 (1H,dd), 7.65 (1H,s), 9.38 (1H,s). MS m/z 310 $[M+H]^+$.

Intermediate 245:

4-amino-N-[(3R)-1-ethylpyrrolidin-3-yl]-3-methoxy-benzamide

To a solution of 4-amino-3-methoxybenzoic acid (Aldrich; 424 mg , 2.54 mmol) and (3R)-1-ethylpyrrolidin-3-amine (Intermediate 246; 312 mg, 2.73 mmol) in DMF (10 mL) was added DIPEA (1.4 ml, 8.04 mmol). The resultant solution was treated with HATU (1.21 g, 3.18 mmol) and stirred, under nitrogen, at ambient temperature overnight.

The reaction mixture was evaporated to a brown, viscous oil, which was partitioned between DCM (20 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The organic phase was separated and aqueous phase re-extracted with DCM (20 mL). Combined organic solutions were evaporated to dryness and the residue purified on a silica column, eluting with a gradient of 0-10% methanol in DCM. Product containing fractions were combined and evaporated. The resultant material was dissolved in methanol and loaded onto an SCX-2 (10 g) cartridge. The cartridge was washed with methanol (75 mL) and then eluted with 2M

ammonia/methanol. The ammoniacal solution was evaporated to yield the title compound as an orange gum (210 mg, 31%).

Intermediate 246:

(3R)-1-ethylpyrrolidin-3-amine

tert-butyl N-[(3R)-1-ethylpyrrolidin-3-yl]carbamate (Intermediate 247; 945 mg, 4.41 mmol) was taken up in DCM (8 mL) and TFA (4 mL) and stirred at ambient temperature for 3 hours.

The reaction mixture was loaded onto an SCX-3 cartridge (5 g), pre-wet with DCM. The cartridge was washed with DCM (30 mL), followed by methanol (30 mL), then eluted with 2M ammonia in methanol (30 mL). The ammoniacal solution was evaporated to dryness to yield the title compound as an amber oil (152 mg)

The SCX-cartridge pre-wash, which was highly coloured, was poured onto an SCX-3 (20 g) cartridge and the cartridge flushed with methanol (150 mL) and then eluted with 2M ammonia in methanol (100 mL). Evaporation of the ammoniacal fraction afforded a further batch of the title compound as an amber oil (165 mg)

Combined yield (317 mg, 63%)

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.99 (3H, t), 1.28 - 1.36 (1H, m), 1.93 - 2.02 (1H, m), 2.08 (1H, dd), 2.32 - 2.42 (3H, m), 2.46 - 2.49 (1H, m), 2.60 - 2.65 (1H, m), 3.26 - 3.33 (1H, m).

Intermediate 247:

tert-butyl N-[(3R)-1-ethylpyrrolidin-3-yl]carbamate

To a solution of (3R)-(+)-3-(t-butyoxycarbonylamino)pyrrolidine (Fluka; 1.54 g, 8.27 mmol) in DMF (25 mL) was added triethylamine (2.3 mL, 16.50 mmol) and ethyl bromide (Aldrich; 1 mL, 13.40 mmol). The reaction mixture was heated by microwave irradiation at 100 °C in for 1 hour.

The reaction mixture was poured into water (400 mL) and the mixture extracted with diethyl ether (2 x 300 mL). The combined organic extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness to yield the title compound as an amber coloured oil (825 mg, 47%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.99 (t, 3H), 1.38 (s, 9H), 1.53 (m, 1H), 1.99 (m, 1H), 2.20 (m, 1H), 2.32 - 2.48 (m, 4H), 2.67 (m, 1H), 3.88 (m, 1H), 6.87 (m, 1H).

Intermediate 248:

4-amino-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide

4-amino-2-fluoro-5-methoxy-benzoic acid (Intermediate 183; 0.75 g, 4.07 mmol), HATU (1.70 g, 4.48 mmol) and DIPEA (2.1 ml, 12.21 mmol) were stirred together in DMF (10 mL) for 10 minutes at ambient temperature. 1-amino-4-dimethylaminocyclohexane (ABChem Inc.; 0.637 g, 4.48 mmol) in DMF (2 mL) was added and the reaction mixture stirred at ambient temperature overnight.

The solvent was evaporated and the residue dissolved in MeOH and loaded onto an SCX-2 (20 g) column pre-wet with MeOH. The column was washed with MeOH (2 column volumes) and the eluted with 2MNH3/MeOH. Product containing fractions were combined and evaporated to give a brown gum which was purified on a silica column eluting with 0-10% 2MNH3/MeOH/DCM to give a single unassigned isoform of the title compound as a pale brown gum (250 mg, 20%)

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.63 (m, 8H), 2.08 (m, 1H), 2.18 (s, 6H), 3.77 (s, 3H), 3.91 (m, 1H), 5.54 (bs, 2H), 6.40 (d, 1H), 7.06 (d, 1H), 7.24 (m, 1H); MS m/z 310 $[M+H]^+$.

A second unassigned isoform was also isolated and designated Intermediate 249 (394 mg, 31%)

Intermediate 249:

4-amino-N-(4-dimethylaminocyclohexyl)-2-fluoro-5-methoxy-benzamide

The title compound was obtained as a single unassigned isoform described above in the preparation of Intermediate 248 as a white solid (394 mg, 31%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.28 (m, 4H), 1.85 (m, 4H), 2.11 (m, 1H), 2.18 (s, 6H), 3.66 (m, 1H), 3.77 (s, 3H), 5.53 (bs, 2H), 6.38 (d, 1H), 7.04 (d, 1H), 7.26 (m, 1H); MS m/z 310 $[M+H]^+$.

Intermediate 250:

10-chloro-2-cyclopentyl-4,4-diethyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a stirred solution of 10-chloro-2-cyclopentyl-4,4-diethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 251; 2.5 g, 7.76 mmol) in DMA (50 mL) under nitrogen was added methyl iodide (0.627 mL, 10.0 mmol). The mixture was cooled on an ice/water bath to 3°C, and sodium hydride (60% mineral oil dispersion; 0.567 g, 11.8 mmol) added in one portion. The reaction mixture was stirred on the ice/water bath for 1 hour before warming to room temperature and the reaction stirred for 4 hours. The reaction mixture was evaporated to dryness to afford a black solid, which was quenched with saturated aqueous NH_4Cl solution (50 mL), extracted with DCM (3 X 100 mL), dried and solvent removed *in vacuo* to yield a black solid which was purified on a silica column eluting with DCM. The obtained solid was added to a diethyl ether and sonicated and the resultant material filtered and dried to yield the title compound as an off white solid (2.1 g, 80%). ^{1}H NMR (400.132 MHz, CDCl3) δ 0.83 (t, 6H), 1.77 - 1.48 (m, 10H), 1.99 - 1.91 (m, 2H), 3.27 (s, 3H), 3.43 (s, 2H), 5.34 (quintet, 1H), 7.82 (s, 1H); MS m/z 337 $[M+H]^+$.

Intermediate 251:

10-chloro-2-cyclopentyl-4,4-diethyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

To a solution of methyl 2-[(cyclopentylamino)methyl]-2-ethyl-butanoate (Intermediate 252; 7.1 g, 31.3 mmol) in acetone (150 mL) was added potassium carbonate (5.3 g, 38.0 mmol) followed by 2,4-dichloro-5-nitropyrimidine (Aldrich; 6.1 g, 31.3 mmol). The black mixture was stirred at room temperature for 18 hours. The reaction was filtered and the solvent removed *in vacuo* to yield a black gum, which was dissolved in acetic acid (175 mL) and iron (7.0 g, 125 mmol) added and the reaction heated at 80 °C overnight. The resulting solution was filtered and the solvent removed *in vacuo*, the black solid/gum was quenched with water (75 mL) and to this was added sodium carbonate until basic, the resultant black emulsion was filtered through a pad of celite. The obtained mixture was extracted with DCM (3 X 150 mL), dried and the solvent removed *in vacuo* to yield a black solid. This was passed through a bond elute column (50 g) eluting with 0-1% MeOH in DCM to afford a brown solid, which was triturated with diethyl ether to yield the title compound as a white solid (3.05 g, 30%)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.90 (t, 6H), 1.57 - 1.48 (m, 2H), 1.81 - 1.61 (m, 6H), 1.98 - 1.91 (m, 2H), 3.36 (s, 2H), 5.31 (quintet, 1H), 7.80 (s, 1H), 8.40 (s, 1H); MS m/z 323 $[M+H]^+$.

Intermediate 252:

methyl 2-[(cyclopentylamino)methyl]-2-ethyl-butanoate

The title compound was prepared by an analogous method to the preparation of Intermediate 200, on a 50 mmol scale utilising Cyclopetanone (Aldrich; 6.33 g, 75 mmol), and distillation at 50 °C and 0.53 mbar pressure, as a clear oil (7.5 g, 65%)

^{1}H NMR (400.132 MHz, CDCl3) δ 0.79 (t, 6H), 1.32 - 1.24 (m, 2H), 1.53 - 1.46 (m, 2H), 1.68 - 1.57 (m, 6H), 1.83 - 1.72 (m, 2H), 2.67 (s, 2H), 2.99 (quintet, 1H), 3.66 (s, 3H).

Intermediate 253:

4-[(2-cyclopentyl-4,4,6-trimethyl-5-oxo-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-10-yl)amino]-3-chloro-benzoic acid

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 130; 496 mg, 1.62 mmol) and 4-amino-3-chlorobenzoic acid (Fluorochem; 278 mg, 1.62 mmol) were taken up in water/ethanol (3:1 v/v; 12 mL). Concentrated hydrochloric acid (330 uL, 3.30 mmol) was added and the reaction heated at reflux overnight.

The reaction mixture was cooled and then poured into 1M $NaOH_{(aq)}$ (75 mL), and DCM (50 mL) added. The aqueous phase was separated and washed with DCM (50 mL) then acidified until a precipitate formed (~pH 2-3) which was collected by suction filtration and dried, under vacuum, at 70°C, for 2 hours to afford a pale pink solid. The material was taken up in 10% MeOH in DCM (10 mL) and a fine suspension resulted. The mixture was filtered and the collected solid dried to yield the title compound as a pink solid, (58 mg, 8%)

MS m/z 442 $[M+H]^+$. Retention time 1.26 minutes

Intermediate 254:

4-amino-2-fluoro-5-methoxy-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

4-amino-2-fluoro-5-methoxy-benzoic acid (Intermediate 183; 500 mg, 2.70 mmol), [1-(pyrrolidin-1-ylmethyl)cyclopropyl]methanamine (Intermediate 33; 417 mg, 2.70 mmol), HATU (1.545 g, 4.05 mmol) and DIPEA (1.415 mL, 8.10 mmol) were dissolved in DMF (8 mL) and left to stir for 3 hours at room temperature. The reaction mixture was loaded onto an SCX-3 column pre-washed with methanol. The column was washed with methanol eluted with 2% 7N ammonia/methanol. Product containing fractions were combined and evaporated and the residue purified on a silica column (5-12% MeOH ammonia/DCM gradient elution) to yield the title compound as an orange-brown solid (200 mg, 23%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ0.29 (2H, broad s), 0.50 (2H, broad s), 1.70 (4H, broad s), 2.45 (4H, s), 2.50 (2H, s), 3.30 (2H, d), 3.75 (3H, s), 5.60 (2H, s), 6.40 (1H, d), 7.15 (1H, d), 8.05 (1H, t); MS m/z 322 $[M+H]^+$.

Intermediate 255:

2'-chloro-9'-cyclopentyl-5'-methyl-8',9'-dihydrospiro[cyclohexane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one

2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclohexane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 256; 300 mg, 0.94 mmol) was dissolved in N,N-dimethylacetamide (10 mL) and methyl iodide (65 mL, 1.03 mmol) added followed by sodium hydride (41 mg of a 60% dispersion in mineral oil, 1.00 mmol). The reaction mixture was stirred for 30 minutes. A drop of water added was added and then the reaction mixture was diluted with water and extracted with ethyl acetate (x2). The combined organic extracts were dried ($MgSO_4$) and concentrated and the residue purified by column chromatography (1% MeOH/DCM) to give a sticky white solid (Note 4) that was suspended in diethyl ether and filtered off to yield the title compound as a white crystalline solid (242 mg, 77%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.30 - 1.37 (2H, m), 1.51 – 1.62 (8H, m), 1.68 – 1.74 (2H, m), 1.84 – 1.91 (2H, m), 1.96 – 2.04 (2H, m), 3.21 (3H, s), 3.47 (2H, s), 4.88 – 4.96 (1H, m), 8.09 (1H, s); MS m/z 335 $[M+H]^+$.

Intermediate 256:

2'-chloro-9'-cyclopentyl-8',9'-dihydrospiro[cyclohexane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one

Methyl 1-(aminomethyl)cyclopentane-1-carboxylate (Intermediate 257; 940 mg, 2.46 mmol) was dissolved in acetic acid (40 mL) and the mixture heated to 70 °C. Iron powder (412 mg, 7.37 mmol) was added and the mixture heated for 4 hours, filtered whilst still warm and concentrated. The residue was suspended between DCM and saturated aqueous sodium hydrogen carbonate solution and the mixture was filtered. The layers were then separated and the organic layer dried ($MgSO_4$) and concentrated to give a green, viscous oil. On addition of methanol a white solid formed which was filtered off to yield the title compound (300mg, 38%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.45 - 1.63 (10H, m), 1.68 – 1.75 (2H, m), 1.79 – 1.86 (2H, m), 1.96 - 2.01 (2H, m), 3.42 (2H, s), 5.06 – 5.15 (1H, m), 7.87 (1H, s), 9.70 (1H, s); MS m/z 321 $[M+H]^+$.

Intermediate 257:

methyl 1-(aminomethyl)cyclopentane-1-carboxylate

Methyl 1-[(cyclopentylamino)methyl]cyclopentane-1-carboxylate (Intermediate 258; 1.60 g, 7.10 mmol), 2,4-dichloro-5-nitropyrimidine (Aldrich; 1.66 g, 8.52 mmol) and triethylamine (1.2 mL, 8.52 mmol) were stirred in acetonitrile (50 mL) for 4 hours. The reaction mixture was evaporated and the residue dissolved in DCM, washed with water, dried ($MgSO_4$) and evaporated. The residue was purified on a silica column eluting with 1% methanol/DCM to yield the title compound as a yellow oil that crystallised on standing (945 mg, 35%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.43 - 1.70 (12H, m), 1.80 - 1.87 (2H, m), 1.97 - 2.01 (2H, m), 3.46 – 3.55 (1H, m), 3.58 (3H, s), 3.77 (2H, s), 8.90 (1H, s); MS m/z 383 $[M+H]^+$.

Intermediate 258:

methyl 1-[(cyclopentylamino)methyl]cyclopentane-1-carboxylate

Methyl 1-(aminomethyl)cyclopentane-1-carboxylate (Intermediate 259; 1.5 g, 9.54 mmol) and cyclopentanone (1.0 mL, 11.45 mmol) were stirred in DCM (40 mL). Sodium acetate (940 mg, 11.45 mmol) and sodium triacetoxyborohydride (3.04 g, 14.31 mmol) were added. The mixture was stirred at room temperature for 48 hours. The reaction mixture was filtered

and the filtrate concentrated. The residue was dissolved in methanol and absorbed on to an SCX column, which was then washed with methanol and eluted with ammonia in methanol. Product containing fractions were combined and evaporated to yield the title compound as a colourless oil (1.64g, 81%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ1.21 - 1.34 (2H, m), 1.39 - 1.70 (13H, m), 1.88 - 1.94 (2H, m), 2.63 (2H, s), 2.90 - 2.96 (1H, m), 3.59 (3H, s).

Intermediate 259:

methyl 1-(aminomethyl)cyclopentane-1-carboxylate

17328/13 Reaction carried out in RSL (P Walker – No.009/07, 09/01/2007)
Methyl 1-cyanocyclopentane-1-carboxylate (Intermediate 260; 6 g, 39.2 mmol) in acetic acid (70 mL) was hydrogenated using Pt O_2 (600 mg) as a catalyst at room temperature under 4 Bar pressure for 4 hours. The reaction mixture was filtered and concentrated. The residue was taken up in methanol and absorbed on to an SCX column (3x 50g), which was then washed with methanol and eluted with ammonia in methanol. Concentration of product containing fractions yielded the title compound as a pale yellow liquid (6.18g, 100%).
^{1}H NMR (399.9 MHz, DMSO-d6) δ1.38 (2H, s), 1.52 - 1.58 (6H, m), 1.87 - 1.93 (2H, m), 2.67 (2H, s), 3.61 (3H, s).

Intermediate 260:

methyl 1-cyanocyclopentane-1-carboxylate

Methyl cyanoacetate (Fluka ; 25 g, 252.3 mmol) and potassium carbonate (83.7 g, 605.5 mmol) were stirred in DMF (250 mL). 1,4-Dibromobutane (Aldrich; 30.1 mL, 252.3 mmol) was slowly added. This caused and exotherm that continued after the addition was completed and a water bath was used to prevent the temperature exceeding 90 °C. The mixture slowly cooled to ambient temperature and was stirred overnight and then heated at 75°C for 3 hours. The reaction mixture was cooled and filtered and the filtrate concentrated to about half volume. The mixture was diluted with water (250 mL) and extracted with diethyl ether (2 x 65 mL). The combined organic extracts were washed with 1N hydrochloric acid, brine, dried ($MgSO_4$) and evaporated to yield the title compound as a pale yellow liquid (31.73 g, 82%).

^{1}H NMR (399.9 MHz, CDCl3) δ1.86 - 1.91 (4H, m), 2.25 - 2.29 (4H, m), 3.83 (3H, s).

Intermediate 261:

10-chloro-6-methyl-2-(2-oxocyclopentyl)-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

10-chloro-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 100; 256 mg, 1.20 mmol) was taken up in DMA (10 mL) and cooled on an ice-bath, with stirring, under nitrogen. Sodium hydride (60% in mineral oil; 232 mg, 5.8 mmol) was carefully added portionwise and the reaction mixture left to stir for 5 minutes, before removing cooling bath and stirring for a further 30 minutes. A solution of 2-chlorocyclopentanone (Aldrich; 600 uL, 6.00 mmol) in DMA (5 mL) was then added. The reaction mixture was heated to 100 °C and stirred for 3.5 hours and then allowed to cool, before addition of saturated aqueous ammonium chloride solution (1 mL). The mixture was partitioned between DCM (40 mL) and water (40 mL). Phases were separated and the aqueous phase re-extracted with DCM (40 mL). Combined extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated. The residue was purified on a silica column eluting with ethyl acetate. Product containing fractions were combined and evaporated to yield the title compound as a sticky brown gum (211 mg, 60%)

MS m/z 295 $[M+H]^+$.

Intermediate 262:

4-bromo-2-chloro-5-fluoro-N-(1-methyl-4-piperidyl)benzamide

4-bromo-2-chloro-5-fluoro-benzoic acid (Apollo Scientific; 5.0 g, 19.8 mmol) was added to DMF (250 mL), to this was added HBTU (9.8 g, 25.7 mmol), N-methyl-4-aminopiperidne (Fluorochem; 2.5 g, 21.8 mmol) and DIPEA (7.0 mL, 39.5 mmol). The reaction was stirred overnight, evaporated to dryness, quenched with 2.0 N NaOH (100 mL), extracted with DCM (3 x 100 mL), dried and solvent removed *in vacuo*. The residue was dissolved in hot acetonitrile, allowed to cool filtered, and the filtrate passed through a SCX column and the residue, after evaporation of product containing fractions, recrystallised from hot acetonitrile to yield the title compound as a white solid (5.0 g, 82%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.64 - 1.55 (m, 2H), 2.07 - 2.03 (m, 2H), 2.19 - 2.14 (m, 2H), 2.29 (s, 3H), 2.79 - 2.76 (m, 2H), 4.04 - 3.95 (m, 1H), 6.13 (brd, 1H), 7.48 (d, 1H), 7.62 (d, 1H); MS m/z 350 $[M+H]^+$.

Intermediate 263:

10-amino-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

10-amino-2-cyclohexyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 264; 1.0 g, 3.83 mmol) was dissolved in DMF (65 ml), to this was added sodium hydride (60% mineral oil dispersion; 0.37 g, 7.66 mmol) in one portion. The reaction was stirred under nitrogen for 30 minutes before being cooling 0 ^{0}C. Methyl Iodide (0.238 mL, 3.83 mmol) in DMF (10 mL) was slowly added to the reaction and the reaction stirred at 0 ^{0}C for 2 hours. The reaction was quenched with MeOH and solvent removed invacuo. The resultant slurry was quenched with saturated aqueous NH_4Cl solution (50 mL), extracted with DCM (3 x 50 mL), dried and solvent evaporated to yield a yellow gum which was purified on a silica column eluting with 0-5% MeOH in DCM. On evaporation of product containing fractions the residue was dissolved in a small amount of DCM, to this was added diethyl ether (50 mL), and the solution slowly evaporated until a precipitate formed. The solution was then sonicated and the precipitate filtered and dried to yield the title compound as a white solid. (0.55g, 52%)

^{1}H NMR (400.132 MHz, CDCl3) δ 1.18 - 1.07 (m, 1H), 1.52 - 1.34 (m, 4H), 1.74 - 1.68 (m, 1H), 1.85 - 1.80 (m, 4H), 2.63 - 2.61 (m, 2H), 3.24 (s, 3H), 3.64 - 3.61 (m, 2H), 4.41 - 4.35 (m, 1H), 4.66 (brs, 2H), 7.77 (s, 1H); MS m/z 276 $[M+H]^+$.

Intermediate 264:

10-amino-2-cyclohexyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

2,4-dichloro-5-nitropyrimidine (Aldrich; 10 g, 0.052 mol) was dissolved in THF (250 mL). To this was added DIPEA (11 mL, 0.062 mol) and the reaction cooled to 0 °C. Methyl 3-(cyclohexylamino)propanoate (9.5 g, 0.052 mol) in THF (30 mL) was slowly added. The cooling bath was removed and the reaction was stirred at room temperature for 1 hour. To the reaction mixture was added saturated $NH_4OH_{(aq)}$ (100 mL), and the reaction heated at 55 °C

for 4 hours using a dry ice condenser. The reaction mixture was extracted with DCM (3 x 100 ml), and combined organic extracts dried and evaporated. The residue was dissolved in methanol (200 mL). Ammonium formate (33 g, 0.52 mol) and 10% palladium (1.5 g) were added. The reaction was heated at reflux for 5 hours, filtered and the methanol evaporated to yield a dark orange solid, which was quenched with 2.0 N $NaOH_{(aq)}$ (100 mL), extracted with DCM (3 x 150 mL), and combined extracts dried and evaporated to yield an orange solid. Hot acetonitrile was added, this was stirred and then sonicated to give a precipitate that was filtered and dried to yield the title compound as a yellow solid (7.5 g, 55%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.18 - 1.05 (m, 1H), 1.48 - 1.37 (m, 4H), 1.84 - 1.68 (m, 5H), 2.68 - 2.66 (m, 2H), 3.62 - 3.59 (m, 2H), 4.74 - 4.65 (m, 1H), 5.34 (brs, 2H), 7.59 (s, 1H), 9.57 (s, 1H); MS m/z 262 $[M+H]^+$.

Intermediate 265:

methyl 3-(cyclohexylamino)propanoate

Cyclohexylamine (Aldrich; 17 g, 0.174 mol) was dissolved in THF (300 mL). To this was added methyl acrylate (Aldrich; 15 g, 0.174 mol) in one portion. The reaction mixture was stirred over the weekend. The solvent was evaporated with care due to the volatility of the product and the residue distilled at 72 ^{0}C at 0.30 mbar to yield the title compound as a clear oil (23.7 g, 74%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.31 - 1.01 (m, 6H), 1.63 - 1.57 (m, 1H), 1.75 - 1.70 (m, 2H), 1.89 - 1.85 (m, 2H), 2.46 - 2.39 (m, 1H), 2.50 (t, 2H), 2.90 (t, 2H), 3.68 (s, 3H).

Intermediate 266:

10-chloro-2-cyclohexyl-6-methyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

10-chloro-2-cyclohexyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one (Intermediate 267; 5.87 g, 20.91 mmol) was suspended in DMA (450 mL) under nitrogen. Methyl iodide (3.26 g, 23 mmol) was added and the suspension cooled to 5 °C on an ice-water bath. Sodium hydride (60% mineral oil dispersion; 920 mg, 23 mmol) was added in a single portion and the resulting mixture stirred on the ice-water bath for 30 minutes allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and the solvent evaporated. The residue was

partitioned between DCM (200 mL) and water (300 mL) and the aqueous phase re-extracted with DCM (100 mL). The combined organic phases were dried ($MgSO_4$) and the evaporated. The residue was taken up in DCM and purified on a silica column eluting with a gradient of 10 – 50% EtOAc / isohexane over 10 column volumes. Fractions containing product were combined and evaporated to yield the title compound as a cream solid (5.02 g, 81%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.13 (m, 1H), 1.47 (m, 4H), 1.72 (m, 1H), 1.85 (m, 4H), 2.66 (m, 2H), 3.28 (s, 3H), 3.69 (m, 2H), 4.47 (m, 1H), 7.93 (s, 1H); MS m/z 295 $[M+H]^+$.

Intermediate 267:

10-chloro-2-cyclohexyl-2,6,9,11-tetrazabicyclo[5.4.0]undeca-7,9,11-trien-5-one

Methyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclohexyl-amino]propanoate (Intermediate 238; 19.03 g, 55.52 mmol) was dissolved in acetic acid (440 mL) and heated to 70 °C under a nitrogen atmosphere. Iron powder (8.37 g, 150 mmol) was added cautiously, giving a slow exotherm to 82 °C, and the mixture stirred at 70 °C for 2 hours. The reaction mixture was cooled to approximately 60 °C and filtered through a pad of celite. The celite was washed through with DCM (500 mL) and the filtrate evaporated and the residue azeotroped with toluene. The resultant material was dissolved in DCM and diluted with EtOAc to give a precipitate which was filtered off. The filtrate was added to a very short pad of silica and eluted with EtOAc and the eluent evaporated to give an orange solid, which was dissolved in DCM (500 mL) and washed with saturated aqueous sodium bicarbonate solution (300 mL). The organic phase contained some insoluble material which was filtered off to give a cream solid. The filtrate was evaporated to dryness and the resulting dark brown gum triturated with DCM (20 mL) and filtered to give a cream solid. The two solids were combined and washed with a small amount of DCM then dried under high vacuum to yield the title compound as a cream solid (5.87 g, 38%)

^{1}H NMR (399.902 MHz, DMSO-d6) δ1.13 (m, 1H), 1.34 (m, 2H), 1.52 (m, 2H), 1.66 (m, 3H), 1.80 (m, 2H), 2.66 (m, 2H), 3.60 (m, 2H), 4.53 (m, 1H), 7.84 (s, 1H), 9.68 (s, 1H); MS m/z 281 $[M+H]^+$.

Intermediate 268:

methyl 3-[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclohexyl-amino]propanoate

To methyl 3-(cyclohexylamino)propanoate (Intermediate 265; 15 g, 80.96 mmol) in acetone (300 mL) at room temperature was added powdered potassium carbonate (16.8 g, 121 mmol). 2,4-Dichloro-5-nitropyrimidine (Frontier Scientific; 17.27 g, 89.06 mmol) in acetone (100 mL) was added over 10 minutes and the resulting yellow mixture stirred at room temperature for 16 hours. The solvent was evaporated and the residue partitioned between EtOAc (500 mL) and water (500 mL). The aqueous phase was re-extracted with EtOAc (2 x 200 mL). The combined organic solutions were evaporated to approx half the volume, washed with brine (200 mL) and evaporated. The residue was taken up in DCM and purified on a silica column, eluting with 10% EtOAc / isohexane. Product containing fractions were combined and evaporated to yield the title compound as a yellow solid (19.03 g, 62%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.27 (m, 2H), 1.49 - 1.68 (m, 4H), 1.85 (m, 4H), 2.70 (m, 2H), 3.20 (m, 1H), 3.71 (s, 3H), 3.82 (m, 2H), 8.63 (s, 1H); MS m/z 343 $[M+H]^+$.

Intermediate 269:

4-amino-2,5-difluoro-N-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methyl]benzamide

4-amino-2,5-difluoro-benzoic acid (Rare Chemicals GmbH; 700 mg, 4.04 mmol), [1-(pyrrolidin-1-ylmethyl)cyclopropyl]methanamine (Intermediate 33; 655 mg, 4.25 mmol), HATU (1.69 g, 4.44 mmol) and DIPEA (2.1 mL, 12.12 mmol) were combined in DMF (10 mL) and stirred at room temperature for 2 hours. The reaction mixture divided into two portions and each loaded on to an SCX-2 column (20 g) pre-wet with MeOH (2 column volumes), flushed with MeOH (2 column volumes) and eluted with 2M ammonia in MeOH. Product containing fractions were evaporated and the residue taken up in DCM and purified on a silica column eluting with a 0 – 5% gradient of 2M ammonia in MeOH / DCM then 5% 2M ammonia in MeOH / DCM. Fractions containing product were combined and evaporated to yield the title compound as an orange gum which solidified on standing to an orange solid (472 mg, 38%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ0.37 (m, 2H), 0.55 (m, 2H), 1.75 (m, 4H), 2.50 (m, 6H), 3.42 (m, 2H), 4.08 (s, 2H), 6.43 (m, 1H), 7.70 (m, 1H), 8.53 (m, 1H); MS m/z 310 $[M+H]^+$.

Intermediate 270:

2'-chloro-9'-cyclohexyl-5'-methyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one

To a stirred solution of 2'-chloro-9'-cyclohexyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one (Intermediate 271; 849 mg, 2.767 mmol) in DMA (60 mL) under nitrogen was added methyl iodide (190 µL, 3.044 mmol). The mixture was cooled on an ice/water bath and sodium hydride (60% mineral oil dispersion; 122 mg, 3.044 mmol) added in one portion. The reaction mixture was stirred on the ice/water bath for 1 hour, the cooling bath removed and allowed it to warm to room temperature. After 1.5 hours the solvent was evaporated and the residue treated with an excess of water. This afforded a solid, which was filtered off and washed well with water and then dried by dessication under high vacuum over P_2O_5 overnight. To yield the title compound as an off-white solid (887 mg, 100%)

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.57 - 0.60 (2H, m), 0.97 - 1.04 (1H, m), 1.05 - 1.08 (2H, m), 1.18 - 1.28 (2H, m), 1.34 - 1.44 (2H, m), 1.60 - 1.67 (1H, m), 1.71 - 1.78 (4H, m), 3.19 (3H, s), 3.40 (2H, s), 4.42 - 4.50 (1H, m), 7.77 (1H, s); MS m/z 321 $[M+H]^+$.

Intermediate 271:

2'-chloro-9'-cyclohexyl-8',9'-dihydrospiro[cyclopropane-1,7'-pyrimido[5,4-b][1,4]diazepin]-6'(5'H)-one

Ethyl 1-[[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclohexyl-amino]methyl]cyclopropane-1-carboxylate (Intermediate 272; 3.89 g, 10.16 mmol) was dissolved in the acetic acid (75 mL) and the solution heated with stirring to 72 °C under nitrogen on an oil bath. Iron powder (1.5 g) was added in one portion giving a small exotherm to 75 ^{0}C over the subsequent 15 minutes. The reaction temperature dropped back to 72 °C and the reaction was maintained at this temperature for 3 hours and then allowed to cool to room temperature overnight.

The reaction mixture was reheated and filtered hot through celite, and the pad washed with more acetic acid. The filtrate was concentrated *in vacuo*, then sonicated in saturated aqueous sodium hydrogen carbonate solution to give a brown suspension. This was filtered, and the resulting solid washed with water. The solid was sucked dry, and suspended in methanol with sonication. The suspension was then diluted with DCM, and sodium sulphate added. This mixture was filtered to give a yellow solution, which was concentrated *in vacuo*

to give a yellow solid, which was triturated under cold methanol to give the product as a white powder. The mother liquors were purified on a silica column, to give more clean product, which was combined with the first batch to yield the title compound as a white solid (850 mg, 27%).

^{1}H NMR (400.13 MHz, DMSO-d_6) δ 0.88 - 0.91 (2H, m), 1.05 - 1.15 (1H, m), 1.15 - 1.18 (2H, m), 1.31 - 1.42 (4H, m), 1.61 - 1.63 (3H, m), 1.74 - 1.81 (2H, m), 3.44 (2H, s), 4.44 (1H, s), 7.93 (1H, s), 9.77 (1H, s); MS m/z 307 $[M+H]^+$.

Intermediate 272:

ethyl 1-[[(2-chloro-5-nitro-pyrimidin-4-yl)-cyclohexyl-amino]methyl]cyclopropane-1-carboxylate

To a solution of ethyl 1-[(cyclohexylamino)methyl]cyclopropane-1-carboxylate (Intermediate 273; 7.175 g, 34 mmol) in acetone (200 mL) was added potassium carbonate 7.05 g, 51 mmol) followed by 2,4-dichloro-5-nitropyrimidine (Aldrich; 9.235 g, 47.6 mmol). The reaction mixture was stirred at room temperature for 5 hours. A further addition of 2,4-dichloro-5-nitropyrimidine (4.62 g, 23.8 mmol) and potassium carbonate (3.5 g, 25.5 mmol) was made and the reaction stirred overnight at room temperature. The reaction mixture was then concentrated *in vacuo* and partitioned between EtOAc and water. The EtOAc layer was separated, dried over sodium sulphate and purified on a silica column eluting with EtOAc / isohexane 10:90, to yield the title compound as a yellow oil (12 g, 92%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.76 - 0.83 (2H, m), 0.90 - 0.97 (1H, m), 1.00 (4H, s), 1.04 - 1.10 (2H, m), 1.13 - 1.15 (2H, m), 1.56 (6H, m), 2.93 - 2.99 (1H, m), 3.69 (2H, s), 3.94 (2H, q), 8.49 (1H, s); MS m/z 383 $[M+H]^+$.

Intermediate 273:

ethyl 1-[(cyclohexylamino)methyl]cyclopropane-1-carboxylate

To a solution of ethyl 1-(aminomethyl)cyclopropane-1-carboxylate (Intermediate 114; 20.65 g, 50 mmol) in DCM (200 mL) was added cyclohexanone (Aldrich; 5.28 mL, 51 mmol). After stirring at room temperature for 15 minutes, sodium acetate (4.185 g, 75 mmol) was added, followed by sodium triacetoxyborohydride (15.905 g, 75 mmol). The suspension was stirred at room temperature for 2 days then partitioned between DCM and saturated aqueous

sodium hydrogen carbonate solution. The organic solution was dried over sodium sulphate and evaporated to yield the title compound as a colourless oil (7.2 g, 64%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.55 - 0.58 (2H, m), 0.81 - 0.97 (4H, m), 0.99 - 1.08 (7H, m), 1.34 - 1.39 (1H, m), 1.47 - 1.51 (2H, m), 1.57 - 1.65 (2H, m), 2.14 - 2.21 (1H, m), 2.49 (2H, s), 3.88 (2H, q).

Intermediate 274:

4-amino-2,5-difluoro-N-[(1S,5R)-9-methyl-9-azabicyclo[3.3.1]non-7-yl]benzamide

A mixture of the 4-Amino-2,5-Difluorobenzoic Acid (Rarechem; 2.4 g, 13.87 mmol) and Endo-9-methyl-9-azabicyclo[3,3,1]-nonan-3-amine (Chempacific; 2.355 g, 15.26 mmol) was dissolved in DMF (150 mL), and to the solution was added DIPEA (5.3 mL, 27.74 mmol). The reaction was cooled on an ice-bath, and HATU(5.805 g, 15.26 mmol) was added, portionwise. The reaction mixture was then stirred at ambient temperature for 18 hours, solvent evaporated, and the residue partitioned between ethyl acetate (200 mL), and saturated aqueous sodium carbonate solution (3 x 50 mL), washed with brine (3 x 50 mL), dried over anhydrous magnesium sulphate, filtered, and the solvent evaporated. The residue was purified on an SCX-2 column (50 g), developing and eluting with 1) water ; 2) MeOH ; and 3) 3.5M NH_3-MeOH.The solvent was evaporated to yield the title compound as a tan crystalline solid (2.58 g, 60%).

^{1}H NMR (400.1MHz; $CDCl_3$) δ 1.00-1.10 (2H,d), 1.23-1.33 (2h,dt), 1.48-1.58 (1H,m), 1.85-2.03 (4H,d+m), 2.50 (3H,s), 2.44-2.56 (2H,m), 3.04-3.12 (2H,d), 4.20 (2H,s), 4.42-4.56 (1H,m), 6.33-6.50 (1H,m), 6.42-6.50 (1H,dd),7.70-7.77 (1H,dd). MS m/z 310 $[M+H]^+$.

Intermediate 275:

4-amino-3-methoxy-N-[(1R,5S)-9-methyl-3-oxa-9-azabicyclo[3.3.1]non-7-yl]benzamide

N-Ethyldiisopropylamine (0.119 mL, 0.68 mmol) was added to 4-amino-3-methoxybenzoic acid (Aldrich; 114 mg, 0.68 mmol), (1R,5S,7s)-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-amine (Bioorganic & Medicinal Chemistry Letters (1992), 2(6), 519-22, 107 mg, 0.68 mmol) and HATU (260 mg, 0.68 mmol) in DMF (5 mL) at 25°C. The resulting solution was stirred at ambient temperature for 6 hours. The DMF was evaporated to give a brown gum as residue, which was purified by ion exchange chromatography, using an SCX-2 (5g) column

pre-wet with methanol. The desired product was eluted from the column using 2M NH3/MeOH and purified fractions were evaporated to dryness to afford a brown gum which was purified by flash silica chromatography, elution gradient 0 to 100% 5% MeOH/DCM in DCM. Pure fractions were combined and evaporated to dryness to afford the title compound as a beige coloured gum (205 mg, 98 %).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.38 (2H, d), 2.39 - 2.45 (2H, m), 2.53 (3H, s), 2.58 - 2.68 (4H, m), 3.64 (2H, d), 3.83 (3H, s), 4.58 - 4.64 (1H, m), 5.60 (2H, s), 6.59 (1H, d), 7.09 (1H, d), 7.33 (1H, d), 8.80 (1H, d); MS m/z 306 $[M+H]^+$.

Supplier Details

Apin Chemicals Ltd
43d Milton Park
Abingdon
Oxon
OX14 4RU
UK

ABChem Inc
5785 Chemin St-Francois
Ville St-Laurent
Quebec H4S 1B6, Canada

ABCR GmbH & Co. KG
Im Schlehert 10
D-76187 Karlsruhe
Germany

Activate Scientific GMBH
Eichenstrasse 36
D-93161 Regensburg
Germany

Sigma-Aldrich Company Ltd.
The Old Brickyard
New Road
Gillingham
Dorset
SP8 4XT
UK

Apollo Scientific Ltd.
Whitefield Rd.
Bredbury,
Stockport,
Cheshire,
SK6 2QR
United Kingdom

ASDI Inc
601 Interchange Blvd.
Newark,
DE, 19711
USA

Asinex Ltd.
6 Schukinskaya Street
Moscow
123182
Russia

CBI Building Blocks
40-144 Leninsky Prospect,
Moscow, 119334

Russia

ChemBridge Corporation
16981 Via Tazon
Suite G
San Diego
CA 92127
USA

ChemPacific Corporation
6200 Freeport Center
Baltimore
MD 21224
USA

Chembasics Pty Ltd
5 Blamey St
Unit 1
O'Connor
WA 6163
Australia

Chemstep
20 Avenue Victor Hugo
Carbon Blanc
33560
France

Enamine Ltd.
23 Alexandra Matrosova Street
Kiev

01103
Ukraine

Maybridge
Treville
Tintagel
Cornwall
PL34 OHW
UK

Fluka Chemie AG
Industriestrasse 25
9471 Buchs
Switzerland

Fluorochem Ltd
Wesley Street
Glossop
Derbyshire
SK13 7RY
UK

Frinton Laboratories, Inc.
P.O. Box 2428
NJ, 08362
United States

Matrix Marketing GMBH
Bahnweg Nord 35
CH-9475 Sevelen
Switzerland

Suzhou ChonTech PharmaChem Technology Company Ltd
77 Jinfeng Rd.
Suzhou
Jiang
China

TimTec LLC
Harmony Business Park Building 301-A
Newark
DE
USA
19711

Zelinsky Institute of Organic Chemistry
47 Leninsky Prospect
Moscow, 117913
Russia

Biological Assays for inhibition of PLK

The following assay was used to measure the effects of the compounds of the present invention as Plk kinase inhibitors.

In Vitro Plk1 Enzyme Assay

The assay uses Scintillation Proximity Assay (SPA) technology (Antonsson et al., Analytical Biochemistry, 1999, 267: 294-299) to determine the ability of test compounds to inhibit phosphorylation by recombinant Plk1. The full-length Plk1 protein is expressed in insect cells as an N-terminal 6His tag fusion and purified by standard Nickel chelate purification techniques using the His tag.

The amino terminal fragment of Cdc25C (encoding residues 1-165) is expressed in E.coli as a GST fusion and purified using the GST tag by standard purification techniques.

Test compounds were prepared as 10mM stock solutions in dimethyl sulphoxide (DMSO) and diluted into water as required to give a range of final assay concentrations. Aliquots (5µl) of each compound dilution were dispensed into a well of a 384-well flat bottom white polystyrene plate (Matrix, Catalogue No. 4316). A 35µl mixture of recombinant purified Plk1 enzyme (12ng/well), purified GST-Cdc25C (150ng/well), adenosine triphosphate (ATP; 64nM), ^{33}P-labelled adenosine triphosphate (^{33}P-ATP; 60 nCi/well) in a buffer solution [comprising 50mM HEPES pH7.5 buffer, 10mM manganese chloride ($MnCl_2$), 1mM dithiothreitol (DTT), 1mg/ml bovine serum albumin (BSA), 100µM sodium vanadate (Na_3VO_4), 100µM sodium fluoride (NaF) and 10mM sodium glycerophosphate] was added and the reactions incubated at ambient temperature for 90 minutes.

Reactions were stopped by addition of EDTA (110mM) and the Cdc25C substrate captured via its GST tag to anti-GST antibody (Molecular Probes, Cat No A-5800) coated Protein A PVT SPA beads (Amersham Biosciences, Catalogue No. RPQ0019; 250µg/well) in 50mM HEPES pH7.5 buffer containing 0.05% (w/v) sodium azide and incubated for up to 2 hours, followed by the addition of 20µl of 4M caesium chloride (final assay concentration of 1M). Plates were then left in the dark overnight before counting on a Packard TopCount NXT.

Radiolabelled phosphorylated substrate is formed *in situ* as a result of Plk1 mediated phosphorylation. The SPA beads contain a scintillant that can be stimulated to emit light. This stimulation only occurs when a radiolabelled phosphorylated substrate is bound to the surface of the coated SPA bead causing the emission of blue light that can be measured on a scintillation counter. Accordingly, the extent of Plk1 mediated Cdc25C phosphorylation was assessed. The raw assay data were then analysed by non-linear regression analysis and Plk1 enzyme inhibition for a given test compound is expressed as an IC50 value.

The following examples were tested in this assay and were measured to have IC50 values less than 100 uM

4, 50, 51, 53, 54, 74, 77, 88, 94, 96, 99, 116, 117, 118, 120, 121, 122, 123, 125, 133, 134, 135, 136, 137, 140, 141, 144, 145, 146, 147, 148, 149, 151, 153, 154, 155, 156, 157, 158, 159, 160, 163, 164, 166, 168, 169, 172, 174,

175, 177, 180, 183, 187, 199, 205, 239, 247, 248, 249, 251, 253, 254, 255, 256, 257, 258, 260, 261, 263, 264, 265, 266, 268, 273, 275, 276, 277, 433,

with the following examples having IC50 values less than 1uM

7, 8, 12, 24, 31, 32, 35, 36, 37, 38, 52, 65, 67, 70, 76, 80, 81, 89, 90, 93, 95, 98, 105, 107, 109, 112, 113, 115, 124, 128, 129, 130, 131, 132, 138, 139, 143, 150, 161, 162, 165, 173, 178, 179, 182, 184, 191, 195, 196, 197, 200, 212, 215, 216, 220, 223, 225, 226, 227, 228, 230, 233, 238, 243, 244, 250, 259, 262, 267, 272, 282, 323, 383, 410,

with the following having IC50 values less than 0.3 uM

1, 2, 5, 6, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 33, 34, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 69, 71, 72, 73, 75, 78, 82, 83, 84, 85, 86, 87, 91, 92, 100, 102, 104, 111, 114, 119, 142, 170, 176, 181, 185, 186, 188, 189, 193, 194, 201, 202, 203, 206, 207, 208, 209, 210, 211, 212, 213, 217, 218, 219, 221, 222, 224, 229, 231, 232, 234, 235, 236, 237, 240, 241, 245, 246, 269, 270, 281, 283, 314, 315, 316, 317, 318, 319, 320, 321, 322, 325, 326, 327, 328, 382, 385, 386, 387, 430, 431, 432.

For example, Example14 was measured to have an IC50 of 110nM, Cell IC50 92 nM.

Cellular Assay

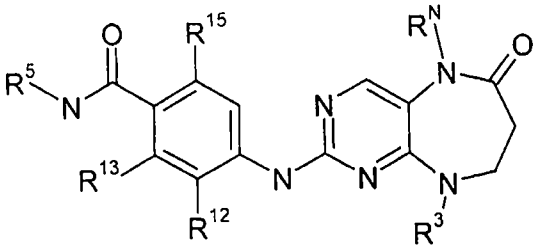
Chromosome condensation in mitosis is accompanied by phosphorylation of histone H3 on serine 10. Dephosphorylation begins in anaphase and ends at early telophase, thus histone H3 serine 10 phosphorylation acts as an excellent mitotic marker and is used to determine the ability of compounds of the present invention to block cells in mitosis.

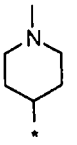
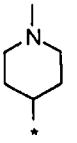
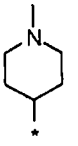
Cells of the human colon tumour cell line HT29 were seeded into 96 well black plates (Costar, Catalogue No 3904) in phenol red free Dulbecco's Modified Eagles Medium (DMEM) supplemented with 10% (v/v) FCS and 1% (v/v) L-Glutamine and incubated overnight at 37°C. Test compounds were solubilised in DMSO, diluted to give a range of final assay concentrations, added to cells and incubated for 24h at 37°C. After 24 hours, cells were fixed in 3.7% (v/v) formaldehyde then permeabilised and blocked for 10 minutes in 100µl 0.5% (v/v) Triton X-100, 1% (w/v) bovine serum albumin (BSA) in phosphate buffered saline (PBS). After washing with PBS, 50µl primary antibody (1:500 dilution of rabbit anti-phosphohistone H3 (Upstate Catalogue No 06-570) in 1% BSA, 0.05% Tween 20) was added to the cells that were left for 1 hour at room temperature. Cells were again washed with PBS and incubated with 50µl secondary antibody (1:1000 Alexa Fluor 488 goat anti-rabbit (Molecular Probes Cat No A-11008) and Hoechst (1:10000) diluted in PBS 0.05% (v/v) Tween 20 and left for 1 hour at room temperature in the dark. Cells were washed with PBS then covered with fresh PBS and stored at 4°C until analysis. Images are acquired and analysed in an automated manner using the Cellomics ArrayScan II or VTi. In this assay both hoechst and phosphohistone H3 staining are measured. Hoechst staining generates a valid cell count while phosphohistone H3 staining determines the number of mitotic cells. Inhibition of Plk leads to an increase in the population of histone H3 Ser10 positive cells, indicating inhibition of proliferation is brought about primarily by arrest of cells in the mitotic phase of the cell cycle. The raw assay data were analysed by non-linear regression analysis and used to determine an IC50 value for each compound.

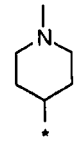
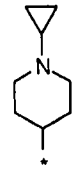
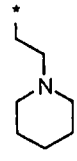
The following example compounds when tested in this assay and had an IC50 value of less than 30uM 5, 23, 24, 40, 42, 89, 103, 105, 107, 112, 115, 122, 123, 124, 125, 126, 127, 128, 129, 131, 132, 133, 138, 143, 159, 165, 167, 170, 171, 173, 177, 178, 179, 180, 186, 187, 192, 195, 212, 215, 218, 220, 221, 223, 224, 228, 229, 230, 231, 232, 233, 248, 253, 256, 257, 263, 264, 265, 270, 271, 272, 275, 277, 284, 286, 287, 296, 297, 332, 410 with the following examples having an IC50 less than 1uM 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451 with the following example have an IC50 of less than 0.3 uM 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35,

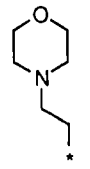
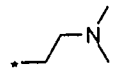
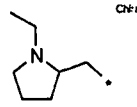
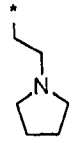
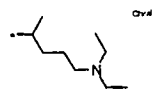
36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453.

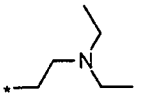
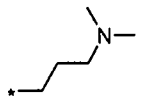
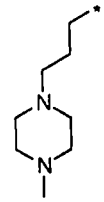
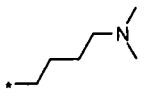
For example, Example14 was measured to have an IC50 92 nM.

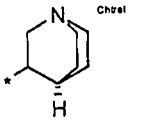
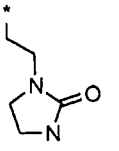
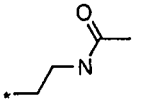
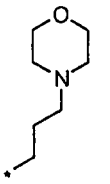


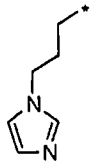
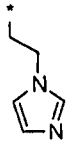
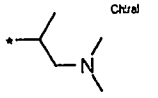
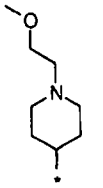
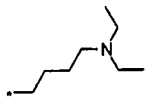
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 1:	Cyclopentyl	Me	OMe	H	H	
Example 2:	Cyclopentyl	Me	H	H	H	
Example 6:	^{i}Pr	Me	OMe	H	H	

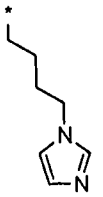
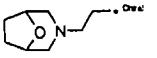
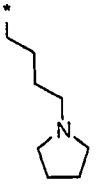
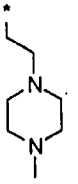
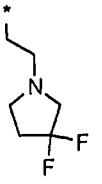
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 8:	Cyclohexyl	Me	OMe	H	H	
Example 10:	Cyclopentyl	Me	OMe	H	H	
Example 11:	Cyclopentyl	Me	OMe	H	H	
Example 12:	Cyclopentyl	Me	OMe	H	H	

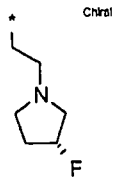
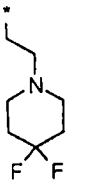
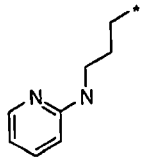
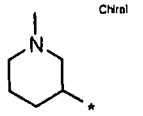
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 13:	Cyclopentyl	Me	OMe	H	H	
Example 14:	Cyclopentyl	Me	OMe	H	H	
Example 15:	Cyclopentyl	Me	OMe	H	H	
Example 16:	Cyclopentyl	Me	OMe	H	H	
Example 17:	Cyclopentyl	Me	OMe	H	H	

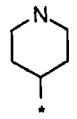
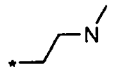
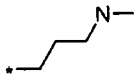
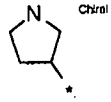
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 18:	Cyclopentyl	Me	OMe	H	H	
Example 19:	Cyclopentyl	Me	OMe	H	H	
Example 20:	Cyclopentyl	Me	OMe	H	H	
Example 21:	Cyclopentyl	Me	OMe	H	H	

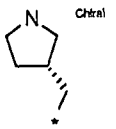
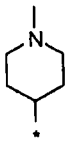
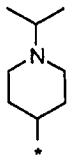
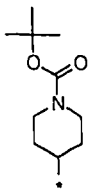
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 22:	Cyclopentyl	Me	OMe	H	H	
Example 23:	Cyclopentyl	Me	OMe	H	H	
Example 24:	Cyclopentyl	Me	OMe	H	H	
Example 25:	Cyclopentyl	Me	OMe	H	H	

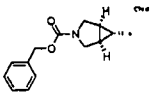
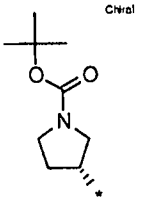
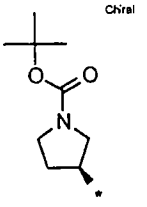
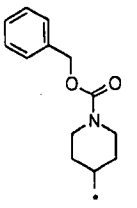
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 26:	Cyclopentyl	Me	OMe	H	H	
Example 27:	Cyclopentyl	Me	OMe	H	H	
Example 28:	Cyclopentyl	Me	OMe	H	H	
Example 29:	Cyclopentyl	Me	OMe	H	H	
Example 30:	Cyclopentyl	Me	OMe	H	H	

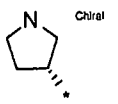
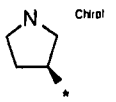
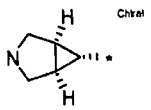
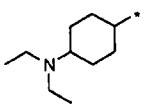
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 31:	Cyclopentyl	Me	OMe	H	H	
Example 32:	Cyclopentyl	Me	OMe	H	H	
Example 33:	Cyclopentyl	Me	OMe	H	H	
Example 34:	Cyclopentyl	Me	OMe	H	H	
Example 35:	Cyclopentyl	Me	OMe	H	H	

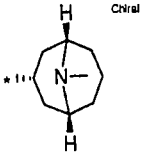
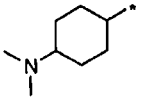
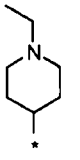
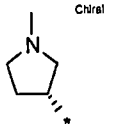
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 36:	Cyclopentyl	Me	OMe	H	H	
Example 37:	Cyclopentyl	Me	OMe	H	H	
Example 38:	Cyclopentyl	Me	OMe	H	H	
Example 39:	Cyclopentyl	Me	OMe	H	H	
Example 40:	Cyclopentyl	Me	OMe	H	H	

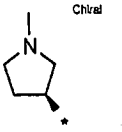
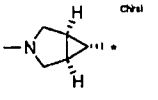
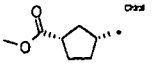
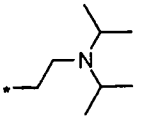
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 41:	Cyclopentyl	Me	OMe	H	H	
Example 42:	Cyclopentyl	Me	OMe	H	H	
Example 43:	Cyclopentyl	Me	OMe	H	H	
Example 44:	Cyclopentyl	Me	OMe	H	H	
Example 45:	Cyclopentyl	Me	OMe	H	H	

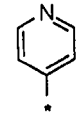
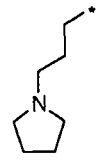
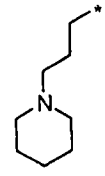
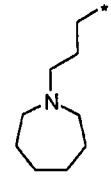
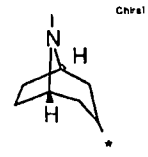
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 46:	Cyclopentyl	Me	OMe	H	H	
Example 47:	Cyclopentyl	Me	OMe	H	H	
Example 48:	Cyclopentyl	Me	OMe	H	F	
Example 49:	Cyclopentyl	Me	OMe	H	H	
Example 50:	Cyclopentyl	Me	OMe	H	H	

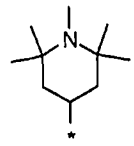
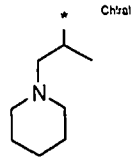
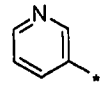
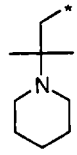
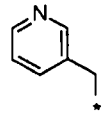
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 51:	Cyclopentyl	Me	OMe	H	H	
Example 52:	Cyclopentyl	Me	OMe	H	H	
Example 53:	Cyclopentyl	Me	OMe	H	H	
Example 54:	Cyclopentyl	Me	OMe	H	H	

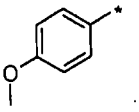
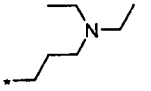
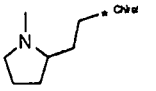
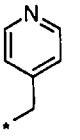
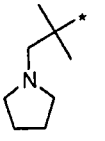
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 55:	Cyclopentyl	Me	OMe	H	H	
Example 56:	Cyclopentyl	Me	OMe	H	H	
Example 57:	Cyclopentyl	Me	OMe	H	H	
Example 58:	Cyclopentyl	Me	OMe	H	H	

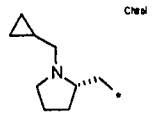
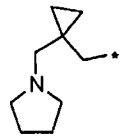
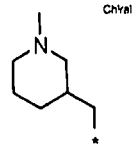
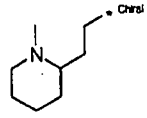
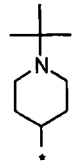
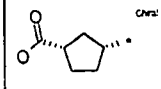
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 59:	Cyclopentyl	Me	OMe	H	H	
Example 60:	Cyclopentyl	Me	OMe	H	H	
Example 61:	Cyclopentyl	Me	OMe	H	H	
Example 62:	Cyclopentyl	Me	OMe	H	H	

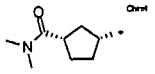
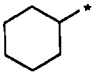
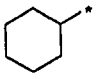
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 63:	Cyclopentyl	Me	OMe	H	H	
Example 64:	Cyclopentyl	Me	OMe	H	H	
Example 65:	Cyclopentyl	Me	OMe	H	H	
Example 66:	Cyclopentyl	Me	OMe	H	H	

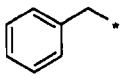
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 67:	Cyclopentyl	Me	OMe	H	H	
Example 68:	Cyclopentyl	Me	OMe	H	H	
Example 69:	Cyclopentyl	Me	OMe	H	H	
Example 70:	Cyclopentyl	Me	OMe	H	H	
Example 71:	Cyclopentyl	Me	OMe	H	H	

Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 72:	Cyclopentyl	Me	OMe	H	H	
Example 73:	Cyclopentyl	Me	OMe	H	H	
Example 74:	Cyclopentyl	Me	OMe	H	H	
Example 75:	Cyclopentyl	Me	OMe	H	H	
Example 76:	Cyclopentyl	Me	OMe	H	H	

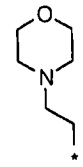
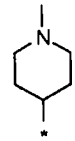
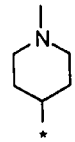
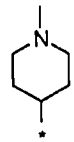
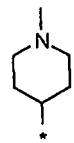
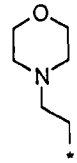
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 77:	Cyclopentyl	Me	OMe	H	H	
Example 78:	Cyclopentyl	Me	OMe	H	H	
Example 79:	Cyclopentyl	Me	OMe	H	H	
Example 80:	Cyclopentyl	Me	OMe	H	H	
Example 81:	Cyclopentyl	Me	OMe	H	H	

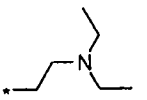
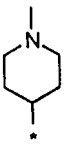
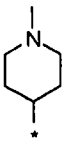
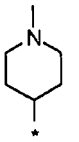
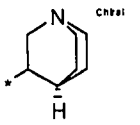
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 82:	Cyclopentyl	Me	OMe	H	H	
Example 83:	Cyclopentyl	Me	OMe	H	H	
Example 84:	Cyclopentyl	Me	OMe	H	H	
Example 85:	Cyclopentyl	Me	OMe	H	H	
Example 86:	Cyclopentyl	Me	OMe	H	H	
Example 87:	Cyclopentyl	Me	OMe	H	H	

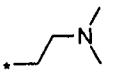
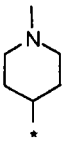
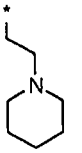
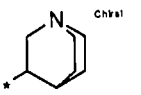
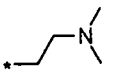
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 88:	Cyclopentyl	Me	OMe	H	H	
Example 89:	Cyclopentyl	Me	H	H	H	
Example 90:	Cyclopentyl	Me	OMe	H	H	
Example 91:	Cyclopentyl	Me	OMe	H	H	

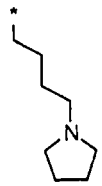
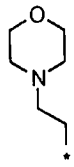
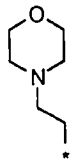
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 92:	Cyclopentyl	Me	OMe	H	H	H
Example 93:	Cyclopentyl	Me	OMe	H	H	
Example 94:	Cyclopentyl	Me	OMe	H	H	
Example 95:	Cyclopentyl	Me	OMe	H	H	
Example 96:	Cyclopentyl	Me	OMe	H	H	
Example 97:	Cyclopentyl	Me	H	H	H	H

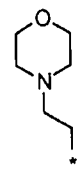
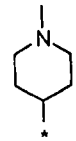
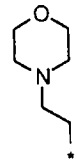
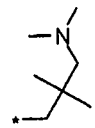
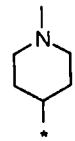
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 98:	Cyclopentyl	Me	OMe	H	H	
Example 99:	Cyclopentyl	Me	OMe	H	H	
Example 100:	Cyclopentyl	Me	H	H	H	
Example 101:	Cyclopentyl	Me	H	H	H	
Example 102:	Cyclopentyl	Me	H	H	H	

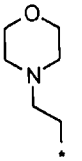
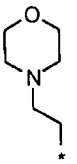
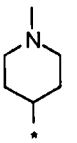
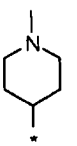
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 184:	Cyclopentyl	Me	Cl	H	H	
Example 185:	Cyclopentyl	Me	Cl	H	H	
Example 187:	Cyclopentyl	Me	H	H	F	
Example 188:	Cyclopentyl	Me	F	H	F	
Example 189:	Cyclopentyl	Me	H	H	H	
Example 191:	Cyclopentyl	Me	H	H	H	

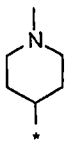
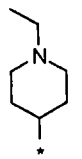
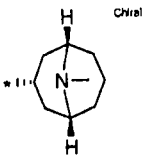
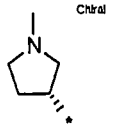
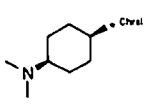
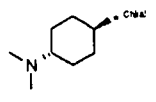
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 192:	Cyclopentyl	Me	H	H	H	
Example 193:	Cyclopentyl	Me	Me	H	H	
Example 194:	Cyclopentyl	Me	F	H	H	
Example 200:	Cyclopentyl	Me	OEt	H	H	
Example 201:	Cyclopentyl	Me	OEt	H	H	

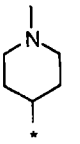
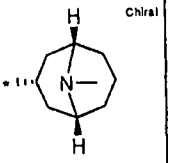
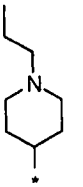
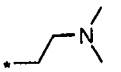
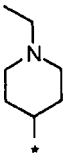
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 202:	Cyclopentyl	Me	OEt	H	H	
Example 203:	^{i}Pr	Me	Cl	H	H	
Example 205:	^{i}Pr	Me	OMe	H	H	
Example 206:	^{i}Pr	Me	OMe	H	H	
Example 207:	^{i}Pr	Me	OMe	H	H	
Example 208:	^{i}Pr	Me	OMe	H	H	

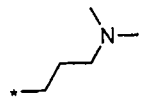
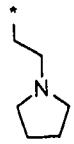
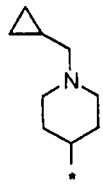
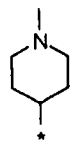
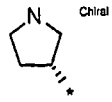
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 209:	^{i}Pr	Me	OMe	H	H	
Example 218:	^{i}Pr	Me	H	H	H	
Example 219:	^{i}Pr	Me	OMe	H	H	
Example 222:	^{i}Pr	Me	H	H	H	

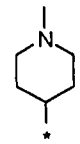
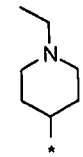
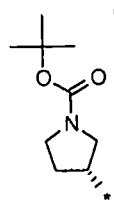
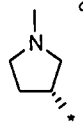
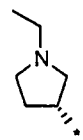
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 228:	^{i}Pr	Me	Cl	H	H	
Example 234:	Cyclopentyl	Me	OMe	H	H	
Example 250:	Cyclopentyl	H	OMe	H	H	
Example 253:	Cyclopentyl	H	H	H	H	
Example 254:	Cyclopentyl	H	H	H	H	

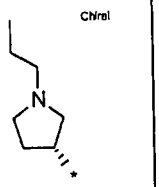
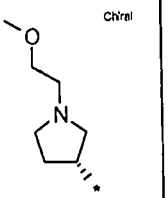
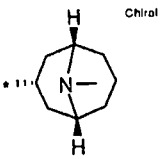
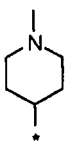
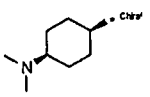
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 255:	Cyclopentyl	H	Cl	H	H	
Example 256:	Cyclopentyl	H	H	H	H	
Example 257:	Cyclopentyl	H	Cl	H	H	
Example 259:	Cyclopentyl	Me	OMe	H	H	
Example 260:	Cyclopentyl	Me	OMe	H	H	

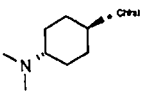
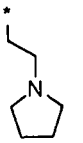
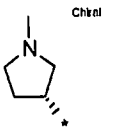
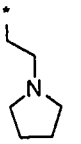
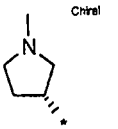
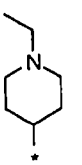
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 281:	^{i}Pr	Me	OEt	H	H	
Example 282:	^{i}Pr	Me	OEt	H	H	
Example 283:	^{i}Pr	Me	OEt	H	H	
Example 284:	^{i}Pr	Me	OEt	H	H	
Example 285:	^{i}Pr	Me	OEt	H	H	
Example 286:	^{i}Pr	Me	OEt	H	H	

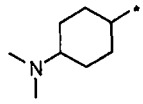
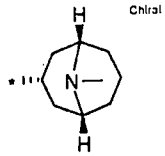
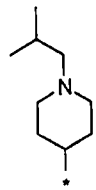
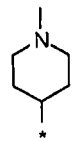
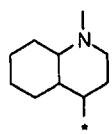
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 287:	^{i}Pr	Me	OEt	H	F	
Example 288:	^{i}Pr	Me	OEt	H	F	
Example 314:	Cyclopentyl	Me	OMe	H	H	
Example 315:	Cyclopentyl	Me	Cl	H	H	
Example 316:	Cyclopentyl	Me	Cl	H	H	

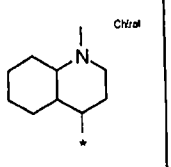
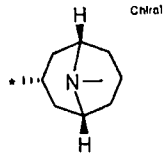
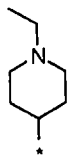
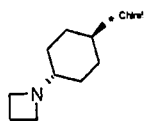
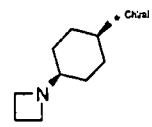
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 317:	Cyclopentyl	Me	Cl	H	H	
Example 318:	Cyclopentyl	Me	Cl	H	H	
Example 319:	Cyclopentyl	Me	OMe	H	H	
Example 320:	Cyclopentyl	Me	OMe	H	Cl	
Example 321:	Cyclopentyl	Me	Cl	H	F	

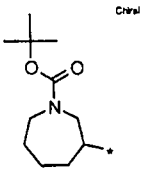
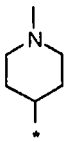
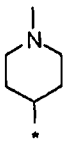
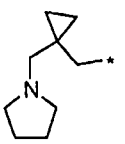
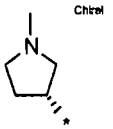
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 322:	Cyclopentyl	Me	Cl	H	F	
Example 323:	Cyclopentyl	Me	Cl	H	F	
Example 324:	Cyclopentyl	Me	Cl	H	F	 Chiral
Example 325:	Cyclopentyl	Me	Cl	H	F	 Chiral
Example 326:	Cyclopentyl	Me	OMe	H	H	 Chiral

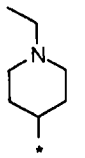
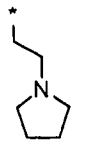
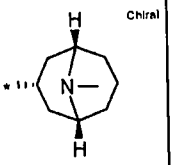
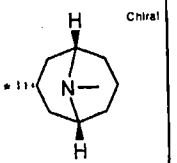
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 327:	Cyclopentyl	Me	OMe	H	H	
Example 328:	Cyclopentyl	Me	OMe	H	H	
Example 329:	Cyclopentyl	Me	F	H	H	
Example 330:	Cyclopentyl	Me	Cl	H	H	
Example 331:	Cyclopentyl	Me	Cl	H	H	

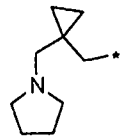
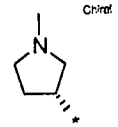
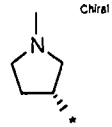
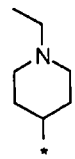
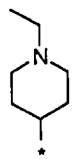
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 332:	Cyclopentyl	Me	Cl	H	H	
Example 333:	Cyclopentyl	Me	OMe	H	F	
Example 334:	Cyclopentyl	Me	F	H	F	
Example 335:	Cyclopentyl	Me	F	H	F	
Example 336:	Cyclopentyl	Me	OMe	H	Cl	
Example 337:	Cyclopentyl	Me	OMe	H	Cl	

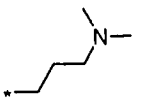
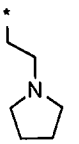
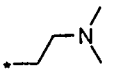
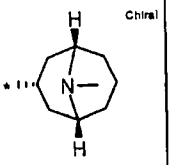
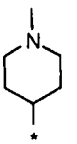
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 338:	Cyclopentyl	Me	OMe	H	Cl	
Example 339:	Cyclopentyl	Me	OMe	H	Cl	
Example 340:	Cyclopentyl	Me	OMe	H	H	
Example 341:	Cyclopentyl	Me	OCH2O		H	
Example 342:	Cyclopentyl	Me	OMe	H	H	

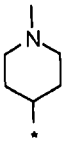
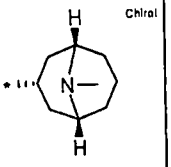
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 343:	Cyclopentyl	Me	OMe	H	H	
Example 344:	Cyclopentyl	Me	OMe	H	F	
Example 345:	Cyclopentyl	Me	F	H	H	
Example 346:	Cyclopentyl	Me	OMe	H	H	
Example 347:	Cyclopentyl	Me	OMe	H	H	

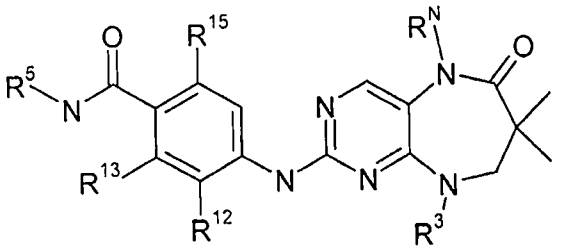
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 348:	Cyclopentyl	Me	OMe	H	H	
Example 411:	Cyclohexyl	Me	F	H	Cl	
Example 412:	Cyclohexyl	Me	F	H	F	
Example 413:	Cyclohexyl	Me	F	H	F	
Example 414:	Cyclohexyl	Me	F	H	F	

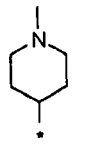
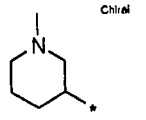
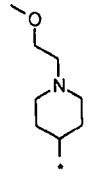
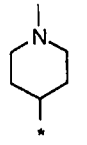
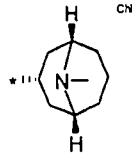
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 415:	Cyclohexyl	Me	F	H	F	
Example 416:	Cyclohexyl	Me	F	H	F	
Example 417:	Cyclohexyl	Me	F	H	H	
Example 418:	Cyclohexyl	Me	OMe	H	H	

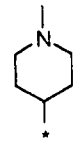
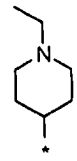
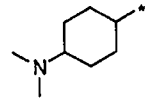
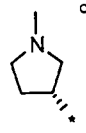
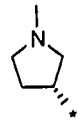
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 419:	Cyclohexyl	Me	OMe	H	F	
Example 420:	Cyclohexyl	Me	OMe	H	F	
Example 421:	Cyclohexyl	Me	OMe	H	H	
Example 422:	Cyclohexyl	Me	OMe	H	F	
Example 423:	Cyclohexyl	Me	OMe	H	H	

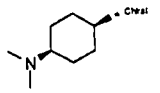
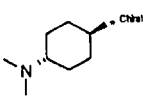
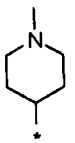
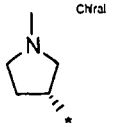
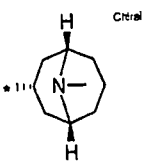
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 424:	Cyclohexyl	Me	OMe	H	H	
Example 425:	Cyclohexyl	Me	OMe	H	F	
Example 426:	Cyclohexyl	Me	OMe	H	H	
Example 427:	Cyclohexyl	Me	OMe	H	F	
Example 428:	Cyclohexyl	Me	H	H	H	

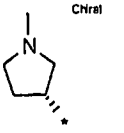
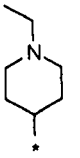
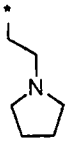
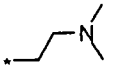
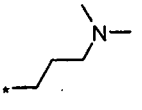
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 429:	Cyclohexyl	Me	F	H	H	
Example 447:	Cyclopentyl	Me	F	H	F	 Chiral

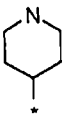
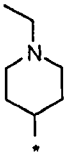
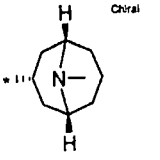
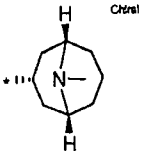


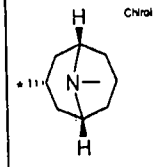
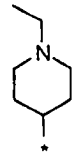
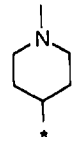
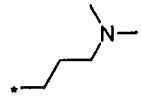
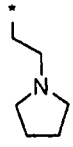
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 235:	Cyclopentyl	Me	OMe	H	H	
Example 243:	Cyclopentyl	Me	OMe	H	H	
Example 244:	Cyclopentyl	Me	OMe	H	H	
Example 245:	Cyclopentyl	Me	H	H	H	
Example 278:	Cyclopentyl	H	OMe	H	H	

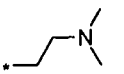
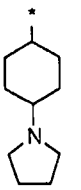
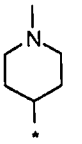
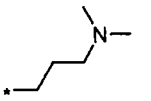
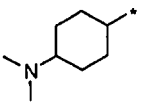
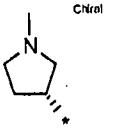
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 289:	^{i}Pr	Me	Cl	H	F	
Example 290:	^{i}Pr	Me	Cl	H	F	
Example 291:	^{i}Pr	Me	Cl	H	F	
Example 292:	^{i}Pr	Me	OMe	H	F	
Example 293:	^{i}Pr	Me	OEt	H	H	

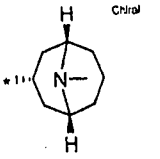
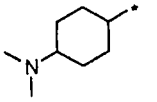
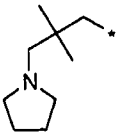
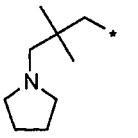
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 294:	^{i}Pr	Me	OEt	H	H	
Example 295:	^{i}Pr	Me	OEt	H	H	
Example 296:	^{i}Pr	Me	OEt	H	F	
Example 297:	^{i}Pr	Me	OEt	H	F	
Example 298:	^{i}Pr	Me	F	H	H	

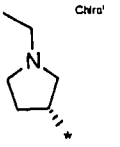
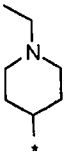
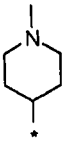
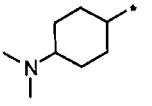
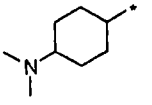
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 299:	^{i}Pr	Me	OMe	H	H	
Example 300:	^{i}Pr	Me	OMe	H	H	
Example 301:	^{i}Pr	Me	OMe	H	H	
Example 302:	^{i}Pr	Me	OMe	H	H	
Example 303:	^{i}Pr	Me	OMe	H	H	

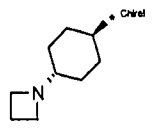
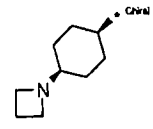
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 349:	Cyclopentyl	Me	OMe	H	H	
Example 350:	Cyclopentyl	Me	OMe	H	H	
Example 351:	Cyclopentyl	Me	OMe	H	H	
Example 352:	Cyclopentyl	Me	OMe	H	F	
Example 353:	Cyclopentyl	Me	F	H	H	

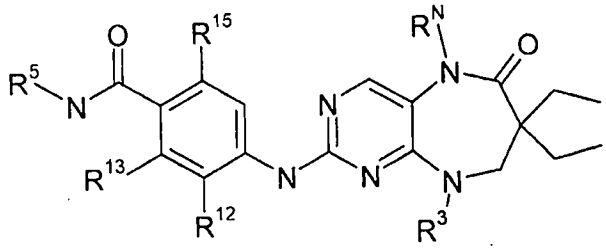
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 354:	Cyclopentyl	Me	OMe	H	H	
Example 355:	Cyclopentyl	Me	F	H	F	
Example 356:	Cyclopentyl	Me	F	H	F	
Example 357:	Cyclopentyl	Me	OMe	H	H	
Example 358:	Cyclopentyl	Me	OMe	H	H	

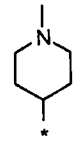
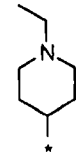
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 359:	Cyclopentyl	Me	OMe	H	H	
Example 360:	Cyclopentyl	Me	OMe	H	H	
Example 361:	Cyclopentyl	Me	OMe	H	F	
Example 362:	Cyclopentyl	Me	Cl	H	H	
Example 363:	Cyclopentyl	Me	OMe	H	H	
Example 364:	Cyclopentyl	Me	OMe	H	F	

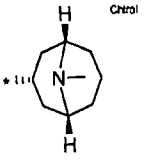
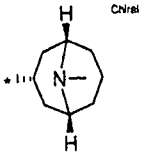
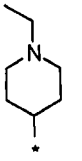
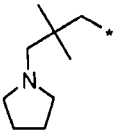
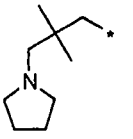
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 365:	Cyclopentyl	Me	H	H	H	
Example 366:	Cyclopentyl	Me	Cl	H	F	
Example 367:	Cyclopentyl	Me	Cl	H	H	
Example 368:	Cyclopentyl	Me	OMe	H	H	

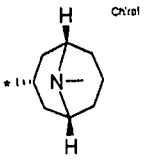
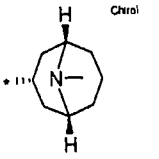
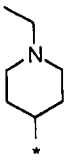
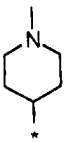
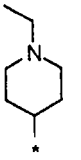
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 369:	Cyclopentyl	Me	OMe	H	H	
Example 370:	Cyclopentyl	Me	OMe	H	F	
Example 371:	Cyclopentyl	Me	F	H	H	
Example 372:	Cyclopentyl	Me	OMe	H	F	
Example 373:	Cyclopentyl	Me	OMe	H	F	

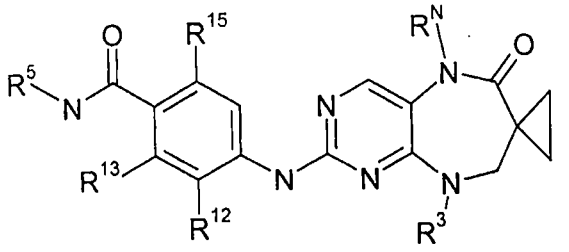
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 374:	Cyclopentyl	Me	OMe	H	H	
Example 375:	Cyclopentyl	Me	OMe	H	H	

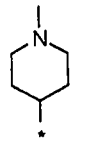
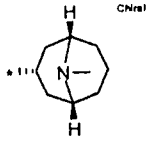
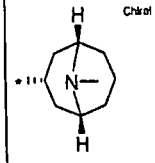
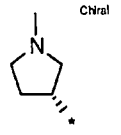
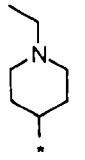


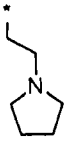
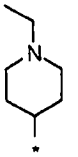
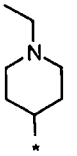
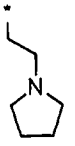
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 304:	^{i}Pr	Me	OMe	H	H	
Example 305:	^{i}Pr	Me	OMe	H	H	

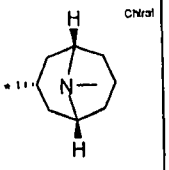
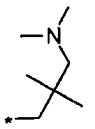
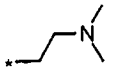
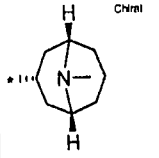
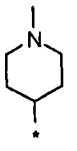
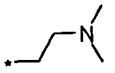
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 306:	^{i}Pr	Me	OMe	H	H	
Example 307:	^{i}Pr	Me	OMe	H	F	
Example 308:	^{i}Pr	Me	OMe	H	F	
Example 309:	^{i}Pr	Me	OMe	H	H	
Example 376:	Cyclopentyl	Me	OMe	H	H	
Example 377:	Cyclopentyl	Me	OMe	H	H	

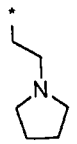
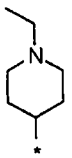
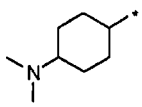
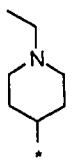
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
						
Example 378:	Cyclopentyl	Me	OMe	H	F	
Example 379:	Cyclopentyl	Me	OMe	H	F	
Example 380:	Cyclopentyl	Me	OMe	H	H	
Example 381:	Cyclopentyl	Me	OMe	H	H	

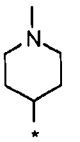
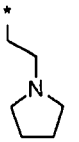
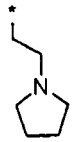
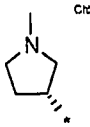
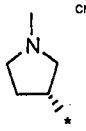


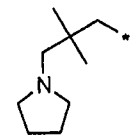
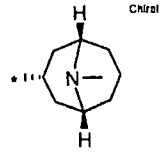
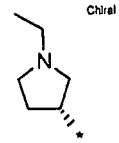
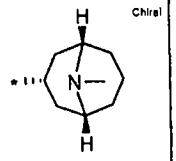
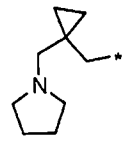
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 246:	Cyclopentyl	Me	OMe	H	H	
Example 279:	Cyclopentyl	H	F	H	H	
Example 280:	Cyclopentyl	H	OMe	H	H	
Example 310:	^{i}Pr	Me	Cl	H	F	
Example 311:	^{i}Pr	Me	Cl	H	F	

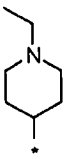
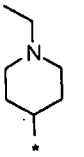
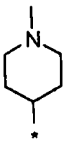
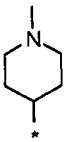
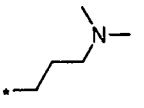
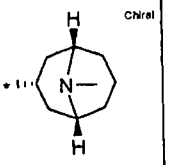
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 312:	^{i}Pr	Me	OMe	H	H	
Example 313:	^{i}Pr	Me	OMe	H	H	
Example 382:	Cyclopentyl	Me	Cl	H	H	
Example 383:	Cyclopentyl	Me	OMe	H	H	
Example 384:	Cyclopentyl	Me	OMe	H	H	

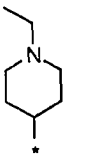
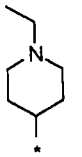
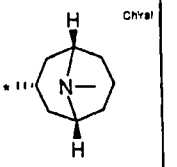
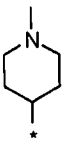
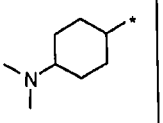
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 385:	Cyclopentyl	Me	OMe	H	H	
Example 386:	Cyclopentyl	Me	OMe	H	H	
Example 387:	Cyclopentyl	Me	OMe	H	H	
Example 388:	Cyclopentyl	Me	F	H	H	
Example 389:	Cyclopentyl	Me	Cl	H	F	
Example 390:	Cyclopentyl	Me	Cl	H	H	

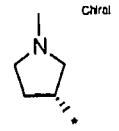
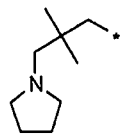
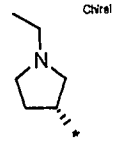
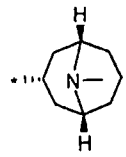
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 391:	Cyclopentyl	Me	Cl	H	H	
Example 392:	Cyclopentyl	Me	Cl	H	H	
Example 393:	Cyclopentyl	Me	Cl	H	F	
Example 394:	Cyclopentyl	Me	Cl	H	F	
Example 395:	Cyclopentyl	Me	F	H	F	

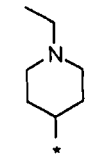
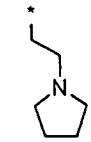
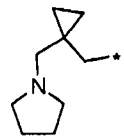
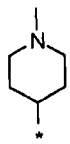
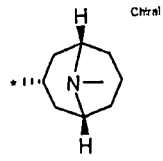
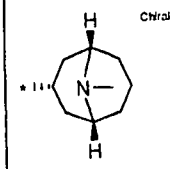
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 396:	Cyclopentyl	Me	F	H	F	
Example 397:	Cyclopentyl	Me	F	H	F	
Example 398:	Cyclopentyl	Me	OMe	H	F	
Example 399:	Cyclopentyl	Me	OMe	H	F	 Chiral
Example 400:	Cyclopentyl	Me	F	H	F	 Chiral

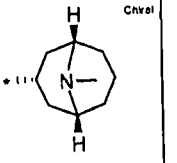
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 401:	Cyclopentyl	Me	OMe	H	H	
Example 402:	Cyclopentyl	Me	Cl	H	H	
Example 403:	Cyclopentyl	Me	OMe	H	H	
Example 404:	Cyclopentyl	Me	OMe	H	F	
Example 405:	Cyclopentyl	Me	OMe	H	F	

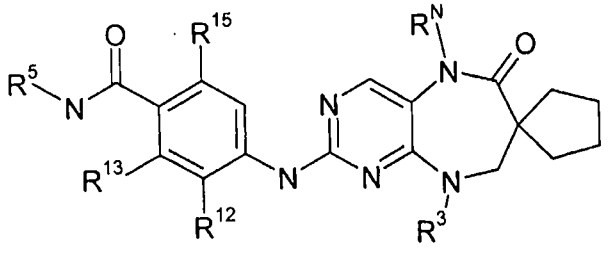
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 406:	Cyclopentyl	Me	F	H	H	
Example 407:	Cyclopentyl	Me	OMe	H	F	
Example 408:	Cyclopentyl	Me	OCH_2O		H	
Example 430:	Cyclohexyl	Me	OMe	H	H	
Example 431:	Cyclohexyl	Me	OMe	H	H	
Example 432:	Cyclohexyl	Me	OMe	H	H	 Chiral

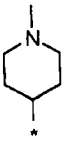
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 433:	Cyclohexyl	Me	OMe	H	H	
Example 434:	Cyclohexyl	Me	F	H	F	
Example 435:	Cyclohexyl	Me	F	H	H	
Example 436:	Cyclohexyl	Me	F	H	F	
Example 437:	Cyclohexyl	Me	Cl	H	F	

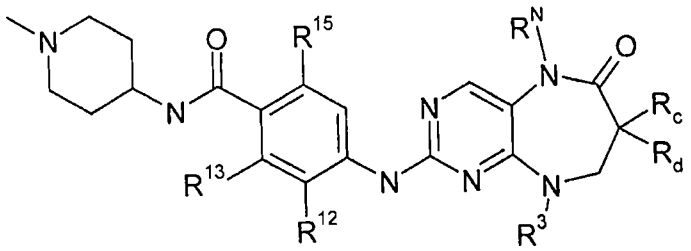
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 438:	Cyclohexyl	Me	OMe	H	F	
Example 439:	Cyclohexyl	Me	OMe	H	H	
Example 440:	Cyclohexyl	Me	OMe	H	H	
Example 441:	Cyclohexyl	Me	OMe	H	H	
Example 442:	Cyclohexyl	Me	OMe	H	F	

Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 443:	Cyclohexyl	Me	OMe	H	F	
Example 444:	Cyclohexyl	Me	OMe	H	F	
Example 445:	Cyclohexyl	Me	OMe	H	F	
Example 446:	Cyclohexyl	Me	F	H	H	
Example 448:	Cyclopentyl	Me	F	H	F	
Example 449:	Cyclohexyl	Me	F	H	F	

Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 450:	Cyclohexyl	H	F	H	H	



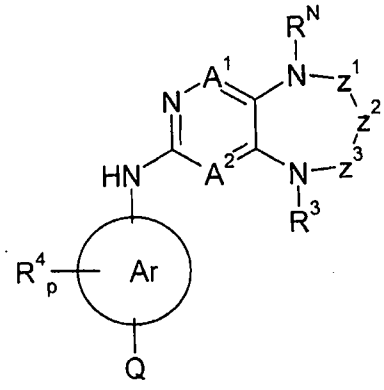
Example	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Example 409:	Cyclopentyl	Me	OMe	H	H	



Example	R^3	R_c	R_d	R^N	R^{12}	R^{13}	R^{15}
Example 3:	Cyclopentyl	Me Racemate		Me	OMe	H	H
Example 236:	Cyclopentyl	Et	H	Me	OMe	H	H
Example 237:	Cyclopentyl	H	Et	Me	OMe	H	H
Example 238:	Cyclopentyl	^{n}Pr	H	Me	OMe	H	H
Example 239:	Cyclopentyl	H	^{n}Pr	Me	OMe	H	H
Example 240:	Cyclopentyl	Me	H	Me	OMe	H	H
Example 241:	Cyclopentyl	H	Me	Me	OMe	H	H

CLAIMS

1. A compound of formula (I):



(I)

wherein

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or an optionally substituted heteroaryl ring comprising 1, 2 or 3 heteroatoms each independently selected from nitrogen, oxygen or sulphur;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered

heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, -OH, -CN, -C=CH, $-C(=O)NH_2$, C_{1-3}alkyl, C_{-1-3}alkylamino, C_{1-3}alkylthio, C_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, -CHO, or $-SO_2Me$

p is 0, 1 or 2;

Q is $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, -(optionally substituted C_{1-3}alkyl)$_g$-$NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ or –(5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur)-L_n-R^5_m;

g is 0 or 1;

k is 0, 1 or 2;

R^a represents H or an optionally substituted C_{1-6}alkyl group, and R^b represents $-L_n-R^5_m$, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a2} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b2} represents $-L_n-R^5_m$, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a3} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b3} represents $-L_n-R^5_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, or R^{a3} and R^{b3} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a4} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b4} represents $-L_n-R^5_m$, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b5} represents $-L_n-R^5_m$, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a6} represents $-L_n-R^5{}_m$;

R^{a7} represents $-L_n-R^5{}_m$;

R^{a8} represents $-L_n-R^5{}_m$;

R^{a9} represents $-L_n-R^5{}_m$;

R^{a10} represents $-L_n-R^5{}_m$;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl, optionally substituted C_{7-12}polycycloalkyl group, optionally substituted C_{7-12}polycycloalkenyl group, optionally substituted C_{5-12}spirocycloalkyl group and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatane, optionally substituted oxogranatane and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group;

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted $-C_{1-4}$alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{1-4}$alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally

substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

X^1 is O or S;

X^2 is O, S or H_2;

Ar represents a 5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur; and

A^1, A^2 each independently represents N or CH;

and wherein

when Z^1 is C=O, Z^2 is CR^cR^d or NR^e and Z^3 is CR^1R^2;

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group; or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d, or R^1 and R^e together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

or when Z^2 is C=O, Z^1 is $CR^{f2}R^{g2}$ and Z^3 is CR^1R^2;

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^{f2}, R^{g2} each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^{f2} and R^{g2} together with

the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^1 and R^3, or R^2 and R^3 together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

or when Z^3 is C=O, Z^2 is $CR^{c3}R^{d3}$ or NR^{e3} and Z^1 is $CR^{f3}R^{g3}$;

R^{c3}, R^{d3} each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^{c3} and R^{d3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^{c3} represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group;

R^{f3}, R^{g3} each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^{f3} and R^{g3} together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^{c3} and R^{f3}, or R^{d3} and R^{g3}, or R^{c3} and R^{f3} together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom

or when Z^1 is CR^fR^g, Z^2 is CR^cR^d or NR^e and Z^3 is CR^1R^2;

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^e represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group;

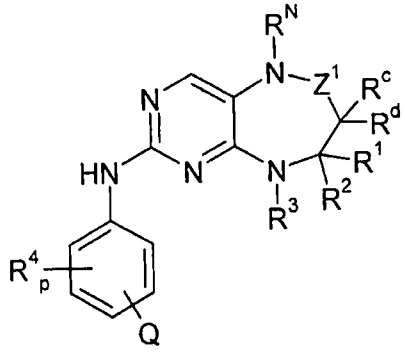
R^f, R^g each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^f and R^g together with the

carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms; or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d, or R^1 and R^{e3} together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom,

or pharmacologically acceptable salts thereof.

2. A compound of formula (II):



(II)

wherein

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an

optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, -OH, -CN, -C=CH, $-C(=O)NH_2$, C_{1-3}alkyl, C_{-1-3}alkylamino, C_{1-3}alkylthio, C_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, -CHO, or $-SO_2Me$;

p is 0, 1 or 2;

Q is $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, -(optionally substituted C_{1-3}alkyl)$_g$-$NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ or –(5- or 6-membered aromatic or heteroaromatic ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur)-L_n-$R^5{}_m$;

g is 0 or 1;

k is 0, 1 or 2;

R^a represents H or an optionally substituted C_{1-6}alkyl group, and R^b represents $-L_n-R^5{}_m$, or R^a and R^b together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a2} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b2} represents $-L_n-R^5{}_m$, or R^{a2} and R^{b2} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a3} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b3} represents $-L_n-R^5{}_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, or R^{a3} and R^{b3} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a4} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b4} represents $-L_n-R^5{}_m$, or R^{a4} and R^{b4} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a5} represents H or an optionally substituted C_{1-6}alkyl group, and R^{b5} represents $-L_n-R^5{}_m$, or R^{a5} and R^{b5} together with the nitrogen atom to which they are attached form a 3- to 7-membered saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms;

R^{a6} represents $-L_n-R^5{}_m$;

R^{a7} represents $-L_n-R^5{}_m$;

R^{a8} represents $-L_n-R^5{}_m$;

R^{a9} represents $-L_n-R^5{}_m$;

R^{a10} represents $-L_n-R^5{}_m$;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl,

optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group;

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted $-C_{1-4}$alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{1-4}$alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and

Z^1 is C=O or CR^fR^g wherein R^f, R^g each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms,

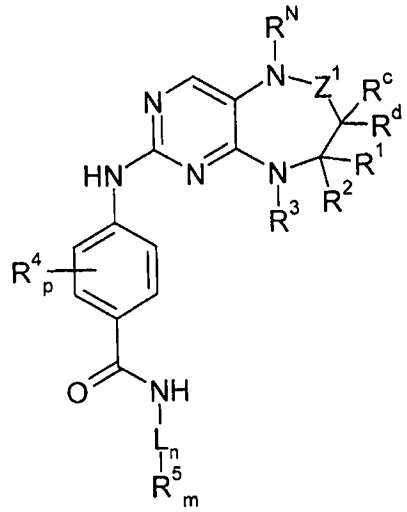
or pharmacologically acceptable salts thereof.

3. A compound according to Claim 1 or 2 wherein R^N represents C_{1-3}alkyl.

4. A compound according to any one of Claims 1 to 3 wherein R^N represents methyl or ethyl.

5. A compound according to any one of Claims 1 to 4 wherein Q represents $-C(=X^1)-NR^aR^b$, wherein X^1 is O, or $-CH_2-NR^{a3}R^{b3}$.

6. A compound of formula (IIa):



(IIa)

wherein

R^1, R^2 each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally

substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

R^N represents hydrogen, $-NH_2$, -OH, -CN, -C=CH, $-C(=O)NH_2$, C_{1-3}alkyl, C_{-1-3}alkylamino, C_{1-3}alkylthio, C_{1-3}alkyloxy, C_{1-3}alkylcarbonyl, -CHO, or $-SO_2Me$;

p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1

m is 1 or 2

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted

azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group;

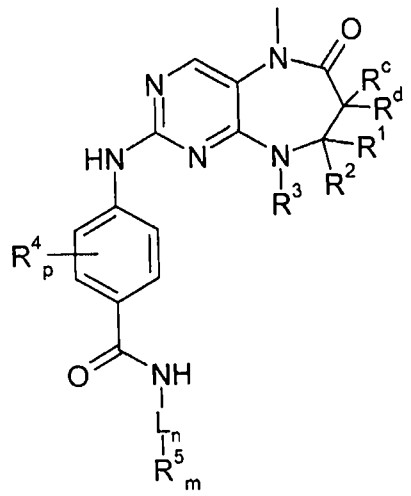
R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted $-C_{1-4}$alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{1-4}$alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms; and

Z^1 is C=O or CR^fR^g wherein R^f, R^g each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^f and R^g together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms,

or pharmacologically acceptable salts thereof.

7. A compound according to Claim 6 wherein Z^1 is C=O or CH_2.

8. A compound of formula (III):



(III)

wherein

R^1, R^2 each independently represents hydrogen or an optionally substituted C_{1-6}alkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^4 each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted $-C_{2-4}$alkyl-C_{6-14}aryl, optionally substituted $-C_{6-14}$aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1;

m is 1 or 2;

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and $-NR^8R^9$;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group; and

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted -C_{1-4}alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{1-4}alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms,

or pharmacologically acceptable salt thereof.

9. A compound according to any one of Claims 6 to 8 wherein R^1 and R^2 are hydrogen.

10. A compound according to Claim 9 wherein one of R^c or R^d is hydrogen.

11. A compound according to Claim 10 wherein one of R^c or R^d is hydrogen and the other is methyl.

12. A compound according to Claim 9 wherein R^c and R^d are methyl.

13. A compound according to Claim 9 wherein R^c and R^d together represent an ethylene bridge.

14. A compound according to Claim 9 wherein R^c and R^d may be identical or different and represent hydrogen or a C_1-C_6alkyl group optionally substituted by one or more substituents selected from C_{1-3}alkyloxy, C_{1-3}alkylthio, C_{1-3}alkyl-$S(O)_2$, C_{1-3}alkylamino and di-(C_{1-3}alkyl)amino.

15. A compound according to any one of Claims 1 to 14 wherein R^3 represents cyclopentyl or cyclohexyl.

16. A compound according to any one of Claims 1 to 15 wherein when p is 1, R^4 represents methoxy, methyl, ethoxy, chlorine or fluorine.

17. A compound according to any one of Claims 1 to 15 wherein when p is 2, each R^4 may be the same or different and selected from methoxy, methyl, ethoxy, ethyl, propargyloxy, chlorine or fluorine.

18. A compound according to any one of Claims 1 to 15 wherein when p is 2 and when each R^4 is adjacent, both R^4 together with the aromatic ring atoms to which they are attached form a 4- to 7-member unsaturated ring optionally comprising 1 to 2 heteroatoms.

19. A compound according to any one of Claims 1 to 18 wherein when n is 1, L represents an optionally substituted a C_{2-10}alkyl or an optionally substituted C_{3-12}cycloalkyl linker.

20. A compound according to Claim 19 wherein when n is 1, L represents cyclohexyl, $-C(CH_3)_2-CH_2-$ or $-CH_2-C(CH_3)_2-CH_2-$.

21. A compound according to any one of Claims 1 to 20 wherein n is 0.

22. A compound according to any one of Claims 1 to 21 wherein m is 1 and R^5 represents hydrogen, $-NR^8R^9$ or a piperidinyl, morpholinyl, pyrrolidinyl, sulphoxomorpholiny, piperazinyl, thiomorpholinyl, tropenyl, granatanyl, oxogranatanyl or azacycloheptyl each optionally substituted by one or more groups as defined for R^8.

23. A compound according to Claim 22 wherein R^5 represents a piperidinyl, pyrrolidinyl, or granatanyl each optionally substituted by one or more groups as defined for R^8.

24. A compound according to Claims 22 or 23 wherein R^8 represents methyl, ethyl or propyl, and/or R^9 represents methyl, ethyl or propyl.

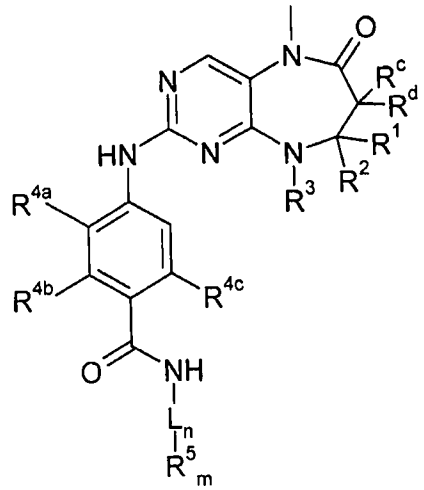
25. A compound according to Claim 8 wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl or optionally substituted C_{6-14}aryl group; p is 0 or 1; R^4 represents OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2, F, CL, Br, O-propargyl, O-butynyl, CN, SMe, NMe_2, $CONH_2$, ethynyl, propynyl, butynyl or allyl; L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{2-4}alkyl-C_{6-14}aryl, optionally substituted -C_{6-14}aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen ring atoms; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes hydrogen or a group, which is bound to L via a carbon atom, selected from among -NR^8R^9, piperidinyl, piperazinyl, pyrrolidinyl, piperazinylcarbonyl, tropenyl, morpholinyl, granatanyl, oxogranatanyl and azacycloheptyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent hydrogen, C_{1-6}alkyl, -C_{1-4}alkyl-C_{3-10}cycloalkyl, C_{3-10}cycloalkyl, C_{6-14}aryl, -C_{1-4}alkyl-C_{6-14}aryl, pyranyl, pyridinyl, pyrimidinyl, C_{1-4}alkyloxycarbonyl, C_{6-14}arylcarbonyl, C_{1-4}alkylcarbonyl, C_{6-14}arylmethyloxycarbonyl, C_{6-14}arylsulphonyl, C_{1-4}alkylsulphonyl or C_{6-14}aryl-C_{1-4}alkylsulphonyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

26. A compound according to Claim 25 wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among -NR^8R^9 and piperidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

27. A compound according to Claim 25 wherein wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

28. A compound according to Claim 25 wherein wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; p is 0, 1 or 2; R^4 each independently represents fluoro or OMe; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and granatanyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge, or pharmacologically acceptable salts thereof.

29. A compound of formula (IIIa):



(IIIa)

wherein

R^1, R^2 each independently represents hydrogen or an optionally substituted C_{1-6}alkyl group, or R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^c, R^d each independently represents hydrogen, an optionally substituted C_{1-6}alkyl group or an optionally substituted C_{3-6}cycloalkyl group, or R^c and R^d together with the carbon atom to which they are attached form a 3- to 6-membered saturated or unsaturated ring optionally comprising 1 to 2 heteroatoms;

R^3 represents hydrogen, an optionally substituted C_{1-12}alkyl group, an optionally substituted C_{2-12}alkenyl group, an optionally substituted C_{2-12}alkynyl group, an optionally substituted C_{6-14}aryl group, an optionally substituted C_{3-12}cycloalkyl group, an optionally substituted C_{3-12}cycloalkenyl group, an optionally substituted C_{7-12}polycycloalkyl group, an optionally substituted C_{7-12}polycycloalkenyl group, an optionally substituted C_{5-12}spirocycloalkyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally substituted 4- to 12-membered heterocycloalkenyl group comprising 1 or 2 heteroatoms, or

optionally one of R^1 and R^3, or R^2 and R^3, or R^1 and R^c, or R^2 and R^d together represent a saturated or unsaturated C_{1-4}alkyl bridge optionally comprising 1 heteroatom;

R^{4a}, R^{4b}, R^{4c} each independently represent -CN, hydroxy, $-NR^6R^7$, $-NR^6SO_2R^7$, halogen, an optionally substituted C_{1-6}alkyl group, an optionally substituted C_{3-7}cycloalkyl group, an optionally substituted C_{2-6}alkenyl group, an optionally substituted C_{2-6}alkynyl group, an optionally substituted C_{1-5}alkyloxy group, an optionally substituted C_{3-6}cycloalkyloxy group, an optionally substituted C_{2-5}alkenyloxy group, an optionally substituted C_{2-5}alkynyloxy group, an optionally substituted C_{1-6}alkythio group, an optionally substituted C_{1-6}alkylsulphoxo group or an optionally substituted C_{1-6}alkylsulphonyl group, an optionally substituted 3- to 12-membered heterocycloalkyl group comprising 1 or 2 heteroatoms, or an optionally

substituted 3- to 12-membered heterocycloalkoxy group comprising 1 or 2 heteroatoms;

p is the number of $R^{4a, 4b, 4c}$ groups that are not hydrogen and is selected from 0, 1 or 2;

L represents a linker selected from optionally substituted C_{2-10}alkyl, optionally substituted C_{2-10}alkenyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{2-4}alkyl-C_{6-14}aryl, optionally substituted -C_{6-14}aryl-C_{1-4}alkyl, optionally substituted C_{3-12}cycloalkyl and optionally substituted heteroaryl comprising 1 or 2 nitrogen atoms;

n is 0 or 1;

m is 1 or 2;

R^5 represents a group selected from among hydrogen, optionally substituted morpholinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, optionally substituted piperazinylcarbonyl, optionally substituted pyrrolidinyl, optionally substituted tropenyl, optionally substituted diketomethylpiperazinyl, optionally substituted sulphoxomorpholinyl, optionally substituted sulphonylmorpholinyl, optionally substituted thiomorpholinyl, optionally substituted azacycloheptyl, optionally substituted granatanyl, optionally substituted oxogranatanyl and -NR^8R^9;

R^6, R^7 each independently represents hydrogen or an optionally substituted C_{1-4}alkyl group; and

R^8, R^9 each independently represents hydrogen, optionally substituted C_{1-6}alkyl, optionally substituted -C_{1-4}alkyl-C_{3-10}cycloalkyl, optionally substituted C_{3-10}cycloalkyl, optionally substituted C_{6-14}aryl, optionally substituted -C_{1-4}alkyl-C_{6-14}aryl, optionally substituted pyranyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted C_{1-4}alkyloxycarbonyl, optionally substituted optionally substituted C_{6-14}arylcarbonyl, optionally substituted C_{1-4}alkylcarbonyl, optionally substituted C_{6-14}arylmethyloxycarbonyl, optionally substituted C_{6-14}arylsulphonyl, optionally substituted C_{1-4}alkylsulphonyl, optionally substituted C_{6-14}aryl-C_{1-4}alkylsulphonyl, or R^8 and R^9 together with the nitrogen atom to which they are attached form a 3- to 7-membered bridged or unbridged, saturated or unsaturated heterocyclic ring optionally comprising 1 to 2 additional heteroatoms,

or pharmacologically acceptable salt thereof.

30. A compound according to Claim 29 wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and piperidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

31. A compound according to Claim 29 wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and pyrrolidinyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

32. A compound according to Claim 29 wherein R^3 represents an optionally substituted C_{1-10}alkyl, optionally substituted C_{3-7}cycloalkyl, optionally substituted C_{3-6}heterocycloalkyl; L represents a linker selected from optionally substituted C_{2-10}alkyl; n denotes 0 or 1; m denotes 1 or 2; R^5 denotes a group selected from among $-NR^8R^9$ and granatanyl each optionally substituted by one or more groups as defined for R^8; R^8, R^9 each independently represent C_{1-6}alkyl; R^1, R^2 are hydrogen; R^c, R^d are each independently selected from hydrogen, Me, or

Et, or R^c and R^d together represent an ethylene bridge; p is 0, 1 or 2; and when p is 1, R^{4b} and R^{4c} are hydrogen and R^{4a} represents methoxy, methyl, ethoxy, chlorine or fluorine; and when p is 2, either R^{4b} is hydrogen and R^{4a} and R^{4c} may be the same or different and selected from methoxy, methyl, ethoxy, chlorine or fluorine, or R^{4c} is hydrogen and R^{4a} and R^{4b} together form a OCH_2O bridge, or pharmacologically acceptable salts thereof.

33. A compound according to any one of Claims 25, 26, 27, 28, 30, 31 or 32 wherein R^3 represents cyclopentyl or cyclohexyl.

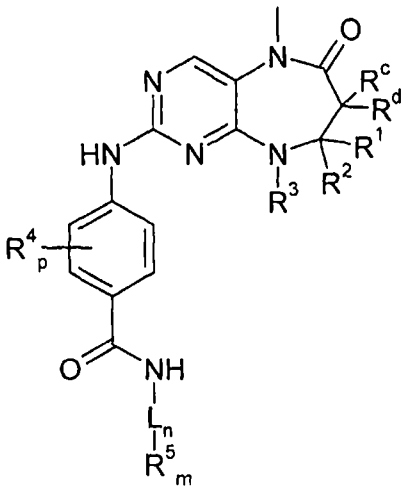
34. A compound according to Claims 33 wherein R^8 represents methyl, ethyl or propyl, and/or R^9 represents methyl, ethyl or propyl.

35. A compound selected from any one of the Examples or pharmacologically acceptable salts thereof.

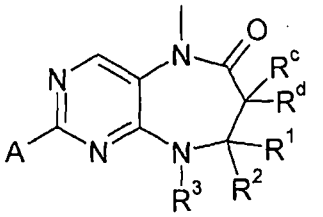
36. A compound selected from any one of Examples 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451, 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453, or pharmacologically acceptable salts thereof.

37. A compound selected from any one of Examples 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 and 453, or pharmacologically acceptable salts thereof.

38. A process for preparing a compound of general formula (III),



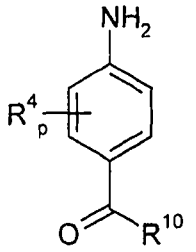
wherein R^1-R^5, R^c, R^d m, n, p and L are as hereinbefore defined, comprising reacting a compound of general formula (IV)



(IV)

wherein R^1-R^3 are as hereinbefore defined and A is a leaving group,

with an optionally substituted compound of general formula (V):



(V)

wherein p and R^4 are as hereinbefore defined; and R^{10} denotes OH, NH-L_m-$R^5{}_n$, OMe, OEt,

and when R^{10} denotes OH, OMe or OEt optionally after previous hydrolysis of the ester group -COR^{10}, reacting with an amine of general formula (VI):

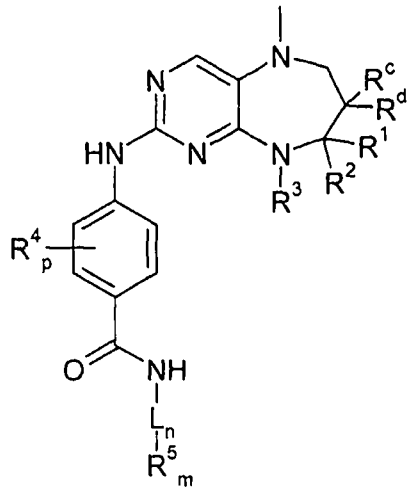
$$NH_2 - L_m - R^5{}_n$$

(VI)

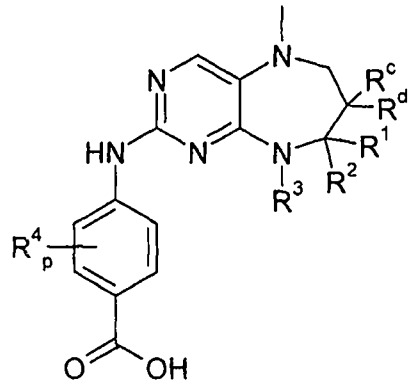
wherein R^5 is as hereinbefore defined,

to give a compound of formula (III).

39. A process for preparing a compound of general formula (XI),



wherein R^1-R^5, R^c, R^d m, n, p and L are as hereinbefore defined, comprising reacting a compound of general formula (XII)



(XII)

with an amine of general formula (VI):

$$NH_2\text{-}L_m\text{-}R^5{}_n$$

(VI)

wherein L and R^5 are as hereinbefore defined.

40. A pharmaceutical composition comprising a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one claims 1 to 37 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

41. A process for the preparation of a pharmaceutical composition as claimed in claim 40 which comprises mixing a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as defined in any one of claim 1 to 37 with a pharmaceutically acceptable adjuvant, diluent or carrier.

42. A compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 37 for use in therapy.

43. Use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 37 in the manufacture of a medicament for the treatment of cancer.

44. Use of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one claims 1 to 37 in the manufacture of a medicament for modulating polo-like kinas (Plk) activity.

45. A method of treating cancer which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 37.

46. A method of modulating polo-like kinase (Plk) activity which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), (II), (IIa), (III) or (IIIa), or a pharmaceutically acceptable salt thereof, as claimed in any one claims 1 to 37.

NUEVOS COMPUESTOS

La presente invención se relaciona con derivados de pirimidina, un proceso para su preparación, composiciones farmacéuticas que los contienen, un proceso para la preparación de las composiciones farmacéuticas, y su uso en terapia y el tratamiento de afecciones mediadas por la quinasa tipo polo.

Muchos de los regímenes de tratamientos actuales para las enfermedades de proliferación celular como el cáncer y la psoriasis utilizan compuestos que inhiben la síntesis de ADN. Los compuestos que inhiben la síntesis de ADN pueden a menudo probar ser tóxicos para muchos tipos de células. Sin embargo, el efecto tóxico marcado de la rápida división de las células tal como las células tumorales es a menudo visto que ofrece un beneficio a la luz de la naturaleza tóxica general de tales compuestos. Por lo tanto, agentes antiproliferativos alternativos que actúan por mecanismos diferentes a la inhibición de la síntesis de ADN pueden ofrecer el potencial para el marcado selectivo de las células proliferantes.

La familia de las quinasas dependientes de las ciclinas (Cdk) han sido ampliamente consideradas los reguladores maestros del ciclo celular pero un número creciente de diversas proteínas quinasas están surgiendo como componentes críticos de la progresión del ciclo celular. Entre estos están la familia de las quinasas tipo polo (Plk), las serina/treonina quinasas que juegan múltiples roles en regular los progresos a través del ciclo celular. En los hombres, cuatro miembros de familias distintas han sido identificados. Estos son Plk1, Plk2 (Snk), Plk3 (Fnk, Prk) y Plk4 (Sak).

El miembro de la familia mejor caracterizado es la Plk1 el cual es conservado de la levadura al hombre y ha sido implicado en numerosos procesos mitóticos incluyendo la activación de Cdc25C y Cdk1/Ciclina B en la transición G2–M, maduración del centrosoma, formación del eje y agrupación (Glover y otros 1998, Genes Dev. 12:3777–87; Barr y otros 2004, Nat. Rev. Mol. Cell Biol 5:429–441). En las últimas etapas de la mitosis, la Plk1 está involucrada en la separación de cromátidos hermanos, la activación de componentes del complejo promotor de la anafase y la regulación de la septina durante la citoquinesis (van Vugt & Medema 2005, Oncogene 24:2844–2859).

La Plk1 es sobre expresada en un amplio espectro de tipos de cánceres incluyendo el de mama, colorectal, endometrial, esofágico, ovario, próstata, pancreático, cánceres y

melanomas del pulmón de células no pequeñas (Wolf y otros 1997, Oncogene 14:543–549; Knecht y otros 1999, Cáncer Res. 59:2794–2797; Wolf y otros 2000, Pathol. Res. Pract. 196:753–759; Takahashi y otros 2003, Cancer Sci. 94:148–152). La expresión de la Plk1 a menudo se correlaciona con pronósticos pobres de los pacientes. La conclusión que la elevación de la Plk1 es una causa y no una consecuencia de la oncogénesis resultó de un estudio que demuestra que la sobre expresión o expresión constitutiva de la Plk1 induce la transformación maligna de las células de mamíferos, provocando la formación del tumor en ratones nude (Smith y otros 1997, Biochem. Biophis. Res. Commun 234:397–405)

El potencial terapéutico para la inhibición de la Plk1 ha sido demostrado en estudios que emplean tanto los oligonucléotidos antisentido (ASO) como los ARN de molécula pequeña (siRNA). La reducción en el nivel de la Plk1 resulta en la inhibición de la proliferación de las células tumorales y la pérdida de la viabilidad celular ambos *in vivo* e *in vitro* pero no inhibe la proliferación de las células primarias (Spankuch–Schmitt y otros 2002, Oncogene 21: 3162–3171; Elez y otros 2003, Oncogene 22:69–80). La microinyección de anticuerpos anti–Plk1 indujeron la catástrofe mitótica en células tumorales HeLa. Estas células exhibieron una distribución anormal de cromatina y microtúbulos monoastrales mientras que las células de fibroblastos normales se detuvieron transitoriamente en la fase G2 del ciclo celular como células mononucleadas simples (Lane y Nigg 1996 J.Cell Biol. 135:1701–1713). Estos resultados sugieren que la inhibición de la Plk1 específicamente está dirigida a las células de cáncer con defectos de punto de chequeo mientras que las células con rutas de punto de chequeo intacto son menos afectadas.

Aunque las funciones exactas de los otros miembros de la familia permanecen ampliamente desconocidas, el silenciamiento de la Plk2 en presencia de taxol o nocodazol significativamente aumenta la apóptosis sugiriendo que la Plk2 puede prevenir la catástrofe mitótica a continuación del daño del eje (Burns y otros 2003, Mol Cell Biol 23: 5556–5571). De igual manera el silenciamiento de la Plk4 en las células de mamíferos induce la apóptosis (Li y otros 2005, Neoplasia 7: 312–323) y los embriones de ratones sin mutación plk4 se detienen con un aumento en las células mitóticas y apoptóticas (Hudson y otros 2001, Curr Biol 11: 441–446).

La Plk3 también parece jugar roles en la mitosis, como la Plk1 esta ha sido reportada para fosforilar el Cdc25C, regular las dinámicas de los microtúbulos y está involucrada en la

función del centrosoma. La sobre expresión de la Plk3 ha sido observada en carcinomas de mama y de ovario, con poca o ninguna expresión en el tejido normal adyacente. El nivel aumentado de proteína estuvo asociado con una mitosis mejorada y estuvo significativamente vinculado al tiempo de supervivencia medio reducido de los pacientes (Weichert y otros 2005, Virchows Arch 446: 442–450; Weichert y otros 2004, Br. J. Cancer 90:815–821).

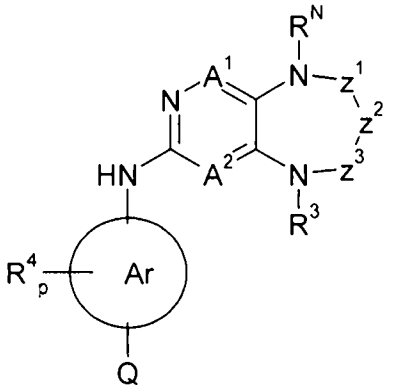
Estos descubrimientos sugieren que los inhibidores farmacológicos de los miembros de la familia de las Plk deben ser de valor terapéutico para el tratamiento de enfermedades proliferativas incluyendo los tumores sólidos tales como carcinomas y sarcomas y las leucemias y malignidades linfoides. Además los inhibidores de la Plk deben ser útiles en el tratamiento de otros trastornos asociados con la proliferación celular descontrolada.

Los derivados de pteridinona son conocidos del arte anterior como sustancias activas con una actividad antiproliferativa. WO 01/019825 y WO 03/020722 describen el uso de derivados de pteridinona para el tratamiento de enfermedades tumorales.

La resistencia de muchos tipos de tumores reclama el desarrollo de nuevas composiciones farmacéuticas para combatir los tumores.

El objeto de la presente invención es proporcionar nuevos compuestos que tienen una actividad antiproliferativa.

De acuerdo a un primer aspecto de la presente invención se proporciona un compuesto de fórmula (I):



(I)

donde

R^3 representa hidrógeno, un grupo opcionalmente sustituido C_{1-12}alquil, un grupo opcionalmente sustituido C_{2-12}alquenil, un grupo opcionalmente sustituido C_{2-12}alquinil, un grupo opcionalmente sustituido C_{6-14}aril, un grupo opcionalmente sustituido C_{3-12}cicloalquil, un grupo opcionalmente sustituido C_{3-12}cicloalquenil, un grupo opcionalmente sustituido C_{7-12}policicloalquil, un grupo opcionalmente sustituido C_{7-12}policicloalquenil, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un anillo heteroaril opcionalmente sustituido que comprende 1, 2 ó 3 heteroátomos cada uno independientemente seleccionado de nitrógeno, oxígeno o azufre;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

R^N representa hidrógeno, $-NH_2$, –OH, –CN, –C=CH, $-C(=O)NH_2$, C_{1-3}alquil, C_{-1-3}alquilamino, C_{1-3}alquiltio, C_{1-3}alquiloxi, C_{1-3}alquilcarbonil, –CHO, o $-SO_2Me$

p es 0, 1 ó 2;

Q es $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, $-(C_{1-3}$alquil opcionalmente sustituido$)_g-NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ o –(anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno y azufre)$-L_n-R^5{}_m$;

g es 0 ó 1;

k es 0, 1 ó 2;

R^a representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^b representa $-L_n-R^5{}_m$, o R^a y R^b junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a2} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b2} representa $-L_n-R^5{}_m$, o R^{a2} y R^{b2} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a3} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b3} representa $-L_n-R^5{}_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, o R^{a3} y R^{b3} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a4} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b4} representa $-L_n-R^5{}_m$, o R^{a4} y R^{b4} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a5} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b5} representa $-L_n-R^5{}_m$, o R^{a5} y R^{b5} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a6} representa $-L_n-R^5{}_m$;

R^{a7} representa $-L_n-R^5{}_m$;

R^{a8} representa $-L_n-R^5{}_m$;

R^{a9} representa $-L_n-R^5{}_m$;

R^{a10} representa $-L_n-R^5{}_m$;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustitutido, C_{2-10}alquenil opcionalmente sustitutido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido, grupo C_{7-12}policicloalquil opcionalmente sustituido, grupo C_{7-12}policicloalquenil opcionalmente sustituido, grupo C_{5-}

$_{12}$espirocicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1

m es 1 ó 2

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azacicloheptil opcionalmente sustituido, granatano opcionalmente sustituido, oxogranatano opcionalmente sustituido y $-NR^8R^9$;

R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido;

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril$-C_{1-4}$alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

X^1 es O o S;

X^2 es O, S o H_2;

Ar representa un anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno y azufre; y

A^1, A^2 cada uno independientemente representa un N o CH;

y donde

cuando Z^1 es C=O, Z^2 es CR^cR^d o NR^c y Z^3 es CR^1R^2;

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c representa hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d, o R^1 y R^c juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

o cuando Z^2 es C=O, Z^1 es $CR^{f2}R^{g2}$ y Z^3 es CR^1R^2;

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^{f2}, R^{g2} cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^{f2} y R^{g2} junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos, u

opcionalmente uno de R^1 y R^3, o R^2 y R^3 juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

o cuando Z^3 es C=O, Z^2 es $CR^{c3}R^{d3}$ o NR^{c3} y Z^1 es $CR^{f3}R^{g3}$;

R^{c3}, R^{d3} cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^{c3} y

R^{d3} junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^{c3} representa hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido;

R^{f3}, R^{g3} cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^{f3} y R^{g3} junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos, u opcionalmente uno de R^{c3} y R^{f3}, o R^{d3} y R^{g3}, o R^{c3} y R^{f3} juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

o cuando Z^1 es CR^fR^g, Z^2 es CR^cR^d o NR^e y Z^3 es CR^1R^2;

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^e representa hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido;

R^f, R^g cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^f y R^g junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos, u opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d, o R^1 y R^{c3} juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo,

o sales farmacéuticamente aceptables del mismo.

El término grupo alquil, incluyendo grupos alquil los cuales son parte de otros grupos, a menos que se indique lo contrario, incluye grupos alquil ramificados y no ramificados con 1

a 12 átomos de carbono. Ejemplos de grupos C_{1-12}alquil incluyen grupos metil, etil, propil, butil, pentil, hexil, heptil, octil, nonil, decil y dodecil. A menos que se indique lo contrario, los términos propil, butil, pentil, hexil, heptil, octil, nonil, decil y dodecil incluyen todas las posibles formas isómericas. Por ejemplo, el término propil incluye los dos grupos isoméricos n–propil e iso–propil, el término butil incluye n–butil, iso–butil, sec–butil y tert–butil, el término pentil incluye iso–pentil, neopentil, etc.

En los grupos alquil anteriormente mencionados, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos alquil pueden ser sustituidos por los siguientes grupos sustituyentes: =O; OH; NO_2; CN; $-NH_2$; halógeno, por ejemplo fluoro o cloro; C_{1-10}alquil opcionalmente sustituido, por ejemplo metil, etil, propil, trifluorometil; $-OC_{1-3}$alquil opcionalmente sustituido, por ejemplo OMe, OEt, $-OCHF_2$, $-OCF_3$; –COOH; $-COO-C_{1-4}$alquil, por ejemplo –COOMe o –COOEt; o $-CONH_2$. "=O" denota un átomo de oxígeno unido a través de un doble enlace. Todos los átomos de hidrógeno del grupo alquil pueden opcionalmente ser reemplazados por los grupos sustituyentes, por ejemplo un grupo trifluorometil es un grupo metil donde todos los átomos de hidrógeno han sido reemplazados con átomos de flúor.

El término puente alquil, a menos que se indique lo contrario, incluye grupos de puente alquil ramificados y no ramificados con 1 a 5 átomos de carbono, por ejemplo puentes metileno, etileno, propileno, butileno y pentileno. A menos que se indique lo contrario, los términos propileno, butileno y pentileno incluyen todas las posibles formas isómericas. En los puentes alquil anteriormente mencionados, 1 ó 2 átomos de C pueden opcionalmente ser reemplazados por uno o más heteroátomos seleccionados de entre oxígeno, nitrógeno o azufre.

El término grupos alquenil (incluyendo aquellos que son parte de otros grupos), a menos que se indique lo contrario, incluye grupos alquileno ramificados y no ramificados con 2 a 10 átomos de carbono que comprenden al menos un doble enlace carbono–carbono. Ejemplos de grupos C_{2-10}alquenil incluyen los grupos etenil, propenil, butenil, pentenil, hexenil, heptenil, octenil, nonenil y decenil. A menos que se indique lo contrario, los términos anteriormente mencionados propenil, butenil, pentenil, hexenil, heptenil, octenil, nonenil y decenil también incluyen todas las posibles formas isómericas. Por ejemplo, el término butenil

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incluye 1–butenil, 2–butenil, 3–butenil, 1–metil–1–propenil, 1–metil–2–propenil, 2–metil–1–propenil, 2–metil–2–propenil y 1–etil–1–etenil.

En los grupos alquenil anteriormente mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos alquenil pueden ser sustituidos por los siguientes grupos sustituyentes: =O; OH; NO_2; CN; $-NH_2$; halógeno, por ejemplo flúor o cloro; C_{1-10}alquil opcionalmente sustituido, por ejemplo metil, etil, propil, trifluorometil; $-OC_{1-3}$alquil opcionalmente sustituido, por ejemplo OMe, OEt, $-OCHF_2$, $-OCF_3$; –COOH; $-COO-C_{1-4}$alquil, por ejemplo –COOMe o –COOEt; o $-CONH_2$. "=O" denota un átomo de oxígeno unido a través de un doble enlace. Todos los átomos de hidrógeno del grupo alquenil pueden opcionalmente ser reemplazados, por ejemplo un grupo trifluoroetileno es un grupo etileno donde todos los átomos de hidrógeno han sido reemplazados con átomos de flúor.

El término grupos alquinil (incluyendo aquellos que son parte de otros grupos), a menos que se indique lo contrario, incluye grupos alquinil ramificados y no ramificados con 2 a 10 átomos de carbono que comprende al menos un triple enlace. Ejemplos de grupos C_{2-10}-alquinil incluyen los grupos etinil, propinil, butinil, pentinil, hexinil, heptinil, octinil, noninil y decinil. A menos que se indique lo contrario, los términos propinil, butinil, pentinil, hexinil, heptinil, octinil, noninil y decinil también incluyen todas las posibles formas isómericas. Por ejemplo, el término butinil incluye 1–butinil, 2–butinil, 3–butinil y 1–metil–2–propinil.

En los grupos alquinil anteriormente mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos alquinil pueden ser sustituidos por los siguientes grupos sustituyentes: =O; OH; NO_2; CN; $-NH_2$; halógeno, por ejemplo flúor o cloro; C_{1-10}alquil opcionalmente sustituido, por ejemplo metil, etil, propil, trifluorometil; $-OC_{1-3}$alquil opcionalmente sustituido, por ejemplo OMe, OEt, $-OCHF_2$, $-OCF_3$; –COOH; $-COO-C_{1-4}$alquil, por ejemplo –COOMe o –COOEt; o $-CONH_2$. "=O" denota un átomo de oxígeno unido a través de un doble enlace. Todos los átomos de hidrógeno del grupo alquinil pueden opcionalmente ser reemplazados.

El término aril incluye sistemas de anillos aromáticos con 6 a 14 átomos de carbono, dichos sistemas de anillos aromáticos comprendiendo uno o más anillos que tienen de 6 a 14 átomos en el anillo donde al menos un anillo es aromático. Ejemplos de grupos C_{6-14}aril

incluyen fenil (C_6), indenil (C_9), naftil (C_{10}), fluorenil (C_{13}), antracil (C_{14}), y fenantril (C_{14}). En los grupos aril anteriormente mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos aril pueden ser sustituidos por los siguientes grupos sustituyentes: OH; NO_2; CN; NH_2; halógeno, por ejemplo flúor o cloro; C_{1-10}alquil opcionalmente sustituido, por ejemplo metil, etil, propil o CF_3; $-OC_{1-3}$alquil opcionalmente sustituido, por ejemplo –OMe, –OEt, $OCHF_2$, o OCF_3; –COOH, $-COO-C_{1-4}$alquil, por ejemplo –COOMe o –COOEt, o $-CONH_2$.

El término heteroaril que comprende 1 ó 2 átomos de nitrógeno incluye sistemas de anillos heteroaromáticos con 5 a 14 átomos en el anillo, dichos sistemas de anillos heteroaromáticos comprendiendo uno o más anillos que tienen de 5 a 14 átomos en el anillo donde al menos un anillo es aromático y donde uno o dos de los átomos en el anillo son remplazados por átomos de nitrógeno, los restantes átomos en el anillo siendo átomos de carbono. Ejemplos de grupos heteroaril donde hasta dos átomos de carbono son reemplazados por uno o dos átomos de nitrógeno que comprenden un anillo incluyen los grupos pirrolil, pirazolil, imidazolil, triazolil, piridinil y pirimidinil. Cada uno de los ejemplos anteriormente mencionados de anillos heteroaril puede opcionalmente también ser fusionado por un anillo adicional, por ejemplo un anillo de benceno. Ejemplos de grupos heteroaril donde hasta dos átomos de carbono son reemplazados por uno o dos átomos de nitrógeno que comprenden dos anillos incluyen indolil, benzimidazolil, quinolinil, isoquinolinil y quinazolinil. En los grupos heteroaril antes mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos heteroaril pueden ser sustituidos por los siguientes grupos sustituyentes: F; Cl; Br; OH; OMe; Me; Et; CN; NH_2; $CONH_2$; fenil opcionalmente sustituido; y heteroaril opcionalmente sustituido, por ejemplo piridil opcionalmente sustituido.

El término anillo heteroaril opcionalmente sustituido que comprende 1, 2 ó 3 heteroátomos cada uno independientemente seleccionado de nitrógeno, oxígeno o azufre incluye los sistemas de anillos heteroaromáticos con 5 a 14 átomos en el anillo, dichos sistemas de anillos heteroaromáticos comprendiendo uno o más anillos que tienen de 5 a 14 átomos en el anillo donde al menos un anillo es aromático y donde uno, dos o tres de los átomos en el anillo son reemplazados por átomos de nitrógeno, oxígeno o azufre, los restantes

átomos en el anillo siendo átomos de carbono. Ejemplos de anillos heteroaril donde hasta tres átomos de carbono son reemplazados por nitrógeno, oxígeno o azufre que comprenden un anillo incluyen grupos furil, imidazolil, isotiazolil, isoxazolil, oxazolil, pirazinil, pirazolil, piridazinil, piridil, pirimidinil, pirrolil, tiazolil, tienil y triazolil. Cada uno de los ejemplos anteriormente mencionados de anillos heteroaril puede opcionalmente también ser fusionado por un anillo adicional, por ejemplo un anillo de benceno. Ejemplos de anillos heteroaril donde hasta tres átomos de carbono son reemplazados por átomos de nitrógeno, oxígeno o azufre que comprenden dos anillos incluyen indolil, benzimidazolil, benzoxazoil, benzioxazoil, quinolinil, isoquinolinil y quinazolinil. En los anillos heteroaril anteriormente mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos heteroaril pueden ser sustituidos por los siguientes grupos sustituyentes: F; Cl; Br; OH; OMe; Me; Et; CN; NH_2; $CONH_2$; fenil opcionalmente sustituido; y heteroaril opcionalmente sustituido, por ejemplo piridil opcionalmente sustituido.

El término grupos cicloalquil, a menos que se indique lo contrario, incluye grupos cicloalquil que comprenden 1 anillo con 3–12 átomos de carbono. Ejemplos de grupos C_{3-12}cicoalquil incluyen los grupos ciclopropil, ciclobutil, ciclopentil, ciclohexil, cicloheptil, ciclooctil, ciclononil, ciclodecil, cicloundecil y ciclododecil. En los grupos cicloalquil anteriormente mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos cicloalquil pueden ser sustituidos por los siguientes grupos sustituyentes: =O; OH; NO_2; CN; $-NH_2$; halógeno, por ejemplo flúor o cloro; C_{1-10}alquil opcionalmente sustituido, por ejemplo metil, etil, propil, trifluorometil; $-OC_{1-3}$alquil opcionalmente sustituido, por ejemplo OMe, OEt, $-OCHF_2$, $-OCF_3$; –COOH; $-COO-C_{1-4}$alquil, por ejemplo –COOMe o –COOEt; o $-CONH_2$. "=O" denota un átomo de oxígeno unido a través de un doble enlace.

El término cicloalquenil, a menos que se indique lo contrario, incluye grupos cicloalquenil con 3–12 átomos de carbono que comprenden un anillo, dicho anillo comprendiendo al menos un doble enlace carbono–carbono. Ejemplos de grupos C_{3-12}cicloalquenil incluyen los grupos ciclopropenil, ciclobutenil, ciclopentenil, ciclohexenil, cicloheptenil, ciclooctenil, ciclononenil, ciclodecenil, cicloundecenil y ciclododecenil. En los

grupos cicloalquenil anteriormente mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos cicloalquenil pueden ser sustituidos por los siguientes grupos sustituyentes: =O; OH; NO_2; CN; $-NH_2$; halógeno, por ejemplo flúor o cloro; C_{1-10}alquil opcionalmente sustituido, por ejemplo metil, etil, propil, trifluorometil; $-OC_{1-3}$alquil opcionalmente sustituido, por ejemplo OMe, OEt, $-OCHF_2$, $-OCF_3$; –COOH; $-COO-C_{1-4}$alquil, por ejemplo –COOMe o –COOEt; o $-CONH_2$. "=O" denota un átomo de oxígeno unido a través de un doble enlace.

Los términos heterocicloalquil y heterocicloalquenil, a menos que se describa lo contrario en las definiciones, incluyen heterociclos de 3 a 12 miembros, por ejemplo de 5, 6 ó 7 miembros, los cuales pueden contener de 1 a 4 heteroátomos seleccionados de nitrógeno, oxígeno o azufre. Heterocicloalquil denota un heterociclo saturado, y heterocicloalquenil denota un heterociclo insaturado. Ejemplos de grupos heterocicloalquil o heterocicloalquenil incluyen tetrahidrofurano, tetrahidrofuranona, *gamma*–butirolactona, *alfa*–pirano, *gamma*–pirano, dioxolano, tetrahidropirano, dioxano, dihidrotiofeno, tiolano, ditiolano, pirrolina, pirrolidina, pirazolina, pirazolidina, imidazolina, imidazolidina, tetrazol, piperidina, piridazina, pirimidina, pirazina, piperazina, triazina, tetrazina, morfolina, tiomorfolina, diazepán, oxazina, tetrahidro–oxazinil, isotiazol, y pirazolidina. En los grupos heterocicloalquil o heterocicloalquenil anteriormente mencionados, a menos que se indique lo contrario, uno o más átomos de hidrógeno pueden opcionalmente ser reemplazados por otros grupos sustituyentes. Por ejemplo, los grupos heterocicloalquil o heterocicloalquenil pueden ser sustituidos por los siguientes grupos sustituyentes: =O; OH; CN; $-NH_2$; halógeno, por ejemplo flúor o cloro; C_{1-4}alquil opcionalmente sustituido, por ejemplo metil, etil, propil, trifluorometil; $-OC_{1-3}$alquil opcionalmente sustituido, por ejemplo OMe, OEt, $-OCHF_2$, $-OCF_3$; –COOH; $-COO-C_{1-4}$alquil, por ejemplo –COOMe o –COOEt; o $-CONH_2$. "=O" denota un átomo de oxígeno unido a través de un doble enlace.

El término policicloalquil, a menos que se indique lo contrario, incluye grupos cicloalquil que comprenden de 3 a 12 átomos de carbono y que comprenden 2 o más anillos. Ejemplos de grupos policicloalquil incluyen los grupos cicloalquil bi–, tri–, tetra– o pentacíclicos opcionalmente sustituidos, por ejemplo pinano, 2,2,2–octano, 2,2,1–heptano o adamantano.

El término policicloalquenil, a menos que se indique lo contrario, incluye los grupos cicloalquenil que comprenden de 7 a 12 átomos de carbono y que comprenden 2 o más anillos donde al menos un anillo comprende un doble enlace carbono–carbono. Ejemplos de grupos policicloalquenil son los grupos cicloalquenil bi–, tri–, tetra– o pentacíclico opcionalmente puenteados y/o sustituidos, por ejemplo grupos bicicloalquenil o tricicloalquenil que tienen al menos un doble enlace, tal como norborneno.

El término espirocicloalquil a menos que se indique lo contrario, incluye los grupos espirocicloalquil que comprenden de 5 a 12 átomos de carbono y que comprenden 2 o más anillos donde dos anillos son unidos a un centro de carbono espiro. Ejemplos de grupos espirocicloalquil incluyen el espiro[4.4]nonil y espiro[3.4]octil.

El término anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno o azufre es un anillo monocíclico aromático completamente insaturado que contiene 5 ó 6 átomos de los cuales uno o más átomos en el anillo son opcionalmente heteroátomos seleccionados de nitrógeno, oxígeno o azufre, con los restantes átomos en el anillo siendo carbono. Ejemplos de un anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno y azufre incluyen los anillos de furil, imidazolil, isotiazolil, isoxazolil, oxazolil, fenil, pirazinil, pirazolil, piridazinil, piridil, pirimidinil, pirrolil, tiazolil, tienil y triazolil.

El término anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos incluye los grupos C_{3-6}cilcoalquil opcionalmente sustituidos y C_{3-6}cilcoalquenil opcionalmente sustituidos, y grupos heterocicloalquil opcionalmente sustituidos de 3 a 6 miembros y heterocilcoalquenil opcionalmente sustituidos de 3 a 6 miembros cada uno con 1 ó 2 heteroátomos.

El término halógeno incluye flúor, cloro, bromo o yodo.

Los términos alquiloxi (–OR donde R es un alquil), alqueniloxi (–OR donde R es un alquenil), alquiniloxi (–OR donde R es un alquinil), cicloalquiloxi (–OR donde R es un cicloalquil) y heterocicloalcoxi (–OR donde R es un heterocicloalquil) denotan un grupo –OR donde el grupo alquil, alquenil, alquinil, cicloalquil o heterocicloalquil respectivo es como el descrito aquí anteriormente.

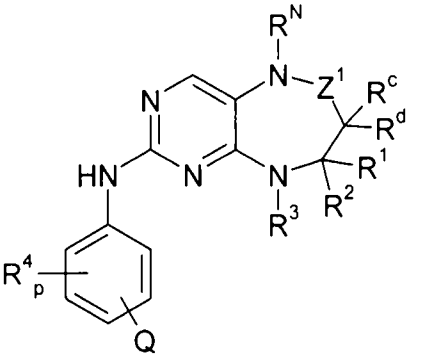
Los términos alquiltio, alquilsulfoxo y alquilsulfono denotan un grupo $-S(O)_xR$ donde x=0, 1 ó 2 respectivamente y R es un grupo alquil como el descrito aquí anteriormente.

El término –alquil–aril se refiere a un grupo alquil con un sustituyente aril. El término –alquil–cicloalquil se refiere a un grupo alquil con un sustituyente cicloalquil. El término –aril–alquil se refiere a un grupo aril con un sustituyente alquil. Los términos alcoxicarbonil (–(C=O)OR), alquilcarbonil (–COR) y arilcarbonil (–COR) se refieren a un grupo carbonil con un sustituyente alcoxi, alquil o aril.

Cuando R^5 representa un morfolinil, piperidinil, homopiperidinil, piperazinil, piperazinilcarbonil, pirrolidinil, tropenil, dicetometilpiperazinil, sulfoxomorfolinil, sulfonilmorfolinil, tiomorfolinil, granatanil, oxogranatanil o azacicloheptil sustituido, uno o más sustituyentes pueden estar presentes y son como los definidos anteriormente para R^8.

Todos los grupos mencionados en la definición de R^1 a R^9 pueden ser opcionalmente ramificados y/o sustituidos.

De acuerdo a un segundo aspecto de la presente invención se proporciona un compuesto de fórmula (II):



(II)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y

R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

R^N representa hidrógeno, $-NH_2$, –OH, –CN, –C=CH, $-C(=O)NH_2$, C_{1-3}alquil, C_{1-3}alquilamino, C_{1-3}alquiltio, C_{1-3}alquiloxi, C_{1-3}alquilcarbonil, –CHO, o $-SO_2Me$;

p es 0, 1 ó 2;

Q es $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, $-(C_{1-3}$alquil opcionalmente sustituido$)_g-NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ o –(anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno y azufre)$-L_n-R^5{}_m$;

g es 0 ó 1;

k es 0, 1 ó 2;

R^a representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^b representa $-L_n-R^5{}_m$, o R^a y R^b junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a2} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b2} representa $-L_n-R^5{}_m$, o R^{a2} y R^{b2} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a3} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b3} representa $-L_n-R^5{}_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, o R^{a3} y R^{b3} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a4} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b4} representa $-L_n-R^5{}_m$, o R^{a4} y R^{b4} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a5} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b5} representa $-L_n-R^5{}_m$, o R^{a5} y R^{b5} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a6} representa $-L_n-R^5{}_m$;

R^{a7} representa $-L_n-R^5{}_m$;

R^{a8} representa $-L_n-R^5{}_m$;

R^{a9} representa $-L_n-R^5{}_m$;

R^{a10} representa $-L_n-R^5{}_m$;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-}

$_{12}$cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1

m es 1 ó 2

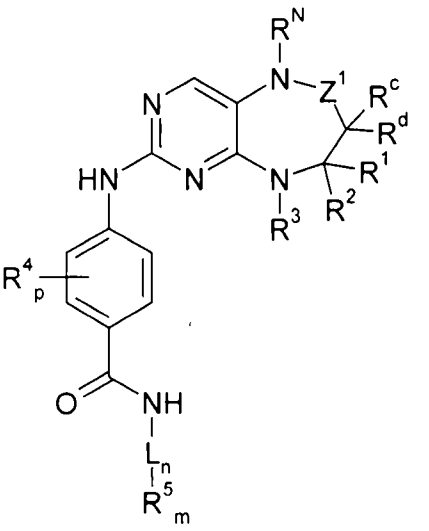
R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azacicloheptil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido;

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril$-C_{1-4}$alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales; y Z^1 es C=O o CR^fR^g donde R^f, R^g cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^f y R^g junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos,

o sales farmacéuticamente aceptables del mismo.

De acuerdo a un tercer aspecto de la presente invención se proporciona un compuesto de fórmula (IIa):



(IIa)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que

comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

R^N representa hidrógeno, $-NH_2$, –OH, –CN, –C=CH, $-C(=O)NH_2$, C_{1-3}alquil, C_{1-3}alquilamino, C_{1-3}alquiltio, C_{1-3}alquiloxi, C_{1-3}alquilcarbonil, –CHO, o $-SO_2Me$;

p es 0, 1 ó 2;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1

m es 1 ó 2

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azacicloheptil opcionalmente

sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

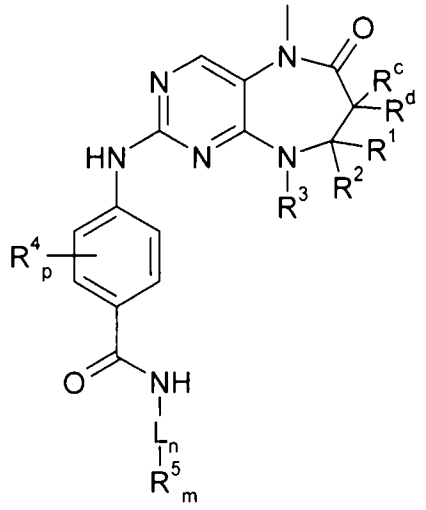
R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido;

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril$-C_{1-4}$alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales; y Z^1 es C=O o CR^fR^g donde R^f, R^g cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^f y R^g junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos,

o sales farmacéuticamente aceptables del mismo.

En una realización del segundo aspecto de la invención, Z^1 es C=O o CH_2.

De acuerdo a un cuarto aspecto de la presente invención se proporciona un compuesto de fórmula (III):



(III)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno o un grupo C_{1-6}alquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

p es 0, 1 ó 2;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1;

m es 1 ó 2;

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azacicloheptil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

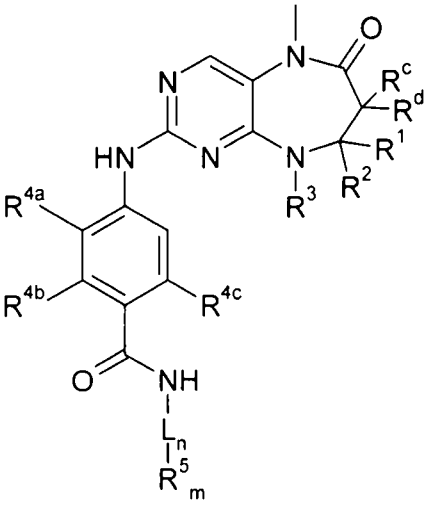
R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido; y

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil–C_{3-10}cicloalquil opcionalmente sustituido, C_{3-}

$_{10}$cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil–C_{6-14}aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril–C_{1-4}alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales,

o una sal farmacológicamente aceptable del mismo.

De acuerdo a un quinto aspecto de la presente invención se proporciona un compuesto de fórmula (IIIa):



(IIIa)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno o un grupo C_{1-6}alquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y

R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^{4a}, R^{4b}, R^{4c} cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

p es el número de grupos $R^{4a, 4b, 4c}$ que no es hidrógeno y es seleccionado de 0, 1 ó 2;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1;

m es 1 ó 2;

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azaciclohéptil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido; y

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil–C_{3-10}cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil–C_{6-14}aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril–C_{1-4}alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales,

o una sal farmacológicamente aceptable del mismo.

En una realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^1 y R^2 pueden ser idénticos o diferentes y representan hidrógeno o un grupo C_1–C_6alquil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^1 y R^2 pueden ser idénticos o diferentes y representan hidrógeno o a metil o etil grupo.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^1 y R^2 son diferentes donde uno de R^1 o R^2 representa hidrógeno y el otro representa un grupo metil o etil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^2 juntos representan un puente alquil de 2 a 5 miembros que comprende opcionalmente de 1 a 2 heteroátomos seleccionados de oxígeno o nitrógeno y opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^2 juntos representan un puente etileno o propileno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^c y R^d pueden ser idénticos o diferentes y representan hidrógeno o un grupo C_1–C_6alquil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^c y R^d pueden ser idénticos o diferentes y representan hidrógeno o un grupo metil o etil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^c y R^d son diferentes donde uno de R^c o R^d representa hidrógeno y el otro representa un grupo metil o etil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^c y R^d juntos representan un puente alquil de 2 a 5 miembros que comprende opcionalmente de 1 a 2 heteroátomos seleccionados de oxígeno o nitrógeno y opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^c y R^d juntos representan un puente etileno, propileno o butileno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, al menos uno de R^1, R^2, R^c, o R^d es hidrógeno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, al menos dos de R^1, R^2, R^c, o R^d son hidrógeno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^2 son hidrógeno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^2 son hidrógeno, y uno de R^c o R^d es hidrógeno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^2 son hidrógeno, y uno de R^c o R^d es hidrógeno y el otro es metil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^2 son hidrógeno, y R^c y R^d son metil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^2 son hidrógeno, y R^c y R^d juntos representan un puente etileno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^3 representa hidrógeno; un C_1–C_{12}alquil, por ejemplo etil, propil, butil, pentil o hexil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; un C_2–C_{12}alquenil, por ejemplo C_5–C_7alquenil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_2–C_{12}alquinil, por ejemplo C_5–C_7alquinil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; un C_6–C_{14}aril, por ejemplo fenil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; un C_3–C_{12}cicloalquil, por ejemplo ciclopentil o ciclohexil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; un C_3–C_{12}cicloalquenil, por ejemplo C_5–C_7cicloalquenil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_7–C_{12}policicloalquil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_7–C_{12}policicloalquenil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_5–C_{12}espirocicloalquil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino

y di–(C_{1-3}alquil)amino; C_3–C_{12}heterocicloalquil el cual contiene de 1 a 2 heteroátomos seleccionados de oxígeno, nitrógeno o azufre, por ejemplo piranil o piperinil, pirrolidinil, pirazinil o morfolinil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; y C_3–C_{12}heterocicloalquenil el cual contiene de 1 a 2 heteroátomos seleccionados de oxígeno, nitrógeno o azufre, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^3 representa isopropil, isobutil, isopentil, ciclopentil, fenil o ciclohexil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^3 representa ciclopentil o ciclohexil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^1 y R^3 o R^2 y R^3 juntos representan un puente C_3–C_4alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo seleccionado de oxígeno o nitrógeno.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, cuando p es 1 ó 2, R^4 representa un grupo seleccionado de entre –CN; hidroxil; –NR^6R^7; halógeno, por ejemplo cloro o flúor; C_1–C_6alquil, por ejemplo metil, etil o propil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_2–C_6alquenil, por ejemplo etenil o propenil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_2–C_6alquinil, por ejemplo etinil, propinil o butinil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_1–C_5alquiloxi, por ejemplo metoxi, etoxi o propargiloxi, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_2–C_5alqueniloxi opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_2–C_5alquiniloxi opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_1–C_6alquiltio opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-}

$_{3}$alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_1–C_6alquilsulfoxo opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino y C_1–C_6alquilsulfonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer y cuarto aspectos, cuando p es 1, R^4 representa metoxi, metil, etoxi, cloro o flúor.

En otra realización, para los compuestos del primer, segundo, tercer, y cuarto aspectos, cuando p es 2, cada R^4 puede ser igual o diferente y seleccionado de metoxi, metil, etoxi, etil, propargiloxi, cloro o flúor.

En otra realización, para los compuestos del primer, segundo, tercer, y cuarto aspectos, cuando p es 2 y cuando cada R^4 es adyacente, ambos R^4 junto con los átomos del anillo aromático al cual están unidos forman un anillo de 4 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos.

En otra realización, para los compuestos del quinto aspecto, cuando p es 1, R^{4b} y R^{4c} son hidrógeno y R^{4a} representa metoxi, metil, etoxi, cloro o flúor.

En otra realización, para los compuestos del quinto aspecto, cuando p es 2, R^{4b} es hidrógeno y R^{4a} y R^{4c} pueden ser iguales o diferentes y seleccionados de metoxi, metil, etoxi, cloro o flúor.

En otra realización, para los compuestos del quinto aspecto, cuando p es 2, R^{4c} es hidrógeno y R^{4a} y R^{4b} juntos forman un puente OCH_2O.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, L representa un enlazador seleccionado de entre C_2–C_{10}alquil, por ejemplo etil, propil, butil o pentil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_2–C_{10}alquenil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_6–C_{14}aril, por ejemplo fenil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; –C_2–C_4alquil–C_6–C_{14}aril opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; –

C_6–C_{14}aril–C_1–C_4alquil opcionalmente sustituido por uno o más sustituyentes seleccionados dè C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_3–C_{12}cicloalquil, por ejemplo ciclohexil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; y heteroaril el cual contiene 1 ó 2 átomos de nitrógeno opcionalmente sustituidos por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, cuando n es 1, L representa un C_{2-10}alquil opcionalmente sustituido o un enlazador C_{3-12}cicloalquil opcionalmente sustituido.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, cuando n es 1, L representa ciclohexil, $-C(CH_3)_2-CH_2-$ o $-CH_2-C(CH_3)_2-CH_2-$.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, n es 0.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, m es 1.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil, tiomorfolinil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido, $-NR^8R^9$ y azacicloheptil opcionalmente sustituido donde cada morfolinil, piperidinil, piperazinil, piperazinilcarbonil, pirrolidinil, tropenil, dicetometilpiperazinil, sulfoxomorfolinil, sulfonilmorfolinil, tiomorfolinil, $-NR^8R^9$ y azacicloheptil es opcionalmente sustituido por uno o más grupos como es definido para R^8.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^5 representa hidrógeno, $-NR^8R^9$ o un piperidinil, morfolinil, pirrolidinil, sulfoxomorfolinil, piperazinil, tiomorfolinil, tropenil, granatanil, oxogranatanil o

azaciclohéptil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^5 representa piperidinil opcionalmente sustituido por uno o más grupos como es definido para R^8.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^5 representa pirrolidinil opcionalmente sustituido por uno o más grupos como es definido para R^8.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^5 representa granatanil opcionalmente sustituido por uno o más grupos como es definido para R^8.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^6 y R^7 pueden ser idénticos o diferentes y representan hidrógeno o C_1–C_4alquil, por ejemplo metil o etil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, los grupos R^8 y R^9 pueden ser idénticos o diferentes y representan hidrógeno; un C_1–C_6alquil, por ejemplo metil, etil o propil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; –C_1–C_4alquil–C_3–C_{10}cicloalquil, por ejemplo –CH_2–ciclopropil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_3–C_{10}cicloalquil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y d–(C_{1-3}alquil)amino; C_6–C_{14}aril, por ejemplo fenil, opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; –C_1–C_4alquil–C_6–C_{14}aril, por ejemplo bencil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; piranil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; piridinil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; pirimidinil

opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; piranil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_1–C_4alquiloxicarbonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_6–C_{14}arilcarbonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_1–C_4alquilcarbonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_6–C_{14} arilmetiloxicarbonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_6–C_{14}arilsulfonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino; C_1–C_4alquilsulfonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino y C_6–C_{14}aril–C_1–C_4alquilsulfonil opcionalmente sustituido por uno o más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^8 representa metil, etil o propil.

En otra realización, para los compuestos del primer, segundo, tercer, cuarto y quinto aspectos, R^9 representa metil, etil o propil.

En otra realización, para el compuesto de fórmula (I), R^N representa C_{1-3}alquil.

En otra realización, para el compuesto de fórmula (I), R^N representa metil o etil.

En otra realización, para el compuesto de fórmula (I), Z^1 representa C=O o CR^fR^g.

En otra realización, para el compuesto de fórmula (I), Z^1 representa C=O o CR^fR^g, y Z^2 representa CR^cR^d.

En otra realización, para el compuesto de fórmula (I), Z^1 representa C=O o CH_2.

En otra realización, para el compuesto de fórmula (I), Q representa $–CH_2–NR^{a3}R^{b3}$ o $–C(=X^1)–NR^aR^b$, donde X^1 es O.

En otra realización, para los compuestos de fórmula (I), (II), (IIa), (III) o (IIIa), n es 1 y L es un enlazador C_{2-10}alquil opcionalmente sustituido.

En otra realización, para los compuestos de fórmula (I), (II), (IIa), (III) o (IIIa), n es 0.

En una realización adicional de la invención se proporciona un subconjunto de compuestos de fórmula (III) o (IIIa) donde R^1 a R^4, R^{4a}, R^{4b}, R^{4c}, R^c, R^d, R^6 y R^7 son como los definidos aquí anteriormente; y L representa un enlazador seleccionado de entre C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, $-C_{6-14}$aril$-C_{1-4}$alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos en el anillo de nitrógeno; n denota 1; m denota 1 ó 2; R^5 denota hidrógeno o un grupo que es enlazado a L a través de un átomo de nitrógeno, seleccionado de morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, $-NR^8R^9$ y azaciclohéptil opcionalmente sustituido; R^8, R^9 independientemente representan hidrógeno, C_{1-6}alquil, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil, C_{3-10}cicloalquil, C_{6-14}aril, $-C_{1-4}$alquil$-C_{6-14}$aril, piranil, piridinil, pirimidinil, C_{1-4}alquiloxicarbonil, C_{6-14}arilcarbonil, C_{1-4}alquilcarbonil, C_{6-14}arilmetiloxicarbonil, C_{6-14}arilsulfonil, C_{1-4}alquilsulfonil o C_{6-14}aril$-C_{1-4}$alquilsulfonil, o sales farmacológicamente aceptables de los mismos.

En aún una realización adicional de la invención se proporciona otro subconjunto de compuestos de fórmula (III) o (IIIa) donde p, R^1 a R^4, R^{4a}, R^{4b}, R^{4c}, R^c, R^d, R^6 y R^7 son como los definidos aquí anteriormente; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, $-C_{6-14}$aril$-C_{1-4}$alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos en el anillo de nitrógeno; n denota 0 ó 1; m denota 1 ó 2; R^5 denota hidrógeno o un grupo que es enlazado a L a través de un átomo de carbono, seleccionado de entre piperidinil, piperazinil, pirrolidinil, piperazinilcarbonil, tropenil, morfolinil, granatanil, oxogranatanil y azaciclohéptil cada uno opcionalmente sustituido por uno o más grupos como

es definido para R^8; y R^8 independientemente representa hidrógeno, C_{1-6}alquil, $-C_{1-4}$alquil–C_{3-10}cicloalquil, C_{3-10}cicloalquil, C_{6-14}aril, $-C_{1-4}$alquil–C_{6-14}aril, piranil, piridinil, pirimidinil, C_{1-4}alquiloxicarbonil, C_{6-14}arilcarbonil, C_{1-4}alquilcarbonil, C_{6-14}arilmetiloxicarbonil, C_{6-14}arilsulfonil, C_{1-4}alquilsulfonil o C_{6-14}aril–C_{1-4}alquilsulfonil, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) o (IIIa) donde L, m, n, p, R^3 to R^9, R^c y R^d son como los definidos aquí anteriormente; y R^1, R^2 cada uno independientemente representa un hidrógeno, Me, Et, Pr, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo cicloalquil de 3 a 5 miembros, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) o (IIIa) donde L, m, n, p y R^1 a R^9 son como los definidos aquí anteriormente; y R^c, R^d cada uno independientemente representa un hidrógeno, Me, Et, Pr, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo cicloalquil de 3 a 5 miembros, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) o (IIIa) donde L, m, n, p y R^3 a R^9 son como los definidos aquí anteriormente; y al menos dos de R^1, R^2, R^c o R^d son hidrógeno.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) o (IIIa) donde L, m, n, p y R^3 a R^9 son como los definidos aquí anteriormente; R^1 y R^2 son hidrógeno, y uno de R^c o R^d es hidrógeno.

En otra realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) o (IIIa) donde R^1, R^2, R^c, R^d, m, n y R^5 a R^8 son como los definidos aquí anteriormente; y R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido o C_{6-14}aril opcionalmente sustituido o R^1 y R^3 o R^2 y R^3 juntos representan un puente C_{3-4}alquil saturado o insaturado que comprende opcionalmente 1 ó 2 heteroátomos; p es 0 ó 1; R^4 representa OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2, F, CL, Br, O–propargil, O–butinil, CN, SMe, NMe_2, $CONH_2$, etinil, propinil, butinil o alil; y L denota un enlazador seleccionado de entre fenil, fenilmetil, ciclohexil opcionalmente sustituidos y C_{1-6}alquil ramificado, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido o C_{6-14}aril opcionalmente sustituido; p es 0 ó 1; R^4 representa OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2, F, CL, Br, O–propargil, O–butinil, CN, SMe, NMe_2, $CONH_2$, etinil, propinil, butinil o alil; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos en el anillo de nitrógeno; n denota 0 ó 1; m denota 1 ó 2; R^5 denota hidrógeno o un grupo, que es enlazado a L a través de un átomo de carbono, seleccionado de entre $-NR^8R^9$, piperidinil, piperazinil, pirrolidinil, piperazinilcarbonil, tropenil, morfolinil, granatanil, oxogranatanil y azaciclohеptil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa hidrógeno, C_{1-6}alquil, $-C_{1-4}$alquil–C_{3-10}cicloalquil, C_{3-10}cicloalquil, C_{6-14}aril, $-C_{1-4}$alquil–C_{6-14}aril, piranil, piridinil, pirimidinil, C_{1-4}alquiloxicarbonil, C_{6-14}arilcarbonil, C_{1-4}alquilcarbonil, C_{6-14}arilmetiloxicarbonil, C_{6-14}arilsulfonil, C_{1-4}alquilsulfonil o C_{6-14}aril–C_{1-4}alquilsulfonil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me, o Et, o R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; p es 0, 1 ó 2; R^4 cada uno independientemente representa un fluoro o OMe; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y piperidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me, o Et, o R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; p es 0, 1 ó 2; R^4 cada uno independientemente representa un fluoro o OMe; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y pirrolidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me, o Et, o R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (III) donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; p es 0, 1 ó 2; R^4 cada uno independientemente representa un fluoro o OMe; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y granatanil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me, o Et, o R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (IIIa) donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y piperidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me, o Et, o R^c y R^d juntos representan un puente etileno; p es 0, 1 ó 2; y cuando p es 1, R^{4b} y R^{4c} son hidrógeno y R^{4a} representa metoxi, metil, etoxi, cloro o flúor; y cuando p es 2, cualquier R^{4b} es hidrógeno y R^{4a} y R^{4c} pueden ser iguales o diferentes y seleccionados de metoxi, metil, etoxi, cloro o flúor, o R^{4c} es

hidrógeno y R^{4a} y R^{4b} juntos forman un puente OCH_2O, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (IIIa) donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y pirrolidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me, o Et, o R^c y R^d juntos representan un puente etileno; p es 0, 1 ó 2; y cuando p es 1, R^{4b} y R^{4c} son hidrógeno y R^{4a} representa metoxi, metil, etoxi, cloro o flúor; y cuando p es 2, cualquier R^{4b} es hidrógeno y R^{4a} y R^{4c} pueden ser iguales o diferentes y seleccionados de metoxi, metil, etoxi, cloro o flúor, o R^{4c} es hidrógeno y R^{4a} y R^{4b} juntos forman un puente OCH_2O, o sales farmacológicamente aceptables de los mismos.

En una realización adicional de la invención se proporciona un subconjunto adicional de compuestos de fórmula (IIIa) donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y granatanil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me, o Et, o R^c y R^d juntos representan un puente etileno; p es 0, 1 ó 2; y cuando p es 1, R^{4b} y R^{4c} son hidrógeno y R^{4a} representa metoxi, metil, etoxi, cloro o flúor; y cuando p es 2, cualquier R^{4b} es hidrógeno y R^{4a} y R^{4c} pueden ser iguales o diferentes y seleccionados de metoxi, metil, etoxi, cloro o flúor, o R^{4c} es hidrógeno y R^{4a} y R^{4b} juntos forman un puente OCH_2O, o sales farmacológicamente aceptables de los mismos.

En un aspecto adicional de la invención, se proporciona un compuesto seleccionado de uno cualquiera de los Ejemplos o sales farmacológicamente aceptables del mismo.

En un aspecto adicional de la invención, se proporciona un compuesto seleccionado de uno cualquiera de los Ejemplos 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451, 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 y 453 o sales farmacológicamente aceptables del mismo.

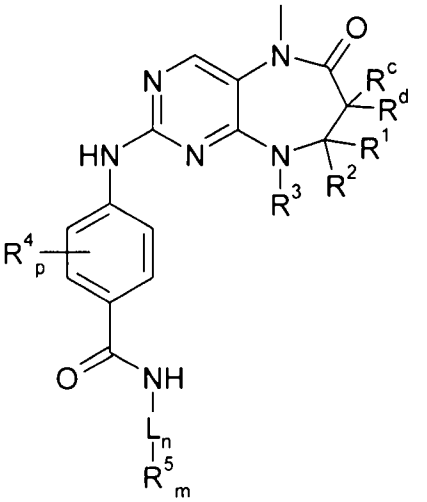
En un aspecto adicional de la invención, se proporciona un compuesto seleccionado de uno cualquiera de los Ejemplos 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 y 453, o sales farmacológicamente aceptables del mismo.

Los compuestos de acuerdo al primer, segundo, tercer, cuarto y quinto aspectos de la invención pueden estar presentes en forma de isómeros ópticos individuales, mezclas de racematos, diastereómeros o enantiómeros individuales, en forma de tautómeros y también como solvatos y/o en forma de bases libres o las sales de adición ácida correspondientes con ácidos farmacológicamente aceptables, tal como por ejemplo sales de adición ácida con ácidos hidrohálicos, por ejemplo ácido clorhídrico o bromhídrico, o ácidos orgánicos, tal como por ejemplo ácido oxálico, fumárico, diglicólico o metanosulfónico o sales de metal como una sal de magnesio, calcio, sodio o potasio.

Los compuestos de fórmula (I), (II), (IIa), (III) o (IIIa) anteriores pueden ser convertidos en una sal farmacéuticamente aceptable de los mismos, preferiblemente una sal de adición ácida tal como una clorhídrica, bromhídrica, fosfato, acetato, fumarato, maleato, tartrato, citrato, oxalato, metanosulfonato o p–toluenosulfonato, o una sal de metal alcalino tal como una de sodio o potasio.

Ciertos compuestos de fórmula (I), (II), (IIa), (III) o (IIIa) son capaces de existir en formas estereoisoméricas. Se entenderá que la invención abarca el uso de todos los isómeros ópticos y geométricos (incluyendo los atropisómeros) de los compuestos de fórmula (I), (II), (IIa), (III) o (IIIa) y mezclas de los mismos incluyendo los racematos. El uso de tautómeros y mezclas de los mismos también forman un aspecto de la presente invención.

La invención también se relaciona con un proceso para preparar un compuesto de la fórmula general (III),

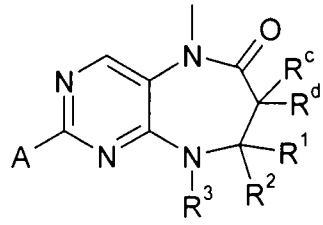


(III)

donde R^1–R^5, R^c, R^d m, n y L son como los definidos aquí anteriormente,

que comprende o bien

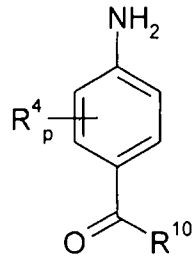
a) reaccionar un compuesto de fórmula general (IV)



(IV)

donde R^1–R^3 son como los definidos aquí anteriormente y A es un grupo de salida,

con un compuesto opcionalmente sustituido de la fórmula general (V):



(V)

donde R^4 es como el definido aquí anteriormente; y R^{10} denota OH, $NH–L_m–R^5{}_n$, OMe, OEt, y cuando R^{10} denota OH, OMe o OEt opcionalmente después de la hidrólisis previa del grupo éster $–COR^{10}$, reaccionar con una amina de fórmula general (VI):

$$NH_2 –L_m–R^5{}_n$$

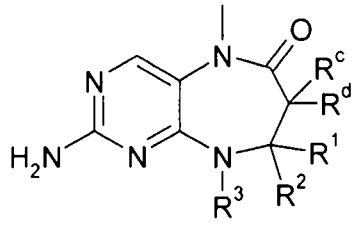
(VI)

donde R^5 es como el definido aquí anteriormente,

para dar un compuesto de fórmula (III);

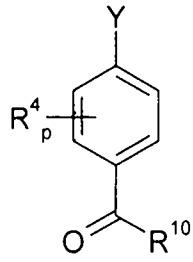
o

b) reaccionar un compuesto de fórmula general (VII)



(VII)

donde R^1–R^3 son como los definidos aquí anteriormente con un compuesto opcionalmente sustituido de la fórmula general (VIII):



(VIII)

donde Y es un grupo de salida, p y R^4 son como los definidos aquí anteriormente; y R^{10} denota OH, NH–L_m–$R^5{}_n$, OMe, OEt, y cuando R^{10} denota OH, OMe o OEt opcionalmente después de la hidrólisis previa del grupo éster –COR^{10}, reaccionar con una amina de fórmula general (VI):

$$NH_2\text{–}L_m\text{–}R^5{}_n$$

(VI)

donde R^5 es como el definido aquí anteriormente,

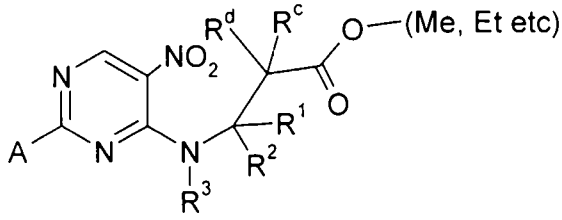
para dar un compuesto de fórmula (III).

En una realización R^{10} es un sustituyente seleccionado de entre OH, NH_2–LR^5, –O–metil y –O–etil.

El término grupo de salida incluye los grupos de salida tal como por ejemplo –O–metil, –SCN, cloro, bromo, yodo, metanosulfonil, trifluorometanosulfonil o p–toluenosulfonil. En una realización el grupo de salida A es cloro.

Los métodos para la preparación de los compuestos de fórmula (V) son descritos en WO04/076454 y WO03/020722 y son incorporados aquí como referencia.

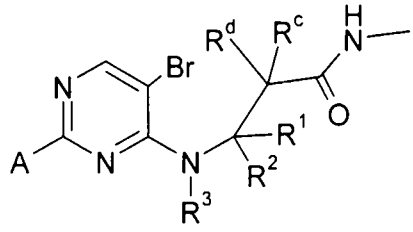
Los compuestos de fórmula (IV) donde A es cloro también pueden ser obtenidos mediante ciclización reductora de un compuesto de fórmula (IX)



(IX)

por ejemplo mediante acoplamiento de paladio.

Los compuestos de fórmula (IV) pueden también ser obtenidos mediante ciclización de un compuesto de fórmula (X)

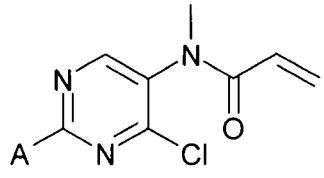


(X)

por ejemplo bajo catálisis mediante un compuesto de acoplamiento de paladio adecuado y en presencia de un ligando adecuado y una base adecuada.

Además, los compuestos de fórmula (IV) pueden ser obtenidos mediante la reacción de otro compuesto de fórmula general (IV), donde R3 es hidrógeno, con un alquil haluro, en un solvente polar, tal como, por ejemplo, N,N–dimetilacetamida, en presencia de una base fuerte, tal como, por ejemplo, hidruro de sodio.

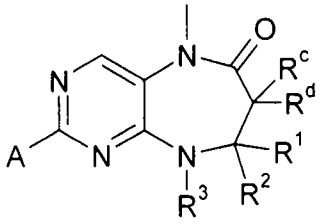
Aún además los compuestos de fórmula (IV), donde R^c, R^d, R^1 y R^2 son hidrógeno, pueden ser obtenidos mediante la reacción de un compuesto de fórmula (XI)



(XI)

con una amina, en presencia de una base, tal como trietilamina, y un ácido de lewis, tal como tetraetóxido de titanio (IV).

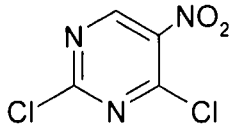
Los compuestos de fórmula (VII) pueden también ser obtenidos mediante la reacción de un compuesto de fórmula (IV), donde A es como el definido aquí anteriormente, pero típicamente cloro,



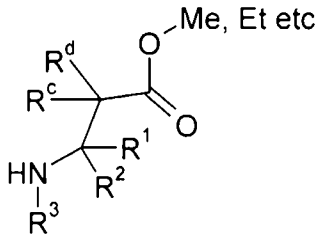
(IV)

con amoniaco o un equivalente adecuadamente protegido.

Los compuestos de fórmula (IX), donde A es cloro, pueden también ser obtenidos mediante la reacción de 5–nitro–2,4–dicloropirimidina



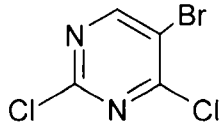
con una amina de fórmula (XII)



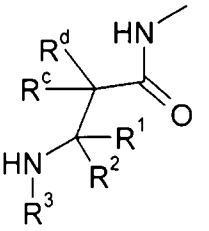
(XII)

por ejemplo mediante calentamiento en presencia de una base, tal como carbonato de potasio, en un solvente orgánico polar tal como acetona.

Los compuestos de fórmula (IX), donde A es cloro, pueden también ser obtenidos mediante la reacción de 5–bromo–2,4dicloropirimida



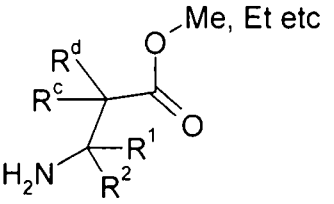
con una amina de fórmula (XIII)



(XIII)

por ejemplo mediante calentamiento en presencia de una base, tal como trietilamina, en un solvente orgánico polar tal como acetonitrilo.

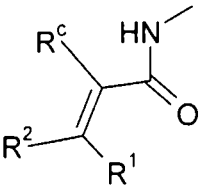
Los compuestos de fórmula (XII), pueden también ser obtenidos mediante la reacción de ésteres de un ácido 3–amino–propanóico apropiadamente sustituido (XIV)



(XIV)

con una cetona o aldehído, en presencia de un agente de reducción adecuado, tal como, por ejemplo, triacetoxiborohidruro de sodio.

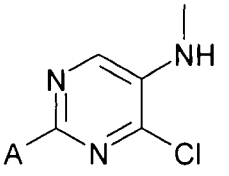
Los compuestos de fórmula (XIII), pueden también ser obtenidos mediante la reacción de amidas de ácido propenoico (XV)



(XV)

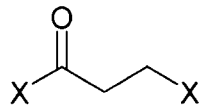
con una amina.

Los compuestos de fórmula (XI) pueden también ser obtenidos mediante la reacción de un compuesto de fórmula (XVI),



(XVI)

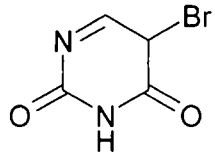
con un compuesto de fórmula (XVII),



(XVII)

donde X es un grupo de salida, típicamente un halógeno, tal como cloro, en presencia de una base, tal como trietilamina, en un solvente orgánico, tal como diclorometano.

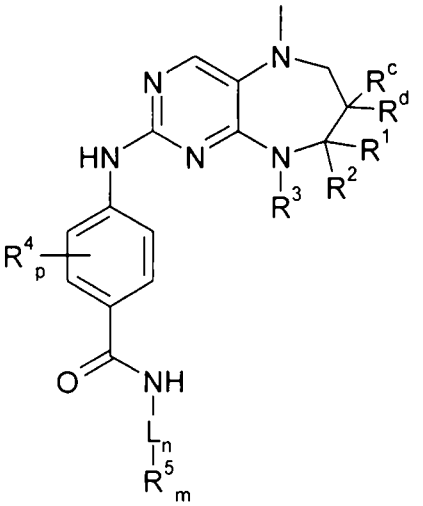
Un compuesto de fórmula (XVI) puede también ser obtenido mediante la reacción secuencial de 5–bromouracil,



con i) metilamina, en un solvente polar, tal como etanol y;

ii) un agente de cloración, tal como oxicloruro de fósforo como es por ejemplo ejemplificado en el Journal of Medicinal Chemistry (1966), 9(1), 121–6.

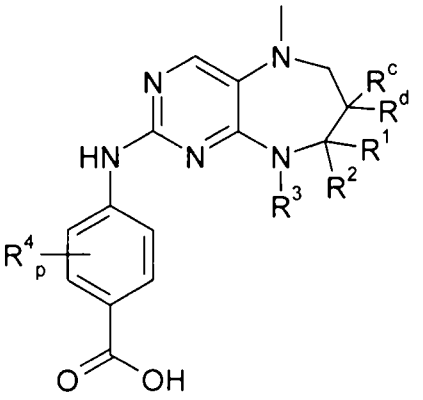
La invención también se relaciona con un proceso para preparar un compuesto de fórmula general (XVIII),



(XVIII)

donde R^1–R^5, R^c, R^d m, n y L son como los definidos aquí anteriormente,

reaccionar un compuesto de fórmula general (XIX)



(XIX)

con una amina de fórmula general (VI):

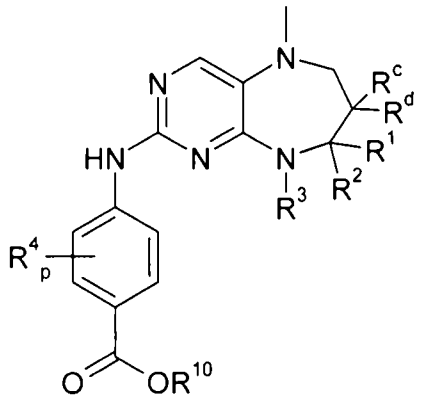
$$NH_2 - L_m - R^5{}_n$$

(VI)

donde L y R^5 son como los definidos aquí anteriormente.

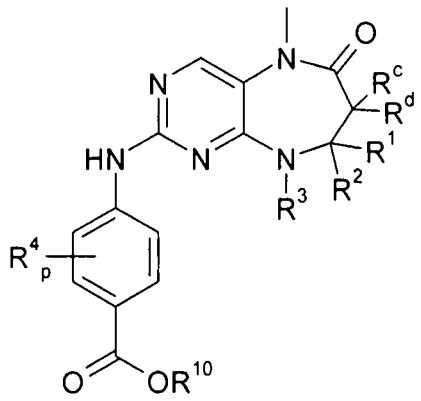
Los compuestos de fórmula (XIX) pueden ser obtenidos mediante hidrólisis de los ésteres correspondientes.

Los ésteres de fórmula general (XX)



(XX)

pueden ser obtenidos mediante la reducción de un compuesto de fórmula (XXI)



(XXI)

el cual puede ser preparado como se describió anteriormente.

Será apreciado por aquellos expertos en el arte que en los procesos de la presente invención ciertos grupos funcionales tales como grupos hidroxil o amino en los reactivos de partida o compuestos intermedios pueden necesitar ser protegidos por grupos de protección. De esta manera, la preparación de los compuestos de fórmula (I), (II), (IIa), (III) o (IIIa) puede involucrar, en varias etapas, la adición y eliminación de uno o más grupos de protección.

La protección y desprotección de grupos funcionales es descrita en 'Protective Groups in Organic Chemistry', editado por J.W.F. McOmie, Plenum Press (1973) y 'Protective Groups in Organic Synthesis', 3ra edición, T.W. Greene y P.G.M. Wuts, Wiley Interscience (1991-1999) y 'Protecting Groups', 3ra edición, P. J. Kocienski, Thieme (2005).

La invención se relaciona adicionalmente con compuestos de fórmula (I), (II), (IIa), (III) o (IIIa) para su uso como composiciones farmacéuticas.

En una realización de la invención, los compuestos de fórmula (I), (II), (IIa), (III) o (IIIa) son de uso como composiciones farmacéuticas con una actividad antiproliferativa.

La invención también se relaciona con el uso de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa) para preparar una composición farmacéutica para el tratamiento y/o prevención del cáncer, infecciones, enfermedades autoimnunes e inflamatorias.

Estos descubrimientos sugieren que los inhibidores farmacológicos de la Plk deben ser un valor terapéutico para el tratamiento de la enfermedad proliferativa incluyendo tumores sólidos tal como carcinomas y sarcomas y las leucemias y malignidades linfoides. Además los inhibidores de la Plk deben ser útiles en el tratamiento de otros trastornos asociados con la proliferación celular no controlada.

Un aspecto de la presente invención por lo tanto se relaciona con el uso de uno o más de los compuestos de fórmula (I), (II), (IIa), (III) o (IIIa) en el tratamiento de trastornos caracterizados por una proliferación de células excesiva o anormal.

Tales enfermedades incluyen por ejemplo: infecciones virales tal como VIH y sarcoma de Kaposi; enfermedades autoinmunes e inflamatorias tal como colitis, artritis reumatoide, enfermedad de Alzheimer, glomerulonefritis y curación de heridas; infecciones bacterianas, fúngicas y parasitarias tal como malaria y enfisema; enfermedades dermatológicas tal como psoriasis; enfermedades de los huesos; enfermedades cardiovasculares tal como restenosis y cardiomiopatía. Los compuestos en la presente invención pueden ser usados para la prevención, tratamiento a corto o largo plazo de las enfermedades anteriormente mencionadas, también en combinación con otras sustancias activas usadas para las mismas indicaciones.

La invención también se relaciona con un método de tratar y/o prevenir el cáncer, infecciones, enfermedades autoimnunes e inflamatorias, donde a un paciente se le da una cantidad efectiva de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa).

La invención también se relaciona con preparaciones farmacéuticas, que contienen como sustancia activa uno o más compuestos de fórmula general (I), (II), (IIa), (III) o (IIIa), o las sales fisiológicamente aceptables de los mismos, opcionalmente combinados con portadores y/o excipientes convencionales.

Los compuestos de fórmula (I), (II) y (III) tienen actividad como productos farmacéuticos, en particular como modulares o inhibidores de la actividad Plk, y pueden ser usados en el tratamiento de enfermedades/afecciones proliferativas e hiperproliferativas, ejemplos de las cuales incluyen los siguientes cánceres:

(1) carcinoma, incluyendo aquel de vejiga, cerebro, mama, colon, riñón, hígado, pulmón, ovario, páncreas, próstata, estómago, cervical, colon, tiroides y piel;

(2) tumores hematopoiéticos de linaje linfoide, incluyendo leucemia linfocítica aguda, linfoma de células B y linfoma de Burketts;

(3) tumores hematopoiéticos de linaje mieloide, incluyendo leucemias mielógenas aguda y crónica y leucemia promielocítica;

(4) tumores de origen mesenquimal, incluyendo fibrosarcoma y rabdomiosarcoma; y

(5) otros tumores, incluyendo melanoma, seminoma, tetratocarcinoma, neuroblastoma y glioma.

En una realización, los compuestos de fórmula (I), (II) y (III) son útiles en el tratamiento de tumores de pulmón, mama y próstata.

De esta manera, la presente invención proporciona un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente para su uso en terapia.

En un aspecto adicional, la presente invención proporciona el uso de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente en la fabricación de un medicamento para su uso en terapia.

En el contexto de la presente descripción, el término "terapia" también incluye "profilaxis" a menos que existan indicaciones específicas en contrario. Los términos "terapéutico" y "terapéuticamente" deben ser interpretados en consecuencia.

La invención también proporciona un método de tratar el cáncer el cual comprende administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente.

La invención aún proporciona adicionalmente un método de modular la actividad kinasa tipo polo (Plk) el cual comprende administrar a un paciente en necesidad del mismo

una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente.

La invención aún proporciona adicionalmente el uso de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para el tratamiento del cáncer.

La invención aún proporciona adicionalmente el uso de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, en la fabricación de un medicamento para modular la actividad quinasa tipo polo (Plk).

Los compuestos de fórmula (I), (II) y (III), y sales farmacéuticamente aceptables de los mismos, pueden ser usados por si mismos pero serán generalmente administrados en forma de una composición farmacéutica en la cual el compuesto/sal/solvato (ingrediente activo) de fórmula (I), (II), (IIa), (III) o (IIIa) está en asociación con un portador, diluente o adyuvante farmacéuticamente aceptable. Dependiendo del modo de administración, la composición farmacéutica preferiblemente comprenderá de 0.05 a 99%p (por ciento en peso), más preferiblemente de 0.05 a 80%p, aún más preferiblemente de 0.10 a 70%p, e incluso más preferiblemente de 0.10 a 50%p, del ingrediente activo, todos los porcentajes en peso estando basados en la composición total.

La presente invención también proporciona una composición farmacéutica que comprende un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente, en asociación con un portador, diluente o adyuvante farmacéuticamente aceptable.

La invención proporciona adicionalmente un proceso para la preparación de una composición farmacéutica de la invención la cual comprende mezclar un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como el definido aquí anteriormente, con un portador, diluente o adyuvante farmacéuticamente aceptable.

Las composiciones farmacéuticas pueden ser administradas de manera tópica (por ejemplo a la piel o el pulmón y/o las vías respiratorias) en forma, por ejemplo, de cremas, soluciones, suspensiones, aerosoles de heptafluoroalcano y formulaciones en polvo seco; o de manera sistémica, por ejemplo por administración oral en forma de tabletas, píldoras, siropes, polvos o gránulos; o por administración parenteral en forma de soluciones o suspensiones; o

por administración subcutánea; o por administración rectal en forma de supositorios; o transdermalmente.

Las composiciones de la invención pueden ser obtenidas mediante procedimientos convencionales usando excipientes farmacéuticos convencionales, bien conocidos en el arte. De esta manera, las composiciones dirigidas al uso oral pueden contener, por ejemplo, uno o más agentes colorantes, edulcorantes, saborizantes y/o conservantes.

Excipientes farmacéuticamente aceptables adecuados para una formulación de tabletas incluyen, por ejemplo, diluentes inertes tal como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes y desintegrantes tal como almidón de maíz o ácido algénico; agentes de enlace tal como almidón; agentes lubricantes tal como estearato de magnesio, ácido esteárico o talco; agentes conservantes tal como etil o propil p–hidroxibenzoato y antioxidantes tal como ácido ascórbico. Las formulaciones de tabletas pueden ser con recubrimiento o sin recubrimiento para modificar su desintegración y subsiguiente absorción del ingrediente activo dentro del tracto gastrointestinal, o para mejorar su estabilidad y/o apariencia, en cualquier caso, usando agentes de recubrimiento convencionales y procedimientos bien conocidos en el arte.

Las composiciones para uso oral pueden estar en forma de cápsulas de gelatina dura en las cuales el ingrediente activo es mezclado con un diluente sólido, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina suave en las cuales el ingrediente activo es mezclado con agua o un aceite tal como aceite de cacahuete, parafina líquida, o aceite de oliva.

Las suspensiones acuosas generalmente contienen el ingrediente activo en forma de polvo fino junto con uno o más agentes de suspensión, tal como sodio carboximetilcelulosa, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinil pirrolidona, goma tragacanto y goma de acacia; agentes dispersantes o humectantes tal como lecitina o productos de condensación de un óxido de alquileno con ácidos grasos (por ejemplo estearato de polioxetileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenooxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como polioxietileno sorbitol monooleato, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenooxicetanol, o productos de

condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como polioxietileno sorbitol monooleato, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y hexitol anhídridos, por ejemplo polietileno sorbitan monooleato. Las suspensiones acuosas pueden también contener uno o más conservantes (tal como etil o propil p–hidroxibenzoato, antioxidantes (tal como ácido ascórbico), agentes colorantes, agentes saborizantes, y/o agentes edulcorantes (tal como sucrosa, sacarina o aspartamo).

Las suspensiones aceitosas pueden ser formuladas suspendiendo el ingrediente activo en un aceite vegetal (tal como aceite de arachis, aceite de oliva, aceite de sésamo o aceite de coco) o en un aceite mineral (tal como parafina líquida). Las suspensiones aceitosas pueden también contener un agente espesante tal como cera de abejas, parafina dura o alcohol cetil. Los agentes edulcorantes tal como aquellos expuestos anteriormente, y los agentes saborizantes pueden ser añadidos para proporcionar una preparación oral agradable. Estas composiciones pueden ser preservadas mediante la adición de un antioxidante tal como ácido ascórbico.

Los gránulos y polvos dispersables adecuados para la preparación de una suspensión acuosa mediante la adición de agua generalmente contienen el ingrediente activo junto con un agente de dispersión o humectante, un agente de suspensión y uno o más conservantes. Agentes de dispersión o humectantes y agentes de suspensión adecuados son ejemplificados por aquellos ya anteriormente mencionados. Excipientes adicionales tal como agentes edulcorantes, saborizantes y colorantes, pueden también estar presentes.

Las composiciones farmacéuticas de la invención pueden también estar en forma de aceite en emulsiones acuosas. La fase aceitosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de arachis, o un aceite mineral, tal como por ejemplo parafina líquida o una mezcla de cualquiera de estos. Agentes emulsificantes adecuados pueden ser, por ejemplo, gomas naturales tal como goma de acacia o goma de tragacanto, fosfátidos naturales tal como frijol de soya, lecitina, un éster o ésteres parciales derivados de ácidos grasos y hexitol anhídridos (por ejemplo sorbitan monooleato) y productos de condensación de dichos ésteres parciales con óxido de etileno tal como polioxietileno sorbitan monooleato. Las emulsiones pueden también contener agentes edulcorantes, saborizantes y conservantes.

Los siropes y elíxires pueden ser formulados con agentes edulcorantes tal como glicerol, propileno glicol, sorbitol, aspartamo o sucrosa, y pueden también contener un agente demulcente, conservante, saborizante y/o colorante.

Las composiciones farmacéuticas pueden también estar en forma de una suspensión aceitosa o acuosa estéril inyectable, la cual puede ser formulada de acuerdo a procedimientos conocidos usando uno o más agentes de dispersión o humectantes y agentes de suspensión apropiados, los cuales han sido mencionados anteriormente. Un preparación estéril inyectable puede también ser una solución o suspensión estéril inyectable en un diluente o solvente no tóxico parenteralmente aceptable, por ejemplo una solución en 1,3 butanediol.

Las formulaciones de supositorios pueden ser preparadas mezclando el ingrediente activo con un excipiente no irritante adecuado el cual es sólido a temperaturas ordinarias pero líquido a la temperatura rectal y por lo tanto se derretirá en el recto para liberar el fármaco. Excipientes adecuados incluyen, por ejemplo, mantequilla de cocoa y polietileno glicoles.

Las formulaciones tópicas, tal como cremas, pomadas, geles y soluciones o suspensiones aceitosas o acuosas, pueden generalmente ser obtenidas formulando un ingrediente activo con un vehículo o diluente convencional, tópicamente aceptable, usando procedimientos convencionales bien conocidos en el arte.

Las composiciones para administración por insuflación pueden ser en forma de polvo finamente dividido que contiene partículas de un diámetro promedio de, por ejemplo, 30μ o mucho menor, el polvo en sí mismo comprendiendo el ingrediente activo solo o diluido con uno o más portadores fisiológicamente aceptables tal como lactosa. El polvo para la insuflación es entonces convenientemente retenido en una cápsula que contiene, por ejemplo, de 1 a 50mg del ingrediente activo para su uso con un dispositivo turbo inhalador, tal como es usado para la insuflación del agente conocido cromoglicato de sodio.

Las composiciones para administración por inhalación pueden ser en forma de un aerosol presurizado convencional dispuesto para dispensar el ingrediente activo como un aerosol que contiene gotitas líquidas o sólidas finamente divididas. Propulsores de aerosol convencionales tal como hidrocarburos fluorados volátiles o hidrocarburos pueden ser usados y el dispositivo de aerosol está convenientemente dispuesto para dispensar una cantidad regulada del ingrediente activo.

Para más información sobre la formulación el lector debe referirse al Capítulo 25.2 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Jefe del Consejo Editorial), Pergamon Press 1990.

El tamaño de la dosis para propósitos terapéuticos de un compuesto de la invención variará naturalmente de acuerdo a la naturaleza y gravedad de las afecciones, la edad y sexo del animal o paciente y la ruta de administración, de acuerdo a los principios bien conocidos de la medicina.

En general, un compuesto de la invención será administrado de manera que una dosis diaria en el rango, por ejemplo, de 0.5 mg a 75 mg del ingrediente activo por kg de peso corporal sean recibidos, dados, si se requiere, en dosis divididas. En general dosis inferiores serán administradas cuando se emplea una ruta parenteral. De esta manera, por ejemplo, para la administración intravenosa, una dosis en el rango, por ejemplo, de 0.5 mg a 30 mg del ingrediente activo por kg de peso corporal será generalmente usada. Similarmente, para la administración por inhalación, una dosis en el rango, por ejemplo, de 0.5 mg a 25 mg del ingrediente activo por kg de peso corporal será generalmente usada. También, por ejemplo, una formulación dirigida a la administración oral para humanos generalmente contendrá, por ejemplo, de 0.5 mg a 2 g del ingrediente activo.

Para más información sobre las Rutas de Administración y Regímenes de Dosificación el lector debe referirse al Capítulo 25.2 en el Volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Jefe del Consejo Editorial), Pergamon Press 1990.

El tratamiento anticáncer definido aquí anteriormente puede ser aplicado como una terapia única o puede involucrar, además del compuesto de la invención, cirugía o radioterapia o quimioterapia convencional. Tal quimioterapia puede incluir una 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 alquilatantes (por ejemplo cisplatino, oxaliplatino, carboplatino, ciclofosfamida, mostaza nitrogenada, melfalán, clorambucil, busulfan, 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 topoisomerasa (por ejemplo epipodofilotoxinas como etopósido y teniposida, amsacrina, topotecan y camptotecina);

(ii) agentes citostáticos tal 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 goserelin, leuprorelin 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 quiinasa 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 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, pp 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 derivado de las plaquetas tal como imatinib, inhibidores de las serina/treonina quinasas (por ejemplo signalling inhibidores de señales Ras/Raf tales como los inhibidores de la farnesil transferasa, por ejemplo sorafenib (BAY 43–9006), inhibidores de señales celulares a través de MEK y/o AKT quinasas, inhibidores de la familia del factor de crecimiento de hepatocitos y, inhibidores de c–kit, inhibidores de la abl quinasa, IGF receptor 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) y 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 anti–vascular bevacizumab (Avastin™), inhibidores de la tirosina quinasa del receptor del VEGF tal como 4–(4–bromo–2–fluoroanilino)–6–metoxi–7–(1–metilpiperidin–4–ilmetoxi)quinazolina (ZD6474; Ejemplo 2 dentro de WO 01/32651), 4–(4–fluoro–2–metilindol–5–iloxi)–6–metoxi–7–(3–pirrolidin–1–ilpropoxi)quinazolina (AZD2171; Ejemplo 240 dentro de WO 00/47212), vatalanib (PTK787; WO 98/35985) y SU11248 (sunitinib; WO 01/60814), compuestos tales como aquellos divulgados 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 avb3 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) terapias antisentido, por ejemplo aquellas que son dirigidas a los objetivos listados anteriormente, tal como ISIS 2503, una antisentido antiras;

(viii) 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;

(ix) 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;

(x) otros inhibidores de ciclo celular tal como inhibidores Eg5, Chk1 o PARP.

Ejemplos

La invención será descrita adicionalmente con referencia a los siguientes ejemplos ilustrativos en los cuales, a menos que se establezca lo contrario:

(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;

(iv) los cartuchos SCX–2 son las columnas de Intercambio Iónico SPE donde la fase estacionaria es el ácido propilsulfónico polimérico. Estos son usados para aislar las aminas.

(v) en general, el curso de las reacciones fue seguido por TLC o LCMS y los tiempos de reacción son dados para ilustración solamente;

(vi) los productos finales tuvieron datos espectrales de masa y/o espectros de resonancia magnética (NMR) de protón satisfactorios;

(vii) 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;

(viii) 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 400 MHz o 500MHz, en $CDCl_3$, DMSO–d_6 o DMSO–d6 + d_4–AcOH a menos que se indique lo contrario;

(ix) los símbolos químicos tienen sus significados habituales; símbolos y unidades SI son usados;

(x) las relaciones de los solventes son dadas en términos de volumen:volumen (v/v); y

(xi) los datos de los espectros de masa (MS) fueron generados en un sistema LCMS donde el componente de la HPLC comprendió generalmente un equipamiento Agilent 1100 o Waters Alliance HT (2790 & 2795) y fueron corridos en una columna Femonenex Gemini C18 5mm, 50 x 2 mm (o similar) eluyendo con eluente ácido (por ejemplo, usando un gradiente entre 0 – 95% agua / acetonitrilo con 5% de un 1% ácido fórmico en una mezcla 50:50 agua:acetonitrilo (v/v); o usando un sistema de solventes equivalente con metanol en lugar de acetonitrilo, o 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;

(xii) la irradiación con microondas de las mezclas de reacción fue realizada usando el instrumento Emrys Optimiser;

(xiii) las siguientes abreviaturas han sido usadas:

AcOH	ácido acético
$CDCl_3$	deuterocloroformo
DCM	diclorometano
DIPEA	*N,N*–diisopropiletilamina
DMA	*N,N*–dimetilacetamida
DMF	*N,N*–dimetilformamida
DMSO	dimetilsulfóxido
DMSO–d_6	hexadeuterodimetilsulfóxido
EtOH	etanol
EtOAc	etil acetato

HATU	2–(1H–7–Azabenzotriazol–1–il)—1,1,3,3–tetrametil uronio hexafluorofosfato Metanaminio
HBTU	O–Benzotriazol–N,N,N',N'–tetrametil–uronio–hexafluoro–fosfato.
HPLC	cromatografía líquida de alta resolución
MeCN	acetonitrilo
MeOH	metanol
MeI	yoduro de metilo
MS	espectroscopía de masas
m/z	relación masa/carga
NMR	resonancia magnética nuclear
SCX–2	columna de intercambio iónico SPE (fase estacionaria del ácido propilsulfónico polimérico)
THF	terahidrofurano
TFA	Ácido trifluoroacético
XANTFOS	9,9–Dimetil–4,5–bis(difenilfosfino)xanteno

Ejemplo 1:

4–[(2–Ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–metoxi–*N*–(1–metil–4–piperidil)benzamida

10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 99 mg, 0.34 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 93 mg, 0.35 mmol) y ácido *p*–toluenosulfónico (167 mg, 0.88 mmol) fueron disueltos en (*R*/S)–4–metil–2–pentanol (8 mL) y calentado a reflujo bajo una manta de nitrógeno durante 24 h. La mezcla de reacción fue enfriada y cargada en una columna SCX–2 luego lavada con MeOH (15 mL). El compuesto crudo fue eluido de la columna SCX–2 con NH_3 (40mL, 7M en MeOH) y los volátiles fueron eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 0–10% NH_3 [7M en MeOH] en DCM), proporcionó el compuesto del título (159 mg, 89%) como un sólido.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.26 (t, 5H), 1.56 – 1.83 (m, 9H), 2.04 (s, 3H), 2.20 – 2.29 (m, 3H), 2.64 – 2.71 (m, 2H), 2.85 – 2.95 (m, 2H), 3.29 (s, 3H), 3.68 – 3.71 (m, 2H), 4.12 (q, 1H), 4.90 (quinteto, 1H), 5.95 (d, 1H), 7.24 (dd, 1H), 7.42 (s, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.51 (d, 1H); MS m/z 508 $[M+H]^+$.

Ejemplo 2:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–*N*–(1–metil–4–piperidil)benzamida

10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 86 mg, 0.31 mmol), 4–amino–*N*–(1–metil–4–piperidil)benzamida (Producto intermedio 4; 72 mg, 0.31 mmol) y ácido *p*–toluenosulfónico (146 mg, 0.76 mmol) fueron disueltos en 4–metil–2–pentanol (5 mL) y refluidos bajo una atmósfera de nitrógeno durante 18 h. La mezcla de reacción fue cargada en una columna SCX–2 luego lavada con MeOH (15 mL). El compuesto crudo fue eluido de la columna SCX–2 con NH_3 (40 mL, 7M en MeOH) y los volátiles fueron eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 0–10% NH_3 [7M en MeOH] en DCM) luego por HPLC preparativa (Columna Sunfire prep RP18, 19 x 100 mm, eluyendo con un gradiente de 0.1% solución de TFA en H_2O y un 0.1% solución de TFA en MeCN). Las fracciones del producto fueron luego cargadas en una columna SCX–2 luego lavadas con MeOH (10 mL). El producto fue eluido de la columna SCX–2 con NH_3 (30 mL, 7M en MeOH) y los volátiles eliminados bajo presión reducida para dar el compuesto del título (38.5 mg, 26%) como un sólido.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ_H 1.58 – 1.78 (10H, m), 1.92 – 2.04 (4H, m), 2.21 (3H, s), 2.58 – 2.60 (2H, m), 2.79 – 2.83 (2H, m), 3.18 (3H, s), 3.60 – 3.65 (2H, m), 3.71 – 3.79 (1H, m), 4.81 – 4.89 (1H, m), 7.76 (2H, d), 7.82 (2H, d), 7.99 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 478 $[M+H]^+$.

Ejemplo 3:

4–[(4*R*/*S*)–(2–Ciclopentil–4,6–dimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–metoxi–*N*–(1–metil–4–piperidil)benzamida

(4*R/S*)–10–Cloro–2–ciclopentil–4,6–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 5; 106 mg, 0.36 mmol), 4–amino–*N*–(1–metil–4–piperidil)benzamida (WO06018220; 95 mg, 0.36 mmol) y ácido *p*–toluenosulfónico (170 mg, 0.89 mmol) fueron disueltos en (*R/S*)–4–metil–2–pentanol (6 mL) y refluidos bajo una manta de nitrógeno durante 24 h. La mezcla de reacción fue enfriada a temperatura ambiente y cargada en una columna SCX–2 y luego lavada con MeOH (40 mL). El compuesto crudo fue eluido de la columna SCX–2 con NH_3 (40 mL, 7M en MeOH) y los volátiles eliminados bajo presión reducida. El material crudo fue luego purificado por cromatografía en columna (SiO_2, gradiente de eluente: 0–10% NH_3 [7M en MeOH] en DCM) luego por HPLC preparativa (columna Sunfire prep RP18, 19 x 100 mm, eluyendo con un gradiente compuesto de un 0.1% solución de TFA en H_2O y una solución de TFA 0.1% en MeCN). Las fracciones del producto fueron cargadas en una columna SCX–2 luego lavadas con MeOH (10 mL). El producto fue eluido de la columna SCX–2 con NH_3 (30 mL, 7M en MeOH) y los volátiles eliminados bajo presión reducida para dar el compuesto del título (43.9 mg, 23%) como un sólido.

^{1}H NMR (400 MHz, DMSO–d6) δ_H 1.04 (d, 3H), 1.51 – 1.84 (m, 12H), 1.99 – 2.13 (m, 3H), 2.81 – 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quinteto, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 522 $[M+H]^+$.

Ejemplo 4:

4–[(2–Ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

A una solución de ácido 4–[(9–ciclopentil–5–metil–6,7,8,9–tetrahidro–5H–pirimido[4,5–b][1,4]diazepin–2–il)amino]–3–metoxibenzoico (Producto intermedio 6; 240 mg, 0.60 mmol) y N–[(dimetilamino)(3H–[1,2,3]triazolo[4,5–b]piridin–3–iloxi)metileno]–N–metilmetanaminio hexafluorofosfato (275 mg, 0.72 mmol) en DMA (10 mL) fue añadido 1–metilpiperidin–4–amina (82 mg, 0.72 mmol) y DIPEA (210 uL, 1.20 mmol), y la reacción agitada a temperatura ambiente durante 2 h. La mezcla de reacción fue cargada en una columna SCX–2 y lavada con MeOH (20 mL). El producto crudo fue luego eluido de la columna SCX–2 con NH_3 (40 mL, 7M en MeOH) y los volátiles eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 5–10% MeOH en DCM) proporcionó el compuesto del título (160 mg, 54%) como un sólido.

^{1}H NMR (400 MHz, DMSO–d6) δ_H 1.65 (m, 10H), 1.94 (m, 6H), 2.21 (s, 3H), 2.71 (s, 3H), 2.82 (d, 2H), 3.00 (t, 2H), 3.48 (m, 2H), 3.94 (s, 3H), 4.86 (m, 1H), 7.36 (s, 1H), 7.46 (m, 2H), 7.53 (s, 1H), 8.02 (d, 1H), 8.46 (d, 1H); MS m/z 494 $[M+H]^+$.

Ejemplo 5:

4–[(2,6–Dimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–*N*–(1–metil–4–piperidil)benzamida

10–Cloro–2,6–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 9; 185 mg, 0.82 mmol), 4–amino–3–metoxi–*N*–(1–metil–4–piperidil)benzamida (215 mg, 0.82 mmol) y ácido *p*–toluenosulfónico (389 mg, 2.05 mmol) en (*R*/S)–4–metil–2–pentanol (6 mL) fueron calentados a 115 °C durante 5 h. La mezcla de reacción fue enfriada a temperatura ambiente luego pasada a través de un cartucho SCX–2 y lavada con MeOH (40 mL). El producto crudo fue eluido fuera del cartucho SCX–2 con NH_3 (40 mL, 7M en MeOH). La purificación por HPLC preparativa (Gemini RP C18 30x100mm, fase móvil del gradiente: 10–80% MeCN/agua + 0.5% NH_3) proporcionó el compuesto del título (180 mg, 48%) como una espuma.

^{1}H NMR (400 MHz, DMSO–d_6) δ_H 1.60 (m, 2H), 1.78 (m, 2H), 1.90 (tr, 2H), 2.19 (s, 3H), 2.62 (tr, 2H), 2.79 (d, 2H), 3.09 (s, 3H), 3.20 (s, 3H), 3.73 (m, 3H), 3.95 (s, 3H), 7.51 (m, 2H), 7.75 (m, 1H), 8.05 (d, 1H), 8.11 (s, 1H), 8.48 (d, 1H); MS m/z 454 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 5 utilizando el derivado de pirimidina apropiado (Productos intermedios 10 – 13) como el electrófilo y 4–amino–3–metoxi–*N*–(1–metil–4–piperidil)benzamida (WO06/018220) como la anilina:

Ejemplo 6:

3–Metoxi–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–*N*–(1–metil–4–piperidil)benzamida

Ejemplo 7:

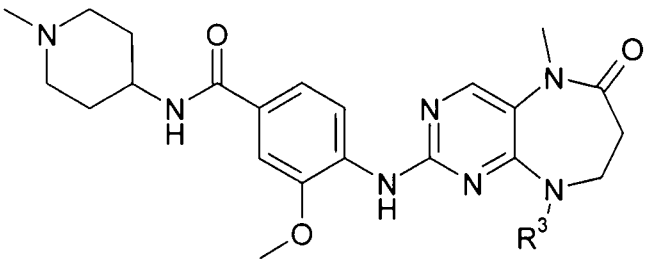
3–Metoxi–4–[[6–metil–2–(3–metilbutil)–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il]amino]–*N*–(1–metil–4–piperidil)benzamida

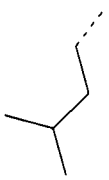
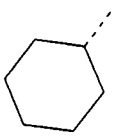
Ejemplo 8:

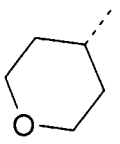
4–[(2–Ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–*N*–(1–metil–4–piperidil)benzamida

Ejemplo 9:

3–Metoxi–4–[[6–metil–2–(oxan–4–il)–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il]amino]–*N*–(1–metil–4–piperidil)benzamida



Ejemplo	R^3	^{1}H NMR (400 MHz, DMSO–d_6)	MS m/z $[M+H]^+$
6		1.25 (d, 6H), 1.60 (m, 2H), 1.77 (m, 2H), 1.95 (tr, 2H), 2.19 (s, 3H), 2.60 (tr, 2H), 2.70 (d, 2H), 3.19 (s, 3H), 3.62 (m, 2H), 3.75 (m, 1H), 3.96 (s, 3H), 4.80 (m, 1H), 7.51 (m, 2H), 7.69 (s, 1H), 8.08 (d, 2H), 8.41 (d, 1H)	482
7		0.92 (d, 6H), 1.58 (m, 5H), 1.76 (m, 2H), 1.93 (tr, 2H), 2.19 (s, 3H), 2.61 (tr, 2H), 2.79 (d, 2H), 3.19 (s, 3H), 3.61 (tr, 2H), 3.71 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.70 (s, 1H), 8.06 (d, 2H), 8.35 (d, 1H)	510
8		1.17 (m, 1H), 1.41 (m, 2H), 1.55–1.90 (m, 11H), 1.95 (tr, 2H), 2.19 (s, 3H), 2.59 (tr, 2H), 2.80 (d, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 3.77 (m, 1H), 4.49 (tr, 1H), 7.49	522

Ejemplo	R^3	^{1}H NMR (400 MHz, DMSO–d_6)	MS m/z $[M+H]^+$
		(m, 2H), 7.70 (s, 1H), 8.08 (m, 2H), 8.39 (d, 1H)	
9		1.61 (m, 2H). 1.72–2.00 (m, 7H), 2.20 (s, 3H), 2.61 (tr, 2H), 2.80 (d, 2H), 3.19 (s, 3H), 3.50 (tr, 2H), 3.67 (m, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.02 (dd, 2H), 4.62 (tr,1H), 7.51 (m, 2H), 7.78 (s, 1H), 8.10 (m, 2H), 8.31 (d, 1H)	524

Ejemplo 10:

4–[(2–Ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–*N*–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida hidrocloruro

10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 238 mg, 0.85 mmol), 4–amino–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida (Producto intermedio 22; 250 mg, 0.85 mmol) y ácido *p*–toluenosulfónico (405 mg, 2.13 mmol) fueron disueltos en (*R*/S)–4–metil–2–pentanol (4 mL) y calentados a reflujo durante 24 h. La mezcla de reacción fue luego enfriada y cargada en una columna SCX–2, la cual fue luego lavada con MeOH (40 mL). El producto crudo fue lavado fuera de la columna SCX–2 con NH_3 (50 mL, 7M en MeOH). La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 0–10% NH_3 [7M en metanol] en DCM) da un aceite amarillo pálido. HCl (0.43 uL, 2N en Et_2O, 0.85 mmol) fue añadido A una solución DCM (5 mL) del aceite amarillo. La concentración bajo presión reducida dio el compuesto del título (188 mg, 40%) como un sólido.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.00 (s, 6H), 1.60 – 1.84 (m, 6H), 2.02 – 2.34 (m, 2H), 2.37 (s, 2H), 2.39 (s, 6H), 2.65 – 2.69 (m, 2H), 3.29 (s, 3H), 3.38 (d, 2H), 3.68 – 3.72 (m, 2H), 3.98 (s, 3H), 4.87 – 4.96 (m, 1H), 7.29 (dd, 1H), 7.51 (d, 1H), 7.67 (s, 1H), 7.95 (s, 1H), 8.51 (d, 1H), 9.14 (t, 1H); MS m/z 524 $[M+H]^+$.

Ejemplo 11:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–ciclopropil–4–piperidil)–3–metoxi–benzamida

Acido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111; 150 mg, 0.36mmol), 1–ciclopropilpiperidin–4–amina (Producto intermedio 24, 77 mg, 0.55mmol) y HATU (208 mg, 0.55mmol) fueron agitados en DMF (92ml). DIPEA (191 mL, 1.09mmol) fue añadido y la mezcla agitada a temperatura ambiente durante 3 h. La mezcla fue absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por HPLC preparativa para dar el compuesto del título como un sólido marrón pálido (127mg, 66%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.29 (2H, s), 0.43 (2H, d), 1.48 – 1.81 (11H, m), 1.94 (2H, m), 2.24 (2H, t), 2.60 (2H, t), 2.96 (2H, d), 3.18 (3H, s), 3.63 (2H, t), 3.78 (1H, m), 3.95 (3H, s), 4.78 – 4.86 (1H, m), 7.46 – 7.51 (2H, m), 7.73 (1H, s), 8.04 (1H, d), 8.09 (1H, s), 8.39 (1H, d); MS m/z 534 $[M+H]^+$.

Ejemplo 12:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[2–(1–piperidil)etil]benzamida

Una solución de HATU (147 mg, 0.385 mmol) en DMA (1 mL) fue añadida a una mezcla de ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111; 144mg, 0.35 mmol), DIPEA (183uL, 1.05 mmol) y 2–(1–piperidil)etanamina (Aldrich, 56 mg 0.44 mmol) en DMA (1 mL). La mezcla resultante fue agitada a temperatura ambiente toda la noche. La mezcla fue absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por HPLC en fase inversa preparativa para dar el compuesto del título (86mg, 47%)

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 12 utilizando el ácido descrito en el Ejemplo 111 y las aminas apropiadas.

Ejemplo 13:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(2–morfolin–4–iletil)benzamida

Ejemplo 14:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–dimetilaminoetil)–3–metoxi–benzamida

Ejemplo 15:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–[(1–etilpirrolidin–2–il)metil]–3–metoxi–benzamida

Ejemplo 16:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(2–pirrolidin–1–iletil)benzamida

Ejemplo 17:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(5–dietilaminopentan–2–il)–3–metoxi–benzamida

Ejemplo 18:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–dietilaminoetil)–3–metoxi–benzamida

Ejemplo 19:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(3–dimetilaminopropil)–3–metoxi–benzamida

Ejemplo 20:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[3–(4–metilpiperazin–1–il)propil]benzamida

Ejemplo 21:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(4–dimetilaminobutil)–3–metoxi–benzamida

Ejemplo 22:

N–(1–azabiciclo[2.2.2]oct–8–il)–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida

Ejemplo 23:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[2–(2–oxoimidazolidin–1–il)etil]benzamida

Ejemplo 24:

N–(2–Acetamidoetil)–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida

Ejemplo 25:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(3–morfolin–4–ilpropil)benzamida

Ejemplo 26:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(3–imidazol–1–ilpropil)–3–metoxi–benzamida

Ejemplo 27:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–imidazol–1–iletil)–3–metoxi–benzamida

Ejemplo 28:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–dimetilaminopropan–2–il)–3–metoxi–benzamida

Ejemplo 29:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[1–(2–metoxietil)–4–piperidil]benzamida

Ejemplo 30:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(4–dietilaminobutil)–3–metoxi–benzamida

Ejemplo 31:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(4–imidazol–1–ilbutil)–3–metoxi–benzamida

Ejemplo 32:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[2–(8–oxa–3–azabiciclo[3.2.1]oct–3–il)etil]benzamida

Ejemplo 33:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(4–pirrolidin–1–ilbutil)benzamida

Ejemplo 34:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[2–(4–metilpiperazin–1–il)etil]benzamida

Ejemplo 35:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–[2–(3,3–difluoropirrolidin–1–il)etil]–3–metoxi–benzamida

Ejemplo 36:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–[2–[(3R)–3–fluoropirrolidin–1–il]etil]–3–metoxi–benzamida

Ejemplo 37:

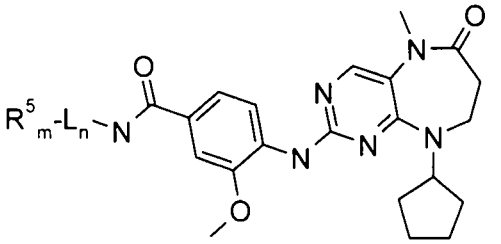
4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–[2–(4,4–difluoro–1–piperidil)etil]–3–metoxi–benzamida

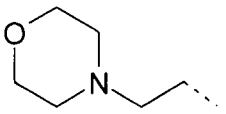
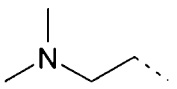
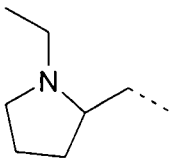
Ejemplo 38:

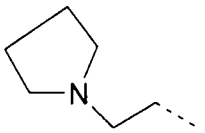
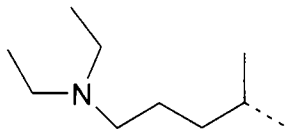
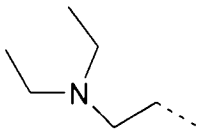
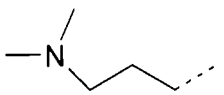
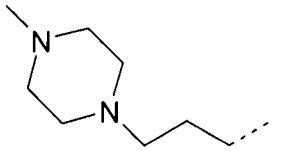
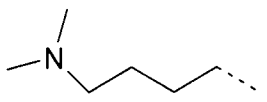
4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[3–(piridin–2–ilamino)propil]benzamida

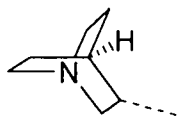
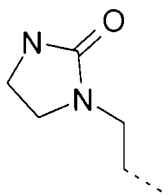
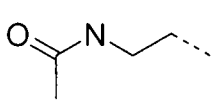
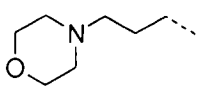
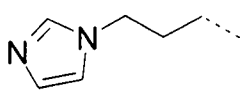
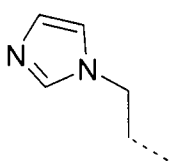
Ejemplo 39:

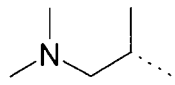
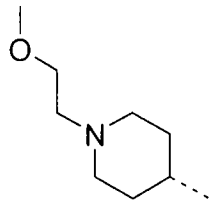
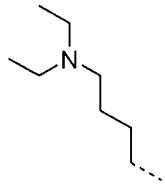
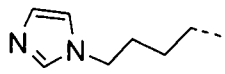
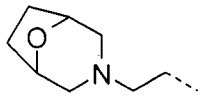
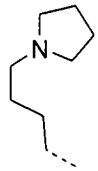
4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-(1-metil-3-piperidil)benzamida

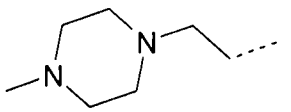
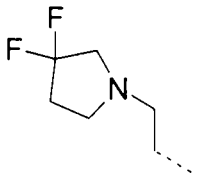
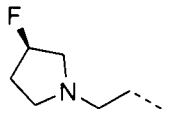
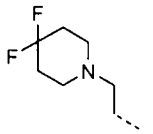
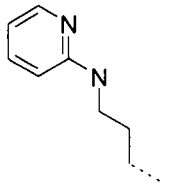
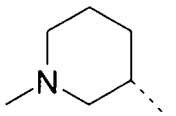


Ejemplo	$R^5{}_m$-L_n-	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
13		Aldrich	524	1.88
14		Aldrich	482	2.00
15		Aldrich	522	2.45

Ejemplo	$R^5{}_m$–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
16		Aldrich	509	2.35
17		Aldrich	553	2.4
18		Aldrich	511	2.2
19		Aldrich	497	1.99
20		ABCR	552	1.74
21		ABCR	511	2.07

Ejemplo	R^5_m–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
22		Aldrich	521	1.97
23		Maybridge	524	1.73
24		Aldrich	497	1.7
25		ABCR	539	1.87
26		Aldrich	520	1.87
27		ABCR	506	1.79

Ejemplo	R^5_m–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
28		Aldrich	497	2.03
29		Chemstep	553	1.96
30		Frinton	539	2.33
31		Asinex	534	1.91
32		US3856783	551	2.07
33		Matrix	537	2.27

Ejemplo	$R^5{}_m$–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
34		Matrix	538	1.74
35		WO2005097750	545	2.2
36		US2005209274	527	2.02
37		Fluorochem	559	2.29
38		US2003069236	546	2.18
39		Fluorochem	509	2.03

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 12 utilizando el ácido descrito en el Ejemplo 111 y las aminas BOC

protegidas apropiadas. Anterior a la purificación SCX la mezcla de reacción fue tratada con HCl 4N en dioxano (1 mL) y agitada a temperatura ambiente durante 24 h. Las mezclas de reacción fueron absorbidas en Columnas SCX, lavadas con metanol y eluidas con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por HPLC preparativa para dar los compuestos del título

Ejemplo 40:

N–(4–aminobutil)–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida

Ejemplo 41:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(4–piperidil)benzamida

Ejemplo 42:

N–(3–aminopropil)–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida

Ejemplo 43:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(2–metilaminoetil)benzamida

Ejemplo 44:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(3–metilaminopropil)benzamida

Ejemplo 45:

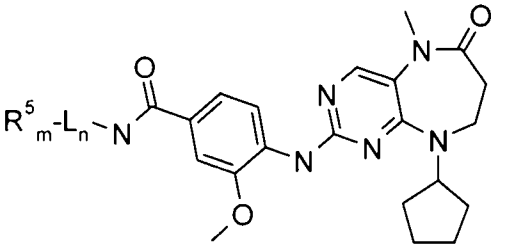
4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–pirrolidin–3–il–benzamida

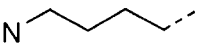
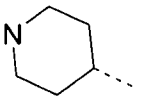
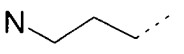
Ejemplo 46:

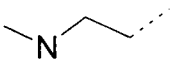
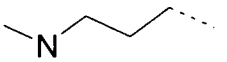
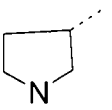
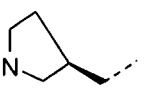
N-(3-amino-2,2-dimetil-propil)-4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzamida

Ejemplo 47:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[[(3R)-pirrolidin-3-il]metil]benzamida



Ejemplo	$R^5{}_m$-L_n-	Suministrador o Fuente de Amina BOC protegida	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
40		Fluka	482	2.02
41		Aldrich	494	2.02
42		Aldrich	468	1.97

Ejemplo	R^5_m–L_n–	Suministrador o Fuente de Amina BOC protegida	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
43		ABCR	468	1.9
44		ABCR	482	2.26
45		ABCR	480	2.02
46		ABCR	496	2.16
47		ABCR	494	2.47

Ejemplo 48:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–2–fluoro–5–metoxi–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 211 mg, 0.75 mmol) y 4–amino–2–fluoro–5–metoxi–N–(1–metil–4–piperidil)benzamida (Producto intermedio 27, 211 mg, 0.75 mmol) fueron combinados con p–

TSA (357 mg, 1.88 mmol) en 4–metil–2–pentanol (1 mL) y calentados a 150 °C durante 18 h. La mezcla de reacción enfriada fue diluida con metanol y agua (aprox. 50 mL) y cargada en un cartucho SCX–2 de 50 g lavando con metanol (100 mL) y eluyendo con amoniaco metanólico 7 *N* (100 mL). La solución concentrada fue purificada por HPLC en fase inversa. El compuesto del título fue obtenido como un sólido beige (178 mg, 45%).

^{1}H NMR (399.902 MHz, DMSO–d_6) δ 1.50 – 1.81 (m, 10H), 1.90 – 2.00 (m, 4H), 2.16 (s, 3H), 2.58 – 2.61 (m, 2H), 2.72 (br d, 2H), 3.17 (s, 3H), 3.63 – 3.65 (m, 2H), 3.68 – 3.75 (m, 1H), 3.92 (s, 3H), 4.83 (quinteto, 1H), 7.19 (d, 1H), 7.79 – 7.82 (m, 2H), 8.11 (s, 1H), 8.33 (d, 1H); MS m/z 526 $[M+H]^+$.

Ejemplo 49:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(1–propan–2–il–4–piperidil)benzamida

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111; 100mg, 0.24 mmol), N–isopropil–4–aminopiperidina (ABCR, 42 mg, 0.29 mmol), HATU (111 mg, 0.29mmol) y DIPEA (127 uL, 0.73 mmol) y DMF (3 mL) fueron combinados y agitados a temperatura ambiente durante 3 horas. El solvente fue evaporado y el residuo particionado entre DCM (10 mL) y agua (10 mL). La fase orgánica fue añadida a una columna SCX–2 de 5g prehumedecida con MeOH (2 volúmenes de columna), purgada con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH y los solventes evaporados. El residuo fue tomado en DCM y purificado en sílice, eluyendo con un gradiente de 0 – 5% MeOH / DCM seguido por 5% luego 10% y finalmente 15% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido blanco (45 mg, 35%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.99 (d, 6H), 1.55 – 1.73 (m, 8H), 2.00 (m, 4H), 2.27 (m, 2H), 2.60 (m, 2H), 2.69 (m, 1H), 2.81 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.92 (m, 4H), 4.83 (m, 1H), 5.82 (d, 1H), 7.14 (m, 1H), 7.35 (d, 1H), 7.59 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 50:

tert–butil 4–[[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzoil]amino]piperidina–1–carboxilato

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111; 113 mg, 0.27 mmol), tert–butil 4–aminopiperidina–1–carboxilato (ABCR, 50mg, 0.25 mmol), HATU (114 mg, 0.3 mmol) y DIPEA (130 uL, 0.75 mmol) y DMF (3 mL) fueron combinados y agitados a temperatura ambiente durante 3 horas. El solvente fue evaporado y el residuo particionado entre DCM (25 mL) y bicarb. sat. ac. (25 mL) y filtrado por gravedad a través de un vaso PTFE. La fase orgánica fue añadida a una columna de sílice y eluida con un gradiente superficial de 0 – 10% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma amarilla a la cual éter fue añadido y reevaporadas para dar el compuesto del título como un sólido naranja. (89mg, 55%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.37 (m, 11H), 1.53 – 1.71 (m, 6H), 1.97 (m, 4H), 2.60 (m, 2H), 2.86 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.91 (s, 3H), 4.05 (m, 3H), 4.83 (m, 1H), 5.83 (d, 1H), 7.15 (m, 1H), 7.35 (m, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 594 $[M+H]^+$.

Ejemplo 51:

Bencil (1S,5R)–6–[[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzoil]amino]–3–azabiciclo[3.1.0]hexano–3–carboxilato

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111; 113 mg, 0.27 mmol), bencil (1S,5R)–6–amino–3–azabiciclo[3.1.0]hexano–3–carboxilato (Producto intermedio 30; 50 mg, 0.25 mmol), HATU (114 mg, 0.3 mmol) y DIPEA (130 uL, 0.75 mmol) y DMF (3 mL) fueron combinados y agitados a temperatura ambiente durante 3 horas. El solvente fue evaporado y el residuo particionado entre DCM (2 mL) y bicarb. sat. ac. (2 mL), filtrado por gravedad a través de un vaso PTFE y los solventes evaporados. El residuo fue tomado en DCM y purificado en sílice eluyendo con un gradiente de 0 – 5% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas. El material resultante fue purificado por HPLC en fase inversa.

^{1}H NMR (400.132 MHz, CDCl3) δ 1.64 (m, 8H), 1.97 (m, 2H), 2.58 (m, 3H), 3.22 (s, 3H), 3.46 (m, 2H), 3.62 (m, 2H), 3.78 (m, 2H), 3.90 (s, 3H), 4.82 (m, 1H), 5.05 (s, 2H), 6.08 (s, 1H), 7.12 (m, 1H), 7.26 (m, 5H), 7.34 (d, 1H), 7.61 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 626 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 51 utilizando el ácido descrito en Ejemplo 111 y las aminas apropiadas.

Ejemplo 52:

tert–butil (3R)–3–[[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzoil]amino]pirrolidina–1–carboxilato

Amina disponible de Chempacific

^{1}H NMR (400.132 MHz, CDCl3) δ 1.41 (s, 9H), 1.63 (m, 3H), 1.94 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 3.26 (m, 4H), 3.43 (m, 2H), 3.65 (m, 3H), 3.91 (s, 3H), 4.59 (m, 1H), 4.84 (m, 1H), 6.01 (d, 1H), 7.15 (m, 5H), 7.35 (d, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 8.45 (d, 1H); MS m/z 580 $[M+H]^+$.

Ejemplo 53:

tert–butil (3S)–3–[[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzoil]amino]pirrolidina–1–carboxilato

Amina disponible de Chempacific

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.64 (m, 6H), 1.93 (m, 3H), 2.19 (m, 1H), 2.60 (m, 2H), 3.26 (m, 4H), 3.43 (m, 2H), 3.65 (m, 3H), 3.91 (s, 3H), 4.59 (m, 1H), 4.84 (m, 1H), 6.02 (d, 1H), 7.15 (m, 1H), 7.35 (d, 1H), 7.62 (s, 1H), 7.88 (s, 1H), 8.45 (d, 1H); MS m/z 580 $[M+H]^+$.

Ejemplo 54:

Bencil 4-[[4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzoil]amino]piperidina-1-carboxilato

Ácido 4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-3-metoxi-benzoico (Ejemplo 111 , 350 mg, 0.85 mmol), Bencil 4-aminopiperidina-1-carboxilato (ABCR, 219 mg, 0.94 mmol), HATU (388 mg, 1.02 mmol) y DIPEA (445 uL, 2.55 mmol) y DMF (5 mL) fueron combinados y agitados a temperatura ambiente durante 3 horas. El solvente fue evaporado y los residuos particionados entre DCM (2 mL) y bicarb. sat. ac. (2 mL), filtrado por gravedad a través de un vaso PTFE y los solventes evaporados. El residuo fue tomado en DCM y purificado en sílice eluyendo con un gradiente de 0 – 5% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas. Para dar el compuesto del título como un sólido naranja.

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.38 (m, 2H), 1.62 (m, 6H), 1.97 (m, 4H), 2.60 (m, 2H), 2.94 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.91 (s, 3H), 4.11 (m, 3H), 4.83 (m, 1H), 5.07 (s, 2H), 5.82 (d, 1H), 7.14 (m, 1H), 7.27 (m, 5H), 7.34 (d, 1H), 7.61 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 628 $[M+H]^+$.

Ejemplo 55:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(3R)-pirrolidin-3-il]benzamida

tert-butil (3R)-3-[[4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzoil]amino]pirrolidina-1-carboxilato (630 mg, 1 mmol) fue disuelto en DCN (10 mL), TFA (10 mL) añadido y agitado a temperatura ambiente durante 2 h. La mezcla de reacción fue añadida a una columna SCX-2 de 10 g prehumedecida con MeOH (2 volumenes de columna), purgada con MeOH (2 volumenes de columna) luego el producto crudo eluido con amoniaco 2M en MeOH y los solventes evaporados. El residuo fue tomado en DCM y purificado en sílice eluyendo con un gradiente de 0 – 10% amoniaco 2M en MeOH / DCM luego 10% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma, éter fue añadido y reevaporado para dar el compuesto del título como un sólido. (300 mg, 74%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.62 (m, 8H), 1.98 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 2.89 (m, 2H), 3.06 (m, 1H), 3.17 (m, 1H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.53 (m,

1H), 4.83 (m, 1H), 6.24 (d, 1H), 7.19 (m, 1H), 7.37 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 480 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 56 utilizando el material BOC protegido descrito en el Ejemplo 54.

Ejemplo 56:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(3S)-pirrolidin-3-il]benzamida

^{1}H NMR (400.132 MHz, CDCl3) δ 1.62 (m, 8H), 1.98 (m, 2H), 2.19 (m, 1H), 2.60 (m, 2H), 2.85 (m, 1H), 2.91 (m, 1H), 3.06 (m, 1H), 3.17 (m, 1H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.53 (m, 1H), 4.83 (m, 1H), 6.24 (d, 1H), 7.19 (m, 1H), 7.37 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 480 $[M+H]^+$.

Ejemplo 57:

N-[(1S,5R)-3-azabiciclo[3.1.0]hex-6-il]-4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzamida

Bencil (1S,5R)-6-[[4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzoil]amino]-3-azabiciclo[3.1.0]hexano-3-carboxilato (Ejemplo 51, 357mg, 0.57 mmol) fue disuelto en MeOH (30 mL) y pasado a través de la cuba de H a 50 °C en modo de hidrógeno total a 1 mL por minuto. La solución añadida a una columna SCX-2 de 10 g prehumedecida con MeOH (2 volumenes de columna), purgada con MeOH (2 volumenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH. Las fracciones básicas fueron evaporadas y el residuo disuelto en DCM y purificado en sílice eluyendo con un gradiente de 0 – 10% amoniaco 2M en MeOH / DCM luego 10% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma a la cual éter fue añadido y reevaporado para dar el compuesto del título como una sólido color crema. (172 mg, 42%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.64 (m, 8H), 1.97 (m, 2H), 2.60 (m, 3H), 2.91 (m, 2H), 3.17 (m, 2H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.82 (m, 1H), 6.02 (s, 1H), 7.13 (m, 1H), 7.35 (d, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.43 (d, 1H); MS m/z 492 $[M+H]^+$.

Ejemplo 58:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(4-dietilaminociclohexil)-3-metoxi-benzamida

Ácido 4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-3-metoxi-benzoico (Ejemplo 111, 100 mg, 0.24 mmol), N,N-dietilciclohexano-1,4-diamina (ABChem, 46 mg, 0.28 mmol), HATU (111 mg, 0.29mmol) y DIPEA (127 uL, 0.73 mmol) y DMF (3 mL) fueron combinados y agitados a temperatura ambiente durante toda la noche. El solvente fue evaporado y los residuos particionados entre DCM (2 mL) y bicarb. sat. ac. (2 mL), filtrado por gravedad a través de un vaso PTFE, los solventes evaporados y el residuo purificado por HPLC en fase inversa para dar el compuesto del título como un sólido color crema (114mg, 83%).

MS m/z 564 [M+H]+. Tiempo de retención 2.20 Minutos

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 58 utilizando las aminas apropiadas.

Ejemplo 59:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(1S,5R)-9-metil-9-azabiciclo[3.3.1]non-7-il]benzamida

Amina disponible de Chontech

^{1}H NMR (399.902 MHz, CDCl3) δ 1.03 (m, 2H), 1.30 (m, 2H), 1.54 (m, 2H), 1.60 – 1.80 (m, 6H), 1.98 (m, 2H), 2.05 (m, 2H), 2.53 (m, 5H), 2.67 (m, 2H), 3.09 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 4.90 (m, 1H), 5.78 (d, 1H), 7.23 (m, 1H), 7.44 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.49 (d, 1H); MS m/z 548 [M+H]+.

Ejemplo 60:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(4-dimetilaminociclohexil)-3-metoxi-benzamida

Amina disponible de ABChem

MS m/z 536 [M+H]+. Tiempo de retención 1.92 Minutos

Ejemplo 61:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(1-etil-4-piperidil)-3-metoxi-benzamida

4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-3-metoxi-N-(4-piperidil)benzamida (Ejemplo 41; 80 mg, 0.16 mmol), Etil bromuro (ABCR, 13 uL, 0.18 mmol), trietilamina (0.45 uL, 0.32 mmol) y DMF (3 mL) fueron combinados y calentados por irradiación de microondas a 75 °C durante 1 h y luego a 80 °C durante 30 minutos. La mezcla de reacción fue purificada por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (56 mg, 66%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.10 (t, 3H), 1.53 – 1.80 (m, 8H), 2.09 (m, 6H), 2.44 (m, 2H), 2.67 (m, 2H), 2.92 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 4.00 (m, 4H), 4.90 (m, 1H), 5.90 (d, 1H), 7.22 (m, 1H), 7.42 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 522 [M+H]+.

Ejemplo 62:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(3R)-1-metilpirrolidin-3-il]benzamida

A 4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(3R)-pirrolidin-3-il]benzamida (Ejemplo 55, 140 mg, 0.29 mmol) disuelto en THF (2 mL) fue añadido ácido acético (17uL, 0.29 mmol) seguido por formaldehído acuoso (1 mL). La mezcla de reacción fue agitada a temperatura ambiente durante 30 min y triacetoxiborohidruro de sodio (100 mg, 0.47 mmol) añadido y la mezcla de reacción agitada durante unas 2 h adicionales. El solvente fue evaporado y el residuo neutralizado conbicarbarbonato de sodio sat. ac. y extraido con DCM (2 x 5ml), filtrado por gravedad a través de un vaso PTFE y los solventes evaporados. El material resultante fue purificado por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (97mg, 67%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.60 – 1.80 (m, 7H), 2.05 (m, 2H), 2.22 (m, 1H), 2.38 (s, 3H), 2.44 (m, 1H), 2.55 (m, 1H), 2.67 (m, 2H), 2.77 (m, 1H), 2.96 (m, 1H), 3.29 (s, 3H), 3.69

(m, 2H), 3.97 (s, 3H), 4.69 (m, 1H), 4.91 (m, 1H), 6.45 (d, 1H), 7.27 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 494 [M+H]+.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 62 utilizando la pirrolidina análoga al Ejemplo 56.

Ejemplo 63:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(3S)-1-metilpirrolidin-3-il]benzamida

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.60 – 1.80 (m, 7H), 2.05 (m, 2H), 2.22 (m, 1H), 2.38 (s, 3H), 2.44 (m, 1H), 2.55 (m, 1H), 2.67 (m, 2H), 2.77 (m, 1H), 2.96 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.97 (s, 3H), 4.68 (m, 1H), 4.91 (m, 1H), 6.45 (d, 1H), 7.27 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.50 (d, 1H); MS m/z 494 [M+H]+.

Ejemplo 64:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(1S,5R)-3-metil-3-azabiciclo[3.1.0]hex-6-il]benzamida

A N-[(1S,5R)-3-azabiciclo[3.1.0]hex-6-il]-4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzamida (Ejemplo 57, 114 mg, 0.23 mmol) disuelto en THF (2 mL) fue añadido ácido acético (13 uL, 0.23 mmol) (material proveniente de la solución), seguido por formaldehído acuoso (0.5 mL, todo el material disuelto nuevamente). La mezcla de reacción fue agitada a temperatura ambiente durante 30 min y triacetoxiborohidruro de sodio (100 mg, 0.47 mmol) añadido y la mezcla de reacción agitada durante unas 2 h adicionales. El solvente fue evaporado y el residuo neutralizado con bicarbonato de sodio sat. ac. y extraído con DCM (15 mL), filtrado a través de un vaso PTFE y evaporado. El material resultante fue purificado por HPLC en fase inversa. ^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.56 – 1.80 (m, 8H), 2.04 (m, 2H), 2.30 (s, 3H), 2.39 (m, 2H), 2.66 (m, 2H), 3.12 (m, 1H), 3.17 (m, 2H), 3.29 (s, 3H), 3.69 (m, 2H), 3.96 (s, 3H), 4.89 (m, 1H), 6.06 (s, 1H), 7.18 (m, 1H), 7.43 (m, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.48 (d, 1H); MS m/z 506 [M+H]+.

Ejemplo 65:

Metil (1S,3R)–3–[[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzoil]amino]ciclopentano–1–carboxilato

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111, 1.1 g, 2.7 mmol), metil (1S,3R)–3–aminociclopentano–1–carboxilato (Producto intermedio 31; 528 mg, 2.94 mmol), HATU (1.22 g, 3.22 mmol) y DIPEA (1.86 mL, 10.68 mmol) y DMF (10 mL) fueron combinados y agitados a temperatura ambiente toda la noche. El solvente fue evaporado y el residuo particionado entre carbonato de sodio saturado y DCM luego filtrado por gravedad a través de un vaso PTFE. La fase orgánica fue pasada a través de una almohadilla de sílice eluyendo con EtOAc. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar una goma marrón la cual fue disuelta en MeOH y añadida a una columna SCX–2 de 50 g prehumedecida con MeOH (2 volúmenes de columna). Purgado con MeOH (2 volúmenes de columna) y el producto eluido con amoniaco 2M en MeOH. El solvente fue evaporado hasta una goma amarilla, éter fue añadido y luego reevaporado para dar el compuesto del título como una espuma amarilla (1.21 g, 84%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.75 (m, 4H), 1.95 (m, 4H), 2.02 – 2.22 (m, 4H), 2.67 (m, 2H), 3.02 (m, 1H), 3.29 (s, 3H), 3.69 (m, 2H), 3.72 (s, 3H), 3.99 (s, 3H), 4.60 (m, 1H), 4.91 (m, 1H), 7.25 (m, 1H), 7.38 (m, 1H), 7.49 (m, 1H), 7.67 (s, 1H), 7.94 (s, 1H), 8.53 (d, 1H); MS m/z 537 [M+H]+.

Ejemplo 66:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–[2–(dipropan–2–ilamino)etil]–3–metoxi–benzamida

Una solución de ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111, 100 mg, 0.24 mmol), DIPEA (0.127 mL, 0.73 mmol) y HATU (120 mg, 0.32 mmol) en DMF (2 mL) fue agitada a temperatura ambiente durante 10 min. La solución marrón pálido fue añadida a N,N–dipropan–2–iletano–1,2–diamina (ABCR, 43 mg, 0.3 mmol) y la solución resultante agitada a temperatura ambiente durante 18 horas. La solución de la reacción fue purificada por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (43 mg, 33%); MS m/z 538 [M+H]+. Tiempo de retención 2.49 min.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 66, utilizando las aminas apropiadas. El dato de NMR fue obtenido en una selección de compuestos como se indicó.

Ejemplo 67:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-piridin-4-il-benzamida

Ejemplo 68:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-(3-pirrolidin-1-ilpropil)benzamida

Ejemplo 69:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[3-(1-piperidil)propil]benzamida

Ejemplo 70:

N-[3-(azepan-1-il)propil]-4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzamida

Ejemplo 71:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-[(1S,5R)-8-metil-8-azabiciclo[3.2.1]oct-3-il]benzamida

Ejemplo 72:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-(1,2,2,6,6-pentametil-4-piperidil)benzamida

Ejemplo 73:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[1–(1–piperidil)propan–2–il]benzamida

Ejemplo 74:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–piridin–3–il–benzamida

Ejemplo 75:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[2–metil–2–(1–piperidil)propil]benzamida

Ejemplo 76:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(piridin–3–ilmetil)benzamida

Ejemplo 77:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(4–metoxifenil)benzamida

Ejemplo 78:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(3–dietilaminopropil)–3–metoxi–benzamida

1H NMR (400.132 MHz, DMSO–d_6) δ 0.95 (t, 6H), 1.66 (m, 8H), 1.94 (m, 2H), 2.45 (m, 6H), 2.59 (m, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.94 (s, 3H), 4.81 (m, 1H), 7.45 (d, 2H), 7.48 (s, 1H), 7.73 (s, 1H), 8.08 (s, 1H), 8.38 (s, 1H), 8.38 (d, 2H)

Ejemplo 79:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[2–(1–metilpirrolidin–2–il)etil]benzamida

Ejemplo 80:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(piridin–4–ilmetil)benzamida

Ejemplo 81:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(2–metil–1–pirrolidin–1–il–propan–2–il)benzamida

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.37 (s, 6H), 1.67 (m, 10H), 1.94 (m, 2H), 2.60 (m, 6H), 2.78 (s, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.94 (s, 3H), 4.80 (m, 1H), 7.37 (d, 1H), 7.42 (s, 1H), 7.48 (s, 1H), 7.72 (s, 1H), 8.08 (s, 1H), 8.36 (d, 1H)

Ejemplo 82:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–[[(2S)–1–(ciclopropilmetil)pirrolidin–2–il]metil]–3–metoxi–benzamida

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.01 (m, 2H), 0.34 (m, 2H), 0.80 (m, 1H), 1.59 (m, 10H), 1.84 (m, 2H), 1.96 (m, 1H), 2.12 (m, 1H), 2.50 (m, 3H), 2.64 (m, 1H), 3.01 (m, 2H), 3.08 (s, 3H), 3.32 (m, 1H), 3.53 (m, 2H), 3.84 (s, 3H), 4.71 (m, 1H), 7.36 (d, 1H), 7.39 (s, 1H), 7.63 (s, 1H), 7.98 (s, 1H), 8.12 (t, 1H), 8.28 (d, 1H)

Ejemplo 83:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.29 (s, 2H), 0.51 (s, 2H), 1.66 (m, 10H), 1.94 (m, 2H), 2.43 (s, 2H), 2.51 (m, 4H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (d, 2H), 3.63 (m, 2H), 3.95 (s, 3H), 4.82 (m, 1H), 7.38 (d, 1H), 7.47 (s, 1H), 7.74 (s, 1H), 8.09 (s, 1H), 8.38 (d, 1H), 8.49 (t, 1H).

Ejemplo 84:

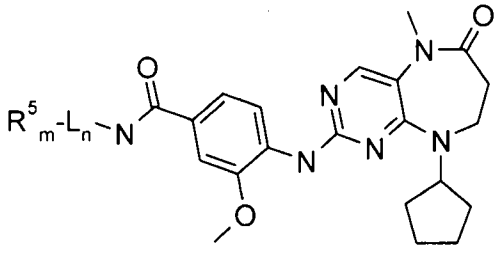
4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[(1–metil–3–piperidil)metil]benzamida

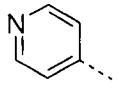
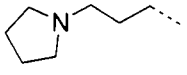
^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.92 (m, 1H), 1.44 (m, 1H), 1.73 (m, 10H), 1.94 (m, 2H), 2.13 (s, 3H), 2.64 (m, 5H), 3.15 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.49 (m, 2H), 7.73 (s, 1H), 8.08 (s, 1H), 8.32 (t, 1H), 8.38 (d, 1H)

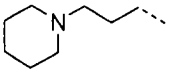
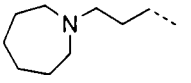
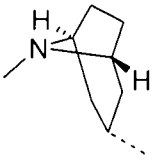
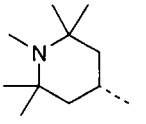
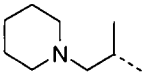
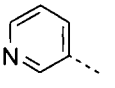
Ejemplo 85:

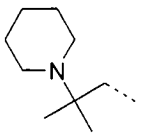
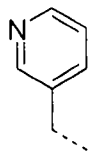
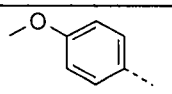
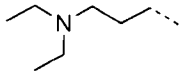
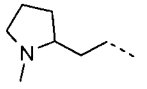
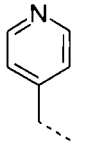
4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[2–(1–metil–2–piperidil)etil]benzamida

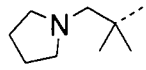
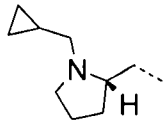
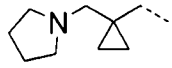
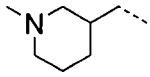
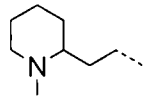
^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.45 (m, 14H), 1.95 (m, 4H), 2.21 (s, 3H), 2.59 (m, 2H), 2.76 (m, 1H), 3.17 (s, 3H), 3.31 (m, 2H), 3.63 (m, 2H), 3.94 (s, 3H), 4.81 (m, 1H), 7.46 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.35 (t, 1H), 8.38 (d, 1H)



Ejemplo	$R^5{}_m$–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
67		Aldrich	488	1.97
68		ABCR	522	2.01

Ejemplo	$R^5{}_m$–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
69		ABCR	536	2.17
70		ABCR	550	2.33
71		Flurochem	534	1.85
72		ABCR	564	2.28
73		Journal of the Chemical Society (1947), p 1511–13.	536	2.31
74		Aldrich	488	1.96

Ejemplo	R^5_m–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
75		Matrix	550	2.67
76		Aldrich	502	1.81
77		Aldrich	517	2.35
78		Aldrich	524	2.11
79		Aldrich	522	1.83
80		Aldrich	502	1.73

Ejemplo	$R^5{}_m$–L_n–	Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
81		Flurochem	536	2.64
82		Producto intermedio 32	548	2.85
83		Producto intermedio 33	548	3.01
84		Chembridge	522	2.19
85		Chembridge	536	2.39

Ejemplo 86:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(1–tert–butil–4–piperidil)benzamida

Una solución de N–[(1S,5R)–3–azabiciclo[3.1.0]hex–6–il]–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida (Ejemplo 57, 250mg, 0.61mmol), 1–tert–butilpiperidin–4–amina (Activate, 96mg, 0.61mmol),

HATU (349mg, 0.92mmol) y DIPEA (321uL, 1.83mmol) en DMF (5 mL) fue agitada a temperatura ambiente toda la noche. La mezcla de reacción fue cargada en una columna SCX-3 prehumedecida con metanol. La columna fue lavada con metanol y luego con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (137mg, 40.8%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.04 (9H, s), 1.55 (2H, s), 1.62 – 1.63 (3H, m), 1.73 (3H, d), 1.80 (2H, d), 1.95 (2H, t), 2.10 (2H, t), 2.60 (2H, t), 3.01 (2H, d), 3.18 (3H, s), 3.62 -3.64 (2H, t), 3.72 (1H, m), 3.95 (3H, s), 4.79 – 4.84 (1H, m), 7.46 (1H, d), 7.50 (1H, d), 7.73 (1H, s), 8.02 (1H, d), 8.09 (1H, s), 8.39 (1H, d); MS m/z 549[M+H]+.

Ejemplo 87:

Ácido (1S,3R)-3-[[4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzoil]amino]ciclopentano-1-carboxílico

A una solución de metil (1S,3R)-3-[[4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzoil]amino]ciclopentano-1-carboxilato (Ejemplo 65, 1.21 g, 2.25 mmol) en THF / agua (20 mL) 4:1 fue añadido hidróxido de litio (472 mg, 11.25 mmol) y la mezcla de reacción agitada a temperatura ambiente toda la noche. El solvente fue evaporado y el residuo diluido con agua. Ácido cítrico 1M fue añadido hasta que la precipitación cesó (pH 3 – 4) y la suspensión resultante agitada durante 20 minutos. El precipitado crema resultante fue filtrado, lavado con agua seguido por isohexano y secado bajo vacío para proporcionar el compuesto del título (1.08 g, 92%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.62 – 1.95 (m, 12H), 2.07 (m, 1H), 2.59 (m, 3H), 2.72 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.28 (m, 1H), 4.81 (m, 1H), 7.51 (m, 2H), 7.74 (s, 1H), 8.09 (s, 1H), 8.38 (d, 1H), 8.85 (s, 1H); MS m/z 523 [M+H]+.

Ejemplo 88:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-[(1R,3S)-3-(dimetilcarbamoil)ciclopentil]-3-metoxi-benzamida

Una solución de ácido (1S,3R)–3–[[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzoil]amino]ciclopentano–1–carboxílico (Ejemplo 87, 100 mg, 0.19 mmol), HATU (80 mg, 0.21 mmol) y DIPEA (100 uL, 0.73 mmol) en DMF (3 mL) fue agitada a temperatura ambiente durante 10 minutos. Una solución dimetilamina en THF (1 mL) fue añadida y la mezcla de reacción agitada a temperatura ambiente toda la noche. El solvente fue evaporado y el material resultante purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido amarillo (80 mg, 86%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.75 (m, 4H), 1.84 (m, 2H), 2.06 (m, 6H), 2.67 (m, 2H), 2.99 (s, 3H), 3.11 (s, 3H), 3.31 (m, 4H), 3.69 (m, 2H), 3.99 (s, 3H), 4.58 (m, 1H), 4.91 (m, 1H), 7.53 (m, 2H), 7.67 (s, 1H), 7.93 (s, 1H), 8.44 (d, 1H), 8.51 (d, 1H); MS m/z 550 [M+H]+.

Ejemplo 89:

N–ciclohexil–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino] benzamida

Una solución de 4–amino–N–ciclohexil–benzamida (TimTec, 108 mg, 0.5 mmol), 10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 140mg, 0.5mmol) y ácido p–toluenosulfónico monohidrato (238mg, 1.25mmol) en 4–metil–2–pentanol (3ml) fue calentado a 140°C durante 3h. La mezcla se dejó enfriar provocando que se forme un sólido. Metanol y DCM fueron añadidos para dar una solución que fue absorbida en una columna SCX–3 y lavada con metanol. El producto eluido con metanol/amoniaco y las fracciones que contienen el producto fueron concentradas. La purificación por cromatografía en fase inversa preparativa (Nota 1) dio el compuesto del título como un sólido blanco (35mg, 15%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.11 – 1.19 (1H, m), 1.26 – 1.37 (4H, m), 1.60 – 1.85 (11H, m), 1.97 – 2.01 (2H, m), 2.59 (2H, m), 3.18 (3H, s), 3.62 – 3.65 (2H, m), 3.72 – 1.76 (1H, m), 4.85 (1H, m), 7.75 – 7.81 (4H, m), 7.93 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 463 [M+H]+.

Ejemplo 90:

N–ciclohexil–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida

Una solución de HATU (147 mg, 0.385 mmol) en DMA (1 mL) fue añadida a una mezcla de ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111, 144mg, 0.35 mmol), DIPEA (183 uL, 0.385 mmol) y Ciclohexilamina (Aldrich, 44 mg, 0.44 mmol) en DMA (1 mL). La mezcla resultante fue agitada a temperatura ambiente toda la noche. La mezcla fue absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas al vacío. El material resultante fue purificado por HPLC en fase inversa preparativa para proporcionar el compuesto del título como un sólido blanco (7 mg, 4%).

m/z 493 [M+H]+. Tiempo de retención 2.57 minutos

Ejemplo 91:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–me toxi–N–metil–benzamida

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 111, 100mg, 0.24 mmol), 2M Metilamina en THF (365 uL, 0.73 mmol), HATU (111 mg, 0.29mmol) y DIPEA (127 uL, 0.73 mmol) y DMF (3 mL) fueron combinados y agitados a temperatura ambiente toda la noche. El solvente fue evaporado y el residuo particionado entre DCM (2 mL) y bicarb. sat. ac. (2 mL), y filtrado por gravedad a través de un vaso PTFE. La fase orgánica fue añadida a una columna de sílice, eluyendo con un gradiente de 0 – 10% MeOH / DCM y solventes evaporados de las fracciones que contienen el producto. El material resultante fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco. (45 mg, 44 %).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.62 (m, 6H), 1.98 (m, 2H), 2.60 (m, 2H), 2.95 (d, 3H), 3.22 (s, 3H), 3.62 (m, 2H), 3.90 (s, 3H), 4.83 (m, 1H), 6.00 (d, 1H), 7.17 (m, 1H), 7.37 (d, 1H), 7.59 (s, 1H), 7.87 (s, 1H), 8.44 (d, 1H); MS m/z 454 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 91 utilizando cloruro de amonio y 3 equivalentes adicionales de DIPEA y recogiendo

el producto como un sólido precipitado del tratamiento final con DCM y solución de bicarbonato de sodio saturada acuosa.

Ejemplo 92:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.73 (m, 6H), 2.00 (m, 2H), 2.64 (m, 2H), 3.23 (s, 3H), 3.68 (m, 2H), 3.99 (s, 3H), 4.86 (m, 1H), 7.22 (s, 1H), 7.57 (m, 2H), 7.78 (s, 1H), 7.92 (s, 1H), 8.13 (s, 1H), 8.44 (d, 1H); MS m/z 411 [M+H]+.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 66, utilizando las aminas apropiadas. El dato de NMR fue obtenido en los compuestos cuando es indicado .

Ejemplo 93:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–propil–benzamida

Ejemplo 94:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(ciclopropilmetil)–3–metoxi–benzamida

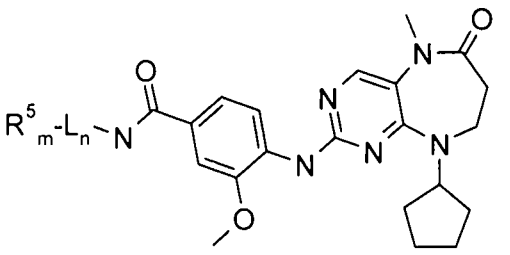
Ejemplo 95:

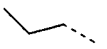
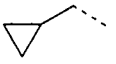
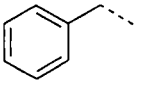
4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–propan–2–il–benzamida

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.19 (d, 6H), 1.67 (m, 6H), 1.95 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.12 (m, 1H), 4.82 (m, 1H), 7.49 (m, 2H), 7.72 (s, 1H), 8.04 (d, 1H), 8.08 (s, 1H), 8.38 (d, 1H)

Ejemplo 96:

N–bencil–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida



Ejemplo	$R^5{}_m$–L_n–	Suministrador o Fuente	MS m/z [M+H]+	Tiempo de retención (Minutos)
93		Aldrich	453	2.04
94		Aldrich	465	2.09
5		Aldrich	453	2.04
96		ABCR	501	2.31

Ejemplo 97:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]benzamida

4–amino–N–ciclohexil–benzamida (TimTec, 108 mg, 0.5 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 100mg, 0.36 mmol), la 4–aminobenzamida (Aldrich, 59 mg, 0.43 mmol) y ácido p–toluenosulfónico (137 mg, 0.72 mmol) fueron calentados juntos en 4–metil–2–pentanol (4ml) a 120°C durante 22 horas. La reacción fue enfriada a temperatura ambiente y pasada bajo una columna SCX–2 de 5g prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y los solventes evaporados. El material resultante fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (37 mg, 27%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.67 (m, 6H), 1.97 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 4.84 (m, 1H), 7.08 (s, 1H), 7.77 (s, 1H), 7.79 (s, 4H), 8.08 (s, 1H), 9.46 (s, 1H); MS m/z 381 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 66 utilizando la amina apropiada.

Ejemplo 98:

N–ciclobutil–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–benzamida

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.67 (m, 8H), 1.95 (m, 2H), 2.09 (m, 2H), 2.23 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.43 (m, 1H), 4.82 (m, 1H), 7.48 (m, 2H), 7.72 (s, 1H), 8.09 (s, 1H), 8.41 (m, 2H); MS m/z 465 $[M+H]^+$.

Ejemplo 99:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–fenil–benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 100 mg, 0.36 mmol), 4–amino–3–metoxi–N–fenil–benzamida (Apin, 104 mg, 0.43 mmol) y ácido p–toluenosulfónico monohidrato (137 mg, 0.72 mmol) fueron agitados en forma de remolino y calentados juntos en 4–metil–2–pentanol (4 mL) a 100°C durante 24 horas. La mezcla de reacción cruda fue cargada en una columna SCX–2 (5g) prehumedecida con MeOH. La columna fue lavada con MeOH y el producto eluido con NH_3

2M/MeOH. El solvente fue evaporado y el material resultante fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (64 mg, 36 %). MS m/z 487 $[M+H]^+$. Tiempo de retención 3.81 minutos.

Ejemplo 100:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–propan–2–il–benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 134mg, 0.48mmol), 4–amino–N–propan–2–il–benzamida (Butt Park, 86 mg, 0.48 mmol) y ácido p–toluenosulfónico monohidrato (227 mg, 1.19 mmol) en 4–metil–2–pentanol (4 mL) fueron calentados a 140°C durante 2h. La mezcla de reacción fue cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol para eliminar ácido p–toluenosulfónico monohidrato y luego eluido con 2% metanol/amoniaco 7N. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (121 mg, 60%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.17 (6H, d), 1.63 (4H, m), 1.74 (2H, m), 1.97 – 1.99 (2H, d), 2.58 – 2.61 (2H, t), 3.18 (3H, s), 3.62 – 3.65 (2H, t), 4.07 – 4.13 (1H, m), 4.85 (1H, m), 7.71 – 7.82 (4H, m), 7.95 – 7.97 (1H, d), 8.09 (1H, s), 9.44 (1H, s); MS m/z 423 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 100 utilizando la anilina apropiada.

Ejemplo 101:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–fenil–benzamida

Amina disponible de Aldrich

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.64 – 1.67 (4H, m), 1.72 – 1.75 (2H, m), 1.99 (2H, m), 2.60 (2H, t), 3.19 (3H, s), 3.63 (2H, t), 4.87 (1H, m), 7.09 (1H, t), 7.35 (2H, m), 7.76 – 7.79 (2H, d), 7.90 (4H, s), 8.11 (1H, s), 9.55 (1H, s), 10.00 (1H, s); MS m/z 423 $[M+H]^+$.

Ejemplo 102:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–metil–benzamida

Amina disponible de TimTec

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.63 (4H, m), 1.70 – 1.74 (2H, m), 1.97 (2H, m), 2.58 – 2.61 (2H, t), 2.78 (3H, d), 3.18 (3H, s), 3.62 – 3.65 (2H, t), 4.84 (1H, m), 7.75 (2H, d), 7.81 (2H, d), 8.09 (1H, s), 8.20 (1H, d), 9.46 (1H, s); MS m/z 395 $[M+H]^+$.

Ejemplo 103:

6–ciclopentil–9–[[2–metoxi–4–(2–pirrolidin–1–iletilamino)fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 140 mg, 0.5 mmol) 2–metoxi–N'–(2–pirrolidin–1–iletil)benceno–1,4–diamina (Producto intermedio 35, 141 mg, 0.6 mmol), y ácido p–toluenosulfónico monohidrato (227 mg, 1.19 mmol) en 4–metil–2–pentanol (4 mL) fueron calentados por irradiación de microondas a 160 °C durante 1 hora. La mezcla de reacción fue absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y el material producido fue purificado por cromatografía en fase normal usando 0–10% metanol/amoniaco para proporcionar el compuesto del título como un sólido (100 mg, 42 %).

^{1}H NMR (500.13 MHz, DMSO–d6) δ 1.55 – 1.62 (4H, m), 1.68 – 1.75 (6H, m), 1.85 – 1.92 (2H, m), 2.54 – 2.56 (6H, m), 2.67 (2H, t), 3.15 – 3.19 (5H, m), 3.58 – 3.60 (2H, m), 3.80 (3H, s), 4.64 – 4.71 (1H, m), 4.87 (1H, t), 6.19 (1H, dd), 6.36 (1H, d), 7.12 (1H, s), 7.67 (1H, d), 7.93 (1H, s); MS m/z 480 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 103, utilizando la anilina apropiada. El datos de NMR es registrado donde fue obtenido.

Ejemplo 104:

6–ciclopentil–9–[[2–metoxi–4–[metil–(1–metil–4–piperidil)amino]fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 105:

6–ciclopentil–9–[[2–metoxi–4–[4–(2–metoxietil)piperazin–1–il]fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 106:

6–ciclopentil–9–[[2–metoxi–4–[4–(1–piperidil)–1–piperidil]fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 107:

6–ciclopentil–9–[[4–(2–dimetilaminoetilamino)–2–metoxi–fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.55 – 1.76 (7H, m), 1.99 – 2.02 (2H, m), 2.31 (6H, s), 2.60 – 2.66 (4H, m), 3.19 (2H, t), 3.27 (3H, s), 3.64 – 3.68 (2H, m), 3.85 (3H, s), 4.80 – 4.88 (1H, m), 6.23 – 6.26 (1H, m), 6.29 (1H, d), 7.09 (1H, s), 7.88 (1H, s), 8.03 (1H, d).

Ejemplo 108:

9–[[4–(4–ciclohexilpiperazin–1–il)–2–metoxi–fenil]amino]–6–ciclopentil–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

1H NMR (400.13 MHz, $CDCl_3$) δ 1.10 – 1.37 (4H, m), 1.55 – 1.78 (8H, m), 1.81 – 1.89 (2H, m), 1.95 – 2.05 (4H, m), 2.44 (1H, s), 2.65 – 2.67 (2H, m), 2.85 (4H, s), 3.24 (4H, s), 3.28 (3H, s), 3.66 – 3.69 (2H, m), 3.89 (3H, s), 4.82 – 4.91 (1H, m), 6.54 – 6.57 (2H, m), 7.24 (1H, s), 7.90 (1H, s), 8.19 (1H, d).

Ejemplo 109:

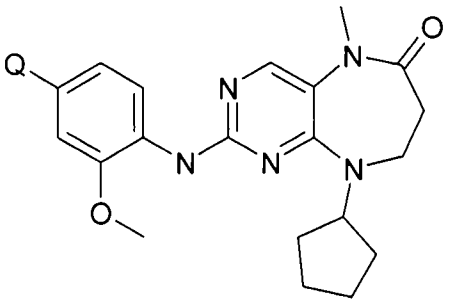
6–ciclopentil–9–[[2–metoxi–4–(4–metil–1,4–diazepan–1–il)fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

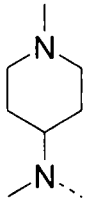
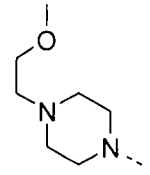
1H NMR (400.13 MHz, $CDCl_3$) δ 1.53 – 1.78 (6H, m), 1.97 – 2.08 (4H, m), 2.42 (3H, s), 2.62 – 2.68 (4H, m), 2.75 – 2.78 (2H, m), 3.27 (3H, s), 3.50 (2H, t), 3.58 – 3.62 (2H, m), 3.64 –

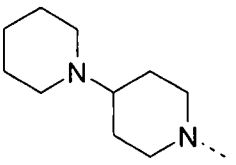
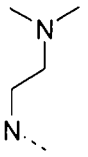
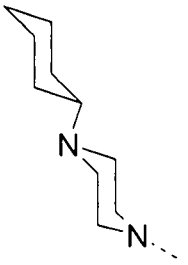
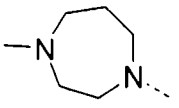
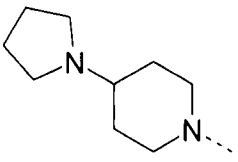
3.67 (2H, m), 3.87 (3H, s), 4.81 – 4.88 (1H, m), 6.27 (1H, d), 6.28 (1H, s), 7.06 (1H, s), 7.88 (1H, m), 8.02 (1H, d).

Ejemplo 110:

6–ciclopentil–9–[[2–metoxi–4–(4–pirrolidin–1–il–1–piperidil)fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona



Ejemplo	Q	Fuente	MS m/z [M+H]+	Tiempo de retención (Minutos)
104		Producto intermedio 36	494	2.10
105		Producto intermedio 37	510	2.14

Ejemplo	Q	Fuente	MS m/z [M+H]+	Tiempo de retención (Minutos)
106		Producto intermedio 38	534	2.82
107		Producto intermedio 39	454	2.00
108		Producto intermedio 40	534	3.49
109		Producto intermedio 41	480	2.33
110		Producto intermedio 42	520	2.68

Ejemplo 111:

Ácido 4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-benzoico

A una solución de 10-cloro-2-ciclopentil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 1, 10.62 g, 36 mmol) y ácido 4-amino-3-metoxibenzoico (Aldrich, 6.795 g, 40.7 mmol) en etanol (150 mL) fue añadido agua (450 mL)

y ácido clorhídrico concentrado 96 mL, 72 mmol). La mezcla fue calentada bajo reflujo durante 36 horas. La reacción fue enfriada y se formó un precipitado sólido marrón el cual fue filtrado, triturado con acetonitrilo frío y secado al vacío para dar el compuesto del título (10.1 g, 68 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.55 – 1.75 (6H, m), 1.87 – 1.95 (2H, m), 2.71 – 2.75 (2H, m), 3.18 (3H, s), 3.71 – 3.76 (2H, m), 3.95 (3H, s), 4.79 – 4.93 (1H, m), 7.58 – 7.62 (2H, m), 8.19 (1H, d), 8.19 (1H, s), 9.37 (1H, s); MS m/z 412 $[M+H]^+$.

Ejemplo 112:

6–ciclopentil–2–metil–9–[(2,4,6–trimetoxifenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

2,4,6–trimetoxianilina (Maybridge, 104 mg, 0.56 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 150 mg, 0.56 mmol) y ácido p–toluenosulfónico monohidrato (268 mg, 1.41 mmol) en 4–metil–2–pentanol (4 mL) fueron calentados a 140°C durante 2 h. La solución de la reacción fue cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol para eliminar ácido p–toluenosulfónico monohidrato y luego lavada con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (140mg, 58%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.32 – 1.68 (8H, m), 2.46 – 2.48 (2H, t), 3.13 (3H, s), 3.50 (2H, t), 3.70 (6H, s), 3.79 (3H, s), 4.32 (1H, m), 6.25 (2H, s), 7.37 (1H, s), 7.85 (1H, s); MS m/z 429 $[M+H]^+$.

Ejemplo 113:

6–ciclopentil–9–[[2–metoxi–4–[(1–metil–4–piperidil)oxi]fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 150 mg, 0.53 mmol), 2–metoxi–4–[(1–metil–4–piperidil)oxi]anilina

(Producto intermedio 43 (124 mg, 0.53 mmol) y ácido p–toluenosulfónico monohidrato (255 mg, 1.34 mmol) calentados en 4–metil–2–pentanol (4 mL) a 140°C durante 2 h. La solución de la reacción fue cargada en una columna SCX–2 prehumedecida con metanol. La columna fue lavada con metanol para eliminar ácido p–toluenosulfónico monohidrato y luego lavada con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para proporcionar el compuesto del título como una goma roja (189 mg, 82 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.53 – 1.56 (4H, m), 1.60 (2H, d), 1.63 – 1.68 (4H, m), 1.84 (2H, d), 1.92 (2H, d), 2.20 (3H, s), 2.18 – 2.22 (2H, m), 2.63 (2H, t), 3.15 (3H, s), 3.56 – 3.59 (2H, t), 3.81 (3H, s), 4.33 (1H, m), 4.64 (1H, m), 6.49 – 6.52 (1H, m), 6.62 (1H, d), 7.51 (1H, s), 7.82 (1H, d), 7.98 (1H, s); MS m/z 481 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 113 utilizando la anilina apropiada indicada.

Ejemplo 114:

6–ciclopentil–9–[[2–metoxi–4–(1–metilpirrolidin–3–il)oxi–fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Anilina de partida – 2–metoxi–4–(1–metilpirrolidin–3–il)oxi–anilina Producto intermedio 45.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.54 (3H, d), 1.58 (1H, s), 1.66 (2H, s), 1.79 – 1.83 (2H, m), 1.85 (1H, s), 2.25 – 2.29 (1H, m), 2.30 (3H, s), 2.43 (1H, m), 2.53 – 2.56 (2H, t), 2.61 – 2.65 (1H, m), 2.66 – 2.68 (1H, m), 2.69 – 2.70 (1H, m), 2.81 – 2.85 (1H, m), 3.15 (3H, s), 3.56 – 3.59 (2H, m), 3.81 (3H, s), 4.65 (1H,m), 4.86 – 4.89 (1H, m), 6.41 – 6.44 (1H, m), 6.56 (1H, d), 7.51 (1H, s), 7.82 (1H, d), 7.98 (1H, s); MS m/z 467 $[M+H]^+$.

Ejemplo 115:

6–ciclopentil–9–[[2–metoxi–4–(2–morfolin–4–iletoxi)fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Anilina de partida – 2–metoxi–4–(2–morfolin–4–iletoxi)anilina Producto intermedio 47

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.55 (3H, d), 1.59 (1H, s), 1.67 (2H, s), 1.85 (2H, s), 2.48 (4H, d), 2.53 – 2.56 (2H, t), 2.69 (2H, t), 3.15 (3H, s), 3.59 (2H, d), 3.59 (4H, d), 3.83 (3H, s),

4.08 (2H, t), 4.67 (1H, s), 6.48 – 6.51 (1H, m), 6.63 (1H, d), 7.50 (1H, s), 7.86 (1H, d), 7.98 (1H, s); MS m/z 497 $[M+H]^+$.

Ejemplo 116:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–2–(trifluorometil)benzonitrilo

10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 157 mg, 0.56 mmol), 4–amino–2–metil–benzonitrilo (Aldrich, 95 mg, 0.51 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (27 mg, 0.05 mmol) fueron disueltos en 1,4–dioxano (7.5 mL). Carbonato de cesio (330 mg, 1.01 mmol) fue añadido y la mezcla purgada con una corriente de nitrógeno durante 5 minutos. Tris(dibencilidenoacetona) paladio (II) (28 mg, 0.03 mmol) fue añadido y el aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y luego calentado a 100°C durante 8 h. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX–3, lavado con metanol y el producto eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase inversa preparativa para dar el compuesto del título como un sólido blanco (21mg, 10%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.57 – 1.72 (6H, m), 1.92 – 2.00 (2H, m), 2.61 (2H, m), 3.19 (3H, s), 3.64 – 3.66 (2H, m), 4.82 – 4.90 (1H, m), 7.99 – 8.07 (2H, m), 8.16 (1H, s), 8.50 (1H, d), 10.15 (1H, s); MS m/z 431 $[M+H]^+$.

Ejemplo 117:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–hidroxietil)bencenosulfonamida

4–amino–N–(2–hidroxietil)bencenosulfonamida (Maybridge; 108 mg, 0.5 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 140 mg, 0.5 mmol) y ácido p–toluenosulfónico monohidrato (238 mg, 1.25 mmol) fueron calentados a 140°C en 4–metil–2–pentanol (3 mL) durante 3 horas. La mezcla se dejó enfriar provocando que se forme un sólido. Metanol y DCM fueron añadidos para dar una solución que fue absorbida en la columna SCX–3 y lavada con metanol. El producto eluido con metanol/amoniaco y las fracciones que contienen el producto fueron concentradas.

La purificación por cromatografía en fase inversa preparativa dio el compuesto del título como un sólido blanco (122mg, 53%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.59 – 1.74 (6H, d), 1.96 – 2.01 (2H, m), 2.57 – 2.61 (2H, m), 2.78 (2H, q), 3.19 (3H, s), 3.35 – 3.40 (2H, m), 3.62 – 3.65 (2H, m), 4.63 (1H, t), 4.80 – 4.88 (1H, m), 7.33 (1H, t), 7.64 – 7.68 (2H, m), 7.90 – 7.94 (2H, m), 8.11 (1H, s), 9.65 (1H, s); MS m/z 461 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 117 utilizando la anilina apropiada disponible de Aldrich.

Ejemplo 118:

6–ciclopentil–9–[[4–(2–dimetilaminoetoxi)fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.55 – 1.71 (6H, m), 1.89 – 1.95 (2H, m), 2.22 (6H, s), 2.55 – 2.57 (2H, m), 2.61 (2H, t), 3.16 (3H, s), 3.58 – 3.61 (2H, m), 4.00 (2H, t), 4.72 – 4.81 (1H, m), 6.82 – 6.86 (2H, m), 7.56 – 7.60 (2H, m), 8.01 (1H, s), 8.95 (1H, s); MS m/z 425 $[M+H]^+$.

Ejemplo 119:

N–[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]fenil]acetamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 100 mg, 0.36 mmol), N–(4–aminofenil)acetamida (Aldrich, 64 mg, 0.43 mmol) y ácido p–toluenosulfónico (137 mg, 0.72 mmol) fueron calentados juntos en 4–metil–2–pentanol (4 mL) a 120^{0}C durante 22 horas. Las reacciones fueron enfriadas a temperatura ambiente y luego pasadas bajo una columna SCX–2 de 5g prehumedecida con metanol. Los productos fueron eluidos con NH_3 2M/MeOH y el solvente evaporado. El material resultante fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (22 mg, 16%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.64 (m, 6H), 1.94 (m, 2H), 2.01 (s, 3H), 2.56 (m, 2H), 3.16 (s, 3H), 3.60 (m, 2H), 4.78 (m, 1H), 7.43 (d, 2H), 7.61 (d, 2H), 8.02 (s, 1H), 9.06 (s, 1H), 9.74 (s, 1H); MS m/z 495 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 119 utilizando las analinas apropiadas sustituidas. Análisis NMR fue asumido donde fue indicado.

Ejemplo 120:

6–ciclopentil–9–[(4–metoxifenil)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.62 (m, 6H), 1.92 (m, 2H), 2.55 (m, 2H), 3.16 (s, 3H), 3.59 (m, 2H), 3.60 (s, 2H), 3.72 (s, 3H), 4.76 (m, 1H), 6.83 (d, 2H), 7.59 (d, 2H), 8.00 (s, 1H), 8.93 (s, 1H)

Ejemplo 121:

6–ciclopentil–2–metil–9–[(4–morfolin–4–ilfenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.63 (m, 6H), 1.92 (m, 2H), 2.55 (m, 2H), 3.02 (m, 4H), 3.15 (s, 3H), 3.59 (m, 2H), 3.74 (m, 4H), 4.76 (m, 1H), 6.85 (d, 2H), 7.56 (d, 2H), 7.99 (s, 1H), 8.89 (s, 1H); MS m/z 423 $[M+H]^+$.

Ejemplo 122:

6–ciclopentil–9–[(4–dimetilaminofenil)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 123:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]bencenosulfonamida

Ejemplo 124:

9-[(1-acetil-2,3-dihidroindol-5-il)amino]-6-ciclopentil-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 125:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(2-metoxietil)bencenosulfonamida

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.66 (m, 6H), 1.96 (m, 2H), 2.59 (m, 2H), 2.88 (m, 2H), 3.17 (s, 3H), 3.18 (s, 3H), 3.30 (m, 2H), 3.63 (m, 2H), 4.83 (m, 1H), 7.44 (t, 1H), 7.66 (d, 2H), 7.91 (d, 2H), 8.10 (s, 1H), 9.64 (s, 1H)

Ejemplo 126:

9-[(3-cloro-4-morfolin-4-il-fenil)amino]-6-ciclopentil-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

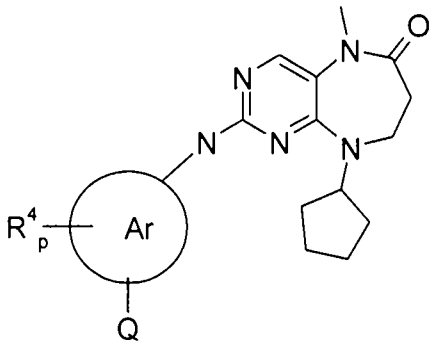
Ejemplo 127:

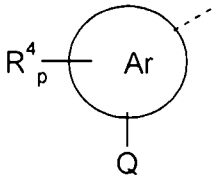
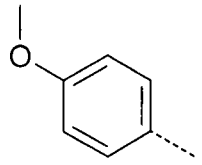
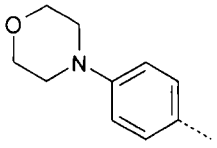
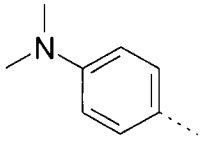
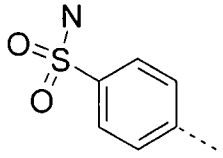
6-ciclopentil-2-metil-9-[(4-metilsulfonilfenil)amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

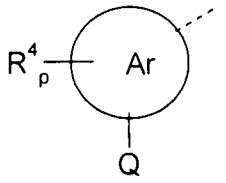
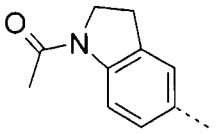
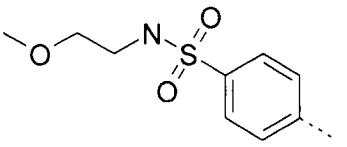
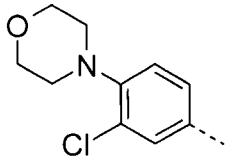
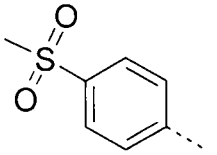
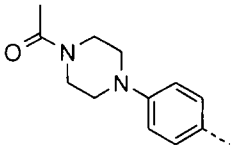
^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.67 (m, 6H), 1.98 (m, 2H), 2.60 (m, 2H), 3.15 (s, 3H), 3.18 (s, 3H), 3.64 (m, 2H), 4.85 (m, 1H), 7.77 (d, 2H), 7.98 (d, 2H), 8.11 (s, 1H), 9.74 (s, 1H)

Ejemplo 128:

9-[[4-(4-acetilpiperazin-1-il)fenil]amino]-6-ciclopentil-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona



Ejemplo		Suministrador o Fuente	MS m/z $[M+H]^+$	Tiempo de retención (Minutos)
120		Aldrich	368	2.16
121		Aldrich	423	1.95
122		Aldrich	381	3.14
123		ABCR	417	2.6

Ejemplo		Suministrador o Fuente	MS m/z [M+H]+	Tiempo de retención (Minutos)
124		Flurochem	421	2.75
125		WO2005/116025	475	2.81
126		Flurochem	457	3.26
127		Flurochem	416	2.78
128		Flurochem	464	2.65

Ejemplo 129:

6–ciclopentil–2–metil–9–[(3,4,5–trimetoxifenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

3,4,5–trimetoxianilina (Aldrich, 104 mg, 0.56 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 150 mg, 0.56 mmol) y ácido p–toluenosulfónico monohidrato (268 mg, 1.41 mmol) fueron calentados a 140°C en 4–metil–2–pentanol (4 mL) durante 2 horas. La solución de la reacción fue cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol para eliminar el ácido p–toluenosulfónico monohidrato y luego lavada con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido púrpura (130mg, 54%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.50 – 1.52 (2H, m), 1.57 – 1.61 (2H, m), 1.70 (2H, m), 1.95 (2H, m), 2.55 – 2.58 (2H, t), 3.17 (3H, s), 3.59 (2H, t), 3.63 (3H, s), 3.76 (6H, s), 4.86 (1H, d), 7.09 (2H, s), 8.04 (1H, s), 8.97 (1H, s); MS m/z 429 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 129 utilizando las analinas apropiadas sustituidas disponibles como se indicó.

Ejemplo 130:

6–ciclopentil–2–metil–9–[(2,3,4–trimetoxifenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Anilina sustituida disponible de Apin.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.53 – 1.56 (2H, m), 1.58 (2H, d), 1.67 – 1.68 (2H, m), 1.88 (2H, t), 2.55 – 2.57 (2H, m), 3.16 (3H, s), 3.58 – 3.60 (2H, t), 3.79 (3H, s), 3.78 – 3.82 (6H, s), 4.69 (1H, m), 6.74 (1H, d), 7.70 (2H, t), 8.00 (1H, s); MS m/z 429 $[M+H]^+$.

Ejemplo 131:

9–[[4–cloro–3–(hidroximetil)fenil]amino]–6–ciclopentil–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Anilina sustituida disponible de Aldrich.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.60 (3H, d), 1.62 – 1.62 (1H, m), 1.67 (2H, d), 1.96 (2H, s), 2.53 – 2.59 (2H, t), 3.17 (3H, s), 3.60 – 3.63 (2H, t), 4.53 (2H, d), 4.88 (1H, m), 5.27 (1H,

t), 7.24 (1H, d), 7.62 – 7.65 (1H, m), 7.96 (1H, d), 8.05 (1H, s), 9.31 (1H, s); MS m/z 402 $[M+H]^+$.

Ejemplo 132:

6–ciclopentil–2–metil–9–[(2–piridin–3–il–1H–benzoimidazol–5–il)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 134 mg, 0.50 mmol), 2–piridin–3–il–1H–benzoimidazol–5–amina (Flurochem, 117 mg, 0.55 mmol) y carbonato de cesio (328 mg, 1.00 mmol) fueron añadidos a dioxano (4 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Bis(dibencilidenoacetona)paladio (28 mg, 0.03 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (27 mg, 0.05 mmol) fueron añadidos y la mezcla calentada a 110 °C toda la noche. La mezcla fue filtrada y el filtrado purificado por cromatografía en columna con un sistema solvente 5% 7N amoniaco en metanol/DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido (73 mg, 32 %).

^{1}H NMR (499.8 MHz, DMSO–d_6 @ 373K) δ 1.64 (4H, m), 1.73 (2H, m), 2.00 (2H, m), 2.53 – 2.56 (2H, t), 3.21 (3H, s), 3.62 – 3.65 (2H, t), 4.82 – 4.85 (1H, m), 7.53 – 7.55 (3H, m), 8.04 (2H, s), 8.45 (1H, d), 8.64 – 8.65 (1H, m), 8.71 (1H, s), 9.32 (1H, d), 12.51 (1H, s); MS m/z 455 $[M+H]^+$.

Ejemplo 133:

N–[[4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]fenil]metil]piridina–2–carboxamida

N–[(4–aminofenil)metil]piridina–2–carboxamida (Producto intermedio 49: 114mg, 0.5mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 141 mg, 0.5 mmol) y ácido p–toluenosulfónico monohidrato (239 mg, 1.25 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140°C durante 2 horas. La mezcla fue enfriada y diluida con metanol / DCM y absorbida en una columna SCX–3, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto

fueron concentradas y purificadas por cromatografía en fase inversa preparativa para dar el compuesto del título como un sólido blanco (63mg, 27%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.54 – 1.71 (6H, m), 1.89 – 1.96 (2H, m), 2.56 – 2.58 (2H, m), 3.16 (3H, s), 3.59 – 3.61 (2H, m), 4.44 (2H, d), 4.79 (1H, m), 7.23 (2H, d), 7.60 – 7.63 (1H, m), 7.65 – 7.67 (2H, m), 7.99 – 8.08 (3H, m), 8.64 – 8.66 (1H, m), 9.13 (1H, s), 9.18 (1H, t); MS m/z 472 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 133 utilizando las analinas apropiadas sustituidas disponible de ABCR.

Ejemplo 134:

6-ciclopentil-2-metil-9-[[4-(1-piperidilsulfonil)fenil]amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.34 – 1.39 (2H, m), 1.52 – 1.75 (10H, m), 1.94 – 2.00 (2H, m), 2.57 – 2.61 (2H, m), 2.87 (4H, t), 3.19 (3H, s), 3.62 – 3.65 (2H, m), 4.84 (1H, m), 7.59 (2H, d), 7.94 – 7.96 (2H, m), 8.11 (1H, s), 9.71 (1H, s); MS m/z 485 $[M+H]^+$.

Ejemplo 135:

6-ciclopentil-2-metil-9-[[4-(2-morfolin-4-iletoxi)fenil]amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.54 – 1.72 (6H, m), 1.89 – 1.95 (2H, m), 2.48 (4H, m), 2.66 – 2.70 (2H, m), 2.68 – 2.69 (2H, m), 3.16 (3H, s), 3.59 (6H, m), 4.05 (2H, t), 4.76 (1H, m), 6.84 – 6.87 (2H, m), 7.57 – 7.60 (2H, m), 8.01 (1H, s), 8.95 (1H, s); MS m/z 467 $[M+H]^+$.

Ejemplo 136:

tert-butil N-[[3-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]fenil]metil]carbamato

10-cloro-2-ciclopentil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 1, 155 mg, 0.55 mmol), tert-butil N-[(3-aminofenil)metil]carbamato

(Chembasics, 111 mg, 0.50 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (27 mg, 0.05 mmol) fueron disueltos en 1,4–dioxano (7.5 mL), carbonato de cesio (326 mg, 1.0 mmol) fue añadido y la mezcla purgada con una corriente de nitrógeno durante 5 minutos. Tris(dibencilidenoacetona) paladio (II) (28 mg, 0.03 mmol) fue añadido y el aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y luego calentado a 100°C durante 8h. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX–3, lavado con metanol y el producto eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase normal (1% metanol/DCM) para dar el compuesto del título como un sólido blanco (57 mg, 24 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.41 (9H, s), 1.59 – 1.71 (6H, m), 1.96 (2H, m), 2.58 (2H, m), 3.17 (3H, s), 3.61 (2H, m), 4.09 (2H, d), 4.85 (1H, m), 6.80 (1H, d), 7.18 (1H, t), 7.30 (1H, t), 7.57 (1H, d), 7.62 (1H, s), 8.04 (1H, s), 9.16 (1H, s); MS m/z 467 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 136 utilizando the anilina apropiada sustituida disponible de Flurochem.

Ejemplo 137:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–2–metil–isoindol–1,3–diona

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.61 – 1.77 (6H, m), 1.95 – 1.98 (2H, m), 2.61 – 2.63 (2H, m), 3.04 (3H, s), 3.20 (3H, s), 3.65 – 3.68 (2H, m), 4.78 (1H, m), 7.39 (1H, d), 7.74 (1H, t), 8.16 (1H, s), 8.81 (1H, d), 9.14 (1H, s); MS m/z 421 $[M+H]^+$.

Ejemplo 138:

N–[2–[3–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–4–metoxi–fenil]etil]acetamida

N–[2–(3–amino–4–metoxi–fenil)etil]acetamida (Compuesto 4– Organic Proces Research & Development 2004, 8, 628–642, 108 mg, 0.5 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 140 mg, 0.5 mmol) y ácido p–toluenosulfónico monohidrato (238 mg, 1.25 mmol) fueron calentados a

140°C en 4–metil–2–pentanol (3 mL) durante 3 horas. La mezcla se dejó enfriar provocando que se forme un sólido. Metanol y DCM fueron añadidos para dar una solución que fue absorbida en una columna SCX–3 y lavada con metanol. El producto fue eluido con metanol/amoniaco y las fracciones que contienen el producto fueron concentradas. La purificación por cromatografía en fase inversa preparativa dio el compuesto del título como un sólido blanco (45 mg, 20 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.55 – 1.70 (6H, m), 1.79 (3H, s), 1.93 – 1.96 (2H, m), 2.56 – 2.59 (2H, m), 2.64 (2H, t), 3.17 (3H, s), 3.20 – 3.26 (2H, m), 3.61 – 3.63 (2H, m), 3.86 (3H, s), 4.85 (1H, m), 6.78 – 6.81 (1H, m), 6.95 (1H, d), 7.55 (1H, s), 7.86 (1H, t), 8.05 (1H, s), 8.12 (1H, d); MS m/z 453 $[M+H]^+$.

Ejemplo 139:

6–ciclopentil–9–[(2–metoxifenil)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

2–metoxianilina (Aldrich, 22 mg, 0.18 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 50 mg, 0.18 mmol) y ácido p–toluenosulfónico monohidrato (84 mg, 0.44 mmol) fueron calentados en 4–metil–2–pentanol (1 mL) a 135°C durante 24 horas. La mezcla fue enfriada y diluida con metanol / DCM y absorbida en una columna SCX–3, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase inversa preparativa para dar el compuesto del título como un sólido blanco (42 mg, 64 %). MS m/z 368 $[M+H]^+$, Tiempo de retención 2.61 min.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 139, utilizando las analinas apropiadas sustituidas disponibles como se indicó.

Ejemplo 140:

6–ciclopentil–9–[(2–etoxifenil)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 141:

6–ciclopentil–2–metil–9–[(2–metilsulfanilfenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 142:

6–ciclopentil–9–[(2–hidroxifenil)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 143:

6–ciclopentil–9–[(2–etilfenil)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 144:

9–[(2–benzoilfenil)amino]–6–ciclopentil–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 145:

2–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]bencenosulfonamida

Ejemplo 146:

6–ciclopentil–2–metil–9–[(2–fenoxifenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 147:

9–[(2–bromofenil)amino]–6–ciclopentil–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 148:

6–ciclopentil–2–metil–9–[(2–fenilfenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 149:

6–ciclopentil–2–metil–9–[(2–metilsulfonilfenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 150:

6–ciclopentil–2–metil–9–[(2–propan–2–ilfenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 151:

9–[(2–butilfenil)amino]–6–ciclopentil–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 152:

6–ciclopentil–2–metil–9–[[2–(1–piperidil)fenil]amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 153:

6–ciclopentil–2–metil–9–[[2–(4–tert–butilfenoxi)fenil]amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 154:

2–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–etil–bencenosulfonamida

Ejemplo 155:

2–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–metil–bencenosulfonamida

Ejemplo 156:

6–ciclopentil–2–metil–9–[[2–(2–morfolin–4–iletilamino)fenil]amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 157:

9–[(2–bencilfenil)amino]–6–ciclopentil–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

Ejemplo 158:

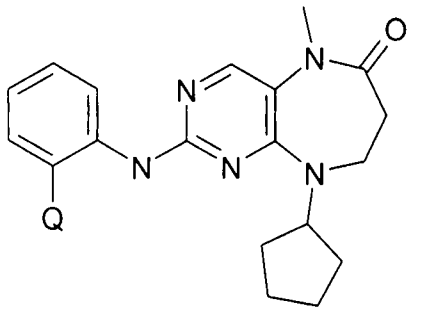
6–ciclopentil–2–metil–9–[(2–pirrol–1–ilfenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

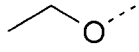
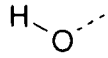
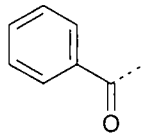
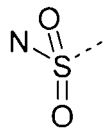
Ejemplo 159:

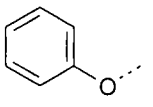
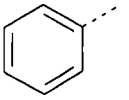
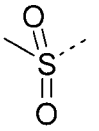
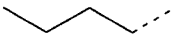
6–ciclopentil–2–metil–9–[[2–(4–metilfenoxi)fenil]amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

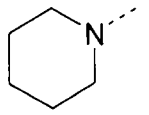
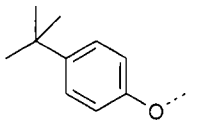
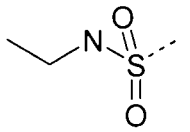
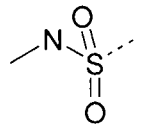
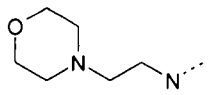
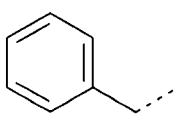
Ejemplo 160:

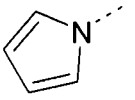
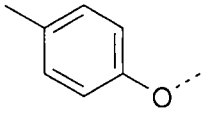
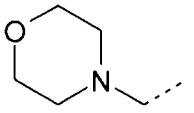
6–ciclopentil–2–metil–9–[[2–(morfolin–4–ilmetil)fenil]amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona



Ejemplo	Q	Suministrador o fuente de Anilina sustituida	MS m/z $[M+H]^+$	Tiempo de Retención (Minutos)
140		Aldrich	382	2.81
141		Aldrich	384	2.76
142		Aldrich	354	2.01
143		Aldrich	366	2.7
144		Aldrich	442	3.11
145		Aldrich	417	1.99

Ejemplo	Q	Suministrador o fuente de Anilina sustituida	MS m/z $[M+H]^+$	Tiempo de Retención (Minutos)
146		Aldrich	430	3.11
147		Aldrich	418	2.82
148		ABCR	414	3
149		Enamina	416	2.38
150		Aldrich	380	2.81
151		ABCR	394	3.07

Ejemplo	Q	Suministrador o fuente de Anilina sustituida	MS m/z $[M+H]^+$	Tiempo de Retención (Minutos)
152		ABCR	421	3.4
153		Tim Tec	486	3.73
154		Farmaco, Edizione Scientifica (1957), 12 41–8	445	2.5
155		Zelinsky	431	2.38
156		Journal of the American Chemical Society (1948), 70 416	466	2.26
157		Aldrich	428	2.99

Ejemplo	Q	Suministrador o fuente de Anilina sustituida	MS m/z $[M+H]^+$	Tiempo de Retención (Minutos)
158		Aldrich	401	2.84
159		Tim Tec	444	3.31
160		Maybridge	437	2.73

Ejemplo 161:

6–ciclopentil–9–[(3–metoxifenil)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

3–metoxianilina (Aldrich, 22 mg, 0.18 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, (50 mg, 0.18 mmol), y ácido p–toluenosulfónico (84 mg, 0.44 mmol) fueron combinados en 4–metil–2–pentanol (1 mL). La solución fue calentada a reflujo bajo una manta de nitrógeno durante 12 horas. La mezcla de reacción fue enfriada y pasada a través de una columna SCX–2 lavada con metanol. El producto crudo fue lavado con amoniaco 7N en metanol y luego concentrado al vacío. El material resultante fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (39 mg, 59%); MS m/z 368 $[M+H]^+$, Tiempo de retención 2.46 min.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 161 utilizando las analinas apropiadas sustituidas disponibles como se indicó.

Ejemplo 162:

6-ciclopentil-9-[(3-etoxifenil)amino]-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 163:

6-ciclopentil-2-metil-9-[(3-metilsulfanilfenil)amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 164:

3-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]benzonitrilo

Ejemplo 165:

9-[(3-acetilfenil)amino]-6-ciclopentil-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 166:

6-ciclopentil-9-[(3-etilfenil)amino]-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 167:

3-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]benzamida

Ejemplo 168:

6-ciclopentil-9-[(3-etinilfenil)amino]-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 169:

9-[(3-benzoilfenil)amino]-6-ciclopentil-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 170:

3-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]bencenosulfonamida

Ejemplo 171:

6-ciclopentil-2-metil-9-[(3-fenilfenil)amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 172:

6-ciclopentil-2-metil-9-[(3-metilsulfonilfenil)amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Ejemplo 173:

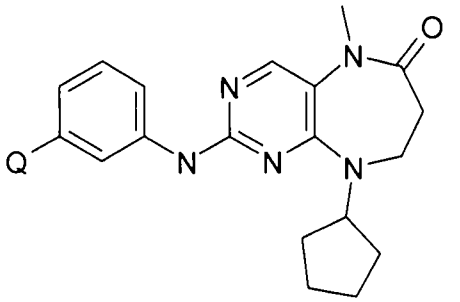
6-ciclopentil-9-[[3-(hidroximetil)fenil]amino]-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

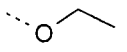
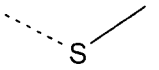
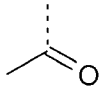
Ejemplo 174:

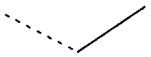
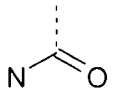
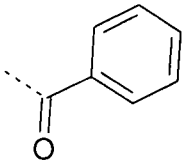
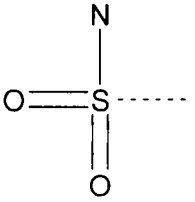
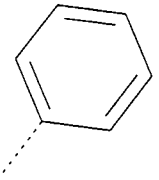
6-ciclopentil-2-metil-9-[(3-propan-2-ilfenil)amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

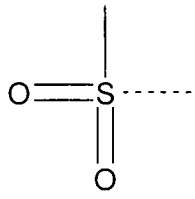
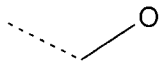
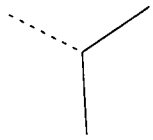
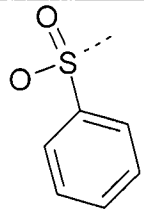
Ejemplo 175:

N-[2-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]fenil]bencenosulfonamida



Ejemplo	Q	Suministrador o fuente de Anilina sustituida	MS m/z $[M+H]^+$	Tiempo de Retención (Minutos)
162		Aldrich	382.23	2.63
163		Aldrich	384.19	2.65
164		Aldrich	363.18	2.4
165		Aldrich	380.23	2.3

Ejemplo	Q	Suministrador o fuente de Anilina sustituida	MS m/z $[M+H]^+$	Tiempo de Retención (Minutos)
166		Aldrich	366.21	2.78
167		Aldrich	381.2	1.78
168		Aldrich	362.17	2.57
169		Aldrich	442.3	2.72
170		ABCR	417.21	1.87
171		ABCR	414.26	2.94

Ejemplo	Q	Suministrador o fuente de Anilina sustituida	MS m/z $[M+H]^+$	Tiempo de Retención (Minutos)
172		Enamina	416.21	2.09
173		Aldrich	368.16	1.96
174		ABCR	380.26	2.92
175		Journal of the Chemical Society (1938), 899–905.	492.19	1.61

Ejemplo 176:

N–[3–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–4–metoxi–fenil]acetamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 100 mg, 0.36 mmol), N–(3–amino–4–metoxi–fenil)acetamida (Aldrich, 77 mg, 0.43 mmol) y ácido p–toluenosulfónico (137 mg, 0.72 mmol) calentados juntos en 4–metil–2–pentanol (4ml) a 120°C durante 22 horas. Las reacciones fueron enfriadas a temperatura ambiente y luego pasadas bajo una columna SCX–2 de 5g prehumedecida con

metanol. La columna fue eluida con NH_3 2M/MeOH y el solvente evaporado . El material resultante fue purificado por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (46 mg, 30%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.58 (m, 6H), 1.88 (m, 2H), 1.99 (s, 3H), 2.56 (m, 2H), 3.17 (s, 3H), 3.59 (m, 2H), 3.83 (s, 3H), 4.85 (m, 1H), 6.93 (d, 1H), 7.05 (d, 1H), 7.56 (s, 1H), 8.02 (s, 1H), 8.37 (s, 1H), 9.68 (s, 1H); MS m/z 425 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 176 utilizando las analinas apropiadas sustituidas disponible de Aldrich.

Ejemplo 177:

N–[3–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]fenil]acetamida

MS m/z 395 $[M+H]^+$. Tiempo de retención 2.65 min

Ejemplo 178:

6–ciclopentil–9–[[5–(hidroximetil)–2–metil–fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

MS m/z 382 $[M+H]^+$. Tiempo de retención 2.76 min

Ejemplo 179:

6–ciclopentil–9–[[3–(2–hidroxietil)fenil]amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 134 mg, 0.48 mmol), 2–(3–aminofenil)etanol (ABChem Inc, 92 mg, 0.48 mmol) y ácido p–toluenosulfónico monohidrato (227 mg, 1.19 mmol) fueron calentados a 140°C en 4–metil–2–pentanol (4 mL) durante 2 horas. La solución de la reacción fue cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol para eliminar el ácido p–toluenosulfónico monohidrato y luego lavada con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto

fueron evaporadas y el material resultante purificado por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (92 mg, 50 %).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.59 – 1.60 (4H, m), 1.69 – 1.71 (2H, m), 1.96 – 1.98 (2H, m), 2.53 – 2.59 (2H, t), 2.69 (2H, t), 3.18 (3H, s), 3.60 (2H, t), 3.62 (2H, t), 4.62 (1H, s), 4.87 (1H, ms), 6.77 (1H, d), 7.14 (1H, t), 7.46 – 7.49 (1H, m), 7.66 (1H, t), 8.04 (1H, s), 9.10 (1H, s); MS m/z 382 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 183 utilizando la anilina apropiada sustituida disponible de fuentes como se indicó.

Ejemplo 180:

6-ciclopentil-2-metil-9-[[3-(2-morfolin-4-iletoxi)fenil]amino]-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

Anilina sustituida disponible de ABCR

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.61 (4H, d), 1.71 (2H, s), 1.97 (2H, s), 2.48 (4H, m), 2.59 (2H, t), 2.68 (2H, t), 3.17 (3H, s), 3.59 (4H, m), 3.62 (2H, m), 4.05 (2H, t), 4.80 – 4.90 (1H, m), 6.49 – 6.52 (1H, d), 7.13 (1H, t), 7.20 (1H, d), 7.51 (1H, t), 8.05 (1H, s), 9.13 (1H, s); MS m/z 467 $[M+H]^+$.

Ejemplo 181:

3-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-4-metoxi-N-(1-metil-4-piperidil)benzamida

Ruta sintética para la anilina sustituida disponible en WO06/018220.

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.48 – 1.62 (8H, m), 1.71 – 1.77 (2H, d), 1.80 – 2.00 (4H, m), 2.17 (3H, s), 2.56 (2H, t), 2.77 (2H, d), 3.17 (3H, s), 3.59 (2H, t), 3.71 (1H, m), 3.91 (3H, s), 4.74 – 4.79 (1H, m), 7.05 (1H, d), 7.48 – 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, d), 8.04 (1H, s), 8.57 (1H, d); MS m/z 509 $[M+H]^+$.

Ejemplo 182:

6-ciclopentil-9-[[5-(3-dimetilaminopirrolidin-1-il)-2-metoxi-fenil]amino]-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 150 mg, 0.53 mmol), 1–(3–amino–4–metoxi–fenil)–N,N–dimetil–pirrolidin–3–amina (Producto intermedio 50; 141 mg, 0.53 mmol) y ácido p–toluenosulfónico monohidrato (255 mg, 1.34 mmol) fueron combinados y calentados en 4–metil–2–pentanol (4 mL) a 140°C durante 2 horas. La mezcla de reacción fue cargada en una columna SCX–2 de 20g que fue prehumedecida con metanol. La columna fue lavada con metanol dos veces para eliminar el ácido p–toluenosulfónico y luego lavada dos veces con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (140mg, 51.6%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.48 – 1.62 (8H, m), 1.71 – 1.77 (2H, d), 1.80 – 2.00 (4H, m), 2.17 (3H, s), 2.56 (2H, t), 2.77 (2H, d), 3.17 (3H, s), 3.59 (2H, t), 3.71 (1H, m), 3.91 (3H, s), 4.74 – 4.79 (1H, m), 7.05 (1H, d), 7.48 – 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, d), 8.04 (1H, s), 8.57 (1H, d); MS m/z 508 $[M+H]^+$.

Ejemplo 183:

6–ciclopentil–2–metil–9–[(3–morfolin–4–ilsulfonilfenil)amino]–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1,150 mg, 0.53 mmol), 3–(morfolinosulfonil)anilina (Fluorochem; 130 mg, 0.53 mmol) y ácido p–toluenosulfónico monohidrato (255 mg, 1.34 mmol) fueron combinados y calentados a 140°C en 4–metil–2–pentanol (4 mL) durante 2 horas. La mezcla fue enfriada y metanol y diclorometano añadidos para disolver el sólido que se formó. La mezcla fue absorbida en una columna SCX–3, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas para dar un sólido cristalino blanco. Esto fue suspendido en metanol y filtrado y secado a 140°C bajo vacío en un desecador para dar el compuesto del título como un sólido cristalino blanco (200mg, 77%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.57 – 1.70 (6H, m), 1.94 – 2.00 (2H, m), 2.57 – 2.60 (2H, m), 2.88 (4H, m), 3.18 (3H, s), 3.61 – 3.66 (6H, m), 4.91 (1H, m), 7.22 – 7.25 (1H, m), 7.53 (1H, t), 7.99 – 8.02 (1H, m), 8.09 (1H, s), 8.23 (1H, t), 9.57 (1H, s)

MS m/z 487 $[M+H]^+$.

Ejemplo 184:

3–cloro–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

4–amino–3–cloro–N–(2–morfolin–4–iletil)benzamida (Producto intermedio 52, 100 mg, 0.35 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 124 mg, 0.44 mmol) y ácido p–toluenosulfónico monohidrato (168 mg, 0.88 mmol) fueron calentados a 140°C en 4–metil–2–pentanol (2.5 mL) durante 3 horas. La mezcla se dejó enfriar provocando que se forme un sólido. Metanol y DCM fueron añadidos para dar una solución que fue absorbida en una columna SCX–3 y lavada con metanol. La elusión del producto con amoniaco / metanol, concentración y cromatografía en columna (2% amoniaco 7N en metanol/DCM) dio el material que fue además purificado por HPLC en fase inversa para dar el compuesto del título como una espuma blanca (87 mg, 47 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.54 – 1.69 (6H, m), 1.86 – 1.89 (2H, m), 2.44 (6H, m), 2.59 (2H, m), 3.18 (3H, s), 3.37 – 3.42 (2H, m), 3.57 – 3.63 (6H, m), 4.69 – 4.77 (1H, m), 7.78 – 7.81 (1H, m), 7.97 (1H, d), 8.09 (1H, s), 8.20 (1H, s), 8.27 (1H, d), 8.40 (1H, t); MS m/z 528 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 184 utilizando 4–amino–3–cloro–N–(1–metil–4–piperidil)benzamida Producto intermedio 55.

Ejemplo 185:

3–cloro–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)benzamida

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.55 – 1.68 (8H, m), 1.77 (2H, s), 1.86 – 1.98 (4H, m), 2.18 (3H, s), 2.59 (2H, m), 2.78 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.69 – 3.77 (1H, m), 4.73 (1H, m), 7.79 – 7.82 (1H, m), 8.00 (1H, d), 8.09 (1H, s), 8.19 (2H, d), 8.26 (1H, d); MS m/z 512 $[M+H]^+$.

Ejemplo 186:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–hidroxi–N–(1–metil–4–piperidil)benzamida

A piridina (1 mL) fue cautelosamente añadido HCl concentrado (1 mL). La mezcla fue calentada a 200°C hasta que no se produjo más agua. La mezcla fue enfriada y 4–[(2–Ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida (Ejemplo 1, 100 mg, 0.2 mmol) fue añadido y la solución recalentada y agitada a 200°C durante 30 minutos. La solución fue enfriada y agua añadida seguido por ajuste de pH a pH neutro por adición de $NaHCO_3$. La solución acuosa fue absorbida en una columna SCX–3 prehumedecida con MeOH. La columna fue lavada con MeOH y agua y MeOH. El producto fue eliminado de la columna por adición de NH_3/MeOH (2N). Las fracciones combinadas fueron evaporadas y el material resultante purificado por HPLC en fase inversa para dar el compuesto del título como una goma la cual en trituración con DCM / hexano dio un sólido amorfo (17 mg, 17 %)
^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.50–1.85 (m, 10H), 1.85–2.10 (m, 4H), 2.20 (s, 3H), 2.55–2.68 (m, 2H), 2.70–2.85 (m, 2H), 3.20 (s, 3H), 3.55–3.70 (m, 2H), 3.60–3.80 (m, 1H), 4.75–4.90 (m, 1H), 7.28–7.35 (d, 1H), 7.38 (s, 1H), 7.83 (s, 1H), 7.95–8.05 (d, 1H), 8.08 (s, 1H), 8.13–8.23 (d, 1H), 10.2–10.5 (bs, 1H); MS m/z 494 $[M+H]^+$.

Ejemplo 187:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–2,6–difluoro–N–(1–metil–4–piperidil)benzamida

10–amino–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 57, 75 mg, 0.29 mmol), 4–bromo–2,6–difluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 58, 105 mg, 0.31 mmol) y carbonato de cesio (187 mg, 0.57 mmol) fueron añadidos a dioxano (3 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Bis(dibencilidenoacetona)paladio (16 mg, 0.028 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (15 mg, 0.026 mmol) fueron añadidos y la mezcla calentada a 100 °C toda la noche. La mezcla de reacción fue enfriada a temperatura ambiente y filtrada. La torta del filtro fue lavada con DCM y el filtrado añadido a una columna SCX–2 de 5g

prehumedecida con MeOH (2 volúmenes de columna), purgado con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH y evaporado hasta una goma marrón. El material resultante fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como una sólido color crema (107 mg, 73%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.59 (m, 4H), 1.72 (m, 4H), 2.04 (m, 4H), 2.16 (m, 2H), 2.29 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.29 (s, 3H), 3.70 (m, 2H), 4.01 (m, 1H), 4.86 (m, 1H), 5.83 (d, 1H), 7.10 (s, 1H), 7.28 (s, 1H), 7.31 (s, 1H), 7.93 (s, 1H); MS m/z 514 $[M+H]^+$.

Ejemplo 188:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–2,5–difluoro–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 100 mg, 0.36 mmol), 4–amino–2,5–difluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 59, 87 mg, 0.32 mmol) y carbonato de cesio (211 mg, 0.65 mmol) fueron añadidos a dioxano (3 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Bis(dibencilidenoacetona)paladio (11 mg, 0.019 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (17 mg, 0.029 mmol) fueron añadidos y la mezcla calentada a 100 °C toda la noche. La mezcla de reacción fue enfriada a temperatura ambiente y filtrada. La torta del filtro fue lavada con DCM y el filtrado añadido a una columna SCX–2 de 5g prehumedecida con MeOH (2 volúmenes de columna), lavada con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH y evaporadas hasta una goma marrón. El material resultante fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (34 mg, 19%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.60 (m, 4H), 1.75 (m, 4H), 2.05 (m, 4H), 2.17 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.30 (s, 3H), 3.71 (m, 2H), 4.01 (m, 1H), 4.88 (m, 1H), 6.59 (m, 1H), 7.29 (m, 1H), 7.82 (m, 1H), 7.96 (s, 1H), 8.46 (m, 1H); MS m/z 515 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 188 utilizando 4–amino–2–fluoro–N–(1–metil–4–piperidil)benzamida Producto intermedio 61.

Ejemplo 189:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–2–fluoro–N –(1–metil–4–piperidil)benzamida

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.59 (m, 4H), 1.73 (m, 4H), 2.05 (m, 4H), 2.18 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.79 (m, 2H), 3.29 (s, 3H), 3.70 (m, 2H), 4.03 (m, 1H), 4.88 (m, 1H), 6.56 (m, 1H), 7.12 (m, 2H), 7.87 (m, 1H), 7.94 (s, 1H), 8.01 (m, 1H); MS m/z 496 $[M+H]^+$.

Ejemplo 190:

metil 4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–hidroxi–benzoato

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 180 mg, 0.64 mmol) y metil 3–hidroxi–4–aminobenzoato (ABCR, 123 mg, 0.73 mmol) fue tomado en etanol (4 mL) y agua (12 mL). A esto fue añadido ácido clorhídrico concentrado(36%; 130 µL). La reacción fue calentada a 80°C y agitada toda la noche. La reacción se dejó reposar y enfriar toda la noche, antes de la evaporación del etanol. El residuo acuoso fue diluido a ~30 mL con agua y la solución basificada a pH 9 por adición de una gotas de Amoniaco ac.. La mezcla resultante fue extraida con DCM (2 x 50 mL). Un sólido persistió en la fase límite. Este sólido fue recogido mediante filtración por succión y secado para dar el compuesto del título como un sólido púrpura/gris (64 mg).

Los extractos orgánicos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio, filtrados y evaporados hasta un sólido rosa/marrón el cual fue tomado en una pequeña cantidad (~5 mL) de DCM y sonicado durante 5 minutos. El sólido fue luego recogido mediante filtración por succión y secado para dar el compuesto del título como un sólido rosa oscuro (79 mg).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.56 – 1.75 (m, 6H), 1.94 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.80 (s, 3H), 4.82 (m, 1H), 7.44 (m, 2H), 7.84 (s, 1H), 8.09 (s, 1H), 8.35 (d, 1H), 10.53 (s, 1H); MS m/z 412 $[M+H]^+$.

Ejemplo 191:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

Una solución de 4–amino–N–(2–morfolin–4–iletil)benzamida (Buttpark; 108mg, 0.43mmol) en EtOH (2 mL) fue añadida a 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 100 mg, 0.36 mmol), agua (6 mL) fue añadida seguido por ácido clorhídrico concentrado (36%, 70 ul) y la solución calentada a 80°C durante 28 horas y luego se dejó enfriar todo el fin de semana. La mezcla de reacción fue cargada en una columna SCX–2 (5g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH. La evaporación del solvente dio el producto crudo como una goma la cual fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (71 mg, 40 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.68 (m, 6H), 1.97 (m, 2H), 2.44 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (m, 2H), 3.58 (m, 4H), 3.63 (m, 2H), 4.84 (m, 1H), 7.77 (m, 4H), 8.08 (s, 1H), 8.16 (t, 1H), 9.45 (s, 1H); MS m/z 494 $[M+H]^+$.

Ejemplo 192:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–dietilaminoetil)benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 100 mg, 0.36 mmol), 4–amino–N–(2–dietilaminoetil)benzamida (Timtec, 101 mg, 0.43 mmol) y ácido p–toluenosulfónico (137 mg, 0.72 mmol) fueron calentados juntos en 4–metil–2–pentanol (4 mL) a 100°C durante 24 horas. La mezcla de reacción cruda fue cargada en una columna SCX–2 (5g) prehumedecida con MeOH. La columna fue lavada con MeOH y el producto eluido con NH_3 2M/MeOH. La evaporación del solvente dio el material que fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (123 mg, 71 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.98 (t, 6H), 1.66 (m, 6H), 1.96 (m, 2H), 2.52 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.30 (s, 2H), 3.63 (m, 2H), 4.84 (m, 1H), 7.73 (d, 2H), 7.80 (d, 2H), 8.08 (s, 1H), 8.12 (t, 1H), 9.45 (s, 1H); MS m/z 480 $[M+H]^+$.

Ejemplo 193:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metil–N–(1–metil–4–piperidil)benzamida

Una solución de 4–amino–3–metil–N–(1–metil–4–piperidil)benzamida (Producto intermedio 63, 53 mg, 0.214 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1, 60 mg, 0.214 mmol) y ácido p–toluenosulfónico monohidrato (102 mg, 0.535 mmol) en 4–metil–2–pentanol (4 mL) fue calentado a 100 °C toda la noche. La reacción fue enfriada a temperatura ambiente (se formó sólido) disuelta en MeOH y añadida en una columna SCX–2 de 2g prehumedecida con MeOH (2 volúmenes de columna). La columna fue lavada con MeOH (2 volúmenes de columna) y luego el producto eluido con amoniaco 2M en MeOH y los solventes evaporados. El material resultante fue tomado en DCM y purificado en sílice eluyendo con un gradiente de 0 – 10% MeOH / DCM luego 10% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma clara a la cual éter fue añadido y reevaporado hasta un sólido blanco el cual fue además purificado por HPLC en fase inversa.

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.54 – 1.70 (m, 6H), 1.75 (m, 2H), 2.02 (m, 4H), 2.17 (m, 2H), 2.31 (s, 3H), 2.37 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.29 (s, 3H), 3.68 (m, 2H), 3.99 (m, 1H), 4.85 (m, 1H), 5.86 (d, 1H), 6.79 (s, 1H), 7.59 (m, 2H), 7.92 (s, 1H), 8.32 (d, 1H); MS m/z 492 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 193 utilizando 4–amino–3–fluoro–N–(1–metil–4–piperidil)benzamida Producto intermedio 65.

<u>Ejemplo 194:</u>

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–fluoro–N–(1–metil–4–piperidil)benzamida

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.53 – 1.80 (m, 8H), 2.03 (m, 4H), 2.16 (m, 2H), 2.30 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.69 (m, 2H), 3.97 (m, 1H), 4.87 (m, 1H), 5.85 (d, 1H), 7.22 (m, 1H), 7.52 (m, 2H), 7.95 (s, 1H), 8.57 (m, 1H); MS m/z 496 $[M+H]^+$.

Ejemplo 195:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-(2-metoxietoxi)-N-(1-metil-4-piperidil)benzamida

A una suspensión de ácido 4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-10-il)amino]-3-(2-metoxietoxi)benzoico (Producto intermedio 66, 55 mg, 0.12 mmol) en DMF (2 mL) fue añadido DIPEA (42 ul, 0.16 mmol) y la mezcla fue agitada durante 5 minutos. HATU (60 mg, 0.16 mmol) fue añadido a la solución resultante color paja. La solución fue agitada por unos 10 minutos adicionales antes de la adición de 4-amino-1-metilpiperidina (18 mg, 0.16 mmol) en DMF (0.5 mL). Las reacción fue agitada a temperatura ambiente durante 6 horas y la mezcla de reacción cruda fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (50 mg, 76 %).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.55 – 1.83 (m, 10H), 1.89 – 2.10 (m, 4H), 2.23 (s, 3H), 2.59 (m, 2H), 2.84 (m, 2H), 3.18 (s, 3H), 3.38 (s, 3H), 3.64 (m, 2H), 3.73 – 3.81 (m, 3H), 4.26 (m, 2H), 4.79 (m, 1H), 7.51 (d, 1H), 7.54 (m, 1H), 7.81 (s, 1H), 8.06 (d, 1H), 8.09 (s, 1H), 8.42 (d, 1H); MS m/z 552 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 195 utilizando una solución de metilamina 2.0M en THF.

Ejemplo 196:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-(2-metoxietoxi)-N-metil-benzamida

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.55 – 1.81 (m, 6H), 2.03 (m, 2H), 2.67 (m, 2H), 3.01 (d, 3H), 3.29 (s, 3H), 3.47 (s, 3H), 3.69 (m, 2H), 3.80 (m, 2H), 4.28 (m, 2H), 4.88 (m, 1H), 6.07 (m, 1H), 7.28 (m, 1H), 7.46 (m, 1H), 7.80 (s, 1H), 7.95 (s, 1H), 8.52 (d, 1H) ; MS m/z 469 $[M+H]^+$.

Ejemplo 197:

4-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(1-metil-4-piperidil)-3-propan-2-iloxi-benzamida

A una solución de ácido 4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–propan–2–iloxi–benzoico (Producto intermedio 69; 49 mg, 0.11 mmol) en DMF (2 mL) fue añadido DIPEA (42 uL, 0.24 mmol) y HATU (61 mg, 0.16 mmol). Las soluciones fueron agitadas durante 5 minutos antes de la adición de 4–amino–1–metilpiperidina (ABCR, 16 mg, 0.14 mmol). La mezcla de reacción fue agitada, a temperatura ambiente, toda la noche.

La mezcla de reacción cruda fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (29 mg, 49%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.36 (d, 6H), 1.54 – 1.80 (m, 10H), 1.94 (m, 4H), 2.17 (s, 3H), 2.59 (m, 2H), 2.78 (m, 2H), 3.18 (s, 3H), 3.64 (m, 2H), 3.74 (m, 1H), 4.78 (m, 2H), 7.48 (m, 1H), 7.52 (m, 1H), 7.67 (s, 1H), 8.04 (d, 1H), 8.08 (s, 1H), 8.41 (d, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 198:

N–ciclohexil–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–(2–dimetilaminoetoxi)benzamida

A una solución agitada de Metil 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–(2–dimetilaminoetoxi)benzoato (Producto intermedio 72; 41 mg, 0.08 mmol) en etanol (2 mL) fue añadida una solución de hidróxido de litio (8 mg, 0.33 mmol) en agua (1 mL). La reacción fue calentada a 100°C por irradiación de microondas con agitación, durante 30 minutos, enfriada, evaporada y el residuo diluido con agua (5 mL). La solución resultante fue tratada con una gotas de HCl 2M (ac.) de manera de ajustar el pH a 2–3. La solución acuosa fue evaporada hasta secarse para dar el ácido carboxílico como una goma amarillo pálido, la cual fue disuelta en DMF (1 mL) y con DIPEA (25 µL, 0.14 mmol) y HATU (40 mg. 0.11 mmol). Ciclohexilamina (11 µL, 0.10 mmol) fue añadida y la mezcla de reacción se dejó agitar, a temperatura ambiente, toda la noche.

La mezcla de reacción cruda fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido color hueso (14 mg, 32 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.10 – 1.37 (m, 6H), 1.55 – 1.99 (m, 12H), 2.28 (s, 6H), 2.59 (m, 2H), 2.65 (t, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.77 (m, 1H), 4.21 (t, 2H), 4.80

(m, 1H), 7.50 (m, 1H), 7.55 (m, 1H), 7.98 (d, 1H), 8.09 (s, 1H), 8.39 (m, 1H), 8.41 (s, 1H); MS m/z 551 $[M+H]^+$.

Ejemplo 199:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)–3–(trifluorometoxi)benzamida

A una solución de 4–amino–N–(1–metil–4–piperidil)–3–(trifluorometoxi)benzamida (Producto intermedio 74, 104 mg, 0.33 mmol) 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]u ndeca–8,10,12–trien–5–ona (Producto intermedio 1, 91 mg, 0.32 mmol) en 1,4–dioxano anhidro (4 mL) fue añadido carbonato de cesio (222 mg ,0.68 mmol). El nitrógeno fue burbujeado a través de la mezcla de reacción durante 10 minutos, antes de la adición de tris(dibencilidenoacetona) paladio (II) (21 mg, 0.07 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (21 mg, 0.11 mmol). La reacción fue calentada por irradiación de microondas a 150°C durante 60 minutos. Las porciones adicionales de 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (19 mg) y tris(dibencilidenoacetona) paladio (II (25 mg) añadidas y la mezcla calentada en una plancha caliente a 100°C toda la noche. La mezcla de reacción fue enfriada y diluida hasta 10 mL con DCM. El material insoluble fue filtrado y la torta del filtro lavada con DCM. La evaporación hasta secarse el filtrado proporcionó una goma marrón, la cual fue tomada en metanol y vertida en un cartucho SCX–2 (5g, Silicycle). El cartucho fue lavado con metanol (~75 mL) antes de eluir los productos con amoniaco 2M en metanol (~50 mL). La fracción amoniacal fue evaporada para proporcionar una goma marrón la cual fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (25 mg, 4 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.51 – 1.97 (m, 14H), 2.17 (s, 3H), 2.59 (m, 2H), 2.78 (m, 2H), 3.18 (s, 3H), 3.62 (m, 2H), 3.74 (m, 1H), 4.74 (m, 1H), 7.86 (m, 2H), 8.08 (s, 1H), 8.25 (d, 1H), 8.30 (d, 1H), 8.57 (s, 1H) MS m/z 562 $[M+H]^+$.

Ejemplo 200:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–etoxi–N–(1–metil–4–piperidil)benzamida

Una solución de HATU (63 mg, 0.165 mmol) en DMA (1 mL) fue añadida a una mezcla de ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–etoxi–benzoico (Producto intermedio 75, 64 mg, 0.15 mmol), DIPEA (79 uL, 0.45 mmol) y la amina en DMA (1 mL). La mezcla resultante fue agitada a temperatura ambiente toda la noche. La mezcla de reacción fue añadida a una columna SCX–3 prehumedecida con metanol, lavada con metanol y el producto eluido con Amoniaco en metanol. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por cromatografía en columna, eluyendo con 0–10% amoniaco metanólico 7N en DCM, para dar el compuesto del título como vidrio claro (64 mg, 82 %).

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.51 (3H, t), 1.61 – 1.82 (8H, m), 2.03 – 2.09 (2H, m), 2.21 – 2.29 (4H, m), 2.38 (3H, s), 2.67 – 2.70 (2H, m), 2.90 – 2.93 (2H, m), 3.31 (3H, s), 3.70 – 3.73 (2H, m), 4.00 – 4.08 (1H, m), 4.22 (2H, q), 4.92 (1H, quin), 6.07 (1H, d), 7.27 (1H, dd), 7.42 (1H, d), 7.72 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 522 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 200 utilizando las aminas apropiadas disponibles de Aldrich.

Ejemplo 201:

N–(1–azabiciclo[2.2.2]oct–8–il)–4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–etoxi–benzamida

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.51 (3H, t), 1.55 – 1.89 (10H, m), 2.06 – 2.03 (6H, m), 2.67 – 2.70 (2H, m), 2.84 – 2.97 (4H, m), 3.07 – 3.13 (1H, m), 3.31 (3H, s), 3.44 – 3.50 (1H, m), 3.70 – 3.73 (2H, m), 4.20 – 4.26 (1H, m), 4.22 (2H, q), 4.91 (1H, quin), 6.55 (1H, d), 7.34 (1H, dd), 7.47 (1H, d), 7.72 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 533 $[M+H]^+$.

Ejemplo 202:

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–dimetilaminoetil)–3–etoxi–benzamida

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.52 (3H, t), 1.62 – 1.82 (6H, m), 2.04 – 2.09 (2H, m), 2.39 (6H, s), 2.64 – 2.71 (4H, m), 3.31 (3H, s), 3.58 – 3.62 (2H, m), 3.70 – 3.73 (2H, m), 4.24 (2H,

q), 4.92 (1H, quin), 7.01 (1H, s), 7.38 (1H, dd), 7.49 (1H, d), 7.71 (1H, s), 7.96 (1H, s), 8.52 (1H, d); MS m/z 494 $[M+H]^+$.

Ejemplo 203:

3-cloro-4-[(2-metil-3-oxo-6-propan-2-il-2,6,8,10-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-9-il)amino]-N-(1-metil-4-piperidil)benzamida

10-cloro-6-metil-2-propan-2-il-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 76, 100mg, 0.39mmol) y 4-amino-3-cloro-N-(1-metil-4-piperidil)benzamida (Producto intermedio 79; 127 mg, 0.47 mmol) fueron suspendidos en 4-metil-2-pentanol (3 mL) y ácido p-toluenosulfónico monohidrato (74 mg, 0.97 mmol) añadido. La mezcla fue calentada a 140°C durante 4 horas. La mezcla fue enfriada provocando que se forme un sólido blanco. La mezcla completa fue diluida con MeOH para dar una solución la cual fue absorbida en una columna SCX-3, lavada con metanol y eluida con metanol/amoniaco. La concentración y cromatografía en columna (1-2-3-5% NH_3 en MeOH/DCM) de las fracciones que contienen el producto dio el compuesto del título como un sólido blanco (58mg, 31%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.23 (6H, d), 1.54 – 1.64 (2H, m), 1.75 – 1.78 (2H, m), 1.91 – 1.97 (2H, m), 2.18 (3H, s), 2.60 (2H, m), 2.78 (2H, d), 3.18 (3H, s), 3.61 (2H, m), 3.69 – 3.75 (1H, m), 4.72 – 4.78 (1H, m), 7.81 – 7.84 (1H, m), 7.99 (1H, d), 8.09 (2H, d), 8.21 (1H, d), 8.32 (1H, d); MS m/z 486 $[M+H]^+$.

Ejemplo 204:

Ácido 3-metoxi-4-[(2-metil-3-oxo-6-propan-2-il-2,6,8,10-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-9-il)amino]benzoico

10-cloro-6-metil-2-propan-2-il-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 76; 739 mg, 2.9 mmol) , ácido 4-amino-3-metoxi-benzoico (Aldrich, 534 mg, 3.2 mmol), 4:1 agua / etanol (6 mL) y ácido clorhídrico concentrado acuoso (0.485 mL, 5.8 mmol) fueron combinados y calentados a reflujo toda la noche bajo nitrógeno. La mezcla de reacción fue enfriada a temperatura ambiente y filtrada. La torta del filtro fue lavada con agua seguido por dietiléter para dar el compuesto del título como un sólido color hueso como la sal de hidrocloruro (673 mg, 55 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) : δ_H : 1.25 (d, 6H), 2.73(m, 2H), 3.19 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.89 (m, 1H), 7.59 (s, 1H), 7.67 (d, 1H), 8.20 (m, 2H), 9.55 (s, 1H); MS m/z 386 $[M+H]^+$.

Ejemplo 205:

3–metoxi–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]–N–[2–(1–piperidil)etil]benzamida

A una solución de la sal de hidrocloruro del ácido 3–metoxi–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]benzoico (Ejemplo 204; 127 mg, 0.33 mmol) y 1–(2–aminoetil)piperidina (Aldrich, 54uL, 0.38 mmol) y DIPEA (157 uL , 0.9 mmol) en DMA anhidro (10 mL) a temperatura ambiente bajo nitrógeno fue añadido HATU (126 mg, 0.33 mmol) como un sólido y la solución resultante agitada a temperatura ambiente toda la noche. La mezcla de reacción fue cargada en una Columna SCX–3 prehumedecida con metanol y la columna lavada con metanol. La columna fue eluida con amoniaco en metanol y el producto que contiene las fracciones evaporado. El material resultante fue disuelto en diclorometano y cromatografiado con 2–5–10–20% metanol/diclorometano seguido por metanol/amoniaco 7N. La evaporación de las fracciones que contienen el producto dio una espuma amarilla la que fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como una goma blanco hueso (75 mg, 46 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) : δ_H : 1.25 (d, 6H), 1.39 (m, 2H), 1.50 (m, 6H), 2.40 (m, 6H), 2.60 (m, 2H), 3.19 (s, 3H), 3.37 (m, 2H), 3.61 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.49 (m, 2H), 7.69 (s, 1H), 8.07 (s, 1H), 8.22 (tr, 1H), 8.41 (m, 1H); MS m/z 496 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 205 utilizando las aminas apropiadas disponibles de Aldrich o Matrix.

Ejemplo 206:

N–(1–azabiciclo[2.2.2]oct–8–il)–3–metoxi–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]benzamida

Ejemplo 207:

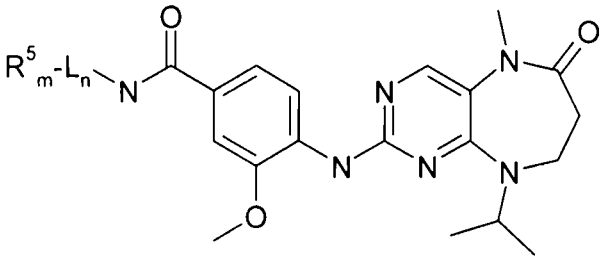
N–(2–dimetilaminoetil)–3–metoxi–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]benzamida

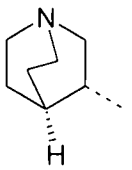
Ejemplo 208:

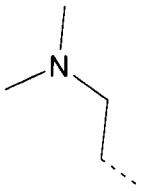
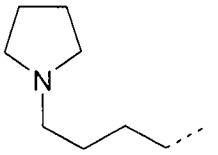
N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]benzamida

Ejemplo 209:

3–metoxi–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]–N–(4–pirrolidin–1–ilbutil)benzamida



Ejemplo	$R^5{}_m$–L_n–	^{1}H NMR (400 MHz, DMSO–d_6)	MS m/z $[M+H]^+$
206		δ_H: 1.23 (d, 6H), 1.30 (m, 1H), 1.60 (m, 2H), 1.85 (m, 2H), 2.60 (m, 2H), 2.70 (m, 4H), 2.90 (m, 1H), 3.11 (m, 1H), 3.20 (s, 3H), 3.62 (m, 2H), 3.95 (m, 4H), 4.81 (m, 1H), 7.49 (s, 1H), 7.56 (d, 1H), 7.30 (s, 1H), 8.06 (m, 2H), 8.42 (d, 1H);	494
207		δ_H: 1.23 (d, 6H), 2.19 (s, 6H), 2.40 (tr, 2H), 2.60 (m, 2H), 3.18 (s, 3H), 3.36 (m , 2H), 3.61 (d, 2H), 3.96 (s, 3H), 4.81 (m, 1H), 7.50 (m, 2H), 7.69 (s, 1H), 8.07 (s, 1H), 8.24 (tr, 1H),	456

Ejemplo	$R^5{}_m$–L_n–	^{1}H NMR (400 MHz, DMSO–d_6)	MS m/z $[M+H]^+$
		8.41 (d, 1H);	
208		δ_H : 0.89 (s, 6H), 1.25 (d, 6H), 2.20 (s, 2H), 2.29 (s, 6H), 2.61 (m, 2H), 3.20 (m, 5H), 3.61 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.46 (m, 2H), 7.70 (s, 1H), 8.08 (s, 1H), 8.41 (m, 2H)	498
209		δ_H : 1.26 (d, 6H), 1.52 (m, 4H), 1.68 (m, 4H), 2.40 (m, 6H), 2.60 (m, 2H), 3.18 (s, 3H), 3.30 (m, 2H), 3.60 (m, 2H), 3.95 (s, 3H), 4.81 (m, 1H), 7.50 (m, 2H), 7.69 (s, 1H), 8.09 (s, 1H), 8.31 (tr, 1H), 8.41 (d, 1H)	510

Ejemplo 210:

4–[(6–etil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

10–cloro–2–etil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona Producto intermedio 81; 180 mg, 0.75 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220, 198 mg, 0.75 mmol) y ácido p–toluenosulfónico (357 mg, 1.88 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) hasta 140 °C durante 18 horas. La mezcla de reacción se dejó enfriar a temperatura ambiente y se cargó en un cartucho SCX–2 de 10 g, lavando con metanol (10 mL), agua (10 mL) y metanol (10 mL) antes que el producto fuera eluido con amoniaco metanólico 7 N el cual al evaporarse las fracciones que contienen el producto proporcionó un aceite amarillo el cual fue purificado por cromatografía flash en sílice (Companion, 40 g, 0–10% amoniaco metanólico/DCM) para dar un vidrio amarillo

pálido el cual fue además purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (192 mg, 49 %).

^{1}H NMR (399.902 MHz, DMSO–d_6) δ 1.24 (t, 3H), 1.60 (qd, 2H), 1.73 – 1.81 (m, 2H), 1.95 (td, 2H), 2.18 (s, 3H), 2.62 – 2.64 (m, 2H), 2.79 (br d, 2H), 3.18 (s, 3H), 3.62 (q, 2H), 3.70 – 3.79 (m, 3H), 3.96 (s, 3H), 7.49 – 7.53 (m, 2H), 7.70 (s, 1H), 8.05 – 8.08 (m, 2H), 8.41 (d, 1H); MS m/z 468 $[M+H]^+$.

Ejemplo 211:

3–metoxi–4–[[2–metil–6–(2–metilpropil)–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il]amino]–N–(1–metil–4–piperidil)benzamida

10–cloro–6–metil–2–(2–metilpropil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 84; 65 mg, 0.24 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220, 57 mg, 0.24 mmol) y ácido p–toluenosulfónico (110 mg, 0.58 mmol) fueron tomados en 4–metil–2–pentanol (1 mL) y calentados hasta 160°C por irradiación de microondas durante 1 hora. La mezcla de reacción fue diluida con metanol (5 mL) y agua (2 mL) y la solución resultante vertida en un cartucho SCX–3 (2 g). El cartucho fue lavado con metanol (~30 mL) antes de eluir los productos con amoniaco 2M metanol (~20 mL). La fracción amoniacal fue evaporada para dar una goma ámbar la cual fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un vidrio incoloro (triturado hasta un sólido blanco) (80 mg, 75 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.90 (d, 6H), 1.60 (m, 2H), 1.77 (m, 2H), 1.94 (m, 2H), 2.11 (m, 1H), 2.17 (s, 3H), 2.64 (m, 2H), 2.78 (m, 2H), 3.19 (s, 3H), 3.50 (d, 2H), 3.68 – 3.79 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.70 (s, 1H), 8.07 (d, 1H), 8.08 (s, 1H), 8.34 (m, 1H); MS m/z 496 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 211 utilizando las cloropirimidinas apropiadas indicadas.

Ejemplo 212A:

4–[(6–butan–2–il–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

La cloropirimidina usada – 2–butan–2–il–10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona Producto intermedio 87.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.87 (t, 3H), 1.23 (d, 3H), 1.49 – 1.70 (m, 4H), 1.77 (m, 2H), 1.95 (t, 2H), 2.18 (s, 3H), 2.55 – 2.68 (m, 2H), 2.79 (m, 2H), 3.18 (s, 3H), 3.50 (m, 1H), 3.62 (m, 1H), 3.74 (m, 1H), 3.95 (s, 3H), 4.63 (m, 1H), 7.48 – 7.52 (m, 2H), 7.68 (s, 1H), 8.05 – 8.08 (m, 2H), 8.38 (m, 1H); MS m/z 496 $[M+H]^+$.

Ejemplo 212B:

4–[(6–ciclobutil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

La cloropirimidina usada – 10–cloro–2–ciclobutil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona Producto intermedio 90.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.55 – 1.80 (m, 6H), 1.95 (m, 2H), 2.10 (m, 2H), 2.18 (s, 3H), 2.25 (m, 2H), 2.58 (m, 2H), 2.79 (m, 2H), 3.18 (s, 3H), 3.66 (m, 2H), 3.74 (m, 1H), 3.95 (s, 3H), 4.52 (m, 1H), 7.49 (m, 1H), 7.53 (m, 1H), 7.74 (s, 1H), 8.06 (d, 1H), 8.14 (s, 1H), 8.45 (d, 1H); MS m/z 494 $[M+H]^+$.

Ejemplo 213:

4–[[6–(ciclopropilmetil)–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il]amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

La cloropirimidina usada 10–cloro–2–(ciclopropilmetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona Producto intermedio 93.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.30 (m, 2H), 0.52 (m, 2H), 1.17 (m, 1H), 1.60 (m, 2H), 1.77 (m, 2H), 1.95 (m, 2H), 2.17 (s, 3H), 2.65 (m, 2H), 2.79 (m, 2H), 3.19 (s, 3H), 3.51 (d, 2H), 3.69 – 3.81 (m, 3H), 3.95 (s, 3H), 7.49 (m, 2H), 7.71 (s, 1H), 8.06 (d, 1H), 8.09 (s, 1H), 8.39 (m, 1H); MS m/z 494 $[M+H]^+$.

Ejemplo 214:

3–metoxi–4–[(2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)benzamida

10–cloro–2–[(2,4–dimetoxifenil)metil]–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 96; 80 mg, 0.23 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 52 mg, 0.20 mmol) y ácido p–toluenosulfónico (110 mg, 0.58 mmol) fueron tomados en 4–metil–2–pentanol (1.5 mL) y calentados a 160°C por irradiación de microondas durante 1 hora. La mezcla de reacción fue disuelta en metanol (5 mL) y agua (~5 mL) y vertida directamente en un cartucho SCX–3 (2 g). El cartucho fue lavado completamente con metanol (~ 30 mL), antes de eluir los productos con amoniaco 2M en metanol (~30 mL). La evaporación de la fracción amoniacal dio una goma marrón la cual fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (9 mg, 10 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.60 (m, 2H), 1.77 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.61 (m, 2H), 2.78 (m, 2H), 3.21 (s, 3H), 3.54 (m, 2H), 3.73 (m, 1H), 3.95 (s, 3H), 7.47 (m, 2H), 7.58 (m, 2H), 8.05 (d, 1H), 8.10 (s, 1H), 8.52 (m, 1H); MS m/z 440 $[M+H]^+$.

Ejemplo 215:

4–[(6–bencil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

2–bencil–10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 99; 42 mg, 0.14 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 33 mg, 0.13 mmol) y ácido p–toluenosulfónico monohidrato (54 mg, 0.28 mmol) fueron tomados en 4–metil–2–pentanol (1.5 mL) y calentados a 160°C por irradiación de microondas durante 1 hora. La mezcla de reacción fue disuelta en metanol (5 mL) y agua (~5 mL) y vertida directamente en un cartucho SCX–3 (2 g). El cartucho fue lavado completamente con metanol (~ 30 mL), antes de eluir los productos con amoniaco 2M en metanol (~30 mL). La evaporación de la fracción amoniacal dio una película ámbar la cual fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido color hueso (33 mg, 48 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.57 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.68 (m, 2H), 2.77 (m, 2H), 3.22 (s, 3H), 3.59 – 3.77 (m, 3H), 3.91 (s, 3H), 4.87 (s, 2H), 7.24 – 7.38 (m, 6H), 7.43 (m, 1H), 7.71 (s, 1H), 8.01 (d, 1H), 8.14 (d, 1H), 8.15 (s, 1H); MS m/z 531 $[M+H]^+$.

Ejemplo 216:

3-metoxi-4-[[2-metil-6-[(2-metil1,3-thiazol-4-il)metil]-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-9-il]amino]-N-(1-metil-4-piperidil)benzamida

10-cloro-6-metil-2-[(2-metil-1,3-thiazol-4-il)metil]-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 101; 58 mg, 0.18 mmol), 4-amino-3-metoxi-N-(1-metil-4-piperidil)benzamida (WO06/018220; 49 mg, 0.19 mmol) y ácido p-toluenosulfónico (70 mg, 0.37 mmol) fueron tomados en 4-metil-2-pentanol (2 mL) y calentados hasta 160°C en un microondas por irradiación de microondas durante 1 hora. La mezcla de reacción fue disuelta en metanol (5 mL) y agua (~5 mL) y vertida directamente en un cartucho SCX-3 (2 g). El cartucho fue lavado completamente con metanol (~ 30 mL), antes de eluir los productos con amoniaco 2M en metanol (~30 mL). La evaporación de la fracción amoniacal dio una película ámbar la cual fue purificada por HPLC en fase inversa para proporcionar el compuesto del título como un sólido color hueso (43 mg, 26 %).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 (m, 2H), 1.76 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.67 (s, 3H), 2.72 (m, 2H), 2.77 (m, 2H), 3.21 (s, 3H), 3.68 – 3.77 (m, 3H), 3.92 (s, 3H), 4.85 (s, 2H), 7.23 (m, 1H), 7.29 (m, 1H), 7.44 (d, 1H), 7.71 (s, 1H), 8.04 (d, 1H), 8.08 (d, 1H), 8.13 (s, 1H); MS m/z 551 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 216 utilizando las cloropirimidinas apropiadas indicadas.

Ejemplo 217:

4-[[6-(ciclobutilmetil)-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il]amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

La cloropirimidina usada – 10-cloro-2-(ciclobutilmetil)-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 102).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.60 (m, 2H), 1.73 – 2.07 (m, 10H), 2.17 (s, 3H), 2.61 (m, 2H), 2.69 – 2.81 (m, 3H), 3.17 (s, 3H), 3.66 – 3.80 (m, 5H), 3.95 (s, 3H), 7.47 – 7.51 (m, 2H), 7.71 (s, 1H), 8.07 (m, 2H), 8.35 (d, 1H); MS m/z 509 $[M+H]^+$.

Ejemplo 218:

4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

4–amino–N–(2–morfolin–4–iletil)benzamida (Buttpark; 188mg, 0.75mmol) y 10–cloro–6–metil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 76; 160mg, 0.63mmol) fueron calentados juntos en EtOH:agua (8 ml) 1:3 en presencia de ácido clorhídrico concentrado (126ul) durante 24 horas. La reacción fue enfriada a temperatura ambiente y luego cargada en una columna SCX–2 (5g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y el solvente evaporado para dar el producto como una goma marrón. Esto fue purificado por HPLC en fase inversa para dar el compuesto del título como un sólido blanco. (125 mg, 42 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.25 (d, 6H), 2.44 (m, 6H), 2.59 (m, 2H), 3.18 (s, 3H), 3.37 (m, 2H), 3.59 (m, 6H), 4.85 (m, 1H), 7.78 (m, 4H), 8.06 (s, 1H), 8.15 (t, 1H), 9.42 (s, 1H); MS m/z 468 $[M+H]^+$.

Los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 218 utilizando las analinas apropiadas sustituidas y cloropirimidinas como se indicó.

Ejemplo 219:

3–metoxi–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

Preparado a partir del Producto intermedio 76 y Producto intermedio 47.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.29 (d, 6H), 2.49 (m, 6H), 2.52 (s, 3H), 2.65 (m, 2H), 3.44 (m, 2H), 3.65 (m, 6H), 4.00 (s, 3H), 4.87 (m, 1H), 7.54 (m, 2H), 7.74 (s, 1H), 8.12 (s, 1H), 8.32 (t,1H), 8.47 (d, 1H).

Ejemplo 220:

3–metoxi–4–[(2–metil–3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

Preparado a partir del Producto intermedio 103 y Producto intermedio 47.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 2.44 (m, 5H), 2.83 (m, 2H), 3.28 (s, 3H), 3.36 (m, 2H), 3.59 (m, 4H), 3.88 (s, 3H), 4.06 (m, 2H), 6.93 (d, 1H), 7.35 (m, 4H), 7.47 (m, 3H), 7.64 (s, 1H), 8.16 (t, 1H), 8.29 (s, 1H).

Ejemplo 221:

3–metoxi–4–[(2–metil–3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)benzamida

Preparado a partir del Producto intermedio 103 y un Producto intermedio descrito en WO06/018220.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.58 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.51 (s, 3H), 2.80 (m, 4H), 3.70 (m, 1H), 3.89 (s, 3H), 4.06 (m, 2H), 6.96 (d, 1H), 7.34 (m, 4H), 7.48 (m, 3H), 7.64 (s, 1H), 7.97 (d, 1H), 8.29 (s, 1H).

Ejemplo 222:

N–(3–dimetilamino–2,2–dimetil–propil)–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]benzamida

Preparado a partir del Producto intermedio 76 y Producto intermedio 22.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.88 (s, 6H), 1.25 (d, 6H), 2.18 (s, 2H), 2.27 (s, 6H), 2.59 (m, 2H), 3.18 (s, 2H), 3.29 (s, 3H), 3.61 (m, 2H), 4.85 (m, 1H), 7.73 (d, 2H), 7.81 (d, 2H), 8.06 (s, 1H), 8.27 (t, 1H), 9.42 (s, 1H).

Ejemplo 223:

N–(3–dimetilamino–2,2–dimetil–propil)–4–[(2–metil–3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]benzamida

Preparado a partir del Producto intermedio 103 y Producto intermedio 22.

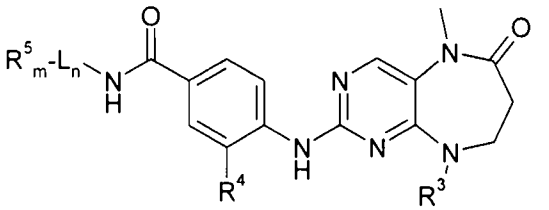
^{1}H NMR (400.132 MHz, DMSO–d_6δ 0.87 (s, 6H), 2.18 (s, 2H), 2.28 (s, 6H), 2.81 (m, 2H), 3.14 (d, 2H), 3.28 (s, 3H), 4.06 (m, 2H), 7.33 (m, 7H), 7.47 (m, 2H), 8.21 (t, 1H), 8.31 (s, 1H), 9.52 (s, 1H).

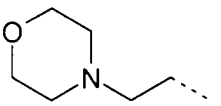
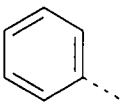
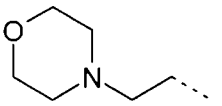
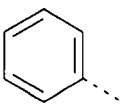
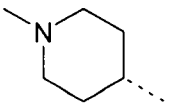
Ejemplo 224:

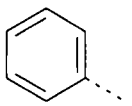
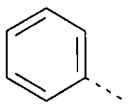
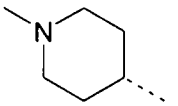
4-[(2-metil-3-oxo-6-fenil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(1-metil-4-piperidil)benzamida

Preparado a partir del Producto intermedio 103 y Producto intermedio 4.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.56 (m, 2H), 1.72 (m, 2H), 1.93 (m, 2H), 2.16 (s, 3H), 2.78 (m, 4H), 3.28 (s, 3H), 3.68 (m, 1H), 4.05 (m, 2H), 7.29 (m, 5H), 7.45 (m, 4H), 7.87 (d, 1H), 8.31 (s, 1H), 9.49 (s, 1H).



Ejemplo	R^3	R^4	$R^5{}_m$-L_n-	MS m/z $[M+H]^+$
219				498
220				532
221				516

Ejemplo	R^3	R^4	$R^5{}_m-L_n-$	MS m/z $[M+H]^+$
222		H		468
223		H		502
224		H		486

Ejemplo 225:

3–cloro–N–(3–dimetilamino–2,2–dimetil–propil)–4–[(2–metil–3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]benzamida

4–amino–3–cloro–N–(3–dimetilamino–2,2–dimetil–propil)benzamida (Producto intermedio 107; 99mg, 0.35mmol), 10–cloro–6–metil–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 103; 99 mg, 0.35 mmol) y ácido p–toluenosulfónico monohidrato (165 mg, 0.87 mmol) fueron calentados a 140°C en 4–metil–2–pentanol (2.5 mL) durante 2 horas. La mezcla se dejó enfriar formando una solución clara naranja oscuro la cual fue cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol para eliminar el p–TsOH y luego eluida con 2% metanol/amoniaco 7N para dar el producto crudo el cual fue purificado por HPLC en fase inversa para proporcionar el compuesto del título como un sólido blanco (15 mg, 8 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.88 (6H, s), 2.17 (2H, s), 2.28 (6H, s), 2.82 – 2.85 (2H, m), 3.16 (2H, d), 4.04 – 4.08 (2H, m), 7.21 – 7.24 (1H, m), 7.28 – 7.30 (1H, m), 7.32 – 7.35 (2H, m), 7.46 (1H, s), 7.48 – 7.50 (1H, m), 7.56 (1H, d), 7.82 (1H, d), 8.02 (1H, s), 8.32 (1H, s), 8.37 (1H, t); MS m/z 537 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 225 utilizando the anilina apropiada sustituida (Producto intermedio 52).

Ejemplo 226:

3–cloro–4–[(2–metil–3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

^{1}H NMR (399.9 MHz, DMSO–d_6) δ2.41 – 2.47 (6H, m), 2.84 (2H, t), 3.33 – 3.41 (2H, m), 3.59 (4H, t), 4.05 – 4.08 (2H, m), 7.24 – 7.27 (1H, m), 7.31 – 7.35 (3H, m), 7.49 (2H, t), 7.55 (1H, q), 7.85 (1H, d), 8.00 (1H, s), 8.31 (2H, s); MS m/z 537 $[M+H]^+$.

Ejemplo 227:

4–[(2–metil–3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

10–cloro–6–metil–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 103; 150 mg, 0.52 mmol), 4–amino–N–(2–morfolin–4–iletil)benzamida (Buttpark; 130 mg, 0.52 mmol) y ácido p–toluenosulfónico monohidrato (248 mg, 1.30mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140°C durante 2 horas. La mezcla de reacción fue enfriada y cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol para eliminar el ácido p–toluenosulfónico monohidrato y luego lavada con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (81 mg, 32.2 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 2.41 – 2.44 (6H, m), 2.82 (2H, t), 3.35 (3H, s), 3.38 – 3.39 (2H, t), 3.59 (4H, t), 4.06 – 4.08 (2H, t), 7.26 (1H, s), 7.29 (1H, s), 7.31 – 7.35 (2H, m), 7.34 – 7.34 (1H, m), 7.40 – 7.42 (2H, m), 7.49 (2H, t), 8.05 (1H, t), 8.31 (1H, s), 9.53 (1H, s); MS m/z 503 $[M+H]^+$.

Ejemplo 228:

3–cloro–4–[(2–metil–3–oxo–6–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

10–cloro–6–metil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 76 ;150 mg, 0.59 mmol), 4–amino–3–cloro–N–(2–morfolin–4–iletil)benzamida (Producto intermedio 52; 168 mg, 0.59 mmol), y ácido p–toluenosulfónico monohidrato (281 mg, 1.47 mmol) fueron calentados en 4–metil–2–pentanol (4 mL) a 140°C durante 2 horas. La mezcla de reacción fue enfriada y cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol para eliminar el ácido p–toluenosulfónico monohidrato y luego lavada con 2% metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa para proporcionar el compuesto del título como una goma naranja (46 mg, 15.6 %).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.20 (6H, d), 2.42 – 2.43 (3H, m), 2.44 – 2.49 (2H, m), 2.60 (2H, t), 3.18 (4H, t), 3.39 (2H, q), 3.60 – 3.62 (6H, m), 4.75 (1H, m), 7.80 – 7.82 (1H, m), 7.96 (1H, d), 8.07 (1H, s), 8.12 (1H, s), 8.32 (1H, d), 8.40 (1H, t); MS m/z 503 $[M+H]^+$.

Ejemplo 229:

3–metoxi–4–[[6–(2–metoxietil)–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il]amino]–N–(1–metil–4–piperidil)benzamida

10–cloro–2–(2–metoxietil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 109; 70 mg, 0.26 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 63 mg, 0.26 mmol), y ácido p–toluenosulfónico monohidrato (123 mg, 0.65 mmol) fueron combinados en 4–Metil–2–pentanol (2 mL) y calentados a 100 °C toda la noche. La reacción fue enfriada a temperatura ambiente y tomada en MeOH y añadida a una columna SCX–2 de 2g prehumedecida con MeOH (2 volúmenes de columna). La columna fue lavada con MeOH (2 volúmenes de columna) y el producto eluido con amoniaco 2M en MeOH y los solventes evaporados. El material resultante fue disuelto en DCM y purificado en sílice eluyendo con un gradiente de 0 – 10% MeOH / DCM luego 10% MeOH / DCM. Las fracciones que contienen el producto combinados y evaporadas hasta una goma clara a la cual éter fue añadido y reevaporado y el material resultante purificado por HPLC en fase inversa para dar el compuesto del título como un sólido blanco (40 mg, 31 %).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.58 (m, 2H), 2.06 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.72 (m, 2H), 2.83 (m, 2H), 3.29 (s, 3H), 3.36 (s, 3H), 3.72 (m, 2H), 3.87 (m, 4H), 4.00 (m,

4H), 5.90 (d, 1H), 7.23 (m, 1H), 7.44 (d, 1H), 7.65 (s, 1H), 7.95 (s, 1H), 8.42 (d, 1H); MS m/z 503 $[M+H]^+$.

Ejemplo 230:

3–metoxi–4–[[6–(1–metoxipropan–2–il)–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il]amino]–N–(1–metil–4–piperidil)benzamida

10–cloro–2–(1–metoxipropan–2–il)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 112 60 mg, 0.21 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 56 mg, 0.21 mmol), y ácido p–toluenosulfónico monohidrato (100 mg, 0.53 mmol) fueron combinados en 4–Metil–2–pentanol (2 mL) y calentados a 100 °C durante 16 h. La mezcla de reacción fue enfriada a temperatura ambiente y disuelta en metanol. La solución resultante fue añadida a una columna SCX–3 prehumedecida con MeOH (2 volúmenes de columna). Purgada con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH y los solventes evaporados. El residuo resultante fue disuelto en DCM y purificado en sílice eluyendo con un gradiente de 5 – 15% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma amarilla cual fue purificada por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido beige (35 mg, 32%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ1.32 (d, 3H), 1.58 (m, 2H), 2.05 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.83 (m, 2H), 3.29 (s, 3H), 3.36 (s, 3H), 3.51 (m, 1H), 3.62 (m, 1H), 3.73 (m, 2H), 4.00 (m, 4H), 5.00 (m, 1H), 5.90 (d, 1H), 7.23 (m, 1H), 7.43 (m, 1H), 7.65 (s, 1H), 7.94 (s, 1H), 8.47 (d, 1H); MS m/z 503 $[M+H]^+$.

Ejemplo 231:

4–[[6–(3–furilmetil)–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il]amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

10–cloro–2–(3–furilmetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 116; 67 mg, 0.23 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 60 mg, 0.23 mmol), y ácido p–toluenosulfónico monohidrato (109 mg, 0.57 mmol) fueron combinados en 4–Metil–2–pentanol (2 mL) y calentados a 100 °C durante 16 h. La mezcla de reacción fue enfriada a temperatura ambiente

y disuelta en metanol. La solución resultante fue añadida a una columna SCX–3 prehumedecida con MeOH (2 volúmenes de columna). Purgada con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH y los solventes evaporados. El residuo resultante fue disuelto en DCM y purificado en sílice eluyendo con un gradiente de 0 – 15% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma amarilla cual fue purificada por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido amarillo (50 mg, 42%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ1.57 (m, 2H), 2.04 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.64 (m, 2H), 2.82 (m, 2H), 3.31 (s, 3H), 3.71 (m, 2H), 3.98 (m, 4H), 4.67 (s, 2H), 5.88 (d, 1H), 6.43 (s, 1H), 7.14 (m, 1H), 7.40 (m, 1H), 7.43 (m, 2H), 7.71 (s, 1H), 7.99 (s, 1H), 8.45 (d, 1H); MS m/z 520 $[M+H]^+$.

Ejemplo 232:

4–[(6–ciclopropil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclopropil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 117 42mg, 0.16 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 44 mg, 0.216 mmol), y ácido p–toluenosulfónico monohidrato (79 mg, 0.41 mmol) fueron combinados en 4–Metil–2–pentanol (2 mL) y calentados a 100 °C durante 16 h. La mezcla de reacción fue enfriada a temperatura ambiente y disuelta en metanol. La solución resultante fue añadida a una columna SCX–3 prehumedecida con MeOH (2 volúmenes de columna). Purgada con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH y los solventes evaporados. El residuo resultante fue disuelto en DCM y purificado en sílice eluyendo con un gradiente de 0 – 15% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma amarilla cual fue purificada por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido blanco (34 mg, 43%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ0.64 (m, 2H), 0.92 (m, 2H), 1.59 (m, 2H), 2.05 (m, 2H), 2.17 (m, 2H), 2.31 (s, 3H), 2.67 (m, 2H), 2.86 (m, 3H), 3.26 (s, 3H), 3.82 (m, 2H), 4.00 (m, 4H), 5.90 (d, 1H), 7.22 (m, 1H), 7.44 (d, 1H), 7.82 (s, 1H), 7.99 (s, 1H), 8.76 (d, 1H); MS m/z 503 $[M+H]^+$.

Ejemplo 233:

N–ciclohexil–3–metoxi–4–[[2–metil–6–(1–metil–4–piperidil)–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il]amino]benzamida

10–cloro–6–metil–2–(1–metil–4–piperidil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 118; 39mg, 0.13 mmol), 4–amino–N–ciclohexil–3–metoxi–benzamida (Producto intermedio 119; 31mg, 0.13 mmol) y ácido p–toluenosulfónico monohidrato (60 mg, 0.31 mmol) fueron combinados en 4–Metil–2–pentanol (2 mL) y calentados a 100 °C durante 16 h. La mezcla de reacción fue enfriada a temperatura ambiente y disuelta en metanol y añadida a una columna SCX–3 prehumedecida con MeOH (2 volúmenes de columna). Purgada con MeOH (2 volúmenes de columna) luego el producto crudo eluido con amoniaco 2M en MeOH y los solventes evaporados. El material resultante fue disuelto en DCM y purificado en sílice eluyendo con un gradiente (25 volúmenes de columna) superficial de 0 – 10% MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma amarilla cual fue purificada por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido blanco (15 mg, 23%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.26 (m, 4H), 1.45 (m, 2H), 1.77 (m, 2H), 1.91 (m, 4H), 2.05 (m, 2H), 2.17 (m, 2H), 2.35 (s, 3H), 2.67 (m, 2H), 3.02 (m, 2H), 3.28 (s, 3H), 3.71 (m, 2H), 3.98 (m, 4H), 4.51 (m, 1H), 5.88 (d, 1H), 7.26 (m, 1H), 7.38 (d, 1H), 7.66 (s, 1H), 7.94 (s, 1H), 8.45 (d, 1H); MS m/z 522 $[M+H]^+$.

Ejemplo 234:

4–[(6–ciclopentil–2,5–dimetil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclopentil–3,6–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 120; 25 mg, 0.42 mmol) y), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 112 mg, 0.42 mmol) fueron combinados con ácido p–toluenosulfónico monohidrato (202 mg, 1.06 mmol) en 4–metil–2–pentanol (1 mL) y calentados hasta 150 °C durante 2 h. La mezcla de reacción enfriada fue diluida con metanol (aprox. 50 mL) y cargada en un cartucho SCX–2 de 50 g lavando con metanol (100 mL) y

eluyendo con amoniaco metanólico 7 N (100 mL). La solución concentrada fue purificada por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido blanco (65 mg, 30%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.29 (d, 3H), 1.54 – 1.89 (m, 9H), 1.95 – 2.23 (m, 6H), 2.32 (s, 3H), 2.56 (dd, 1H), 2.72 (dd, 1H), 2.84 (br d, 2H), 3.31 (s, 3H), 3.98 (s, 3H), 4.00 – 4.07 (m, 1H), 4.63 – 4.71 (m, 1H), 5.91 (d, 1H), 7.23 (dd, 1H), 7.42 (d, 1H), 7.67 (s, 1H), 7.97 (s, 1H), 8.47 (d, 1H); MS m/z 522 $[M+H]^+$.

Ejemplo 235:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

Una solución de HATU (221 mg, 0.55 mmol) en DMA (10 mL) fue añadida a una mezcla del ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 242; 220 mg, 0.5 mmol), DIPEA(261 uL, 1.5 mmol) y 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 72 mg, 0.62 mmol) en DMA (10 mL). La mezcla resultante fue agitada a temperatura ambiente durante 2 horas, luego parcialmente purificada por SCX. El compuesto fue recuperado de la columna SCX usando amoniaco 7N en metanol, luego concentrado al vacío, y purificado adicionalmente por cromatografía en columna, eluyendo con 0–10% amoniaco (7N en metanol) en DCM. El material puro fue recuperado como un aceite naranja, el cual se hizo una espuma y se solidificó bajo alto vacío. La trituración bajo éter dio el compuesto del título como un sólido amorfo amarillo pálido (154 mg, 58%).

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.22 (6H, s), 1.56 – 1.63 (2H, m), 1.72 – 1.93 (6H, m), 1.99 – 2.03 (2H, m), 2.14 (2H, d), 2.41 – 2.45 (2H, m), 2.48 (3H, s), 3.06 – 3.09 (2H, m), 3.32 (3H, s), 3.40 (2H, s), 4.00 (3H, s), 4.10 – 4.14 (1H, m), 5.29 – 5.38 (1H, m), 6.12 (1H, d), 7.28 (1H, dd), 7.44 (1H, d), 7.65 (1H, s), 7.88 (1H, s), 8.52 (1H, d); MS m/z 536 $[M+H]^+$.

Ejemplo 236: Ejemplo 237:

4–[[(4S)–2–ciclopentil–4–etil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il]amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

y

4-[[(4R)-2-ciclopentil-4-etil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-10-il]amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

10-cloro-2-ciclopentil-4-etil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 123; 186 mg, 0.6 mmol), 4-amino-3-metoxi-N-(1-metil-4-piperidil)benzamida (WO06/018220; 159 mg, 0.6 mmol) fueron combinados con ácido p-toluenosulfónico monohidrato (286 mg, 1.5 mmol) en 4-metil-2-pentanol (01 mL) y a 115°C toda la noche. La mezcla enfriada de reacción fue disuelta en metanol, pasada a través de una columna SCX-2 y lavada con metanol. El producto fue eluido con metanol/amoniaco 7N. Las fracciones que contienen el producto fueron evaporadas y el material resultante fue purificado usando HPLC en fase inversa modificada base para dar una mezcla de los compuestos del título como una espuma marrón (110 mg).

Los enantiómeros individuales fueron separados por cromatografía en columna quiral como espumas blancas.

Enantiómero 1 (26 mg)

^{1}H NMR (399.9 MHz, DMSO-d6) : δ_H : 0.89 (tr, 3H), 1.31 (m, 2H), 1.50-1.90 (m, 12H), 2.11 (m, 2H), 2.36 (m, 5H), 2.61 (m, 1H), 3.00 (m, 2H), 3.21 (s, 3H), 3.42 (m, 2H), 3.84 (m, 1H), 3.97 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.77 (m, 1H), 8.12 (m, 2H), 8.39 (d, 1H); MS m/z 536 $[M+H]^+$.

Enantiómero 2 (26 mg)

^{1}H NMR (399.9 MHz, DMSO-d6) : δ_H : 0.89 (tr, 3H), 1.31 (m, 2H), 1.50-1.90 (m, 12H), 2.11 (m, 2H), 2.36 (m, 5H), 2.61 (m, 1H), 3.00 (m, 2H), 3.21 (s, 3H), 3.42 (m, 2H), 3.84 (m, 1H), 3.97 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.77 (m, 1H), 8.12 (m, 2H), 8.39 (d, 1H).; MS m/z 536 $[M+H]^+$.

Ejemplo 238: Ejemplo 239:

4-[[(4S)-2-ciclopentil-6-metil-5-oxo-4-propil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-10-il]amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

y

4-[[(4R)-2-ciclopentil-6-metil-5-oxo-4-propil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-10-il]amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

10–cloro–2–ciclopentil–6–metil–4–propil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 124; 194 mg, 0.6 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 159 mg, 0.6 mmol) fueron combinados con ácido p–toluenosulfónico monohidrato (286 mg, 1.5 mmol) en 4–metil–2–pentanol (01 mL) y a 115°C toda la noche. La mezcla de reacción enfriada fue disuelta en metanol, pasada a través de una columna SCX–2 y lavada con metanol. El producto fue eluido con metanol/amoniaco 7N. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado usando HPLC prep básica para dar una mezcla de los compuestos del título como una espuma marrón claro (65 mg).

Los enantiómeros individuales fueron separados por cromatografía en columna quiral como espumas blancas.

Enantiómero 1 (15 mg)

^{1}H NMR (399.9 MHz, DMSO–d6) : δ 0.84 (tr, 3H), 1.29 (m, 3H), 1.50–1.90 (m, 13H), 2.11 (m, 2H), 2.41 (m, 5H), 2.69 (m, 1H), 3.02 (m, 2H), 3.20 (s, 3H), 3.40 (m, 2H), 3.85 (m, 1H), 3.95 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.76 (m, 1H), 8.12 (s, 1H), 8.14 (d, 1H), 8.40 (d, 1H); MS m/z 550 $[M+H]^+$.

Enantiómero 2 (22 mg)

^{1}H NMR (399.9 MHz, DMSO–d6) : δ 0.84 (tr, 3H), 1.29 (m, 3H), 1.50–1.90 (m, 13H), 2.11 (m, 2H), 2.41 (m, 5H), 2.69 (m, 1H), 3.02 (m, 2H), 3.20 (s, 3H), 3.40 (m, 2H), 3.85 (m, 1H), 3.95 (s, 3H), 4.79 (tr, 1H), 7.50 (m, 2H), 7.76 (m, 1H), 8.12 (s, 1H), 8.14 (d, 1H), 8.40 (d, 1H); MS m/z 550 $[M+H]^+$.

Ejemplo 240: Ejemplo 241:

4–[[(4S)–2–ciclopentil–4,6–dimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il]amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

y

4–[[(4R)–2–ciclopentil–4,6–dimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il]amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclopentil–4,6–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 125; 674 mg, 2.29 mmol), 4–amino–3–metoxi–N–(1–metil–4–

piperidil)benzamida (WO06/018220; 602 mg, 2.29 mmol) y ácido p–toluenosulfónico (1.09 g, 0.89 mmol) fueron disueltos en 4–metil–2–pentanol (15 mL) y refluidos bajo una manta de nitrógeno durante 24 horas. La mezcla de reacción fue enfriada y pasada a través de una columna SCX–2 lavada con metanol. El producto crudo fue eluido con amoniaco 7N en metanol. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por cromatografía en columna, eluyendo con 0–10% amoniaco metanol (7N) en DCM. El material resultante fue purificado por HPLC en fase inversa modificada base para dar una mezcla de los compuestos del título como un sólido blanco (480 mg, 40%).

Los enantiómeros individuales fueron separados por cromatografía en columna quiral como gomas blancas las cuales fueron disueltas separadamente en DCM luego pasadas a través de columnas SCX–2 y lavadas con metanol. Los productos fueron eluidos fuera de las columnas usando amoniaco 7N en metanol y concentrados bajo presión reducida para proporcionar los enantiómeros como sólidos blancos.

Enantiómero 1 (118 mg)

^{1}H NMR (399.902 MHz, DMSO–d6) δ 1.04 (d, 3H), 1.51 – 1.84 (m, 12H), 1.99 – 2.13 (m, 3H), 2.81 – 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quinteto, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 523 $[M+H]^+$.

Enantiómero 2 (59 mg)

^{1}H NMR (399.902 MHz, DMSO–d6) δ 1.04 (d, 3H), 1.51 – 1.84 (m, 12H), 1.99 – 2.13 (m, 3H), 2.81 – 2.91 (m, 6H), 3.20 (s, 3H), 3.45 (q, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 4.08 (s, 1H), 4.75 (quinteto, 1H), 7.49 (d, 1H), 7.75 (s, 1H), 8.09 (d, 1H), 8.40 (d, 1H); MS m/z 523 $[M+H]^+$.

Ejemplo 242:

Ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico

A una solución de 10–cloro–2–ciclopentil–4,4,6–trimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 126; 616 mg, 2. 0 mmol) y ácido 4–amino–3–metoxibenzoico (378 mg, 2.2 mmol) en etanol (5 mL) fue añadida agua (15 mL) y ácido clorhídrico concentrado (0.335 mL). La mezcla fue calentada bajo

reflujo durante 36 horas. La reacción fue enfriada y un sólido marrón precipitado. Esto fue filtrado, secado y triturado bajo acetonitrilo frío y luego secado al vacío para dar el producto como un sólido marrón pálido (420 mg, 48%).

^{1}H NMR (400.13 MHz, DMSO–d_6) δ 1.15 (6H, s), 1.55 – 1.90 (8H, m), 3.19 (3H, s), 3.53 (2H, s), 3.95 (3H, s), 5.07 – 5.16 (1H, m), 7.59 – 7.61 (2H, m), 8.11 (1H, s), 8.13 (1H, d), 9.53 (1H, s); MS m/z 440 $[M+H]^+$.

Ejemplo 243:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(1–metil–3–piperidil)benzamida

Una solución de HATU (126 mg, 0.33 mmol) en DMA (5 mL) fue añadido a una mezcla del ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 242 132 mg, 0.3 mmol), DIPEA (261 uL, 1.5 mmol) y 3–amino N–metilpiperidina dihidrocloruro (71 mg, 0.375 mmol) en DMA (5 mL). La mezcla resultante fue agitada a temperatura ambiente durante 2 horas, luego parcialmente purificada por SCX. El compuesto fue eluido de la columna SCX usando amoniaco 7N en metanol, luego concentrado al vacío, y purificado adicionalmente por cromatografía en columna, eluyendo con 0–10% amoniaco (7N en metanol) en DCM. El material puro fue recuperado como un aceite naranja, el cual se hizo una espuma y se solidificó bajo alto vacío. La trituración bajo éter dio el compuesto del título como un sólido amorfo amarillo pálido (65 mg, 41%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.03 (6H, s), 1.34 – 1.87 (12H, m), 2.17 (5H, s), 2.41 (2H, s), 3.13 (3H, s), 3.20 (2H, s), 3.82 (3H, s), 4.19 (1H, s), 5.10 – 5.20 (1H, m), 7.09 (1H, s), 7.20 (1H, s), 7.34 (1H, s), 7.43 (1H, s), 7.68 (1H, s), 8.31 (1H, d); MS m/z 536 $[M+H]^+$.

Ejemplo 244:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–[1–(2–metoxietil)–4–piperidil]benzamida

Una solución de HATU (126 mg, 0.33 mmol) en DMA (5 mL) fue añadida a una mezcla de ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Ejemplo 242 132 mg, 0.3 mmol), DIPEA (261 uL,

1.5 mmol) y 4–amino N–(2–metoxietil)piperidina (60 mg, 0.375) en DMA (5 mL). La mezcla resultante fue agitada a temperatura ambiente durante 2 horas, luego parcialmente purificada por SCX. El compuesto fue recuperado de la columna SCX usando amoniaco 7N en metanol, luego concentrado al vacío, y purificado adicionalmente por cromatografía en columna, eluyendo con 0–10% amoniaco (7N en metanol) en DCM. El material puro fue recuperado como un aceite naranja, el cual se hizo una espuma y se solidificó bajo alto vacío. La trituración bajo éter dio un sólido amorfo amarillo pálido (55 mg, 32%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.13 (6H, s), 1.43 – 1.56 (2H, m), 1.58 – 1.74 (4H, m), 1.87 – 1.97 (4H, m), 2.04 (2H, d), 2.44 (2H, t), 2.76 (2H, t), 3.10 – 3.12 (2H, m), 3.23 (3H, s), 3.29 – 3.30 (2H, m), 3.30 (3H, s), 3.59 – 3.62 (2H, m), 3.90 (2H, s), 4.03 – 4.07 (1H, m), 5.20 – 5.28 (1H, m), 6.04 (1H, d), 7.17 – 7.20 (2H, m), 7.34 (1H, d), 7.55 (1H, s), 7.79 (1H, s), 8.42 (1H, d). MS m/z 580 $[M+H]^+$.

Ejemplo 245:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–metil–4–piperidil)benzamida

Una solución de HATU (126 mg, 0.33 mmol) en DMA (5 mL) fue añadida a una mezcla de ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzoico, (Producto intermedio 129; 123 mg, 0.3 mmol) DIPEA (261 uL, 1.5 mmol) y 4–amino N–metilpiperidina (43 mg, 0.375) en DMA (5 mL). La mezcla resultante fue agitada a temperatura ambiente durante 2 horas, luego parcialmente purificada por SCX. El compuesto fue eluido de la columna SCX usando amoniaco 7N en metanol, luego concentrado al vacío, y purificado adicionalmente por cromatografía en columna, eluyendo con 0–10% amoniaco (7N en metanol) en DCM. El material puro fue recuperado como un aceite naranja, el cual se hizo una espuma y se solidificó bajo alto vacío. La trituración bajo éter dio un sólido amorfo amarillo pálido (100 mg, 66%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.13 (6H, s), 1.43 – 1.53 (2H, m), 1.60 – 1.73 (4H, m), 1.83 – 1.95 (4H, m), 2.01 – 2.09 (2H, m), 2.37 – 2.42 (2H, m), 2.44 (3H, s), 3.06 (2H, d), 3.22 (3H, s), 3.30 (2H, s), 4.01 – 4.07 (1H, m), 5.16 – 5.25 (1H, m), 6.07 (1H, d), 6.99 (1H, s), 7.58 (2H, d), 7.65 (2H, d), 7.77 (1H, s); MS m/z 506 $[M+H]^+$.

Ejemplo 246:

4-(9'-ciclopentil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-N-(1-metilpiperidin-4-il)-3-metoxibenzamida

2'-cloro-9'-ciclopentil-5'-metil-8',9'-dihidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepin]-6'(5'H)-ona (Producto intermedio 130; 153 mg, 0.5 mmol) 4-amino-3-metoxi-N-(1-metil-4-piperidil)benzamida (WO06/018220; 158 mg, 0.6 mmol) fueron combinados con ácido p-toluenosulfónico monohidrato (190 mg, 1.0 mmol) en 4-metil-2-pentanol (4 mL) mezclado y calentado por irradiación de microondas a 160°C durante 1 hora, limpiado parcialmente por SCX, luego purificado por cromatografía en columna, eluyendo con 0-6% amoniaco metanólico en DCM, para dar el producto como un aceite claro, el cual se solidificó en trituración con éter para dar el compuesto del título como un sólido blanco (160 mg, 60%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.61 – 0.64 (2H, m), 1.09 – 1.12 (2H, m), 1.42 – 1.52 (2H, m), 1.61 – 1.76 (6H, m), 1.98 – 2.11 (4H, m), 2.23 (2H, t), 2.35 (3H, s), 2.89 (2H, d), 3.30 (3H, s), 3.47 (2H, s), 3.99 (3H, s), 3.99 – 4.10 (1H, m), 4.93 – 4.99 (1H, m), 5.99 (1H, d), 7.26 (1H, dd), 7.43 (1H, d), 7.65 (1H, s), 7.87 (1H, s), 8.53 (1H, d)MS m/z 534 $[M+H]^+$.

Ejemplo 247:

3-cloro-N-(2-morfolin-4-iletil)-4-[(3-oxo-6-fenil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-9-il)amino]benzamida

4-amino-3-cloro-N-(2-morfolin-4-iletil)benzamida (Producto intermedio 104; 104mg, 0.36mmol), 10-cloro-2-fenil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 52; 100 mg, 0.36 mmol) y ácido p-toluenosulfónico monohidrato (174 mg, 0.91mmol) fueron calentados a 140°C en 4-metil-2-pentanol (2.5ml) durante 4.5 h. La mezcla de reacción fue enfriada y absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Despues de la concentración de las fracciones que contienen el producto fue añadido metanol al residuo y la suspensión filtrada para dar el compuesto del título como un sólido blanco color hueso (42 mg, 22%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 2.41 – 2.47 (6H, m), 2.89 (2H, m), 3.36 (2H, t), 3.59 (4H, m), 4.01 – 4.03 (2H, m), 7.19 – 7.22 (1H, m), 7.36 – 7.43 (3H, m), 7.51 – 7.55 (3H, m), 7.69 (1H, s), 7.83 (1H, d), 7.97 (1H, s), 8.27 (1H, t), 9.66 (1H, s); MS m/z 522 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 255 utilizando 4–amino–3–cloro–N–(1–metil–4–piperidil)benzamida Producto intermedio 55 para dar el compuesto del título como un sólido blanco (31 mg, 17%).

Ejemplo 248:

3–cloro–N–(1–metil–4–piperidil)–4–[(3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]benzamida

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.54 – 1.58 (2H, m), 1.74 (2H, d), 1.91 – 1.97 (2H, m), 2.17 (3H, s), 2.74 – 2.79 (2H, m), 2.89 (2H, m), 3.64 – 3.74 (1H, m), 4.00 – 4.03 (2H, m), 7.20 – 7.23 (1H, m), 7.35 – 7.41 (3H, m), 7.53 (3H, d), 7.68 (1H, s), 7.87 (1H, d), 7.96 (1H, s), 8.10 (1H, d), 9.65 (1H, s); MS m/z 506 $[M+H]^+$.

Ejemplo 249:

N–(2–morfolin–4–iletil)–4–[(3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–9–il)amino]benzamida

4–amino–N–(2–morfolin–4–iletil)benzamida (Buttpark; 188mg, 0.75mmol) y 10–cloro–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 104; 160mg, 0.63mmol) fueron calentados juntos en EtOH:agua (8ml, 1:3) en presencia de ácido clorhídrico concentrado (126ul) durante 24 horas. La mezcla fue enfriada a temperatura ambiente y luego cargada en una columna SCX–2 (5g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y el solvente evaporado para dar producto como una goma marrón, el cual fue purificado por HPLC en fase inversa modificada, base para proporcionar el compuesto del título como un sólido blanco (35 mg , 13%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 2.43 (m, 4H), 2.88 (m, 3H), 3.34 (m, 2H), 3.59 (m, 4H), 3.99 (m, 3H), 7.18 (d, 2H), 7.38 (m, 5H), 7.53 (t, 2H), 7.93 (s, 1H), 8.00 (m, 1H), 9.28 (s, 1H), 9.57 (s, 1H); MS m/z 488 $[M+H]^+$.

Ejemplo 250:

4–[(6–ciclopentil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(2–morfolin–4–iletil)benzamida

4–amino–3–metoxi–N–(2–morfolin–4–iletil)benzamida (Producto intermedio 135 176 mg, 0.75 mmol) y 10–cloro–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 2 168 mg, 0.63mmol) fueron calentados juntos en EtOH:agua (8ml, 1:3) en presencia de ácido clorhídrico concentrado(126ul) durante 24 horas. La mezcla fue enfriada a temperatura ambiente y luego cargada en una columna SCX–2 (5g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y el solvente evaporado para dar el producto como una goma marrón, el cual fue purificado por HPLC en fase inversa modificada, base para proporcionar el compuesto del título como un sólido blanco (154 mg, 54%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.73 (m, 8H), 2.45 (m, 6H), 2.62 (m, 2H), 3.39 (m, 4H), 3.58 (m, 6H), 3.94 (s, 3H), 5.09 (m, 1H), 7.46 (m, 2H), 7.60 (s, 1H), 7.80 (s, 1H), 8.25 (t, 1H), 8.38 (d, 1H), 9.41 (s, 1H); MS m/z 510 $[M+H]^+$.

Ejemplo 251:

3–metoxi–N–(1–metil–4–piperidil)–4–[(3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]benzamida

4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 173 mg, 0.66 mmol) y 10–cloro–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 104; 150mg, 0.55mmol) fueron calentados juntos en EtOH:agua (8 mL, 1:3) en presencia de ácido clorhídrico concentrado(110 ul) durante 24 horas. Ácido p–toluenosulfónico monohidrato (105 mg, 0.55 mmol) fue añadido y la mezcla calentada a 150 grados durante 3h por irradiación de microondas. La mezcla fue enfriada a temperatura ambiente y cargada en una Columna SCX–2 (5 g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y los solventes evaporados para dar una goma marrón la cual fue purificada por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido blanco (73 mg, 27%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.57 (m, 2H), 1.75 (m, 2H), 1.93 (m, 2H), 2.17 (s, 3H), 2.84 (m, 4H), 3.70 (m, 1H), 3.87 (s, 3H), 4.01 (m, 2H), 6.91 (d, 1H), 7.39 (m, 6H), 7.53 (m, 2H), 7.93 (s, 1H), 7.95 (s, 1H), 9.60 (s, 1H); MS m/z 502 $[M+H]^+$.

Ejemplo 252:

N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–4–[(3–oxo–6–fenil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]benzamida

4–amino–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida (Producto intermedio 22; 183mg, 0.66mmol) y 10–cloro–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 104; 150 mg, 0.55 mmol) fueron calentados juntos en EtOH:agua (8 mL, 1:3) en presencia de ácido clorhídrico concentrado(110ul) durante 24 horas. IPA/DMA fue añadido para ayudar a la solución seguido por ácido p–toluenosulfónico monohidrato (52mg, 0.27mmol) y la mezcla calentada por irradiación de microondas durante 1 hora a 150°C. La mezcla fue enfriada a temperatura ambiente y cargada en una columna SCX–2 (5g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y el solvente evaporado para dar producto como una goma marrón la cual fue purificada por HPLC en fase inversa modificada base para proporcionar el compuesto del título como una goma (13 mg, 5%).

ES+518 (M+H), ES– 516 (M–H). Tiempo de retención 2.18 minutos.

Ejemplo 253:

4–[(6–ciclopentil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(3–dimetilamino–2,2–dimetil–propil)benzamida

4–amino–N–(3–dimetilamino–2,2–dimetil–propil)benzamida (Producto intermedio 136; 113mg, 0.45mmol) y 10–cloro–2–ciclopentil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 2; 120mg, 0.45mmol) fueron calentados juntos en EtOH:agua (8ml, 1:3) en presencia de ácido 4–toluenosulfónico (214mg, 1.13mmol) durante 23 horas. La mezcla de reacción fue calentada por irradiación de microondas a 150°C durante 20 minutos enfriada a temperatura ambiente y cargada en una columna SCX–2 (5g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y el solvente

evaporado para dar producto como una goma, la cual fue purificada por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido blanco (77 mg, 36%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.88 (s, 6H), 1.61 (m, 4H), 1.74 (m, 2H), 1.90 (m, 2H), 2.19 (s, 2H), 2.27 (s, 6H), 2.61 (m, 2H), 3.18 (d, 2H), 3.57 (m, 2H), 5.14 (m, 1H), 7.69 (d, 2H), 7.78 (d, 2H), 7.79 (s, 1H), 8.30 (t, 1H), 9.31 (s, 1H), 9.38 (s, 1H); MS m/z 480 $[M+H]^+$.

Ejemplo 254:

4–[(6–ciclopentil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)benzamida

4–amino–N–(1–metil–4–piperidil)benzamida (Producto intermedio 4; 131mg, 0.56mmol) y 10–cloro–2–ciclopentil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 2; 150mg, 0.56mmol) fueron calentados juntos en 4–metil–2–pentanol (4ml) en presencia de ácido p–toluenosulfónico (266mg, 1.40mmol) durante 24 horas. La mezcla fue enfriada a temperatura ambiente y luego cargada en una columna SCX–2 (5g) prehumedecida con metanol. El producto fue eluido con NH_3 2M/MeOH y el solvente evaporado para dar producto crudo, el cual fue purificado por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido blanco (56 mg, 22%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.58 (m, 6H), 1.75 (m, 4H), 1.92 (m, 4H), 2.17 (s, 3H), 2.61 (m, 2H), 2.77 (m, 2H), 3.57 (m, 2H), 3.72 (m, 1H), 5.14 (m, 1H), 7.75 (m, 4H), 7.79 (s, 1H), 7.95 (d, 1H), 9.29 (s, 1H), 9.38 (s, 1H); MS m/z 464 $[M+H]^+$.

Ejemplo 255:

3–cloro–4–[(6–ciclopentil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(3–dimetilamino–2,2–dimetil–propil)benzamida

4–amino–3–cloro–N–(3–dimetilamino–2,2–dimetil–propil)benzamida (Producto intermedio 107; 118mg, 0.37mmol), 10–cloro–2–ciclopentil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 2; 100mg, 0.37mmol) y ácido p–toluenosulfónico monohidrato (179mg, 0.94mmol) fueron calentados a 140°C en 4–metil–2–pentanol durante

2h. La LC–MS indicó que la reacción no había llegado al completamiento con ~50% del producto en la mezcla. Una columna SCX–3 fue lavada con metanol luego la solución fue cargada en ella. La columna fue lavada con metanol y eluida con metanol/amoniaco 7N para dar el producto crudo. La mezcla fue concentrada el material resultante purificado por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido blanco raro (24mg, 12.6%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.89 (6H, s), 1.56 (4H, m), 1.71 (2H, s), 1.83 – 1.85 (2H, m), 2.18 (2H, s), 2.27 (6H, s), 2.62 (2H, t), 3.18 – 3.20 (2H, s), 3.57 (2H, t), 5.03 (1H, m), 7.73 – 7.76 (1H, m), 7.80 (1H, s), 7.94 (1H, d), 8.03 (1H, s), 8.28 (1H, d), 8.46 (1H, s), 9.44 (1H, s); MS m/z 514 $[M+H]^+$.

Ejemplo 256:

4–[(6–ciclopentil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(2–morfolin–4–iletil)benzamida

10–cloro–2–ciclopentil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 2; 150mg, 0.56mmol), 4–amino–N–(2–morfolin–4–iletil)benzamida (Buttpark ; 141mg, 0.56mmol) y ácido p–toluenosulfónico monohidrato (268mg, 1.41mmol) fueron calentados en 4–metil–2–pentanol (4 mL) durante 2 horas a 140°C. La mezcla de reacción fue cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol y metanol/amoniaco 7N para eluir el producto crudo. Las fracciones que contienen el producto fueron evaporadas, disueltas en DMF y purificadas por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido blanco (77 mg, 28.5%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.62 (2H, m), 1.67 (2H, m), 1.76 (2H, m), 1.91 (2H, m), 2.43 – 2.46 (6H, m), 2.62 (2H, t), 3.38 (2H, q), 3.58 (6H, t), 5.12 – 5.16 (1H, m), 7.74 – 7.77 (3H, m), 7.77 (2H, d), 8.15 (1H, t), 9.33 (1H, s), 9.40 (1H, s); MS m/z 481 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 256 utilizando 4–amino–3–cloro–N–(2–morfolin–4–iletil)benzamida Producto intermedio 50 para dar el compuesto del título como un sólido amarillo (44 mg, 15%).

Ejemplo 257:

3-cloro-4-[(6-ciclopentil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(2-morfolin-4-iletil)benzamida

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.57 (4H, d), 1.68 – 1.72 (2H, m), 1.85 (2H, s), 2.43 (6H, m), 2.62 (2H, t), 3.39 (2H, q), 3.58 (6H, t), 5.03 (1H, m), 7.78 (2H, t), 7.95 (1H, d), 8.00 (1H, s), 8.30 (1H, d), 8.39 (1H, t), 9.44 (1H, s); MS m/z 515 $[M+H]^+$.

Ejemplo 258:

3-metoxi-4-[[6-(1-metoxipropan-2-il)-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-9-il]amino]-N-(1-metil-4-piperidil)benzamida

10-cloro-2-(1-metoxipropan-2-il)-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 137; 35 mg, 0.13 mmol)), 4-amino-3-metoxi-N-(1-metil-4-piperidil)benzamida (WO06/018220; 34 mg, 0.13 mmol) y ácido p-toluenosulfónico monohidrato (61 mg, 0.32 mmol) fueron disueltos en 4-metil-2-pentanol (2 mL) y calentados a 100 °C durante 18 h. La mezcla de reacción fue enfriada a temperatura ambiente disuelta en MeOH y añadida a una columna SCX-2 de 2g prehumedecida con MeOH (2 volúmenes de columna). Purgada con MeOH (2 volúmenes de columna) y el producto eluido con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido color crema (13 mg, 20%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.29 (d, 3H), 1.61 (m, 2H), 2.06 (m, 2H), 2.18 (m, 2H), 2.31 (s, 3H), 2.77 (m, 2H), 2.84 (m, 2H), 3.36 (s, 3H), 3.54 (m, 2H), 3.68 (m, 2H), 3.97 (s, 3H), 4.00 (m, 1H), 5.27 (m, 1H), 5.90 (d, 1H), 6.94 (s, 1H), 7.23 (m, 1H), 7.42 (d, 1H), 7.60 (s, 1H), 7.70 (s, 1H), 8.43 (d, 1H); MS m/z 498 $[M+H]^+$.

Ejemplo 259:

4-[(6-ciclopentil-2-etil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

10-cloro-2-ciclopentil-6-etil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 139; 221 mg, 0.75 mmol), 4-amino-3-metoxi-N-(1-metil-4-piperidil)benzamida (WO06/018220; 198 mg, 0.75 mmol) y ácido p-toluenosulfónico (357

mg, 1.88 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140 °C durante 18 horas. La mezcla de reacción se dejó enfriar a temperatura ambiente y cargada en un cartucho SCX–2 de 10 g, lavando con metanol (10 mL), agua (10 mL) y metanol (10 mL) antes que el producto fuera eluido con amoniaco metanólico 7 N para proporcionar un aceite amarillo con la evaporación de las fracciones que contienen el producto. El material resultante fue purificado por cromatografía flash en sílice, 0–10% amoniaco metanólico/DCM para dar un vidrio amarillo pálido el cual fue purificado por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido blanco (192 mg, 0.36 mmol, 49%). ^{1}H NMR (399.902 MHz, DMSO–d_6) δ 1.00 (t, 3H), 1.55 – 1.82 (m, 12H), 1.91 – 1.98 (m, 4H), 2.18 (s, 3H), 2.79 (d, 2H), 3.60 – 3.63 (m, 2H), 3.69 – 3.79 (m, 3H), 3.96 (s, 3H), 4.74 (quinteto, 1H), 7.48 – 7.51 (m, 2H), 7.77 (s, 1H), 8.08 (d, 1H), 8.13 (s, 1H), 8.39 (d, 1H); MS m/z 523 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 259 utilizando 10–cloro–2–ciclopentil–6–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 142 para dar el compuesto del título como un sólido blanco (77 mg, 14%).

Ejemplo 260:

4–[(6–ciclopentil–3–oxo–2–propan–2–il–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

^{1}H NMR (399.902 MHz, DMSO–d_6) δ 1.14 (d, 6H), 1.54 – 1.81 (m, 12H), 1.92 – 1.98 (m, 4H), 2.18 (s, 3H), 2.79 (br d, 2H), 3.56 – 3.59 (m, 2H), 3.70 – 3.80 (m, 1H), 3.96 (s, 3H), 4.40 (septeto, 1H), 4.63 (quinteto, 1H), 7.48 – 7.51 (m, 2H), 7.80 (s, 1H), 8.03 (s, 1H), 8.08 (d, 1H), 8.40 (d, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 261:

2–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)1,3–tiazol–4–carboxamida

10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 150 mg, 0.53 mmol), 2–amino–N–(1–metil–4–piperidil)–1,3–tiazol–4–carboxamida (Producto intermedio 145; 123 mg, 0.48 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (26 mg, 0.04 mmol) fueron disueltos en 1,4–dioxano (4.5 mL) carbonato de cesio (315 mg, 0.97 mmol) fue añadido y la mezcla purgada con una corriente de nitrógeno durante 5 minutos. Tris(dibencilidenoacetona) paladio (II) (27mg, 0.03 mmol) fue añadido y el aparato fue evacuado y llenado nuevamente tres veces con nitrógeno y luego calentado a 100°C toda la noche. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, lavado con metanol y el producto eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase inversa preparativa para dar el compuesto del título como un sólido marrón pálido (80 mg, 34%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.49 – 1.83 (10H, m), 1.99 – 2.05 (4H, m), 2.18 (3H, s), 2.61 (2H, t), 2.67 – 2.75 (2H, m), 3.19 (3H, s), 3.64 – 3.72 (3H, m), 5.00 (1H, m), 7.48 (1H, d), 7.66 (1H, s), 8.14 (1H, s), 11.28 (1H, s); MS m/z 485 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 261 utilizando 2–amino–4–metil–N–(1–metil–4–piperidil)–1,3–tiazol–5–carboxamida Producto intermedio 146. Un sólido que precipitó de las fracciones básicas de la columna SCX fue filtrado. El filtrado fue concentrado y metanol añadido al residuo dando material precipitado adicional, el cual fue filtrado y combinado con el precipitado original para dar el compuesto del título como un sólido blanco (95mg, 40%).

Ejemplo 262:

2–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–4–metil–N–(1–metil–4–piperidil)1,3–tiazol–5–carboxamida

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.50 – 1.76 (10H, m), 1.90 – 2.03 (4H, m), 2.16 (3H, s), 2.43 (3H, s), 2.61 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.60 – 3.67 (3H, m), 5.07 (1H, m), 7.60 (1H, d), 8.13 (1H, s), 11.33 (1H, s);

1H NMR (399.9 MHz, DMSO–d6) +d4 AcOH δ 1.63 – 1.90 (10H, m), 1.86 – 1.92 (2H, m), 2.01 (2H, s), 2.44 (3H, s), 2.46 (3H, s), 2.61 (2H, t), 3.08 (2H, m), 3.18 (3H, s), 3.65 (2H, m), 3.78 – 3.85 (1H, m), 5.05 (1H, d), 8.12 (1H, s); MS m/z 499 $[M+H]^+$.

Ejemplo 263:

2–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)1,3–tiazol–5–carboxamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 148 mg, 0.53 mmol), 2–amino–N–(1–metil–4–piperidil)–1,3–tiazol–5–carboxamida (Producto intermedio 147; 115 mg, 0.48 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (25 mg, 0.04 mmol) fueron disueltos en 1,4–dioxano (5 mL) carbonato de cesio (312 mg, 0.96 mmol) fue añadido y la mezcla purgada con una corriente de nitrógeno durante 5 minutos. Tris(dibencilidenoacetona) paladio (II) (27mg, 0.03 mmol) fue añadido y el aparato fue evacuado y llenado nuevamente tres veces con nitrógeno y luego calentado a 100°C toda la noche. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, lavada con metanol y el producto eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase normal (5% amoniaco en metanol/DCM) para dar un sólido amarillo el cual fue suspendido en DCM, filtrado y secado en el filtro para dar el compuesto del título como un sólido blanco (48mg, 21%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.50 – 1.79 (10H, m), 1.90 – 2.04 (4H, m), 2.17 (3H, s), 2.62 (2H, t), 2.77 (2H, d), 3.19 (3H, s), 3.65 – 3.71 (3H, m), 5.09 (1H, m), 8.03 (1H, s), 8.07 (1H, d), 8.15 (1H, s), 11.45 (1H, s) ; MS m/z 485 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 263 utilizando 2–amino–N–(1–metil–4–piperidil)–1,3–oxazol–5–carboxamida Producto intermedio 148 el producto final es purificado por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido marrón pálido (25 mg, 41%).

Ejemplo 264:

2-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(1-metil-4-piperidil)1,3-oxazol-5-carboxamida

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.48 – 1.76 (10H, m), 1.85 – 1.97 (4H, m), 2.17 (3H, s), 2.56 – 2.61 (2H, m), 2.76 (2H, d), 3.18 (3H, s), 3.59 – 3.68 (3H, m), 4.79 (1H, m), 7.63 (1H, s), 8.03 (1H, d), 8.07 (1H, s), 10.64 (1H, s); MS m/z 469 $[M+H]^+$.

Ejemplo 265:

2-[(6-ciclopentil-2-metil-3-oxo-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-9-il)amino]-N-(1-metil-4-piperidil)1,3-oxazol-4-carboxamida

Ácido 2-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-1,3-oxazol-4-carboxílico (Producto intermedio 150; 85 mg, 0.23 mmol), HATU (131 mg, 0.34 mmol) y 4-amino-1-metilpiperidina (40 mg, 0.34 mmol) fueron agitados en DMF (5 mL) y DIPEA (120 µL, 0.68 mmol) añadido. La mezcla fue agitada toda la noche, absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase normal (5% amoniaco en metanol/DCM) para dar el compuesto del título como un sólido blanco (66 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.50 – 1.74 (10H, m), 1.88 – 1.98 (4H, m), 2.16 (3H, s), 2.58 (2H, t), 2.82 (2H, d), 3.18 (3H, s), 3.60 – 3.63 (2H, m), 3.66 – 3.75 (1H, m), 4.71 – 4.80 (1H, m), 7.54 (1H, d), 8.06 (1H, s), 8.26 (1H, s), 10.46 (1H, s); MS m/z 469 $[M+H]^+$.

Ejemplo 266:

9-[(6-cloropiridin-3-il)amino]-6-ciclopentil-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-3-ona

10-cloro-2-ciclopentil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 1; 157 mg, 0.56 mmol), 5-amino-2-cloropiridina (65 mg, 0.51mmol) y 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (27 mg, 0.05 mmol) fueron disueltos en 1,4-dioxano (7.5 mL). Carbonato de cesio (330 mg, 1.01 mmol) fue añadido y la mezcla purgada con una corriente de nitrógeno durante 5 minutos. Tris(dibencilidenoacetona) paladio (II) (28 mg, 0.03 mmol) fue añadido y el aparato fue evacuado y llenado nuevamente tres veces con nitrógeno y luego calentado a 100°C durante 8 h. La mezcla fue enfriada, filtrada y el filtrado

absorbido en una columna SCX, lavada con metanol y el producto eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase inversa preparativa para dar el compuesto del título como un sólido blanco (14mg, 7%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.56 – 1.74 (6H, m), 1.93 – 1.98 (2H, m), 2.57 – 2.60 (2H, m), 3.18 (3H, s), 3.61 – 3.64 (2H, m), 4.79 (1H, m), 7.40 (1H, d), 8.09 (1H, s), 8.18 – 8.20 (1H, m), 8.75 (1H, d), 9.51 (1H, s); MS m/z 373 $[M+H]^+$.

Utilizando las anilinas disponibles comercialmente apropiadas , los siguientes ejemplos fueron preparados por un proceso análogo a aquel usado en la preparación del Ejemplo 266.

Ejemplo 267:

6–ciclopentil–9–[(6–metoxipiridin–3–il)amino]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.52 – 1.73 (6H, m), 1.89 – 2.08 (2H, m), 2.53 – 2.58 (2H, m), 3.16 (3H, s), 3.58 – 3.61 (2H, m), 3.81 (3H, s), 4.69 – 4.77 (1H, m), 6.75 (1H, d), 7.98 – 8.04 (2H, m), 8.39 – 8.40 (1H, m), 9.04 (1H, s); MS m/z 369 $[M+H]^+$.

Ejemplo 268:

6–ciclopentil–2–metil–9–(piridin–4–ilamino)–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.61 – 1.78 (6H, m), 1.97 – 2.08 (2H, m), 2.59 – 2.62 (2H, m), 3.19 (3H, s), 3.63 – 3.66 (2H, m), 4.81 – 4.89 (1H, m), 7.76 – 7.78 (2H, m), 8.13 (1H, s), 8.34 (2H, d), 9.81 (1H, s) MS m/z 339 $[M+H]^+$.

Ejemplo 269:

6–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)piridina–3–carboxamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 100 mg, 0.36 mmol), 6–amino–N–(1–metil–4–piperidil)piridina–3–carboxamida (Producto intermedio 152; 76 mg, 0.32 mmol) y carbonato de cesio (211 mg,

0.65 mmol) fueron añadidos a dioxano (3 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Tris(dibencilidenoacetona)dipaladio(0) (18 mg, 0.02 mmol) y 9,9–dimetil–4,5–bis(difenilfosfino)xanteno (17 mg , 0.03mmol) fueron añadidos y la mezcla calentada a 100 °C toda la noche. La mezcla de reacción fue enfriada a temperatura ambiente filtrada y la torta del filtro lavada con DCM. El filtrado añadido a una columna SCX–2 de 5g prehumedecida con MeOH (2 volúmenes de columna). Purgado con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron evaporadas para dar una goma marrón la cual fue purificada por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido blanco (117 mg, 75%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.54 – 1.80 (m, 8H), 2.03 (m, 4H), 2.17 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.70 (m, 2H), 4.00 (m, 1H), 4.84 (m, 1H), 5.85 (d, 1H), 7.94 (s, 1H), 7.99 (s, 1H), 8.05 (m, 1H), 8.40 (d, 1H), 8.63 (m, 1H); MS m/z 479 $[M+H]^+$.

El siguiente ejemplo fue preparado por un proceso análogo a aquel usado en la preparación del Ejemplo 269 utilizando 5–amino–N–(1–metil–4–piperidil)piridina–2–carboxamida (Producto intermedio 153), para dar el compuesto del título como un sólido amarillo (104 mg, 61%).

Ejemplo 270:

5–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–N–(1–metil–4–piperidil)piridina–2–carboxamida

^{1}H NMR (399.902 MHz, CDC_{13}) δ 1.68 (m, 8H), 2.02 (m, 4H), 2.18 (m, 2H), 2.31 (s, 3H), 2.67 (m, 2H), 2.82 (m, 2H), 3.30 (s, 3H), 3.69 (m, 2H), 3.98 (m, 1H), 4.85 (m, 1H), 7.11 (s, 1H), 7.78 (d, 1H), 7.94 (s, 1H), 8.13 (d, 1H), 8.31 (m, 1H), 8.59 (d, 1H); MS m/z 479 $[M+H]^+$.

Ejemplo 271:

3–metoxi–4–[(6–metil–5–oxo–2–prop–2–inil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–metil–4–piperidil)benzamida

9–cloro–2–metil–6–prop–2–inil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–3–ona (Producto intermedio 154; 53 mg, 0.21 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 66 mg, 0.25 mmol) ácido p–toluenosulfónico monohidrato (80 mg, 0.42 mmol) e isopropanol (4 mL) fueron combinados en un tubo reactor de microondas de 10 mL y calentados por irradiación de microondas a 150 °C durante 80 minutos. La muestra fue transferida a un cartucho SCX (10 g) prehumedecido con metanol, lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como una goma blanco hueso (4 mg, 3%).

MS m/z 478 $[M+H]^+$. Tiempo de retención 1.03 minutos. Monitor Ácido.

Ejemplo 272:

3–metoxi–4–[[6–metil–2–[(4–metilpentan–2–iloxiCarbónimidoil)metil]–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il]amino]–N–(1–metil–4–piperidil)benzamida

2–(10–cloro–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–2–il)acetonitrilo (Producto intermedio 155; 97 mg, 0.39 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 124mg, 0.47mmol) y ácido p–toluenosulfónico monohidrato (148 mg, 0.78 mmol) fueron calentados juntos en 4–metil–2–pentanol (4 mL) a 100 °C durante 24 horas. La mezcla de reacción fue diluida con agua y metanol y la solución cargada en una columna SCX–2 (5 g) prehumedecida con metanol. La columna fue lavada con metanol (x2) y eluida con NH_3 2M/MeOH. Las fracciones que contienen el producto identificadas como el producto de adición del solvente y el grupo nitrilo fueron combinados y evaporados. Al residuo fue añadido 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220 62 mg, 0.24 mmol) y ácido p–toluenosulfónico monohidrato (74 mg, 0.39 mmol) y la mezcla calentada por irradiación de microondas en isopropanol (4 mL) durante 20 minutos a 150 °C. La mezcla enfriada fue cargada en una columna SCX–2 (5 g) prehumedecida con MeOH. La columna fue lavada con MeOH y eluida con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar

el compuesto del título como un sólido marrón claro (21 mg, 9%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 0.75 (m, 2H), 0.81 (d, 3H), 1.13 (d, 3H), 1.24 (m, 1H), 1.52 (m, 5H), 1.76 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.46 (m, 2H), 2.75 (m, 4H), 3.22 (s, 3H), 3.75 (m, 3H), 3.95 (s, 3H), 4.22 (s, 1H), 4.91 (m, 1H), 7.48 (m, 2H), 7.59 (s, 1H), 7.80 (s, 1H), 8.04 (d, 1H), 8.43 (d, 1H); MS m/z 582 $[M+H]^+$.

Ejemplo 273:

4-[[2-[(3,5-dimetil-1,2-oxazol-4-il)metil]-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il]amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

9-cloro-6-[(3,5-dimetil-1,2-oxazol-4-il)metil]-2-metil-2,6,8,10-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-3-ona (Producto intermedio 156; 81 mg, 0.25 mmol), 4-amino-3-metoxi-N-(1-metil-4-piperidil)benzamida (WO06/018220; 80 mg, 0.30 mmol) ácido p-toluenosulfónico monohidrato (96 mg, 0.5 mmol) e isopropanol (4 mL) fueron combinados en un tubo reactor de microondas de 10 mL y calentados por irradiación de microondas a 150 °C durante 80 minutos. La muestra fue transferida a un cartucho SCX (20 g) prehumedecido con metanol, lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como una goma blanco hueso (61 mg, 45%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.58 (2H, m), 1.76 (2H, m), 1.94 (2H, m), 2.08 (3H, s), 2.17 (3H, s), 2.36 (3H, s), 2.61 (2H, m), 2.78 (2H, m), 3.17 (3H, s), 3.53 (2H, m), 3.73 (1H, m), 3.95 (3H, s), 4.61 (2H, s), 7.49 (2H, m), 7.83 (1H, s), 8.05 (1H, d), 8.19 (1H, s), 8.35 (1H, d).

Ejemplo 274:

4-[[2-(2-fluoroetil)-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il]amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

10-cloro-2-(2-fluoroetil)-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 157; 86 mg, 0.33 mmol), 4-amino-3-metoxi-N-(1-metil-4-

piperidil)benzamida (WO06/018220; 104 mg,0.40 mmol) y ácido p–toluenosulfónico monohidrato (126 mg, 0.66 mmol) fueron calentados juntos en 4–metil–2–pentanol (4 mL) a 100 °C durante 24 horas. La mezcla de reacción fue diluida con agua y metanol y la solución cargada en una columna SCX–2 (5 g) prehumedecida con metanol. La columna fue lavada con metanol (x2) y el producto eluido con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas. El material resultante fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido amarillo (60 mg, 37%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.59 (m, 2H), 1.75 (m, 2H), 1.94 (m, 2H), 2.17 (s, 3H), 2.73 (m, 4H), 3.13 (s, 3H), 3.57 (m, 2H), 3.72 (s, 3H), 3.72 (m, 1H), 3.83 (t, 2H), 4.05 (t, 2H), 6.91 (d, 1H), 7.32 (m, 2H), 7.89 (s, 1H), 7.91 (d, 1H); MS m/z 466 $[M+H]^+$–HF.

Ejemplo 275:

N–ciclohexil–4–[[2–(2–dimetilaminoetil)–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il]amino]–3–metoxi–benzamida

10–cloro–2–(2–dimetilaminoetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 158; 84 mg, 0.30 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 90 mg, 0.36 mmol) y ácido p–toluenosulfónico monohidrato (113 mg, 0.60 mmol) fueron calentados juntos en IPA (4 mL) por irradiación de microondas a 150 °C durante 20 minutos. La mezcla de reacción fue cargada en una columna SCX–2 (5g) prehumedecida con metanol; la columna fue lavada con metanol y el producto eluido con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas. El material resultante fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (59 mg, 40%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.24 (m, 5H), 1.72 (m, 6H), 2.19 (s, 6H), 2.54 (t, 2H), 2.62 (m, 2H), 3.17 (s, 3H), 3.70 (t, 3H), 3.75 (m, 2H), 3.95 (s, 3H), 7.48 (m, 2H), 7.70 (s, 1H), 8.01 (d, 1H), 8.07 (s, 1H), 8.35 (d, 1H); MS m/z 496 $[M+H]^+$.

Ejemplo 276:

N–ciclohexil–3–metoxi–4–[[6–metil–5–oxo–2–[2–(1–piperidil)etil]–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il]amino]benzamida

10–cloro–6–metil–2–[2–(1–piperidil)etil]–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 159; 90 mg, 0.28 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 83 mg, 0.34 mmol) y ácido p–toluenosulfónico monohidrato (107 mg, 0.56 mmol) fueron calentados juntos en IPA (4 mL) por irradiación de microondas a 150 °C durante 20 minutos. La mezcla de reacción fue cargada en una columna SCX–2 (5g) prehumedecida con metanol; la columna fue lavada con metanol y el producto eluido con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas. El material resultante fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (40 mg, 27%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.15 (m, 1H), 1.34 (m, 6H), 1.47 (m, 4H), 1.72 (m, 6H), 2.35 (m, 4H), 2.54 (t, 2H), 2.62 (m, 2H), 3.17 (s, 3H), 3.69 (t, 2H), 3.74 (m, 2H), 3.94 (s, 3H), 7.49 (m, 2H), 7.69 (s, 1H), 8.01 (d, 1H), 8.06 (s, 1H), 8.33 (d, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 277:

N–ciclohexil–3–metoxi–4–[[6–metil–2–(2–morfolin–4–iletil)–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il]amino]benzamida

10–cloro–6–metil–2–(2–morfolin–4–iletil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 160; 95 mg, 0.29 mmol), –amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 86 mg, 0.35 mmol) y ácido p–toluenosulfónico monohidrato (110 mg, 0.58 mmol) fueron calentados juntos en IPA (4 mL) por irradiación de microondas a 150 °C durante 20 minutos. La mezcla de reacción fue cargada en una columna SCX–2 (5g) prehumedecida con metanol; la columna fue lavada con metanol y el producto eluido con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas. El material resultante fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (56 mg, 36%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.15 (m, 1H), 1.32 (m, 4H), 1.72 (m, 6H), 2.39 (m, 4H), 2.60 (m, 4H), 3.17 (s, 3H), 3.55 (t, 4H), 3.73 (m, 4H), 3.94 (s, 3H), 7.48 (m, 2H), 7.72 (s, 1H), 8.01 (d, 1H), 8.06 (s, 1H), 8.30 (d, H); MS m/z 538 $[M+H]^+$.

Ejemplo 278:

4–[(2–ciclopentil–4,4–dimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 127; 62 mg, 0.21 mmol) y 4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 161; 63 mg, 0.21 mmol) fueron tomados en 4–metil–2–pentanol (2 mL) y ácido p–toluenosulfónico monohidrato (81 mg, 0.42 mmol) añadido. La mezcla de reacción fue calentada a 160 °C por irradiación de microondas durante 60 minutos. La mezcla de reacción enfriada fue tratada con una mezcla de metanol y agua (5:2 v/v, 7 mL) . La solución resultante fue cargada en un cartucho SCX–3 (5 g) prehumedecido con metanol. El cartucho fue lavado completamente con metanol (~40 mL). Los productos fueron luego eluidos con amoniaco 2M en metanol (~30 mL). La solución amoniacal fue evaporada y el material resultante fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (64 mg, 54%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.90 – 0.95 (2H, m), 1.14 (6H, s), 1.41 – 1.50 (3H, m), 1.54 – 1.68 (4H, m), 1.71 – 1.78 (2H, m), 1.83 – 1.96 (4H, m), 2.01 – 2.10 (1H, m), 2.15 – 2.23 (2H, m), 2.42 (3H, s), 2.95 – 3.01 (2H, m), 3.27 – 3.28 (2H, m), 3.95 (3H, s), 4.28 – 4.39 (1H, m), 5.23 (1H, quinteto), 7.45 – 7.49 (2H, m), 7.59 (1H, s), 7.88 – 7.90 (2H, m), 8.35 (1H, d), 9.45 (1H, s); MS m/z 562 $[M+H]^+$.

Ejemplo 279:

4–(9'–ciclopentil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–fluoro–N–((1R,3r,5S)–9–metil–9–azabiciclo[3.3.1]nonan–3–il)benzamida

2'–cloro–9'–ciclopentil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[4,5–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 131; 256 mg, 0.875 mmol) y 4–amino–3–fluoro–N–

[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 162; 255 mg, 0.875 mmol) y el ácido p–toluenosulfónico monohidrato (416 mg, 2.19 mmol) y 4–Metil–2–pentanol (5 mL) fueron calentados por irradiación de microondas durante 30 minutos a 160 °C. La mezcla de reacción enfriada fue disuelta en metanol (50 mL) y cargada en un cartucho SCX–2 (20 g) prehumedecido con metanol. El cartucho fue lavado completamente con metanol (3 x 35 mL) y el producto eluido con amoniaco metanólico 7 N (~100 mL). La solución amoniacal fue evaporada y el material resultante purificado en una columna de sílice cargada como una solución en DCM (20 mL) y eluido con un ggradiente lineal de 0 a 10% 7N NH_3/MeOH en DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco después de la trituración bajo dietil éter (104 mg, 22%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.77 – 0.80 (2H, m), 0.93 – 1.00 (2H, m), 1.17 – 1.30 (4H, m), 1.34 – 1.37 (2H, m), 1.47 (1H, s), 1.62 – 1.68 (4H, m), 1.88 – 1.93 (5H, m), 2.43 (3H, s), 2.40 – 2.49 (2H, m), 3.02 (2H, d), 3.27 (2H, s), 4.37 – 4.49 (1H, m), 4.98 – 5.07 (1H, m), 5.67 (1H, d), 7.11 (1H, d), 7.20 (1H, s), 7.41 – 7.44 (1H, m), 7.45 – 7.48 (1H, m), 7.63 (1H, s), 8.46 (1H, t); MS m/z 548 $[M+H]^+$.

Ejemplo 280:

4–(9'–ciclopentil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–metoxi–N–((1R,3r,5S)–9–metil–9–azabiciclo[3.3.1]nonan–3–il)benzamida

2'–cloro–9'–ciclopentil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[4,5–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 131; 293 mg, 1.0 mmol) y 4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 161; 303 mg, 1.0 mmol) y el ácido p–toluenosulfónico monohidrato (476 mg, 2.5 mmol) y 4–Metil–2–pentanol (10 mL) fueron combinados y calentados con agitación a 120 °C toda la noche. La mezcla de reacción enfriada fue disuelta en metanol (60 mL) y cargada en un cartucho SCX–2 (20 g) prehumedecido con metanol. El cartucho fue lavado completamente con metanol (3 x 35 mL) y el producto eluido con amoniaco metanólico 7 N (~100 mL). La solución amoniacal fue evaporada y el material resultante purificado en una columna de sílice cargada como una

solución en DCM (17 mL) y eluido con un gradiente lineal de 0 a 10% 2N NH_3/MeOH en DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante triturado bajo dietil éter. El sólido filtrado resultante fue tratado con DMF caliente (3 mL) y acetonitrilo (8 mL) al calentar en un baño de hielo/agua se formó un precipitado sólido el cual fue filtrado y secado para proporcionar el compuesto del título como un sólido blanco (251 mg, 45%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.77 – 0.79 (2H, m), 0.96 (2H, d), 1.19 – 1.33 (4H, m), 1.35 – 1.37 (2H, m), 1.44 – 1.48 (1H, m), 1.60 – 1.68 (4H, m), 1.85 – 1.98 (5H, m), 2.41 – 2.50 (2H, m), 2.43 (3H, s), 3.02 (2H, d), 3.25 (2H, s), 3.90 (3H, s), 4.41 – 4.46 (1H, m), 5.00 – 5.09 (1H, m), 5.75 (1H, d), 7.16 (1H, dd), 7.36 (1H, d), 7.55 (1H, s), 7.67 (1H, s), 7.75 (1H, s), 8.39 (1H, d); MS m/z 560 $[M+H]^+$.

Ejemplo 281:

3–etoxi–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–metil–4–piperidil)benzamida

A una solución agitada de ácido 3–etoxi–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzoico (Producto intermedio 163; 80 mg, 0.20 mmol), HATU (115 mg, 0.30 mmol) y 4–amino–1–metilpiperidina (Fluorochem; 35 mg, 0.30 mmol) en DMF (5 mL) fue añadido diisopropiletilamina (105 µL, 0.60 mmol). La mezcla fue agitada durante 2 horas a temperatura ambiente y luego absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (5% amoniaco en metanol/DCM) para proporcionar el compuesto del título como una espuma blanca (87 mg, 88%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.26 (6H, d), 1.44 (3H, t), 1.55 – 1.65 (2H, m), 1.77 (2H, d), 1.92 – 1.98 (2H, m), 2.18 (3H, s), 2.60 (2H, m), 2.79 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.70 – 3.78 (1H, m), 4.21 (2H, q), 4.78 – 4.85 (1H, m), 7.49 – 7.53 (2H, m), 7.67 (1H, s), 8.05 (2H, m), 8.41 (1H, d); MS m/z 496 $[M+H]^+$.

Ejemplo 282:

3–etoxi–N–(1–etil–4–piperidil)–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 281, en una escala de 0.2 mmol, utilizando 4–amino–1–etilpiperidina (Fluorochem; 39 mg, 0.3 mmol), como una espuma blanca (67 mg, 66%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.01 (3H, t), 1.26 (6H, d), 1.44 (3H, t), 1.52 – 1.62 (2H, m), 1.77 – 1.80 (2H, m), 1.94 (2H, m), 2.34 (2H, q), 2.60 (2H, m), 2.89 (2H, d), 3.18 (3H, s), 3.62 (2H, m), 3.72 – 3.80 (1H, m), 4.21 (2H, q), 4.78 – 4.85 (1H, m), 7.48 – 7.52 (2H, m), 7.67 (1H, s), 8.05 (2H, m), 8.41 (1H, d); MS m/z 510 $[M+H]^+$.

Ejemplo 283:

3–etoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 281, en una escala de 0.2 mmol, utilizando endo–9–metil–9–azabiciclo[3,3,1]nonano–3–ona (Chempacific; 47 mg, 0.3 mmol), como una espuma blanca (71 mg, 66%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.94 (2H, d), 1.27 (6H, d), 1.41 – 1.49 (6H, m), 1.89 – 1.96 (2H, m), 2.06 (1H, m), 2.15 – 2.23 (2H, m), 2.42 (3H, s), 2.61 (2H, m), 2.99 (2H, d), 3.18 (3H, s), 3.63 (2H, m), 4.22 (2H, q), 4.30 – 4.38 (1H, m), 4.78 – 4.85 (1H, m), 7.49 – 7.53 (2H, m), 7.67 (1H, s), 7.90 (1H, d), 8.07 (1H, s), 8.42 (1H, d); MS m/z 536 $[M+H]^+$.

Ejemplo 284:

3–etoxi–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–[(3R)–1–metilpirrolidin–3–il]benzamida

10–cloro–6–metil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 10; 100 mg, 0.39mmol), 4–amino–3–etoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 166; 104 mg, 0.39 mmol) y ácido 4–toluenosulfónico monohidrato (187 mg, 0.98 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140 °C durante 3 horas. La mezcla de reacción enfriada fue absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto

fueron concentradas y purificadas por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (114 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.26 (6H, d), 1.44 (3H, t), 1.73 – 1.81 (1H, m), 2.12 – 2.20 (1H, m), 2.27 (3H, s), 2.37 – 2.46 (2H, m), 2.57 – 2.70 (4H, m), 3.18 (3H, s), 3.62 (2H, m), 4.21 (2H, q), 4.38 – 4.44 (1H, m), 4.78 – 4.85 (1H, m), 7.51 – 7.55 (2H, m), 7.67 (1H, s), 8.07 (1H, s), 8.28 (1H, d), 8.41 (1H, d); MS m/z 482 $[M+H]^+$.

Ejemplo 285:

N–(4–dimetilaminociclohexil)–3–etoxi–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 284, en una escala de 0.26 mmol, utilizando 4–amino–N–((1s,4s)–4–(dimetilamino)ciclohexil)–3–etoxibenzamida (Producto intermedio 167; 66 mg, 0.36 mmol), como un sólido blanco (39 mg, 29%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.26 (6H, d), 1.42 – 1.54 (7H, m), 1.72 – 1.80 (2H, m), 1.86 – 1.90 (2H, m), 2.99 – 2.03 (1H, m), 2.19 (6H, s), 2.60 (2H, m), 3.18 (3H, s), 3.62 (2H, m), 3.89 – 3.93 (1H, m), 4.21 (2H, q), 4.78 – 4.85 (1H, m), 7.51 – 7.56 (2H, m), 7.66 (1H, s), 8.00 (1H, d), 8.07 (1H, s), 8.41 (1H, d); MS m/z 525 $[M+H]^+$.

Ejemplo 286:

N–(4–dimetilaminociclohexil)–3–etoxi–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 284, en una escala de 0.26 mmol, utilizando 4–amino–N–((1r,4r)–4–(dimetilamino)ciclohexil)–3–etoxibenzamida (Producto intermedio 168; 66 mg, 0.26 mmol), como un sólido blanco (80 mg, 59%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.23 – 1.39 (10H, m), 1.44 (3H, t), 1.83 – 1.91 (4H, m), 2.11 – 2.19 (7H, m), 2.60 (2H, m), 3.18 (3H, s), 3.62 (2H, m), 3.71 – 3.75 (1H, m), 4.21 (2H, q), 4.78 – 4.85 (1H, m), 7.48 – 7.52 (2H, m), 7.67 (1H, s), 8.01 (1H, d), 8.07 (1H, s), 8.41 (1H, d); MS m/z 525 $[M+H]^+$.

Ejemplo 287:

5–etoxi–2–fluoro–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–metil–4–piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 284, en una escala de 0.39 mmol, utilizando 4–amino–5–etoxi–2–fluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 169; 116mg, 0.39 mmol), calentando a 140 °C durante 2 horas, como un sólido blanco (73 mg, 37%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.27 (6H, d), 1.42 (3H, t), 1.52 – 1.62 (2H, m), 1.78 (2H, d), 1.99 (2H, t), 2.17 (3H, s), 2.62 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.64 (2H, m), 3.69 – 3.79 (1H, m), 4.18 (2H, q), 4.77 – 4.84 (1H, m), 7.20 (1H, d), 7.74 (1H, d), 7.79 – 7.82 (1H, m), 8.10 (1H, s), 8.35 (1H, d); MS m/z 515 $[M+H]^+$.

Ejemplo 288:

5–etoxi–2–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 284, en una escala de 0.39 mmol, utilizando 4–amino–5–etoxi–2–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 170; 132mg, 0.39 mmol), calentando a 140 °C durante 2 horas, como un sólido blanco (92 mg, 43%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.92 (2H, d), 1.28 (6H, d), 1.39 – 1.46 (6H, m), 1.87 – 1.94 (2H, m), 1.99 – 2.10 (1H, m), 2.17 – 2.25 (2H, m), 2.42 (3H, s), 2.62 (2H, m), 2.98 (2H, d), 3.19 (3H, s), 3.64 (2H, m), 4.18 (2H, q), 4.26 – 4.34 (1H, m), 4.78 – 4.85 (1H, m), 7.22 (1H, d), 7.65 – 7.68 (1H, m), 7.75 (1H, d), 8.11 (1H, s), 8.36 (1H, d); MS m/z 555 $[M+H]^+$.

Ejemplo 289:

5–cloro–2–fluoro–N–(1–metil–4–piperidil)–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

4–amino–5–cloro–2–fluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 173; 91 mg, 0.32 mmol), 10–cloro–4,4,6–trimetil–2–propan–2–il–2,6,9,11–

tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 178; 100 mg, 0.35 mmol) y XANTFOS (17 mg, 0.03 mmol) fueron disueltos en 1,4–dioxano (7.5 mL). Carbonato de cesio (225 mg, 0.64 mmol) fue añadido y el sistema purgado con una corriente de nitrógeno durante 15 minutos antes de que tris(dibencilidenoacetona) paladio (II) (18 mg, 0.02 mmol) fue añadido. El aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y luego calentado a 100 °C durante 3 horas. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, el cual fue lavado con metanol y eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (2.5% 3.5N amoniaco en metanol/DCM) para proporcionar el compuesto del título como un sólido blanco (96mg, 56%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.12 (6H, s), 1.21 (6H, d), 1.50 – 1.60 (2H, m), 1.77 – 1.80 (2H, m), 1.93 – 2.00 (2H, m), 2.17 (3H, s), 2.74 (2H, d), 3.21 (3H, s), 3.38 (2H, s), 3.67 – 3.72 (1H, m), 5.07 – 5.14 (1H, m), 7.67 (1H, d), 8.03 – 8.08 (3H, m), 8.31 – 8.36 (1H, m); MS m/z 532 $[M+H]^+$.

Ejemplo 290:

5–cloro–N–(1–etil–4–piperidil)–2–fluoro–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 289, en una escala de 0.39 mmol, utilizando 4–amino–5–cloro–N–(1–etil–4–piperidil)–2–fluoro–benzamida (Producto intermedio 174; 96 mg, 0.32 mmol), como un sólido blanco (67 mg, 38%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.00 (3H, t), 1.12 (6H, s), 1.21 (6H, d), 1.48 – 1.58 (2H, m), 1.80 (2H, d), 1.96 (2H, t), 2.32 (2H, q), 2.84 (2H, d), 3.21 (3H, s), 3.38 (2H, s), 3.68 – 3.76 (1H, m), 5.07 – 5.14 (1H, m), 7.67 (1H, d), 8.03 – 8.07 (3H, m), 8.32 – 8.36 (1H, m); MS m/z 546 $[M+H]^+$.

Ejemplo 291:

5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 289, en una escala de 0.39 mmol, utilizando 4–amino–5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida (Producto intermedio 175; 100 mg, 0.32 mmol), como un sólido blanco (109 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.12 (6H, s), 1.17 – 1.37 (8H, m), 1.46 – 1.58 (2H, m), 1.68 – 1.94 (4H, m), 2.13 – 2.18 (7H, m), 3.20 (3H, s), 3.38 (2H, s), 3.64 – 3.71 y 3.91 – 4.95 (each 0.5H, m), 5.08 – 5.15 (1H, m), 7.62 – 7.67 (1H, m), 7.98 – 8.04 (3H, m), 8.29 – 8.34 (1H, m); MS m/z 560 $[M+H]^+$.

Ejemplo 292:

2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

10–cloro–4,4,6–trimetil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 178; 100 mg, 0.35mmol), 4–amino–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 182; 95 mg, 0.35 mmol) y ácido p–toluenosulfónico monohidrato (169 mg, 0.88 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140 °C durante 3 horas. La mezcla fue enfriada y absorbida en una columna SCX, la cual fue lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (60 mg, 33%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.12 (6H, s), 1.23 (6H, d), 1.68 – 1.76 (1H, m), 2.13 – 2.22 (1H, m), 2.27 (3H, s), 2.36 – 2.45 (2H, m), 2.59 – 2.64 (1H, m), 2.67 – 2.71 (1H, m), 3.20 (3H, s), 3.39 (2H, s), 3.93 (3H, s), 4.35 – 4.43 (1H, m), 5.09 – 5.16 (1H, m), 7.22 (1H, d), 7.75 (1H, d), 7.96 – 7.99 (1H, m), 8.03 (1H, s), 8.34 (1H, d); MS m/z 516 $[M+H]^+$.

Ejemplo 293:

3–etoxi–N–[(3R)–1–metilpirrolidin–3–il]–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 292, en un escala de 0.35 mmol, utilizando 4–amino–3–etoxi–N–[(3R)–1–metilpirrolidin–3–

il]benzamida (Producto intermedio 166; 94 mg, 0.35 mmol), como un sólido blanco (106 mg, 59%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.11 (6H, s), 1.23 (6H, d), 1.44 (3H, t), 1.74 – 1.80 (1H, m), 2.15 – 2.19 (1H, m), 2.27 (3H, s), 2.38 – 2.47 (2H, m), 2.61 – 2.71 (2H, m), 3.20 (3H, s), 3.38 (2H, s), 4.21 (2H, q), 4.39 – 4.43 (1H, m), 5.09 – 5.16 (1H, m), 7.51 – 7.54 (2H, m), 7.63 (1H, s), 7.98 (1H, s), 8.28 (1H, d), 8.38 (1H, d); MS m/z 511 $[M+H]^+$.

Ejemplo 294:

N–(4–dimetilaminociclohexil)–3–etoxi–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 292, en una escala de 0.26 mmol, utilizando 4–amino–N–((1s,4s)–4–(dimetilamino)ciclohexil)–3–etoxibenzamida (Producto intermedio 167; 80 mg, 0.26 mmol), como un sólido blanco (91 mg, 59%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.11 (6H, s), 1.23 (6H, d), 1.40 – 1.55 (7H, m), 1.72 – 1.81 (2H, m), 1.86 – 1.90 (2H, m), 2.01 – 2.05 (1H, m), 2.19 (6H, s), 3.20 (3H, s), 3.38 (2H, s), 3.88 – 3.95 (1H, m), 4.21 (2H, q), 5.09 – 5.16 (1H, m), 7.51 – 7.55 (2H, m), 7.62 (1H, s), 7.97 – 8.01 (2H, m), 8.37 (1H, d); MS m/z 553 $[M+H]^+$.

Ejemplo 295:

N–(4–dimetilaminociclohexil)–3–etoxi–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 292, en una escala de 0.26 mmol, utilizando 4–amino–N–((1r,4r)–4–(dimetilamino)ciclohexil)–3–etoxibenzamida (Producto intermedio 168; 80 mg, 0.26 mmol), como un sólido blanco (77 mg, 54%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.11 (6H, s), 1.23 (6H, d), 1.27 – 1.39 (4H, m), 1.44 (3H, t), 1.83 – 1.92 (4H, m), 2.15 – 2.21 (7H, m), 3.20 (3H, s), 3.38 (2H, s), 3.71 – 3.75 (1H, m), 4.21 (2H, q), 5.09 – 5.15 (1H, m), 7.48 – 7.51 (2H, m), 7.63 (1H, s), 7.98 – 8.02 (2H, m), 8.37 (1H, d); MS m/z 553 $[M+H]^+$.

Ejemplo 296:

5–etoxi–2–fluoro–N–(1–metil–4–piperidil)–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 292, en una escala de 0.39 mmol, utilizando 4–amino–5–etoxi–2–fluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 169; 116 mg, 0.39 mmol), como un sólido blanco (92 mg, 48%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.12 (6H, s), 1.21 – 1.24 (6H, d), 1.42 (3H, t), 1.52 – 1.62 (2H, m), 1.77 – 1.80 (2H, m), 1.94 – 2.00 (2H, m), 2.17 (3H, s), 2.69 – 2.75 (2H, m), 3.20 (3H, s), 3.39 (2H, s), 3.69 – 3.76 (1H, m), 4.18 (2H, q), 5.07 – 5.14 (1H, m), 7.20 (1H, d), 7.71 (1H, d), 7.77 – 7.80 (1H, m), 8.02 (1H, s), 8.31 (1H, d); MS m/z 543 $[M+H]^+$.

Ejemplo 297:

5–etoxi–2–fluoro–N–[(3R)–1–metilpirrolidin–3–il]–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 292, en una escala de 0.32 mmol, utilizando 4–amino–5–etoxi–2–fluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 186; 90 mg, 0.32 mmol), como una espuma blanca (61 mg, 36%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.12 (6H, s), 1.24 (6H, d), 1.42 (3H, t), 1.67 – 1.75 (1H, m), 2.13 – 2.22 (1H, m), 2.26 (3H, s), 2.34 – 2.47 (2H, m), 2.58 – 2.63 (1H, m), 2.66 – 2.70 (1H, m), 3.20 (3H, s), 3.39 (2H, s), 4.18 (2H, q), 4.34 – 4.43 (1H, m), 5.07 – 5.14 (1H, m), 7.21 (1H, d), 7.71 (1H, s), 7.95 – 7.98 (1H, m), 8.02 (1H, s), 8.31 (1H, d); MS m/z 529 $[M+H]^+$.

Ejemplo 298:

3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]benzamida

10–cloro–4,4,6–trimetil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 178; 43 mg, 0.15 mmol) y 4–amino–3–fluoro–N–(9–metil–9–azabiciclo[3.3.1]non–7–il)benzamida (Producto intermedio 162; 44 mg, 0.15 mmol) fueron

combinados con ácido p–toluenosulfónico monohidrato (72 mg, 0.38 mmol) en 4–metil–2–pentanol (1 mL) y calentado por irradiación de microondas durante 50 minutos a 160 °C. La mezcla de reacción enfriada fue diluida con metanol (5 mL) y cargada en un cartucho SCX–3 (2 g) prehumedecido con metanol. El cartucho fue lavado con metanol (2 x 3 mL) y el producto eluido con amoniaco metanólico 7 N (10 mL). La fracción básica fue evaporada para dar una goma amarilla cual fue purificada por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido blanco (46 mg, 57 %).

^{1}H NMR (400 MHz, DMSO–d6) δ 0.9 (2H, d), 1.1 (6H, s), 1.15 (6H, d), 1.45 (4H, t), 1.9 (2H, m), 2.05 (1H, m), 2.2 (3H, m), 2.4 (3H, s), 2.95 (2H, d), 3.20 (3H, s), 3.3 (2H, s), 4.3 (1H, m), 5.1 (1H, m), 7.65 (2H, m), 7.95 (2H, m), 8.15 (2H, m), 8.15 (1H, t), 8.55 (1H, s); MS m/z 539 $[M+H]^+$.

Ejemplo 299:

3–metoxi–N–[(3R)–1–metilpirrolidin–3–il]–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

10–cloro–4,4,6–trimetil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 178; 75 mg, 0.27 mmol), 4–amino–3–metoxi–N–(1–metilpirrolidin–3–il)benzamida (Producto intermedio 187; 67 mg, 0.27 mmol) y ácido p–toluenosulfónico monohidrato (127 mg, 0.66 mmol) fueron calentados a 140 °C en 4–metil–2–pentanol (4 mL) durante 2 horas. La mezcla de reacción fue cargada en una columna SCX–3 prehumedecida con metanol. La columna fue lavada con metanol y eluida con 2% metanol/amoniaco 7N. Las fracciones que contienen el producto fueron evaporadas y el residuo disuelto en DMF y purificado por HPLC en fase inversa modificada base para dar el compuesto del título como un sólido blanco (23 mg, 17.5%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.08 (6H, s), 1.22 (6H, d), 1.78 (1H, m), 2.18 (1H, m), 2.23 (3H, s), 2.38 (1H, m), 2.41 (1H, m), 2.61 (1H, m), 2.64 (1H, m), 3.18 (3H, s), 3.37 (2H, s), 3.95 (3H, s), 4.41 (1H, m), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 496 $[M+H]^+$.

Ejemplo 300:

N–(1–etil–4–piperidil)–3–metoxi–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 299, en una escala de 0.27 mmol, utilizando 4–amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida (Producto intermedio 190; 74 mg, 0.27 mmol), como un sólido blanco (31 mg, 22%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.00 (3H, t), 1.10 (6H. s), 1.22 (6H. d), 1.55 (2H, q), 1.78 (2H, d), 1.95 (2H, t), 2.31 (2H, q), 2.89 (2H, d), 3.17 (3H, s), 3.37 (2H, s), 3.75 (1H, m), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 524 $[M+H]^+$.

Ejemplo 301:

3–metoxi–N–(2–pirrolidin–1–iletil)–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 299, en una escala de 0.27 mmol, utilizando 4–amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida (Producto intermedio 192; 70 mg, 0.27 mmol), como un sólido blanco (52 mg, 38%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.10 (6H, s), 1.22 (6H, d), 1.68 (4H, m), 2.49 (4H, m), 2.60 (2H, t), 3.18 (3H, s), 3.38 (2H, s), 3.40 (2H, m), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 510 $[M+H]^+$.

Ejemplo 302:

N–(2–dimetilaminoetil)–3–metoxi–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 299, en una escala de 0.27 mmol, utilizando 4–amino–N–(2–dimetilaminoetil)–3–metoxi–benzamida (Producto intermedio 194; 63 mg, 0.27 mmol), como un sólido blanco (38 mg, 30%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.10 (6H, s), 1.22 (6H, d), 2.18 (6H, s), 2.39 (2H, t), 3.18 (3H, s), 3.35 (2H, t), 3.37 (2H, s), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 510 $[M+H]^+$.

Ejemplo 303:

N–(3–dimetilaminopropil)–3–metoxi–4–[(4,4,6–trimetil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 299, en una escala de 0.27 mmol, utilizando 4–amino–N–(2–dimetilaminoetil)–3–metoxi–benzamida (Producto intermedio 196; 67 mg, 0.27 mmol), como un sólido blanco (8 mg, 6%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.10 (6H, s), 1.22 (6H, d), 1.68 (2H, m), 2.18 (3H, s), 2.28 (2H, t), 3.17 (3H, s), 3.29 (2H, t), 3.37 (2H, s), 3.95 (3H, s), 5.16 (1H, m), 7.52 (1H, s), 7.53 (1H, dd), 7.65 (1H, s), 7.99 (1H, s), 8.29 (1H, d), 8.40 (1H, d); MS m/z 498 $[M+H]^+$.

Ejemplo 304:

4–[(4,4–dietil–6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(1–metil–4–piperidil)benzamida

10–cloro–4,4–dietil–6–metil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 198; 100 mg, 0.322 mmol), ácido p–toluenosulfónico monohidrato (153 mg, 0.81 mmol) y 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 84 mg, 0.322 mmol) fueron añadidos a 4–metil–2–pentanol (7 mL). La reacción fue calentada a 120 °C todo el fin de semana. La mezcla de reacción fue cargada en a una columna SCX (10 g), prehumedecida con metanol, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título, después de secar bajo vacío a 70 °C, como un sólido blanco (97 mg, 56%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.25 (d, 6H), 1.63 – 1.49 (m, 4H), 1.70 (sextet, 2H), 2.07 – 2.04 (m, 2H), 2.19 – 2.13 (m, 2H), 2.30 (s, 3H), 2.84 – 2.81 (m, 2H), 3.28 (s, 3H), 3.40 (s, 2H), 4.04 – 3.92 (m, 4H), 5.32 (sextet, 1H), 5.93 (d, 1H), 7.24 (dd, 1H), 7.43 (d, 1H), 7.59 (s, 1H), 7.83 (s, 1H), 8.48 (d, 1H); MS m/z 538 $[M+H]^+$.

Ejemplo 305:

4–[(4,4–dietil–6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 304, en una escala de 0.322 mmol, utilizando 4–amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida (Producto intermedio 190; 89 mg, 0.322 mmol), como un sólido blanco (89 mg, 30%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.10 (t, 3H), 1.25 (d, 6H), 1.63 – 1.49 (m, 4H), 1.75 – 1.66 (m, 2H), 2.17 – 2.06 (m, 4H), 2.44 (q, 2H), 2.93 – 2.90 (m, 2H), 3.28 (s, 3H), 3.40 (s, 2H), 4.05 – 3.97 (m, 4H), 5.32 (septeto, 1H), 5.91 (d, 1H), 7.23 (dd, 1H), 7.43 (d, 1H), 7.59 (s, 1H), 7.83 (s, 1H), 8.47 (d, 1H); MS m/z 552 $[M+H]^+$.

Ejemplo 306:

4–[(4,4–dietil–6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 304, en una escala de 0.322 mmol, utilizando 4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida (Producto intermedio 202; 97 mg, 0.322 mmol), como un sólido blanco (83 mg, 45%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.78 (t, 6H), 1.22 (d, 6H), 1.60 – 1.40 (m, 6H), 1.89 – 1.77 (m, 2H), 2.16 – 2.03 (m, 2H), 2.42 – 2.33 (m, 2H), 3.18 (s, 3H), 3.29 (s, 4H), 3.41 (s, 2H), 3.69 – 3.57 (m, 2H), 3.97 (s, 3H), 4.70 – 4.52 (m, 1H), 5.24 – 5.18 (m, 1H), 7.53 – 7.51 (m, 2H), 7.67 (s, 1H), 7.98 (s, 1H), 8.31 – 8.22 (m, 1H), 8.41 (d, 1H), 9.27 – 9.18 (m, 1H); MS m/z 578 $[M+H]^+$.

Ejemplo 307:

4–[(4,4–dietil–6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 304, en una escala de 0.322 mmol, utilizando 4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida (Producto intermedio 204; 103 mg, 0.322 mmol), como un sólido blanco (100 mg, 52%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.85 (t, 6H), 1.05 – 1.03 (m, 2H), 1.34 – 1.26 (m, 8H), 1.59 – 1.49 (m, 3H), 1.70 (sextet, 2H), 2.02 – 1.91 (m, 3H), 2.57 – 2.50 (m, 5H), 3.10 – 3.07 (m, 2H), 3.29 (s, 3H), 3.42 (s, 2H), 3.95 (s, 3H), 4.57 – 4.46 (m, 1H), 5.30 (septeto, 1H), 6.55 (dd, 1H), 7.57 (d, 1H), 7.64 (s, 1H), 7.85 (s, 1H), 8.38 (d, 1H); MS m/z 596 $[M+H]^+$.

Ejemplo 308:

4–[(4,4–dietil–6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 304, en una escala de 0.322 mmol, utilizando 4–amino–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida (Producto intermedio 205; 95 mg, 0.322 mmol), como un sólido blanco (87 mg, 48%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.85 (t, 6H), 1.10 (t, 3H), 1.27 (d, 6H), 1.75 – 1.49 (m, 6H), 2.08 – 2.06 (m, 2H), 2.20 – 2.14 (m, 2H), 2.44 (q, 2H), 2.88 – 2.85 (m, 2H), 3.29 (s, 3H), 3.42 (s, 2H), 3.95 (s, 3H), 4.10 – 4.00 (m, 1H), 5.33 – 5.26 (m, 1H), 6.68 (dd, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 7.85 (s, 1H), 8.38 (d, 1H); MS m/z 570 $[M+H]^+$.

Ejemplo 309:

4–[(4,4–dietil–6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 304, en una escala de 0.33 mmol, utilizando 4–amino–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida (Producto intermedio 206; 100 mg, 0.33 mmol), como un sólido blanco (76 mg, 40%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.01 (s, 6H), 1.24 (d, 6H), 1.53 (sextet, 2H), 1.71 (sexteto, 2H), 1.86 – 1.81 (m, 4H), 2.57 (s, 2H), 2.72 – 2.68 (m, 4H), 3.28 (s, 3H), 3.40 –

3.39 (m, 4H), 3.97 (s, 3H), 5.34 (septeto, 1H), 7.20 (dd, 1H), 7.58 (d, 1H), 7.62 (s, 1H), 7.84 (s, 1H), 8.44 (d, 1H), 9.28 (s, 1H); MS m/z 5780 $[M+H]^+$.

Ejemplo 310:

(R)–5–cloro–2–fluoro–4–(9'–isopropil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–metilpirrolidin–3–il)benzamida

2'–cloro–9'–isopropil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 208; 88 mg, 0.32mmol), 4–amino–5–cloro–2–fluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 207; 101 mg, 0.36 mmol) y XANTFOS (17 mg, 0.03 mmol) fueron disueltos en 1,4–dioxano (7.5 mL). Carbonato de cesio (229 mg, 0.65 mmol) fue añadido y el sistema purgado con una corriente de nitrógeno durante 15 minutos antes de que tris(dibencilidenoacetona) paladio (II) (18 mg, 0.02 mmol) fue añadido. El aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y luego calentado a 100 °C durante 3 horas. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, la cual fue lavada con metanol y eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (2.5% amoniaco 7N en MeOH/DCM) para proporcionar el compuesto del título como una espuma amarillo pálido (148 mg, 90%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.70 – 0.73 (2H, m), 0.94 – 0.96 (2H, m), 1.15 (6H, d), 1.67 – 1.75 (1H, m), 2.12 – 2.21 (1H, m), 2.26 (3H, s), 2.33 – 2.43 (2H, m), 2.56 – 2.62 (1H, m), 2.67 – 2.71 (1H, m), 3.19 (3H, s), 3.49 (2H, s), 4.31 – 4.40 (1H, m), 4.79 – 4.86 (1H, m), 7.69 (1H, d), 8.04 (2H, m), 8.23 – 8.25 (1H, m), 8.36 – 8.41 (1H, m); MS m/z 516 $[M+H]^+$.

Ejemplo 311:

5–cloro–N–(1–etilpiperidin–4–il)–2–fluoro–4–(9'–isopropil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 310, en una escala de 0.29 mmol, utilizando 4–amino–5–cloro–N–(1–etil–4–piperidil)–2–

fluoro–benzamida (Producto intermedio 174; 87 mg, 0.29 mmol), después de la purificación HPLC en fase inversa preparativa modificada base, como un sólido blanco (98 mg, 62%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.72 (2H, m), 0.94 (2H, m), 1.00 (3H, t), 1.17 (6H, d), 1.51 – 1.57 (2H, m), 1.80 (2H, d), 1.96 (2H, t), 2.32 (2H, q), 2.84 (2H, d), 3.18 (3H, s), 3.49 (2H, s), 3.67 – 3.78 (1H, m), 4.79 – 4.86 (1H, m), 7.67 (1H, d), 8.02 – 8.07 (3H, m), 8.38 (1H, d); MS m/z 544 $[M+H]^+$.

Ejemplo 312:

4–(9'–isopropil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–metoxi–N–(2–(pirrolidin–1–il)etil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 284, en una escala de 0.36 mmol, utilizando 4–amino–3–metoxi–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 192; 94 mg, 0.36 mmol), calentando a 140 °C durante 2 horas, como un sólido blanco (65 mg, 36%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.69 (2H, t). 0.93 (2H, t), 1.19 (6H, d), 1.69 – 1.72 (4H, s), 2.71 (4H, s), 2.80 (2H, s), 3.17 (3H, s), 3.39 – 3.41 (2H, t), 3.48 (2H, s), 3.95 (3H, s), 4.82 – 4.86 (1H, m), 7.49 (1H, d), 7.50 (1H, s), 7.63 (1H, s), 7.99 (1H, s), 8.32 (1H, t), 8.43 (1H, d); MS m/z 509 $[M+H]^+$.

Ejemplo 313:

N–(3–(dimetilamino)–2,2–dimetilpropil)–4–(9'–isopropil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–metoxibenzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 284, en una escala de 0.36 mmol, utilizando 4–amino–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida (Producto intermedio 206; 100 mg, 0.36 mmol), calentando a 140 °C durante 2 horas, como un sólido blanco (78 mg, 42%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.69 (2H, t), 0.89 (6H, s), 0.93 (2H, t), 1.18 (6H, d), 2.21 (2H, s), 2.25 (6H, s), 3.17 (3H, s), 3.21 (2H, d), 3.48 (2H, s), 3.95 (3H, s), 4.82 – 4.86 (1H,

m), 7.49 (1H, d), 7.50 (1H, s), 7.63 (1H, s), 7.99 (1H, s), 8.32 (1H, t), 8.43 (1H, d); MS m/z 525 $[M+H]^+$.

Ejemplo 314:

4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-3-metoxi-N-(1-propil-4-piperidil)benzamida

Ácido 4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-3-metoxi-benzoico (Ejemplo 111; 231 mg, 0.56 mmol), DIPEA (0.3 mL, 1.68 mmol) y HATU (283 mg, 0.75 mmol) fueron agitados juntos en DMA (4 mL) a temperatura ambiente durante 10 minutos. 4-amino-1-propilpiperidina (Fluorochem; 100 mg, 0.70 mmol) fue añadido y la mezcla agitada a temperatura ambiente durante 4 horas. La mezcla de reacción fue cargada en una columna SCX-2 (10g) prehumedecida con MeOH. La columna fue lavada con MeOH (x2) y el producto eluido con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como una goma (194 mg, 65%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.86 (t, 3H), 1.44 (m, 2H), 1.66 (m, 10H), 1.94 (m, 4H), 2.24 (t, 2H), 2.59 (m, 2H), 2.87 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.76 (m, 1H), 3.95 (s, 3H), 4.82 (m, 1H), 7.48 (m, 2H), 7.72 (s, 1H), 8.05 (d, 1H), 8.08 (s, 1H), 8.38 (d, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 315:

3-cloro-4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(2-dimetilaminoetil)benzamida

10-cloro-2-ciclopentil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 1; 80 mg, 0.285 mmol) y 4-amino-3-cloro-N-(2-dimetilaminoetil)benzamida (Producto intermedio 213; 69 mg, 0.285 mmol), ácido p-toluenosulfónico monohidrato (136 mg, 0.713 mmol) fueron combinados en 4-Metil-2-pentanol (2 mL) y calentados a 100 °C toda la noche. Metanol fue añadido a la mezcla de reacción enfriada y la solución cargada en una columna SCX-3 (5 g) prehumedecida con

MeOH (2 volúmenes de columna). La columna fue purgada con MeOH (2 volúmenes de columna) y eluido con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron evaporadas y el residuo disuelto en DCM con un poco de MeOH. La solución resultante fue purificada en una columna de sílice, eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM luego 10% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (21 mg, 15%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.56 – 1.79 (m, 6H), 2.02 (m, 2H), 2.29 (s, 6H), 2.53 (m, 2H), 2.68 (m, 2H), 3.30 (s, 3H), 3.51 (m, 2H), 3.70 (m, 2H), 4.87 (m, 1H), 6.71 (s, 1H), 7.53 (s, 1H), 7.68 (m, 1H), 7.83 (m, 1H), 7.95 (s, 1H), 8.63 (d, 1H); MS m/z 486 $[M+H]^+$.

Ejemplo 316:

3–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 80 mg, 0.285 mmol) y 4–amino–3–cloro–N–(1–etil–4–piperidil)benzamida (Producto intermedio 212; 76 mg, 0.285 mmol), ácido p–toluenosulfónico monohidrato (136 mg, 0.713 mmol) fueron combinados en 4–Metil–2–pentanol (2 mL) y calentados a 100 °C toda la noche. Metanol fue añadido a la mezcla de reacción enfriada y la solución cargada en una columna SCX–3 (5 g) prehumedecida con MeOH (2 volúmenes de columna). La columna fue purgada con MeOH (2 volúmenes de columna) y eluido con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron evaporadas y el residuo disuelto en DCM con un poco de MeOH. La solución resultante fue purificada en una columna de sílice, eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM luego 10% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (22 mg, 15%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.11 (t, 3H), 1.54 – 1.79 (m, 8H), 2.08 (m, 6H), 2.44 (q, 2H), 2.68 (m, 2H), 2.92 (m, 2H), 3.30 (s, 3H), 3.70 (m, 2H), 3.99 (m, 1H), 4.87 (m, 1H), 5.84

(d, 1H), 7.54 (s, 1H), 7.62 (m, 1H), 7.80 (m, 1H), 7.96 (s, 1H), 8.64 (d, 1H); MS m/z 526 $[M+H]^+$.

Ejemplo 317:

3–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(3–dimetilaminopropil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 316, en una escala de 0.356 mmol, utilizando 4–amino–3–cloro–N–(3–dimetilaminopropil)benzamida (Producto intermedio 214; 91 mg, 0.356 mmol), como un sólido blanco (31 mg, 17%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.55 – 1.80 (m, 8H), 2.03 (m, 2H), 2.33 (s, 6H), 2.53 (m, 2H), 2.68 (m, 2H), 3.30 (s, 3H), 3.56 (m, 2H), 3.70 (m, 2H), 4.88 (m, 1H), 7.54 (s, 1H), 7.65 (d, 1H), 7.84 (s, 1H), 7.96 (s, 1H), 8.57 (s, 1H), 8.63 (d, 1H); MS m/z 500 $[M+H]^+$.

Ejemplo 318:

3–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 316, en una escala de 0.356 mmol, utilizando 4–amino–3–cloro–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 215; 95 mg, 0.356 mmol), como un sólido blanco (39 mg, 21%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.56 – 1.82 (m, 10H), 2.02 (m, 2H), 2.58 (m, 4H), 2.70 (m, 4H), 3.30 (s, 3H), 3.55 (m, 2H), 3.70 (m, 2H), 4.87 (m, 1H), 6.74 (s, 1H), 7.53 (s, 1H), 7.67 (m, 1H), 7.84 (m, 1H), 7.95 (s, 1H), 8.63 (d, 1H); MS m/z 512 $[M+H]^+$.

Ejemplo 319:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–[1–(ciclopropilmetil)–4–piperidil]–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 314, en una escala de 0.24 mmol, utilizando 1–(ciclopropilmetil)–4–piperidinamina dihidrocloruro (Aldrich; 95 mg, 0.356 mmol) y DIPEA (210 µL, 1.3 mmol) y agitando a temperatura ambiente durante 24 horas, como un sólido blanco (85 mg, 64%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.00 (m, 2H), 0.38 (m, 2H), 0.75 (m, 1H), 1.60 (m, 10H), 1.90 (m, 4H), 2.11 (d, 2H), 2.51 (m, 2H), 2.91 (m, 2H), 3.10 (s, 3H), 3.55 (m, 2H), 3.68 (m, 1H), 3.87 (s, 3H), 4.74 (m, 1H), 7.40 (m, 2H), 7.64 (s, 1H), 7.98 (d, 1H), 8.00 (s, 1H), 8.30 (d, 1H); MS m/z 548 $[M+H]^+$.

Ejemplo 320:

2–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–5–metoxi–N–(1–metil–4–piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 316, en a una escala de 0.285 mmol, utilizando 4–amino–2–cloro–5–metoxi–N–(1–metil–4–piperidil)benzamida (Producto intermedio 216; 85 mg, 0.285 mmol), como un sólido blanco (108 mg, 70%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.61 (m, 4H), 1.76 (m, 4H), 2.09 (m, 4H), 2.20 (m, 2H), 2.31 (s, 3H), 2.68 (m, 2H), 2.78 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.03 (m, 1H), 4.97 (m, 1H), 6.56 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.62 (s, 1H); MS m/z 542 $[M+H]^+$.

Ejemplo 321:

5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–N–[(3R)–pirrolidin–3–il]benzamida

tert–butil (3R)–3–[[5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoil]amino]pirrolidina–1–carboxilato (Ejemplo 324; 175 mg, 0.29 mmol) fue disuelto en 1,4–dioxano (5 mL) y 4M $HCl_{(ac)}$ en 1,4–dioxano (10 mL) añadido. La mezcla fue agitada a temperatura ambiente durante 2 horas. TFA (2 mL) fue añadido y la reacción agitada durante 1 hora adicional. La reacción fue concentrada, disuelta en DCM (10 mL) y TFA (3 mL) añadido. La reacción fue agitada a temperatura ambiente durante 1 hora, concentrada y el residuo disuelto en metanol, absorbido en una columna SCX, lavado con metanol y eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por cromatografía en columna (7.5% amoniaco en metanol/DCM) para proporcionar el compuesto del título como una espuma blanca (112 mg, 77%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.58 – 1.77 (8H, m), 1.92 – 2.02 (3H, m), 2.60 – 2.77 (5H, m), 2.87 – 3.01 (2H, m), 3.19 (3H, s), 3.65 (2H, m), 4.23 – 4.31 (1H, m), 4.76 – 4.84 (1H, m), 7.70 (1H, d), 8.07 – 8.17 (3H, m), 8.33 (1H, d); MS m/z 502 $[M+H]^+$.

Ejemplo 322:

5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–N–(1–metil–4–piperidil)benzamida

Ácido 5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoico (Producto intermedio 219; 100 mg, 0.23 mmol), 4–amino–1–metilpiperidina (Fluorochem; 40 mg, 0.35 mmol) y HATU (132 mg, 0.35 mmol) fueron agitados en DMF (3 mL). *N,N*–diisopropiletilamina (121 µL, 0.69 mmol) fue añadida y la mezcla calentada a 50 °C durante 2 horas. La mezcla fue enfriada y absorbida en una columna SCX, la cual fue posteriormente lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y el residuo purificado por cromatografía en fase inversa preparativa de la base modificada para proporcionar el compuesto del título como un sólido blanco (58 mg, 48%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.50 – 1.80 (10H, m), 1.92 – 1.99 (4H, m), 2.17 (3H, s), 2.61 (2H, m), 2.74 (2H, d), 3.19 (3H, s), 3.63 – 3.74 (3H, m), 4.76 – 4.84 (1H, m), 7.67 (1H, d), 8.07 (1H, d) 8.14 (1H, m), 8.31 – 8.36 (1H, m); MS m/z 530 $M+H]^+$.

Ejemplo 323:

5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 322, en una escala de 0.23 mmol, utilizando 4–amino–1–etilpiperidina (Fluorochem; 45 mg, 0.35 mmol), como un sólido blanco (60 mg, 48%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.00 (3H, t), 1.59 (8H, d), 1.80 (2H, d), 1.93 – 1.98 (4H, m), 2.32 (2H, q), 2.61 (2H, m), 2.84 (2H, d), 3.19 (3H, s), 3.63 – 3.76 (3H, m), 4.76 – 4.84 (1H, m), 7.67 (1H, d), 8.08 (1H, d), 8.14 (2H, d), 8.31 – 8.36 (1H, m); MS m/z 544 $[M+H]^+$.

Ejemplo 324:

tert–butil (3R)–3–[[5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoil]amino]pirrolidina–1–carboxilato

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 322, en una escala de 0.46 mmol, utilizando boc–R–(3R)–aminopirrolidina (Aldrich; 130 mg, 0.75 mmol) y purificación por cromatografía en fase normal (5% MeOH/DCM), como una espuma blanca (179 mg, 65%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.42 (9H, s), 1.56 – 1.74 (7H, m), 1.87 – 1.97 (3H, m), 2.09 – 2.13 (1H, m), 2.60 – 2.64 (2H, m), 3.19 (4H, m), 3.37 – 3.44 (1H, m), 3.49 – 3.57 (1H, m), 3.63 – 3.67 (2H, m), 4.38 (1H, m), 4.80 (1H, m), 7.70 (1H, d), 8.09 – 8.25 (2H, m), 8.32 – 8.37 (1H, m), 8.44 (1H, d); MS m/z 602 $[M+H]^+$.

Ejemplo 325:

5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida

5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–N–[(3R)–pirrolidin–3–il]benzamida (Ejemplo 321; 95 mg, 0.19 mmol) fue disuelto en 37% solución de formaldehído acuoso (1.1 mL) y ácido acético (120 µL, 1.89 mmol). Acetato de sodio (156 mg, 1.89 mmol) fue añadido y la mezcla enfriada en un baño de hielo/agua. Cianoborohidruro de sodio (12 mg, 0.19 mmol) fue añadido y la mezcla se dejó calentar a temperatura ambiente. Después de agitar durante 1 hora, la mezcla fue absorbida en una columna SCX, y posteriormente lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (2% amoniaco 7N en metanol/DCM) para proporcionar el compuesto del título como una espuma blanca (69mg, 70%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.58 – 1.73 (7H, m), 1.90 – 1.96 (2H, m), 2.12 – 2.21 (1H, m), 2.26 (3H, s), 2.38 – 2.43 (3H, m), 2.56 – 2.64 (3H, m), 2.67 – 2.71 (1H, m), 3.19 (3H, s), 3.63 – 3.67 (2H, m), 4.34 – 4.36 (1H, m), 4.80 (1H, m), 7.69 (1H, d), 8.14 (2H, m), 8.27 (1H, d), 8.33 (1H, d); MS m/z 516 $[M+H]^+$.

Ejemplo 326:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–[(3R)–1–etilpirrolidin–3–il]–3–metoxi–benzamida

4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–metoxi–N–[(3R)–pirrolidin–3–il]benzamida (Ejemplo 55; 100 mg, 0.21 mmol) en DMF (3 mL) fue añadida trietilamina (59 ul, 0.42 mmol) y etil bromuro (Acros; 24 ul, 0.31 mmol). La mezcla de reacción fue calentada hasta 90 °C por irradiación de microondas durante 1 hora. La mezcla de reacción enfriada fue vertida en un cartucho SCX–3 (5 g) y el cartucho lavado completamente con metanol (40 mL) y luego eluido con amoniaco 2M en metanol. Las fracciones amoniacales fueron combinadas y evaporadas. El residuo fue purificado por HPLC en fase inversa preparativa modificada base y las fracciones que contienen el producto combinadas y evaporadas para proporcionar el compuesto del título como un sólido blanco (27 mg, 25%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.97 (t, 3H), 1.51 – 1.75 (m, 7H), 1.87 (m, 2H), 2.08 (m, 1H), 2.32 – 2.68 (m, 8H), 3.10 (s, 3H), 3.56 (m, 2H), 3.88 (s, 3H), 4.32 (m, 1H), 4.75 (m, 1H), 7.44 (m, 2H), 7.65 (s, 1H), 8.01 (s, 1H), 8.22 (d, 1H), 8.31 (d, 1H); MS m/z 508 $[M+H]^+$.

Ejemplo 327:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–[(3R)–1–propilpirrolidin–3–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 326, en una escala de 0.21 mmol, utilizando n–propil bromuro (Aldrich; 29 µL, 0.31 mmol) y calentando durante 45 minutos a 90 °C, como una goma blanco hueso (63 mg, 58%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.88 (t, 3H), 1.45 (m, 2H), 1.56 – 1.82 (m, 7H), 1.95 (m, 2H), 2.14 (m, 1H), 2.35 (m, 2H), 2.44 (m, 2H), 2.61 (m, 3H), 2.74 (m, 1H), 3.17 (s, 3H), 3.63 (m, 2H), 3.95 (s, 3H), 4.39 (m, 1H), 4.82 (m, 1H), 7.50 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.27 (d, 1H), 8.38 (d, 1H); MS m/z 522 $[M+H]^+$.

Ejemplo 328:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–[(3R)–1–(2–metoxietil)pirrolidin–3–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 326, en una escala de 0.21 mmol, utilizando 2–bromoetil metiléter (Aldrich; 30 µL, 0.31 mmol) 45 minutos a 90 °C , como una goma blanco hueso (57 mg, 50%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.57 – 1.82 (m, 7H), 1.95 (m, 2H), 2.13 (m, 1H), 2.52 (d, 2H)[oscurecido por DMSO], 2.59 (m, 4H), 2.69 (m, 1H), 2.79 (m, 1H), 3.17 (s, 3H), 3.24 (s, 3H), 3.43 (t, 2H), 3.63 (m, 2H), 3.95 (s, 3H), 4.39 (m, 1H), 4.82 (m, 1H), 7.51 (m, 2H), 7.72 (s, 1H), 8.08 (s, 1H), 8.29 (d, 1H), 8.38 (d, 1H); MS m/z 538 $[M+H]^+$.

Ejemplo 329:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida

4–amino–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 162; 1.0 g, 3.43 mmol), 10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 0.96 g, 3.43 mmol) y ácido p–toluenosulfónico monohidrato (1.63 g, 8.56 mmol) fueron agitados y calentados juntos a 110 °C en 4–metil–2–pentanol (30 mL) durante 18 horas. La mezcla de reacción enfriada fue diluida con agua y metanol y la solución cargada en una columna SCX–2 (20g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volúmenes de columna) y el producto eluido con NH_3 2M/MeOH (2 volúmenes de columna). Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por cromatografía en una columna de sílice eluyendo con un 0–100% gradiente de 10% NH_3 2M–MeOH en DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar una espuma la cual en trituración con etil acetato produjo, en filtración, el compuesto del título como un sólido blanco (473 mg, 26%) 536 (M+H), ES– 534 (M–H)

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.94 (m, 2H), 1.55 (m, 9H), 1.90 (m, 4H), 2.03 (m, 1H), 2.19 (m, 3H), 2.42 (s, 3H), 2.58 (m, 2H), 2.98 (m, 2H), 3.17 (s, 3H), 3.60 (m, 2H), 4.32 (m, 1H), 4.74 (m, 1H), 7.69 (m, 2H), 8.00 (d, 1H), 8.06 (s, 1H), 8.12 (m, 1H), 8.72 (s, 1H); MS m/z 536 [M+H]+.

Ejemplo 330:

3,5–dicloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–N–(1–metil–4–piperidil)benzamida

Ácido 3,5–dicloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoico (Producto intermedio 221; 85 mg, 0.18 mmol), HATU (104 mg, 0.27 mmol) y 4–amino–1–metilpiperidina (32 mg, 0.27m mol) fueron agitados en DMF (3 mL) y diisopropiletilamina (95 µL, 0.54 mmol) añadida. La mezcla fue agitada durante 2 horas y absorbida en una columna SCX, la cual fue posteriormente lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por cromatografía en columna (4% amoniaco en metanol/DCM) para proporcionar el compuesto del título como un sólido blanco (67 mg, 66%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.26 – 1.65 (10H, m), 1.79 (2H, d), 1.98 (2H, t), 2.17 (3H, s), 2.55 (2H + DMSO, m), 2.73 (2H, d), 3.15 (3H, s), 3.53 – 3.55 (2H, m), 3.67 – 3.74 (1H, m), 4.37 (1H, t), 7.65 (1H, d), 7.96 (1H, s), 8.43 (1H, d), 9.01 (1H, s); MS m/z 564 [M+H]+.

Ejemplo 331:

3,5–dicloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 330, en una escala de 0.21 mmol, utilizando 1–amino–4–dimetilaminociclohexano (ABChem Inc.; 30 µL, 0.31 mmol) y la separación del cis–isómero por cromatografía en columna, como un sólido blanco (21 mg, 19%).

^{1}H NMR (500.13 MHz, DMSO–d_6) δ 1.38 – 1.92 (16H, m), 2.04 – 2.08 (1H, m), 2.18 (6H, s), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.53 – 3.55 (2H, m), 3.9 1 –3.95 (1H, m), 4.39 (1H, m), 7.63 (1H, d), 7.95 (1H, s), 8.39 (1H, d), 9.00 (1H, s); MS m/z 592 [M+H]+.

Ejemplo 332:

3,5–dicloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 330, en una escala de 0.21 mmol, utilizando 1–amino–4–dimetilaminociclohexano (ABChem Inc.; 30 µL, 0.31 mmol) y la separación del trans isómero por cromatografía en columna, como un sólido blanco (42 mg, 39%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.22 – 1.68 (12H, m), 1.80 – 1.85 (2H, m), 1.90 – 1.95 (2H, m), 2.10 – 2.14 (1H, m), 2.18 (6H, s), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.53 – 3.56 (2H, m), 3.63 – 3.71 (1H, m), 4.33 – 4.42 (1H, m), 7.64 (1H, d), 7.95 (1H, s), 8.39 (1H, d), 9.01 (1H, s); MS m/z 592 [M+H]+.

Ejemplo 333:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–5–metoxi–N–(2–pirrolidin–1–iletil)benzamida

10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 80 mg, 0.285 mmol), 4–amino–2–fluoro–5–metoxi–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 228; 80 mg, 0.285 mmol), ácido p–toluenosulfónico monohidrato (136 mg, 0.732 mmol) y 4–Metil–2–pentanol (3 mL) fueron combinados y calentados a 100 °C toda la noche. La mezcla de reacción enfriada fue añadida a una columna SCX–2 (5 g), prehumedecida con MeOH (2 volumenes de columna). La columna fue purgada con MeOH (2 volumenes de columna) y eluida con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base y las fracciones que contienen el producto combinadas y evaporadas para proporcionar el compuesto del título como una sólido color crema (94 mg, 36%)

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.63 (m, 2H), 1.77 (m, 8H), 2.06 (m, 2H), 2.58 (m, 4H), 2.68 (m, 2H), 2.72 (m, 2H), 3.30 (s, 3H), 3.60 (m, 2H), 3.71 (m, 2H), 3.95 (s, 3H), 4.91 (m, 1H), 7.31 (m, 1H), 7.57 (d, 1H), 7.72 (s, 1H), 7.95 (s, 1H), 8.40 (d, 1H); MS m/z 526 [M+H]+.

Ejemplo 334:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 100 mg, 0.356 mmol), 4–amino–2,5–difluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 229; 83 mg, 0.324 mmol) y carbonato de cesio (211 mg, 0.648 mmol) fue añadido a dioxano (3 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Tris(dibencilidenoacetona) paladio (II) (11 mg, 0.019 mmol) y XANTFOS (17 mg, 0.029 mmol) fueron añadidos y la mezcla calentada a 100 °C toda la noche. La mezcla de reacción enfriada fue filtrada y la torta del filtro lavada con DCM y el filtrado evaporado. El residuo fue disuelto en DCM y purificado en una columna de sílice eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM sobre 30 volumenes de columnas. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido amarillo (91 mg, 56%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.64 (m, 2H), 1.75 (m, 5H), 2.05 (m, 2H), 2.30 (m, 1H), 2.41 (m, 4H), 2.67 (m, 4H), 2.89 (m, 1H), 3.30 (s, 3H), 3.71 (m, 2H), 4.65 (m, 1H), 4.88 (m, 1H), 6.95 (m, 1H), 7.30 (m, 1H), 7.81 (m, 1H), 7.96 (s, 1H), 8.45 (m, 1H); MS m/z 500 [M+H]+.

Ejemplo 335:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 334, en una escala de 0.324 mmol, utilizando 4–amino–2,5–difluoro–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 230; 87 mg, 0.324 mmol), como un sólido blanco (117 mg, 70%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.63 (m, 2H), 1.77 (m, 8H), 2.05 (m, 2H), 2.57 (m, 4H), 2.70 (m, 4H), 3.30 (s, 3H), 3.58 (m, 2H), 3.71 (m, 2H), 4.88 (m, 1H), 7.28 (m, 2H), 7.82 (m, 1H), 7.96 (s, 1H), 8.46 (m, 1H); MS m/z 514 [M+H]+.

Ejemplo 336:

2–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

Ácido 2–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–5–metoxi–benzoico (Producto intermedio 231; 100mg, 0.224 mmol), (3R)–1–metilpirrolidin–3–amina dihidrocloruro (Producto intermedio 184; 40 mg, 0.235 mmol), HATU (94 mg, 0.246 mmol) y DIPEA (195 µL, 1.12 mmol) fueron combinados en DMF (3 mL) y agitados a temperatura ambiente toda la noche. La mezcla de reacción fue añadida a una columna SCX–2 (5 g) prehumedecida con MeOH (2 volúmenes de columna), purgada con MeOH (2 volúmenes de columna) y eluida con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (76 mg, 64%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.62 (m, 2H), 1.78 (m, 5H), 2.11 (m, 2H), 2.31 (m, 1H), 2.42 (m, 4H), 2.69 (m, 4H), 2.90 (m, 1H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.68 (m, 1H), 4.97 (m, 1H), 6.97 (m, 1H), 7.38 (s, 1H), 7.63 (s, 1H), 7.93 (s, 1H), 8.61 (s, 1H); MS m/z 528 [M+H]+.

Ejemplo 337:

2–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–5–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 336, en una escala de 0.224 mmol, utilizando 4–amino–1–etil piperidina (Fluorochem; 32 mg, 0.246 mmol), como un sólido blanco (97 mg, 79%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.11 (t, 3H), 1.60 (m, 4H), 1.75 (m, 4H), 2.09 (m, 4H), 2.19 (m, 2H), 2.44 (m, 2H), 2.68 (m, 2H), 2.88 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.06 (m, 1H), 4.97 (m, 1H), 6.58 (d, 1H), 7.40 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.61 (s, 1H); MS m/z 556 [M+H]+.

Ejemplo 338:

2–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(4–dimetilaminociclohexil)–5–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 336, en una escala de 0.224 mmol, utilizando 1–amino–4–dimetilaminociclohexano (ABChem Inc.; 35 mg, 0.246 mmol), como un sólido blanco (84 mg, 66%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.26 – 1.76 (m, 11H), 1.94 (m, 2H), 2.10 (m, 2H), 2.21 (m, 2H), 2.30 (m, 6H), 2.68 (m, 2H), 3.29 (m, 3H), 3.71 (m, 2H), 3.94 (m, 3.5H), 4.25 (m, 0.5H), 4.97 (m, 1H), 6.46 (d, 0.5H), 6.85 (d, 0.5H), 7.39 (s, 0.5H), 7.45 (s, 0.5H), 7.63 (m, 1H), 7.94 (m, 1H), 8.62 (m, 1H); MS m/z 570 [M+H]+.

Ejemplo 339:

2–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 336, en una escala de 0.224 mmol, utilizando endo–9–metil–9–azabiciclo[3,3,1]–nonan–3–amina (Chempacific; 38 mg, 0.246 mmol), como un sólido blanco (84 mg, 64%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.05 (m, 2H), 1.30 (m, 2H), 1.52 – 1.66 (m, 4H), 1.76 (m, 4H), 1.97 (m, 2H), 2.11 (m, 2H), 2.55 (m, 5H), 2.68 (m, 2H), 3.10 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 3.94 (s, 3H), 4.52 (m, 1H), 4.98 (m, 1H), 6.42 (d, 1H), 7.41 (s, 1H), 7.63 (s, 1H), 7.94 (s, 1H), 8.61 (s, 1H); MS m/z 582 [M+H]+.

Ejemplo 340:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–[1–(2–metilpropil)–4–piperidil]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 316, en una escala de 0.49 mmol, utilizando 1–isobutilpiperidin–4–amina hidrocloruro (Ambinter; 96 mg, 0.61 mmol) y DIPEA (340 µL, 1.6 mmol) y agitar a temperatura ambiente durante 24 horas, como un sólido blanco (159 mg, 59%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.87 (d, 6H), 1.68 (m, 11H), 1.94 (m, 4H), 2.04 (d, 2H), 2.59 (m, 2H), 2.84 (m, 2H), 3.17 (s, 3H), 3.63 (m, 2H), 3.77 (m, 1H), 3.95 (s, 3H), 4.81 (m, 1H), 7.47 (s, 1H), 7.50 (s, 1H), 7.72 (s, 1H), 8.04 (d, 2H), 8.08 (s, 1H), 8.38 (d, 1H); MS m/z 550 [M+H]+.

Ejemplo 341:

7-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(1-metil-4-piperidil)benzo[1,3]dioxol-4-carboxamida

7-amino-N-(1-metil-4-piperidil)benzo[1,3]dioxol-4-carboxamida (Producto intermedio 223; 60mg, 0.21mmol), 10-cloro-2-ciclopentil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 1; 60 mg, 0.21 mmol) y ácido p-toluenosulfónico monohidrato (102 mg, 0.53 mmol) fueron calentados en 4-metil-2-pentanol (3 mL) a 140 °C durante 2 horas. La mezcla de reacción enfriada fue absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron evaporadas y el residuo purificado por cromatografía en fase normal (2.5% 7N NH_3 en metanol/DCM) y luego HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (35 mg, 32%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.48 – 1.60 (6H, m), 1.63 – 1.69 (2H, m), 1.79 – 1.83 (4H, m), 2.00 – 2.05 (2H, m), 2.17 (3H, s), 2.55 – 2.58 (2H, m), 2.67 – 2.70 (2H, m), 3.17 (3H, s), 3.59 (2H, m), 3.74 – 3.78 (1H, m), 4.69 – 1.77 (1H, m), 6.14 (2H, s), 7.23 (1H, d), 7.27 (1H, d), 7.48 – 7.51 (1H, m), 8.04 (1H, s), 8.60 (1H, s); MS m/z 522 $[M+H]^+$.

Ejemplo 342:

4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-3-metoxi-N-(1-metil-3,4,4a,5,6,7,8,8a-octahidro-2H-quinolin-4-il)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 314, en una escala de 0.49 mmol, utilizando 1-metil-3,4,4a,5,6,7,8,8a-octahidro-2H-quinolin-4-amina (CBI Building Blocks; 103 mg, 0.61 mmol) y DIPEA (260 µL, 1.47 mmol) y agitando a temperatura ambiente durante 2 horas, como un isómero simple de estereoquímica no especificada, como un sólido blanco (52 mg, 19%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.09 (6H, m), 1.66 (11H, m), 1.94 (2H, m), 2.07 (2H, m), 2.16 (3H, s), 2.59 (2H, m), 2.81 (1H, m), 3.18 (3H, s), 3.63 (3H, m), 3.95 (3H, s), 4.81 (1H, m), 7.49 (2H, m), 7.73 (1H, s), 7.97 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 562 $[M+H]^+$.

Ejemplo 343:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(1–metil–3,4,4a,5,6,7,8,8a–octahidro–2H–quinolin–4–il)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 314, en una escala de 0.49 mmol, utilizando 1–metil–3,4,4a,5,6,7,8,8a–octahidro–2H–quinolin–4–amina (CBI Building Blocks; 103 mg, 0.61 mmol) y DIPEA (260 µL, 1.47 mmol) y agitando a temperatura ambiente durante 2 horas, como un isómero simple de estereoquímica no especificada, como un sólido blanco (102 mg, 37%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.94 (1H, m), 1.21 (3H, m), 1.44 (2H, m), 1.66 (10H, m), 1.88 (3H, m), 2.10 (2H, m), 2.19 (3H, s), 2.59 (2H, m), 3.18 (3H, s), 3.63 (2H, m), 3.96 (3H, s), 4.17 (1H, m), 4.81 (1H, m), 7.40 (1H, s), 7.45 (2H, d), 7.56 (1H, d), 7.75 (1H, s), 8.08 (1H, s), 8.37 (1H, d); MS m/z 562 $[M+H]^+$.

Ejemplo 344:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

4–amino–2–fluoro–5–metoxi–N–(9–metil–9–azabiciclo[3.3.1]non–7–il)benzamida (Producto intermedio 204; 50 mg, 0.16 mmol), 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 1; 45 mg, 0.16 mmol) y ácido p–toluenosulfónico monohidrato (76 mg, 0.40 mmol) fueron agitados y calentados juntos en 4–metil–2–pentanol (3 mL) a 110 °C durante 18 horas.

Una porción adicional de 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 1; 20 mg, 0.07 mmol) fue añadida y la mezcla calentada por irradiación de microondas a 150 °C durante 1 hora y 30 minutos.

La mezcla de reacción enfriada fue cargada en una columna SCX–3 (5 g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volumenes de columna) y eluida con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron evaporadas y el residuo

purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (48 mg, 53%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.90 (m, 2H), 1.42 (m, 3H), 1.69 (m, 6H), 1.96 (m, 5H), 2.21 (m, 2H), 2.41 (s, 3H), 2.61 (m, 2H), 2.97 (m, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 3.93 (s, 3H), 4.30 (m, 1H), 4.84 (m, 1H), 7.22 (d, 1H), 7.67 (m, 1H), 7.81 (s, 1H), 8.12 (s, 1H), 8.34 (d, 1H); MS m/z 566 [M+H]+.

Ejemplo 345:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–N–(1–etil–4–piperidil)–3–fluoro–benzamida

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 1; 212 mg, 0.75 mmol), 4–amino–N–(1–etilpiperidin–4–il)–3–fluorobenzamida (Producto intermedio 225; 200 mg, 0.75 mmol) y ácido p–toluenosulfónico monohidrato (0.335 mL, 1.88 mmol) fueron suspendidos en 4–Metil–2–pentanol (5 mL) y sellados en un tubo de microondas. La reacción fue calentada hasta 160 °C durante 30 minutos en el reactor de microondas y se dejó enfriar a temperatura ambiente.

El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando NH_3 7M /MeOH y las fracciones puras fueron evaporadas hasta secarse para proporcionar el producto crudo como un aceite naranja el cual fue purificado por HPLC en fase inversa preparativa modificada base. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar el compuesto del título como un sólido blanco (35 mg, 9%).

^{1}H NMR DMSO–d6 δ 0.65 (t, 2H), 0.9 (t, 2H), 1.0 (t. 3H), 1.5 (m, 7H), 1.6 (m, 2H), 1.9 (t, 2H), 2.3 (q, 2H), 2.9 (d, 2H), 3.2 (s, 3H), 3.4 (s, 2H), 3.6 (m, 1H), 4.75 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.6 (s, 1H); MS m/z 510 [M+H]+.

Ejemplo 346:

N–[4–(azetidin–1–il)ciclohexil]–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzamida

A una solución de 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 1; 70 mg, 0.17 mmol) en DMF (3 mL) fue añadida

una solución de 4–(azetidin–1–il)ciclohexan–1–amina (Producto intermedio 226; 39 mg, 0.25 mmol) en DMF (1 mL). DIPEA (90 uL, 0.51 mmol) fue añadido, seguido por HATU (98 mg, 0.26 mmol). La mezcla resultante fue agitada a temperatura ambiente durante 4 horas.

La mezcla de reacción fue evaporada y el residuo particionado entre DCM (5 mL) y solución de bicarbonato de sodio saturada acuosa. (5 mL). La fase orgánica fue separada mediante elusión por gravedad a través de un vaso PTFE y evaporadas hasta una goma ámbar la cual fue purificada por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (29 mg, 31%) asignado como el isómero trans. El isómero cis (Ejemplo 347) fue aislado como un sólido color canela (32 mg, 34%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.92 – 1.00 (2H, m), 1.29 – 1.38 (2H, m), 1.57 – 1.99 (15H, m), 2.58 – 2.60 (2H, m), 3.07 (4H, t), 3.17 (3H, s), 3.61 – 3.65 (2H, m), 3.66 – 3.76 (1H, m), 3.95 (3H, s), 4.82 (1H, quinteto), 7.45 – 7.48 (2H, m), 7.72 (1H, s), 8.01 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 548 $[M+H]^+$.

Ejemplo 347:

N–[4–(azetidin–1–il)ciclohexil]–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzamida

El compuesto del título fue aislado de la reacción anterior para producir el Ejemplo 346 como un sólido color canela (32 mg, 34%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.30 – 1.40 (2H, m), 1.43 – 1.50 (2H, m), 1.56 – 1.77 (10H, m), 1.86 – 1.98 (4H, m), 2.18 – 2.23 (1H, m), 2.58 – 2.60 (2H, m), 3.07 (4H, t), 3.18 (3H, s), 3.62 – 3.65 (2H, m), 3.77 – 3.87 (1H, m), 3.95 (3H, s), 4.82 (1H, quinteto), 7.50 – 7.54 (2H, m), 7.71 (1H, s), 8.04 (1H, d), 8.08 (1H, s), 8.37 (1H, d); MS m/z 548 $[M+H]^+$.

Ejemplo 348:

tert–butil 3–[[4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoil]amino]azepan–1–carboxilato

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 314, en una escala 0.30 mmol, utilizando tert–butil 3–aminoazepan–1–carboxilato (Anichem; 78 mg, 0.36 mmol) y DIPEA (151 µL, 0.91 mmol) y agitando a temperatura ambiente durante 19 horas, como una goma ámbar (153 mg, 83%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.24 – 1.46 (11H, m), 1.50 – 2.00 (14H, m), 2.57 – 2.61 (2H, m), 3.06 – 3.19 & 3.30 – 3.37 (1H, m), 3.18 (3H, s), 3.54 – 3.70 (3H, m), 3.95 (3H, s), 4.08 – 4.22 (1H, m), 4.75 – 4.87 (1H, m), 7.36 – 7.49 (2H, m), 7.74 (1H, s), 8.01 & 8.16 (2 x d, 1H), 8.09 (1H, s), 8.39 (1H, d); MS m/z 608 $(M+H)^+$

Ejemplo 349:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(4–piperidil)benzamida

10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 127; 50 mg, 0.16 mmol) y tert–butil 4–[(4–amino–3–metoxi–benzoil)amino]piperidina–1–carboxilato (Producto intermedio 234; 85 mg, 0.24 mmol) fueron disueltos en 4–metil–2–pentanol (1 mL) y ácido p–toluenosulfónico monohidrato (44 mg, 0.32 mmol) añadido. La mezcla de reacción fue calentada a 90°C por irradiación de microondas durante 20 minutos y luego a 150°C durante unos 45 minutos adicionales. La mezcla de reacción fue diluida con agua (3 mL) y metanol (3 mL) y la solución vertida directamente en un cartucho SCX–3 (2 g). El cartucho fue lavado con metanol (30 mL) y luego eluido con amoniaco 2M en metanol. La evaporación hasta secarse de las fracciones amoniacales proporcionó una goma ámbar, la cual fue purificada HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (32 mg, 38%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.10 (s, 6H), 1.43 (m, 2H), 1.55 – 1.79 (m, 10H), 1.89 (m, 2H), 2.96 (m, 2H), 3.19 (s, 3H), 3.38 (s, 2H), 3.83 (m, 1H), 3.95 (s, 3H), 5.19 (m, 1H), 7.48 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.05 (d, 1H), 8.36 (d, 1H); MS m/z 522 $[M+H]^+$.

Ejemplo 350:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–3–metoxi–benzamida

10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 127; 115 mg, 0.37 mmol) y 4–amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida (Producto intermedio 190; 104 mg, 0.37 mmol) fueron disueltos 4–metil–

2–pentanol (3 mL). Ácido p–toluenosulfónico monohidrato (142 mg, 0.74 mmol) fue añadido y la mezcla calentada por irradiación de microondas a 160 °C durante 1 hora.

Después de enfriar, la mezcla de reacción fue diluida con MeOH (5 mL) y vertida directamente en un cartucho SCX–3 (5 g). El cartucho fue lavado con metanol (40 mL) y eluido con amoniaco 2M en metanol (40 mL). La evaporación hasta secarse de las fracciones amoniacales proporcionó una goma amarilla cual fue purificada por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (125 mg, 61%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.01 (t, 3H), 1.11 (s, 6H), 1.53 – 1.97 (m, 14H), 2.34 (q, 2H), 2.90 (m, 2H), 3.20 (s, 3H), 3.39 (s, 2H), 3.78 (m, 1H), 3.96 (s, 3H), 5.20 (m, 1H), 7.48 (m, 2H), 7.68 (s, 1H), 8.00 (s, 1H), 8.07 (d, 1H), 8.37 (d, 1H); MS m/z 550 $[M+H]^+$.

Ejemplo 351:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.24 mmol, utilizando 4–amino–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida (Producto intermedio 22; 68 mg, 0.24 mmol), como una espuma blanca (47 mg, 53%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.90 (s, 6H), 1.11 (s, 6H), 1.62 (m, 4H), 1.75 (m, 2H), 1.90 (m, 2H), 2.21 (s, 2H), 2.29 (s, 6H), 3.21 (m, 5H), 3.40 (s, 2H), 3.96 (s, 3H), 5.20 (m, 1H), 7.42 (m, 1H), 7.47 (d, 1H), 7.70 (s, 1H), 8.00 (s, 1H), 8.39 (d, 1H), 8.44 (t, 1H); MS m/z 552 $[M+H]^+$.

Ejemplo 352:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.31 mmol, utilizando 4–amino–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 204; 96 mg, 0.31 mmol)

calentando por irradiación de microondas a 150 °C durante 1 hora, como una espuma blanca (47 mg, 53%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.16 – 1.23 (8H, m), 1.52 – 1.65 (4H, m), 1.73 – 1.83 (5H, m), 1.97 – 2.11 (5H, m), 2.54 – 2.65 (5H, m), 3.17 – 3.26 (2H, m), 3.31 (3H, s), 3.40 (2H, s), 3.96(3H, s), 4.51 – 4.62 (1H, m), 5.29 (1H, quinteto), 6.60 – 6.74 (1H, m), 7.57 (1H, d), 7.70 (1H, s), 7.88 (1H, s), 8.39 (1H, d); MS m/z 594 $[M+H]^+$.

Ejemplo 353:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.34 mmol, utilizando 4–amino–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 162; 100 mg, 0.34 mmol) calentando por irradiación de microondas a 150 °C durante 40 minutos, como una espuma blanca (52 mg, 27%).

^{1}H NMR (399.902 MHz, DMSO–d6) δ 0.9 (2H, d), 1.1 (6H, s), 1.45 (3H, m), 1.55 (4H, m), 1.7 (2H, m), 1.8 (2H, m), 1.9 (2H, m), 2.05 (1H, m) 2.2 (2H, m), 2.40 (2H, s), 3.0 (2H, d), 3.2 (3H, s), 3.35 (2H, s) 4.3 (1H, m), 5.2 (1H, m), 7.65 (1H, d), 7.70 (1H, d), 8.0 (2H, m), 8.15 (1H, t), 8.65 (1H, s); MS m/z 564 $[M+H]^+$.

Ejemplo 354:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.32 mmol, utilizando 4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida (Producto intermedio 202; 99 mg, 0.32 mmol) calentando térmicamente a 140 °C durante 2 horas, como un sólido blanco (104 mg, 56%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.94 (2H, d), 1.10 (6H, s), 1.42 – 1.49 (3H, m), 1.63 (4H, s), 1.75 (2H, s), 1.89 – 1.96 (3H, m), 1.92 – 1.95 (2H, m), 2.16 – 2.21 (2H, m), 2.42 (3H, s),

2.99 (2H, d), 3.20 (3H, s), 3.39 (2H, s), 3.96 (3H, s), 4.32 – 4.38 (1H, m), 5.21 (1H, m), 7.47 (1H,d), 7.50 (1H, s), 7.68 (1H, s), 7.92 (1H, d), 8.00 (1H, s), 8.38 (1H, d); MS m/z 576 $[M+H]^+$.

Ejemplo 355:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida

10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 127; 100mg, 0.32mmol), 4–amino–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida (Producto intermedio 235; 101 mg, 0.36 mmol) y carbonato de cesio (22 mg, 0.65 mmol) añadido a dioxano (5 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Tris(dibencilidenoacetona) paladio (II) (18 mg, 0.02 mmol) y XANTFOS (17 mg, 0.03 mmol) fueron añadidos y la mezcla calentada a 110 °C toda la noche. La mezcla fue filtrada y el filtrado cargado en un cartucho SCX (10 g) prehumedecido con metanol, lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido cristalino blanco (97mg, 54%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.00 (3H, t), 1.11 (6H, s), 1.48 – 1.55 (2H, m), 1.60 (4H, d), 1.73 (2H, s), 1.77 – 1.82 (2H, m), 1.88 (2H, d), 1.93 – 1.99 (2H, m), 2.32 (2H, q), 2.83 (2H, d), 3.20 (3H, s), 3.39 (2H, s), 3.70 – 3.74 (1H, m), 5.21 (1H, m), 7.40 – 7.45 (1H, m), 7.95 – 7.98 (1H, m), 8.02 (1H, s), 8.20 – 8.25 (1H, m), 8.88 (1H, s); MS m/z 556 $[M+H]^+$.

Ejemplo 356:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–(1–metil–4–piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 355, en una escala de 0.32 mmol, utilizando 4–amino–2,5–difluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 59; 96 mg, 0.32 mmol), como un sólido blanco (38 mg, 22%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.11 (6H, s), 1.54 – 1.58 (2H, m), 1.59 (3H, s), 1.74 (3H, d), 1.79 (2H, s), 1.87 (2H, s), 1.95 (1H, d), 1.99 (1H, s), 2.17 (3H, s), 2.75 (2H, d), 3.20 (3H, s), 3.37 (2H, s), 3.70 (1H, m), 5.22 (1H, m), 7.40 – 7.45 (1H, m), 7.95 – 7.98 (1H, m), 8.02 (1H, s), 8.20 – 8.25 (1H, m), 8.88 (1H, s); MS m/z 540 $[M+H]^+$.

Ejemplo 357:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(3–dimetilaminopropil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.32 mmol, utilizando 4–amino–N–(3–dimetilaminopropil)–3–metoxi–benzamida (Producto intermedio 196; 82 mg, 0.32 mmol) calentando térmicamente a 140 °C durante 2 horas, como un sólido blanco (84 mg, 50%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.11 (6H, s), 1.63 (2H, m), 1.65 – 1.71 (4H, m), 1.75 (2H, s), 1.86 – 1.89 (2H, t), 2.16 (6H, s), 2.28 – 2.34 (2H, t), 3.15 – 3.20 (3H, s), 3.28 – 3.31 (2H, m), 3.36 – 3.39 (2H, s), 3.95 (3H, s), 5.18 – 5.22 (1H, m), 7.47 – 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.37 (1H, s), 8.39 (1H, t); MS m/z 524 $[M+H]^+$.

Ejemplo 358:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.32 mmol, utilizando 4–amino–3–metoxi–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 192; 86 mg, 0.32 mmol) calentando térmicamente a 140 °C durante 2 horas, como un sólido blanco (56 mg, 32%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.11 (6H, s), 1.63 (3H, m), 1.68 – 1.71 (3H, m), 1.74 (3H, d), 1.86 – 1.89 (3H, m), 2.48 (4H, m), 2.58 (2H, t), 3.18 (3H, s), 3.39 (4H, t), 3.92 – 3.98 (3H, s), 5.18 (1H, m), 7.47 – 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.29 (1H, 4), 8.39 (1H, d); MS m/z 536 $[M+H]^+$.

Ejemplo 359:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(2–dimetilaminoetil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.32 mmol, utilizando 4–amino–N–(2–dimetilaminoetil)–3–metoxi–benzamida (Producto intermedio 194; 77 mg, 0.32 mmol) calentando térmicamente a 140 °C durante 2 horas, como un sólido blanco (37 mg, 22%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.11 (6H, s), 1.63 – 1.68 (4H, m), 1.75 (2H, m), 1.92 (2H, m), 2.15 (6H, s), 2.40 (2H, t), 3.19 (3H, s), 3.33 – 3.37 (4H, m), 3.95 (3H, s), 5.18 (1H, m), 7.47 – 7.50 (1H, m), 7.51 (1H, s), 7.68 (1H, s), 8.02 (1H, s). 8.29 (1H, 4), 8.39 (1H, d); MS m/z 510 $[M+H]^+$.

Ejemplo 360:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(4–pirrolidin–1–ilciclohexil)benzamida

A una solución de ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico (Producto intermedio 236; 83 mg, 0.19 mmol) en DMF (3 mL) fue añadida una solución de 4–pirrolidin–1–ilciclohexan–1–amina (Producto intermedio 237; 78 mg, 0.46 mmol). DIPEA (100 uL, 0.57 mmol) fue añadido, seguido por HATU (107 mg, 0.28 mmol). La mezcla resultante fue agitada a temperatura ambiente durante 2 horas. La mezcla de reacción fue evaporada hasta una goma, la cual fue particionada entre DCM (20 mL) y solución de bicarbonato de sodio saturada acuosa. (20 mL). La fase orgánica fue separada mediante elusión por gravedad a través de un vaso filtro PTFE y evaporadas hasta una goma ámbar la cual fue purificada por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido color hueso (34 mg, 30%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.29 (m, 2H), 1.41 – 1.83 (m, 12H), 1.95 – 2.20 (m, 7H), 2.60 (m, 4H), 3.30 (s, 3H), 3.37 (s, 2H), 3.94 (m, 1H), 3.97 (s, 3H), 5.31 (m, 1H), 5.83 (d, 1H), 7.20 (m, 1H), 7.42 (d, 1H), 7.60 (s, 1H), 7.85 (s, 1H), 8.47 (d, 1H); MS m/z 590 $[M+H]^+$.

Ejemplo 361:

4-[(2-ciclopentil-4,4,6-trimetil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-2-fluoro-5-metoxi-N-(1-metil-4-piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.49 mmol, utilizando 4-amino-2-fluoro-5-metoxi-N-(1-metil-4-piperidil)benzamida (Producto intermedio 27; 144 mg, 0.51 mmol), como una espuma blanca (66 mg, 24%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 1.11 (s, 6H), 1.52 – 1.68 (m, 6H), 1.76 (m, 4H), 1.95 (m, 4H), 2.16 (s, 3H), 2.73 (m, 2H), 3.20 (s, 3H), 3.40 (s, 2H), 3.73 (m, 1H), 3.92 (s, 3H), 5.19 (m, 1H), 7.19 (d, 1H), 7.79 (m, 2H), 8.02 (s, 1H), 8.31 (d, 1H); MS m/z 554 $[M+H]^+$.

Ejemplo 362:

3-cloro-4-[(2-ciclopentil-4,4,6-trimetil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(3-dimetilaminopropil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 355, en una escala de 0.34 mmol, utilizando 4-amino-3-cloro-N-(3-dimetilaminopropil)benzamida (Producto intermedio 214; 98 mg, 0.38 mmol), como un sólido color hueso (27 mg, 15%).

^{1}H NMR (400.132 MHz, DMSO-d6) d 1.10 (s, 6H), 1.50 – 1.74 (m, 8H), 1.83 (m, 2H), 2.15 (s, 6H), 2.27 (t, 2H), 3.19 (s, 3H), 3.28 (m, 2H), 3.37 (s, 2H), 5.11 (m, 1H), 7.77 (m, 1H), 7.96 (d, 1H), 7.99 (s, 1H), 8.11 (s, 1H), 8.27 (d, 1H), 8.48 (t, 1H); MS m/z 528 $[M+H]^+$.

Ejemplo 363:

4-[(2-ciclopentil-4,4,6-trimetil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(4-dimetilaminociclohexil)-3-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.49 mmol, utilizando 4-amino-N-(4-dimetilaminociclohexil)-3-metoxi-benzamida (Producto intermedio 239; 144 mg, 0.51 mmol), como una espuma blanca (39 mg, 14%).

^{1}H NMR (400.132 MHz, DMSO-d6) d 1.10 (s, 6H), 1.21 – 2.04 (m, 16H), 2.10 – 2.21 (m, 7H), 3.19 (s, 3H), 3.38 (s, 2H), 3.72 & 3.92 (m, 1H), 3.95 (s, 3H), 5.19 (m, 1H), 7.49 (m, 2H), 7.66 (d, 1H), 7.99 (s, 1H), 8.01 (d, 1H), 8.36 (d, 1H); MS m/z 564 [M+H]+.

Ejemplo 364:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.32 mmol, utilizando 4–amino–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 182; 77 mg, 0.32 mmol) calentando térmicamente a 140 °C durante 3 horas, como un sólido blanco (84 mg, 49%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.11 (6H, s), 1.64 – 1.76 (7H, m), 1.87 – 1.94 (2H, m), 2.13 – 2.22 (1H, m), 2.26 (3H, s), 2.34 – 2.45 (2H, m), 2.58 – 2.64 (1H, m), 2.66 – 2.71 (1H, m), 3.20 (3H, s), 3.41 (2H, s), 3.93 (3H, s), 4.36 – 4.41 (1H, m), 5.15 – 5.24 (1H, m), 7.22 (1H, d), 7.78 (1H, d), 7.97 – 8.00 (1H, m), 8.03 (1H, s), 8.32 (1H, d); MS m/z 540 [M+H]+.

Ejemplo 365:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–2–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 355, en una escala de 0.32 mmol, utilizando 4–amino–2–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 241; 93 mg, 0.34 mmol), como un sólido color hueso (113 mg, 62%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.91 (2H, d), 1.11 (6H, s), 1.38 (1H, m), 1.42 (2H, m), 1.61 (2H, s), 1.64 (2H, t), 1.75 (1H, s), 1.84 (2H, m), 1.89 (2H, m), 2.03 (1H, m), 2.20 (2H, m), 2.39 (3H, s), 2.98 (2H, d), 3.17 (3H, s), 3.40 (2H, s), 4.28 (1H, m), 5.23 (1H, m), 7.38 (1H, d), 7.52 (1H, t), 7.64 (1H, m), 7.89 (1H, d), 8.01 (1H, s), 9.62 (1h, s); MS m/z 565 $[M+H]^+$.

Ejemplo 366:

5–cloro–4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 355, en una escala de 0.29 mmol, utilizando 4–amino–5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida (Producto intermedio 175; 92 mg, 0.29 mmol) calentando a 110 °C durante 3 horas, como un sólido color hueso (55 mg, 32%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.11 (6H, s), 1.25 – 1.37 (3H, m), 1.47 – 2.01 (13.5H, m), 2.13 (6.5H, d), 3.20 (3H, s), 3.40 (2H, s), 3.62 – 3.71 y 3.88 – 3.95 (each 0.5H, m), 5.12 – 5.20 (1H, m), 7.65 – 7.68 (1H, m), 7.99 – 8.04 (2H, m), 8.10 (1H, d), 8.30 – 8.35 (1H, m); MS m/z 587 $[M+H]^+$.

Ejemplo 367:

3–cloro–4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(2,2–dimetil–3–pirrolidin–1–il–propil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 355, en una escala de 0.34 mmol, utilizando 4–amino–3–cloro–N–(2,2–dimetil–3–pirrolidin–1–il–propil)benzamida (Producto intermedio 244; 123 mg, 0.39 mmol) calentando a 110 °C durante 3 horas, como un sólido color hueso (35 mg, 18%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.90 (s, 6H), 1.10 (s, 6H), 1.49 – 1.85 (m, 12H), 2.42 (s, 2H), 2.60 (m, 4H), 3.19 (s, 3H), 3.21 (d, 2H), 3.36 (s, 2H), 5.09 (m, 1H), 7.73 (m, 1H), 7.88 (d, 1H), 7.98 (s, 1H), 8.15 (s, 1H), 8.25 (d, 1H), 8.69 (t, 1H); MS m/z 582 [M+H]+.

Ejemplo 368:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.33 mmol, utilizando 4–amino–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida (Producto intermedio 206; 100 mg, 0.33 mmol) calentando térmicamente a 120 °C durante 3 días, como un sólido blanco (55 mg, 29%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.20 (s, 3H), 1.54 – 160 (m, 8H), 1.80 – 1.63 (m, 8H), 2.03 – 1.95 (m, 2H), 2.56 (s, 2H), 2.72 – 2.65 (m, 4H), 3.29 (s, 3H), 3.37 (s, 2H), 3.39 (d, 2H), 3.98 (s, 3H), 5.34 (quinteto, 1H), 7.20 (d, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.86 (s, 1H), 8.43 (d, 1H), 9.16 – 9.10 (m, 1H); MS m/z 578 $[M+H]^+$.

Ejemplo 369:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–[(3R)–1–etilpirrolidin–3–il]–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.22 mmol, utilizando 4–amino–N–[(3R)–1–etilpirrolidin–3–il]–3–metoxi–benzamida (Producto intermedio 245; 70 mg, 0.26 mmol) calentando por irradiación de microondas a 160 °C durante 1 hora, como un sólido blanco (50 mg, 42%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.04 (t, 3H), 1.10 (s, 6H), 1.55 – 1.93 (m, 9H), 2.15 (m, 1H), 2.43 (m, 4H), 2.65 (m, 1H), 2.73 (m, 1H), 3.19 (s, 3H), 3.38 (s, 2H), 3.95 (s, 3H), 4.40 (m, 1H), 5.19 (m, 1H), 7.51 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.28 (d, 1H), 8.37 (d, 1H); MS m/z 536 [M+H]+.

Ejemplo 370:

4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida

10–cloro–2–ciclopentil–4,4,6–trimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 127; 52 mg, 0.17 mmol), 4–amino–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida (Producto intermedio 205; 50 mg, 0.17mmol) y ácido p–toluenosulfónico monohidrato (81 mg, 0.43 mmol) fueron agitados y calentados juntos en 4–metil–2–pentanol (2 mL) por irradiación de microondas a 150 °C durante 1 hora. Una porción adicional de 10–cloro–2–ciclopentil–4,4,6–trimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (10mg) fue añadida y la reacción continuó durante 1 hora adicional. La solución enfriada fue cargada en una columna SCX–3 (5g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volumenes de columna) y eluida con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (49 mg, 51%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.00 (t, 3H), 1.11 (s, 6H), 1.74 (m, 12H), 2.32 (q, 2H), 2.83 (m, 2H), 3.17 (s, 3H), 3.40 (s, 2H), 3.73 (m, 1H), 3.92 (s, 3H), 5.19 (m, 1H), 7.19 (d, 1H), 7.77 (s, 1H), 7.80 (m, 1H), 8.02 (s, 1H), 8.31 (d, 1H); MS m/z 568 [M+H]+.

Ejemplo 371:

4-[(2-ciclopentil-4,4,6-trimetil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-10-il)amino]-3-fluoro-N-(1-metil-4-piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.45 mmol, utilizando 4-amino-3-fluoro-N-(1-metil-4-piperidil)benzamida (Producto intermedio 65; 114 mg, 0.45 mmol) calentando por irradiación de microondas a 160 °C durante 30 minutos, como un sólido blanco (96 mg, 41%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.1 (s, 6H), 1.55 (m, 6H), 1.7 – 1.85 (m, 6H), 1.95 (t, 2H), 2.8 (d, 2H), 3.2 (s, 3H), 3.35 (s, 2H), 3.75 (m, 1H), 5.15 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.85 (s, 1H); MS m/z 525 $[M+H]^+$.

Ejemplo 372:

4-[(2-ciclopentil-4,4,6-trimetil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(4-dimetilaminociclohexil)-2-fluoro-5-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.16 mmol, utilizando 4-amino-N-(4-dimetilaminociclohexil)-2-fluoro-5-metoxi-benzamida (isómero simple no definido) (Producto intermedio 248; 50 mg, 0.16 mmol) calentando por irradiación de microondas a 150 °C durante 1 hora, como un sólido blanco (30 mg, 32%).

^{1}H NMR (400.132 MHz, DMSO-d_6) δ 1.11 (6H, s), 1.63 (14H, m), 1.90 (2H, m), 2.07 (1H, m), 2.17 (6H, s), 3.20 (3H, s), 3.40 (2H, s), 3.92 (3H, s), 3.94 (1H, m), 5.19 (1H, m), 7.19 (1H, d), 7.71 (1H, m), 7.77 (1H, s), 8.02 (1H, s), 8.31 (1H, d); MS m/z 582 $[M+H]^+$.

Ejemplo 373:

4-[(2-ciclopentil-4,4,6-trimetil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(4-dimetilaminociclohexil)-2-fluoro-5-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, en una escala de 0.16 mmol, utilizando 4-amino-N-(4-dimetilaminociclohexil)-2-fluoro-5-metoxi-benzamida (isómero simple no definido) (Producto intermedio 249; 50 mg,

0.16 mmol) calentando por irradiación de microondas a 150 °C durante 1 hora, como un sólido blanco (50 mg, 54%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.11 (6H, s), 1.30 (4H, m), 1.75 (12H,m), 2.12 (1H, m), 2.18 (6H, s), 3.20 (3H, s), 3.40 (2H, s), 3.69 (1H, m), 3.92 (3H, s), 5.18 (1H, m), 7.19 (1H, d), 7.73 (1H, m), 7.76 (1H, s), 8.02 (1H, s), 8.30 (1H, d); MS m/z 582 $[M+H]^+$.

Ejemplo 374:

N–[4–(azetidin–1–il)ciclohexil]–4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 346, utilizando 10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 127; 75 mg, 0.17 mmol) y 4–(azetidin–1–il)ciclohexan–1–amina (Producto intermedio 226; 39 mg, 0.25 mmol) como un sólido color hueso (35 mg, 36%) asignado como el trans isómero.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.92 – 1.00 (2H, m), 1.10 (6H, s), 1.29 – 1.39 (2H, m), 1.58 – 1.94 (15H, m), 3.07 (4H, t), 3.19 (3H, s), 3.38 (2H, s), 3.67 – 3.76 (1H, m), 3.94 (3H, s), 5.19 (1H, quinteto), 7.45 – 7.48 (2H, m), 7.67 (1H, s), 7.99 (1H, s), 8.00 (1H, d), 8.36 (1H, d); MS m/z 576 $[M+H]^+$.

Ejemplo 375:

N–[4–(azetidin–1–il)ciclohexil]–4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzamida

El compuesto del título fue aislado de la reacción anterior para producir el Ejemplo 374, como un sólido color hueso (35 mg, 36%) asignado como el cis isómero.

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.03 (6H, s), 1.24 – 1.31 (2H, m), 1.37 – 1.42 (2H, m), 1.50 – 1.70 (10H, m), 1.78 – 1.86 (4H, m), 2.12 – 2.16 (1H, m), 2.96 – 3.04 (4H, m), 3.12 (3H, s), 3.31 (2H, s), 3.69 – 3.79 (1H, m), 3.87 (3H, s), 5.12 (1H, quinteto), 7.42 – 7.46 (2H, m), 7.58 (1H, s), 7.91 (1H, s), 7.96 (1H, d), 8.28 (1H, d); MS m/z 576 $[M+H]^+$.

Ejemplo 376:

4-[(2-ciclopentil-4,4-dietil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(2,2-dimetil-3-pirrolidin-1-il-propil)-3-metoxi-benzamida

10-cloro-2-ciclopentil-4,4-dietil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 250; 111 mg, 0.33 mmol), ácido p-toluenosulfónico monohidrato (155 mg, 0.81 mmol) y 4-amino-N-(2,2-dimetil-3-pirrolidin-1-il-propil)-3-metoxi-benzamida (Producto intermedio 206; 100 mg, 0.33 mmol) fueron añadidos a 4-metil-2-pentanol (7 mL). La reacción fue calentada a 120 °C todo el fin de semana. La muestra fue transferida a un cartucho SCX (10 g) prehumedecido con metanol, luego lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (55 mg, 27%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.01 (s, 6H), 1.80 – 1.48 (m, 14H), 2.02 – 1.94 (m, 2H), 2.56 (s, 2H), 2.69 (s, 4H), 3.28 (s, 3H), 3.39 (d, 2H), 3.42 (s, 2H), 3.98 (s, 3H), 5.42 (quinteto, 1H), 7.20 (d, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.84 (s, 1H), 8.43 (d, 1H), 9.14 (s, 1H); MS m/z 606 $[M+H]^+$.

Ejemplo 377:

4-[(2-ciclopentil-4,4-dietil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-10-il)amino]-3-metoxi-N-[(1S,5R)-9-metil-9-azabiciclo[3.3.1]non-7-il]benzamida

10-cloro-2-ciclopentil-4,4-dietil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona (Producto intermedio 250; 100 mg, 0.30 mmol), ácido p-toluenosulfónico monohidrato (142 mg, 0.75 mmol) y 4-amino-3-metoxi-N-[(1S,5R)-9-metil-9-azabiciclo[3.3.1]non-3-il]benzamida (Producto intermedio 202; 91 mg, 0.30 mmol) fueron añadidos a 4-metil-2-pentanol (7 mL). La reacción fue calentada a 120 °C todo el fin de semana. La muestra fue transferida a un cartucho SCX (10 g) prehumedecido con metanol, luego lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (80 mg, 44%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.09 – 1.07 (m, 2H), 1.44 – 1.38 (m, 2H), 1.63 – 1.48 (m, 6H), 1.80 – 1.66 (m, 6H), 2.03 – 1.94 (m, 3H), 2.56 – 2.49 (m, 4H), 3.14 – 3.11 (m, 2H), 3.28 (s, 3H), 3.42 (s, 2H), 3.97 (s, 3H), 4.58 – 4.47 (m, 1H), 5.42 – 5.32 (m, 1H), 5.94 (d, 1H), 7.25 (dd, 1H), 7.25 (d, 1H), 7.25 (d, 1H), 7.44 (d, 1H), 7.60 (s, 1H), 7.83 (s, 1H), 8.47 (d, 1H); MS m/z 604 $[M+H]^+$.

Ejemplo 378:

4–[(2–ciclopentil–4,4–dietil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 377, utilizando 4–amino–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 204; 96 mg, 0.30 mmol), como un sólido blanco (25 mg, 13%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.84 (t, 6H), 1.07 – 1.04 (m, 2H), 1.36 – 1.30 (m, 2H), 1.63 – 1.49 (m, 6H), 1.82 – 1.66 (m, 7H), 2.04 – 1.91 (m, 4H), 2.57 – 2.51 (m, 4H), 3.11 – 3.08 (m, 2H), 3.29 (s, 3H), 3.44 (s, 2H), 3.95 (s, 3H), 4.58 – 4.46 (m, 1H), 5.36 (quinteto, 1H), 6.55 (dd, 1H), 7.57 (d, 1H), 7.67 (s, 1H), 7.85 (s, 1H), 8.37 (d, 1H); MS m/z 622 $[M+H]^+$.

Ejemplo 379:

4–[(2–ciclopentil–4,4–dietil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 377, utilizando 4–amino–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida (Producto intermedio 205; 89 mg, 0.30 mmol), como un sólido blanco (35 mg, 20%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.10 (t, 3H), 1.62 – 1.49 (m, 6H), 1.81 – 1.65 (m, 6H), 2.08 – 1.98 (m, 4H), 2.19 – 2.13 (m, 2H), 2.43 (q, 2H), 2.89 – 2.86 (m, 2H), 3.29 (s, 3H), 3.44 (s, 2H), 3.95 (s, 3H), 4.09 – 3.99 (m, 1H), 5.34 (quinteto, 1H), 6.68 (dd, 1H), 7.55 (d, 1H), 7.67 (s, 1H), 7.84 (s, 1H), 8.37 (d, 1H); MS m/z 596 $[M+H]^+$.

Ejemplo 380:

4-[(2-ciclopentil-4,4-dietil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-3-metoxi-N-(1-metil-4-piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 377, utilizando 4-amino-3-metoxi-N-(1-metil-4-piperidil)benzamida (WO06/018220; 79 mg, 0.30 mmol), como un sólido blanco (30 mg, 18%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (t, 6H), 1.64 – 1.48 (m, 6H), 1.80 – 1.66 (m, 6H), 2.00 – 1.92 (m, 2H), 2.07 – 2.05 (m, 2H), 2.20 – 2.14 (m, 2H), 2.31 (s, 3H), 2.84 – 2.81 (m, 2H), 3.28 (s, 3H), 3.42 (s, 2H), 4.03 – 3.92 (m, 4H), 5.38 (quinteto, 1H), 5.89 (d, 1H), 7.22 (dd, 1H), 7.41 (d, 1H), 7.59 (s, 1H), 7.84 (s, 1H), 8.48 (d, 1H); MS m/z 564 $[M+H]^+$.

Ejemplo 381:

4-[(2-ciclopentil-4,4-dietil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(1-etil-4-piperidil)-3-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 377, utilizando 4-amino-N-(1-etil-4-piperidil)-3-metoxi-benzamida (Producto intermedio 190; 83 mg, 0.30 mmol), como un sólido blanco (90 mg, 52%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.77 (t, 6H), 1.03 (t, 3H), 1.56 – 1.41 (m, 6H), 1.73 – 1.59 (m, 6H), 1.95 – 1.87 (m, 2H), 2.10 – 1.98 (m, 4H), 2.37 (q, 2H), 2.86 – 2.83 (m, 2H), 3.22 (s, 3H), 3.35 (s, 2H), 3.98 – 3.91 (m, 4H), 5.31 (quinteto, 1H), 5.82 (d, 1H), 7.15 (dd, 1H), 7.34 (d, 1H), 7.52 (s, 1H), 7.77 (s, 1H), 8.41 (d, 1H); MS m/z 578 $[M+H]^+$.

Ejemplo 382:

3-cloro-4-(9'-ciclopentil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-N-(1-etilpiperidin-4-il)benzamida

2'-cloro-9'-ciclopentil-5'-metil-8',9'-dihidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepin]-6'(5'H)-ona (Producto intermedio 130; 108 mg, 0.35 mmol) 4-amino-3-cloro-N-(1-etil-4-piperidil)benzamida (Producto intermedio 212; 118 mg, 0.42 mmol), y ácido p-toluenosulfónico monohidrato (133 mg, 0.7 mmol) fueron combinados en 4-metil-2-pentanol (4 mL) y calentados por irradiación de microondas a 160 °C durante 1 hora. La mezcla de reacción fue cargada en un cartucho SCX (10 g) prehumedecido con metanol, luego lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el

producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (38 mg, 20%).

^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.66 – 0.69 (2H, m), 0.90 – 0.93 (2H, m), 1.00 (3H, t), 1.41 – 1.70 (8H, m), 1.77 – 1.85 (4H, m), 1.90 – 1.96 (2H, m), 2.32 (2H, q), 2.88 (2H, d), 3.18 (3H, s), 3.47 (2H, s), 3.72 – 3.76 (1H, m), 4.74 – 4.82 (1H, m), 7.79 (1H, dd), 7.98 – 8.00 (2H, m), 8.08 (1H, s), 8.20 (1H, d), 8.30 – 8.34 (1H, m)

MS m/z 552 $[M+H]^+$.

Ejemplo 383:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–3–metoxi–benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 100 mg, 0.33 mmol), 4–amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida (Producto intermedio 190; 91 mg, 0.33 mmol) y ácido p–toluenosulfónico monohidrato (156 mg, 0.81 mmol) fueron calentados a 140 °C en 4–metil–2–pentanol (4 mL) durante 2 horas. La mezcla de reacción fue cargada en un cartucho SCX–3 (10 g) prehumedecido con metanol, luego lavado con metanol y eluido con 2% metanol/amoniaco 7N. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (89 mg, 50%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.67 – 0.69 (2H, t), 0.90 – 0.93 (2H, t), 1.01 (3H, t), 1.51 – 1.51 (1H, m), 1.52 (1H, d), 1.56 – 1.62 (4H, m), 1.68 (1H, s), 1.70 (1H, d), 1.78 (1H, d), 1.81 (1H, s), 1.93 (4H, d), 2.33 (2H, q), 2.90 (2H, d), 3.19 (3H, s), 3.49 (2H, s), 3.61 – 3.65 (1H, m), 3.96 (3H, s), 4.86 (1H, m), 7.47 (1H, t), 7.50 (1H, d), 7.68 (1H, s), 8.00 (1H, s), 8.07 (1H, d), 8.40 (1H, d); MS m/z 549 $[M+H]^+$.

Ejemplo 384:

4-(9'-ciclopentil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-3-metoxi-N-(2-pirrolidin-1-iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 383, utilizando 4-amino-3-metoxi-N-(2-pirrolidin-1-iletil)benzamida (Producto intermedio 192; 86 mg, 0.30 mmol), como un sólido blanco (20 mg, 11%).

^{1}H NMR (399.9 MHz, DMSO-d6) δ 0.67 – 0.69 (2H, t), 0.90 – 0.93 (2H, t), 1.52 (2H, d), 1.61 (2H, t), 1.65 – 1.71 (7H, m), 1.89 – 1.92 (3H, m), 2.58 (2H, t), 3.18 (3H, s), 3.20 (2H, t) – encontrado bajo agua, 3.39 (2H, q), 3.49 (2H, s), 3.95 (3H, s), 4.86 (1H, s), 7.46 (1H, d), 7.48 – 7.51 (1H, m), 7.69 (1H, s), 7.99 (1H, s), 8.31 (1H, t), 8.40 – 8.42 (1H, m); MS m/z 535 $[M+H]^+$.

Ejemplo 385:

4-(9'-ciclopentil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-3-metoxi-N-[(1S,5R)-9-metil-9-azabiciclo[3.3.1]non-7-il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 383, utilizando 4-amino-3-metoxi-N-[(1S,5R)-9-metil-9-azabiciclo[3.3.1]non-3-il]benzamida (Producto intermedio 202; 99 mg, 0.30 mmol), como un sólido blanco (114 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 0.67 – 0.70 (2H, t), 0.90 – 0.93 (2H, t), 0.95 (2H, s), 1.42 – 1.48 (2H, m), 1.43 – 1.49 (2H, m), 1.54 (2H, t), 1.60 – 1.63 (1H, m), 1.68 (1H, s), 1.70 (1H, d), 1.89 – 1.97 (4H, m), 2.08 (1H, d), 2.16 – 2.24 (2H, m), 2.42 (3H, s), 2.98 – 3.01 (2H, d), 3.18 (3H, s), 3.49 (2H, s), 3.97 (3H, s), 4.34 (1H, m), 4.87 (1H, m), 7.47 (1H, d), 7.50 (1H, t), 7.68 (1H, s), 7.92 (1H, d), 8.00 (1H, s), 8.40 (1H, d); MS m/z 575 $[M+H]^+$.

Ejemplo 386:

4-(9'-ciclopentil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-N-(3-dimetilamino-2,2-dimetil-propil)-3-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 383, utilizando 4–amino–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida (Producto intermedio 22; 92 mg, 0.30 mmol), como un sólido blanco (89 mg, 50%).
^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.67 – 0.69 (2H, m), 0.89 (6H, s), 0.90 – 0.93 (2H, t), 1.51 (1H, d), 1.54 (1H, s), 1.58 (1H, d), 1.61 – 1.62 (1H, m), 1.69 (2H, d), 1.90 (2H, d), 2.21 (2H, s), 2.29 (6H, s), 3.19 (3H, s), 3.21 (2H, d), 3.48 (2H, s), 3.96 (3H, s), 4.86 (1H, m), 7.41 – 7.43 (1H, m), 7.47 (1H, d), 7.70 (1H, s), 7.99 (1H, s), 8.41 (1H, d), 8.44 (1H, t); MS m/z 551 $[M+H]^+$.

Ejemplo 387:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(2–dimetilaminoetil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 383, utilizando 4–amino–N–(2–dimetilaminoetil)–3–metoxi–benzamida (Producto intermedio 194; 78 mg, 0.30 mmol), como un sólido blanco (82 mg, 50%).
^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.67 – 0.70 (2H, t), 0.92 (2H, t), 1.51 (1H, d), 1.55 (1H, d), 1.60 – 1.63 (2H, m), 1.70 (2H, t), 1.90 (2H, s), 2.19 (6H, s), 2.41 (2H, t), 3.18 (3H, s), 3.37 (2H, q), 3.49 (2H, s), 3.95 (3H, s), 4.86 (1H, m), 7.46 (1H, d), 7.48 – 7.51 (1H, d), 7.69 (1H, s), 7.99 (1H, d), 8.27 (1H, t), 8.39 – 8.42 (1H, m); MS m/z 509 $[M+H]^+$.

Ejemplo 388:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 108 mg, 0.35 mmol) y 4–amino–3–fluoro–N–(9–metil–9–azabiciclo[3.3.1]non–7–il)benzamida (Producto intermedio 162; 102 mg, 0.35 mmol) fueron combinados con ácido p–toluenosulfónico monohidrato (167 mg, 0.88 mmol) en 4–metil–2–pentanol (2 mL) y calentado por irradiación de microondas durante 25 minutos a 160 °C La mezcla de reacción enfriada fue diluida con metanol (10 mL) y cargada

en un cartucho SCX–3 (5 g) prehumedecido con metanol. El cartucho fue lavado con metanol (2 x 5 mL) y eluido con amoniaco metanólico 7 N (10 mL). Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para dar el compuesto del título como un sólido blanco (54 mg, 28 %).

^{1}H NMR (400 MHz, DMSO–d_6) δ 0.65 (t, 2H), 0.9 (m, 4H), 1.5 (m. 7H), 1.65 (m, 2H), 1.85 (m, 4H), 2.05 (m, 1H), 2.2 (m, 2H), 2.4 (s, 3H), 3.0 (d, 2H), 3.2 (s, 3H), 3.45 (s, 2H), 4.3 (m, 1H), 4.8 (m, 1H) 7.65 (m, 1H), 7.75 (m, 1H), 7.95 (m, 2H), 8.15 (t, 1H), 8.65 (s, 1H); MS m/z 562 $[M+H]^+$.

Ejemplo 389:

5–cloro–4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–N–(1–metil–4–piperidil)benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 85 mg, 0.30 mmol), 4–amino–5–cloro–2–fluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 173; 101 mg, 0.33 mmol) y XANTFOS (16 mg, 0.03 mmol) fueron disueltos en 1,4–dioxano (7.5 mL). Carbonato de cesio (210 mg, 0.59 mmol) fue añadido y el sistema purgado con una corriente de nitrógeno durante 15 minutos antes que tris(dibencilidenoacetona) paladio (II) (17 mg, 0.02 mmol) fuera añadido. El aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y luego calentado a 100 °C durante 3 horas. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, la cual fue posteriormente lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (100 mg, 60%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.69 – 0.71 (2H, m), 0.92 – 0.95 (2H, m), 1.51 – 1.64 (6H, m), 1.66 – 1.71 (2H, m), 1.77 – 1.80 (2H, m), 1.85 – 1.99 (4H, m), 2.17 (3H, s), 2.74 (2H, d), 3.19 (3H, s), 3.50 (2H, s), 3.66 – 3.73 (1H, m), 4.80 – 4.88 (1H, m), 7.68 (1H, d), 8.04 – 8.09 (3H, m), 8.35 – 8.39 (1H, m); MS m/z 556 $[M+H]^+$.

Ejemplo 390:

3–cloro–4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(2–dimetilaminoetil)benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 100 mg, 0.33 mmol) y 4–amino–3–cloro–N–(2–dimetilaminoetil)benzamida (Producto intermedio 213; 89 mg, 0.37 mmol) fueron disueltos en 1,4 dioxano (4 mL) y carbonato de cesio (234 mg, 0.72 mmol) fue añadido. La mezcla de reacción fue burbujeada con nitrógeno durante 15 minutos antes de la adición de tris–dibencilidenoacetonadipaladio (II) (19 mg, 0.02 mmol) seguido por XANTFOS (19 mg, 0.03 mmol). La mezcla de reacción fue calentada a 100 °C toda la noche, enfriada a temperatura ambiente y diluida con DCM (20 mL). La mezcla resultante fue filtrada y el filtrado cargado en un cartucho SCX–3 (5 g). El cartucho fue lavado completamente con metanol (50 mL) y luego eluido con amoniaco 2M en metanol (50 mL). La evaporación de la fracción amoniacal proporcionó una goma ámbar la cual fue purificada por HPLC en fase inversa preparativa del ácido modificado. El material resultante fue disuelto en MeOH/Agua y vertido en un cartucho SCX–3 (2 g) y el cartucho el cual fue luego lavado con metanol y eluido con amoniaco 2M en metanol, y la solución amoniacal evaporados para proporcionar el compuesto del título como un sólido (7 mg, 3%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.67 (m, 2H), 0.91 (m, 2H), 1.41 – 1.69 (m, 6H), 1.83 (m, 2H), 2.19 (s, 6H), 2.41 (t, 2H), 3.18 (s, 3H), 3.35 (m, 2H), 3.47 (s, 2H), 4.78 (m, 1H), 7.78 (m, 1H), 7.97 (d, 1H), 7.99 (s, 1H), 8.10 (s, 1H), 8.32 (d, 1H), 8.37 (t, 1H); MS m/z 512 $[M+H]^+$.

Ejemplo 391:

3–cloro–4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 390, utilizando 4–amino–3–cloro–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 215; 97 mg, 0.36 mmol), como un sólido blanco (7 mg, 3%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.67 (m, 2H), 0.91 (m, 2H), 1.50 (m, 4H), 1.67 (m, 6H), 1.83 (m, 2H), 2.58 (t, 2H), 3.18 (s, 3H), 3.38 (m, 2H), 3.47 (s, 2H), 4.78 (m, 1H), 7.79 (m, 1H), 7.97 (d, 1H), 7.99 (s, 1H), 8.10 (s, 1H), 8.32 (d, 1H), 8.42 (t, 1H); MS m/z 538 $[M+H]^+$.

Ejemplo 392:

3–cloro–4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(3–dimetilamino–2,2–dimetil–propil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 390, utilizando 4–amino–3–cloro–N–(3–dimetilamino–2,2–dimetil–propil)benzamida (Producto intermedio 107; 103 mg, 0.36 mmol), como un sólido blanco (4 mg, 2%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.67 (m, 2H), 0.88 (s, 6H), 0.91 (m, 2H), 1.41 – 1.70 (m, 6H), 1.83 (m, 2H), 2.18 (s, 2H), 2.27 (s, 6H), 3.19 (m, 5H), 3.46 (s, 2H), 4.77 (m, 1H), 7.75 (m, 1H), 7.94 (d, 1H), 7.99 (s, 1H), 8.13 (s, 1H), 8.29 (d, 1H), 8.46 (t, 1H); MS m/z 554 $[M+H]^+$.

Ejemplo 393:

5–cloro–4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 389, utilizando 4–amino–5–cloro–N–(1–etil–4–piperidil)–2–fluoro–benzamida (Producto intermedio 174; 90 mg, 0.30 mmol), como un sólido blanco (102 mg, 60%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.69 – 0.71 (2H, m), 0.92 – 0.95 (2H, m), 1.00 (3H, t), 1.49 – 2.01 (14H, m), 2.32 (2H, q), 2.84 (2H, d), 3.19 (3H, s), 3.50 (2H, s), 3.68 – 3.74 (1H, m), 4.82 – 4.88 (1H, m), 7.68 (1H, d), 8.04 – 8.08 (3H, m), 8.35 – 8.39 (1H, m); MS m/z 570 $[M+H]^+$.

Ejemplo 394:

5–cloro–4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 389, utilizando 4–amino–5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida (Producto intermedio 175; 94 mg, 0.30 mmol), como un sólido blanco (65 mg, 37%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.69 – 0.71 (2H, m), 0.92 – 0.95 (2H, m), 1.340 – 1.35(2H, m), 1.49 – 1.94 (14H, m), 2.25 – 2.30 (7H, m), 3.19 (3H, s), 3.50 (2H, s), 3.67 – 3.71 y 3.91 – 3.97 (cada 0.5H. m), 4.80 – 4.88 (1H, m), 7.65 – 7.68 (1H, m), 8.01 – 8.04 (2H, m), 8.08 (1H, d), 8.34 – 8.38 (1H, m); MS m/z 584 $[M+H]^+$.

Ejemplo 395:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 100 mg, 0.33 mmol), 4–amino–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida (Producto intermedio 235; 102 mg, 0.36 mmol) y carbonato de cesio (213 mg, 0.65 mmol) añadido a dioxano (5 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Tris–dibencilidenoacetonadipaladio (II) (18 mg, 0.02 mmol) y XANTFOS (17 mg, 0.03 mmol) fueron añadidos y la mezcla calentada a 110 °C toda la noche. La mezcla fue filtrada, y el filtrado cargado en un cartucho SCX–3 (10 g) prehumedecido con metanol, luego lavado con metanol y eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como una goma naranja clara (99 mg, 55%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.69 (2H, t), 0.93 (2H, t), 1.05 (3H, t), 1.52 – 1.58 (4H, m), 1.61 (2H, m), 1.65 – 1.67 (2h, m), 1.80 (2H, d), 1.85 (2H, d), 2.10 – 2.12 (2H, t), 2.41 (2h, q), 2.91 (2H, d), 3.17 (3H, s), 3.45 (2H, s), 3.75 (1H, m), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 554 $[M+H]^+$.

Ejemplo 396:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2,5–difluoro–N–(1–metil–4–piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 395, utilizando 4–amino–2,5–difluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 59; 97 mg, 0.36 mmol), como un sólido color hueso (122 mg, 69%) ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.69 (2H, t), 0.93 (2H, t), 1.05 (3H, t), 1.52 – 1.58 (4H, m), 1.61 (2H, m), 1.65 – 1.67 (2h, m), 1.80 (2H, d), 1.85 (2H, d), 2.10 – 2.12 (2H, t), 2.22 (3H, s), 2.91 (2H, d), 3.17 (3H, s), 3.45 (2H, s), 3.75 (1H, m), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 540 $[M+H]^+$.

Ejemplo 397:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2,5–difluoro–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 395, utilizando 4–amino–2,5–difluoro–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 230; 97 mg, 0.36 mmol), como una goma amarillo pálido (121 mg, 69%). ^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.69 (2H, t), 0.93 (2H, t), 1.48 – 1.55 (4H, m), 1.58 – 1.64 (6H, m), 1.85 – 1.92 (2H, m), 2.57 (4H, m), 2.68 (2H, t), 3.17 (3H, s), 3.40 (2H, m), 3.45 (2H, s), 4.80 – 4.85 (1H, m), 7.40 (1h, dd), 7.95 (1h, d), 8.19 (1H, s), 8.25 (1H, dd), 8.84 (1h, s); MS m/z 540 $[M+H]^+$.

Ejemplo 398:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–5–metoxi–N–(2–pirrolidin–1–iletil)benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 80 mg, 0.26 mmol), 4–amino–3–metoxi–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 192; 73 mg, 0.26 mmol) y

4.92 (1H, m), 7.22 (1H, d), 7.66 – 7.69 (1H, m), 7.77 (1H, s), 8.03 (1H, s), 8.35 (1H, d); MS m/z 592 $[M+H]^+$.

Ejemplo 405:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–5–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 70 mg, 0.23 mmol), 4–amino–2–fluoro–5–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida (Producto intermedio 254; 70 mg, 0.22 mmol), y ácido p–toluenosulfónico monohidrato (136 mg, 0.71 mmol) fueron agitados y calentados juntos en 4–metil–2–pentanol (3 mL) a 110 °C durante 18 horas.

La solución de reacción enfriada fue cargada en una columna SCX–3 (5g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volumenes de columna) y el producto eluido con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (38 mg, 29%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.34 (2H, m), 0.50 (2H, m), 0.69 (2H, m), 0.92 (2H, m), 1.61 (12H, m), 1.92 (2H, m), 2.44 (2H, s), 2.50 (2H, s), 3.18 (3H, s), 3.36 (2H, d), 3.51 (2H, s), 3.93 (3H, s), 4.89 (1H, m), 7.37 (1H, d), 7.80 (1H, s), 8.03 (1H, s), 8.37 (2H, d), 8.41 (1H, m); MS m/z 592 $[M+H]^+$.

Ejemplo 406:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–3–fluoro–benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 231 mg, 0.75 mmol), 4–amino–N–(1–etilpiperidin–4–il)–3–fluorobenzamida (200 mg, 0.75 mmol) y ácido p–toluenosulfónico monohidrato (335 mg, 1.88 mmol) fueron suspendidos en 4–Metil–2–pentanol (5 mL) y sellados en un tubo de microondas. La reacción fue calentada hasta 160 °C durante 30

minutos en el reactor de microondas y se dejó enfriar a temperatura ambiente.

El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando NH_3 7M/MeOH y las fracciones puras fueron evaporadas hasta secarse para proporcionar un aceite naranja/marrón el cual fue purificado por HPLC preparativa usando mezclas decrecientemente polares de agua (que contienen 1% NH_3) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar el compuesto del título como un sólido blanco (48 mg, 12%).

^{1}H NMR (400 MHz, DMSO–d6) δ 0.65 (t, 2H), 0.9 (t, 2H), 1.0 (t. 3H), 1.5 (m, 7H), 1.6 (m, 2H), 1.9 (t, 2H), 2.3 (q, 2H), 2.9 (d, 2H), 3.2 (s,3H), 3.4 (s, 2H), 3.6 (m, 1H), 4.75 9m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s, 1H), 8.15 (m, 1H), 8.6 (s, 1H); MS m/z 537 $[M+H]^+$.

Ejemplo 407:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 121 mg, 0.39 mmol) y 4–amino–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida (Producto intermedio 205; 116 mg, 0.39 mmol) fueron tomados en 4–metil–2–pentanol (4 mL) y ácido p–toluenosulfónico monohidrato (150 mg, 0.79 mmol) añadido. La mezcla de reacción fue calentada a 160 °C por irradiación de microondas durante 1 hora. La mezcla de reacción enfriada fue vertida en una mezcla de metanol y agua (5:2 v/v, 7 mL) y la solución resultante cargada en un cartucho SCX–3 (5 g), el cual había sido prehumedecido con metanol. El cartucho fue lavado completamente con metanol (40 mL) y eluido con amoniaco 2M en metanol (30 mL). La solución amoniacal fue evaporada para dar una goma ámbar proporcionada la cual fue purificada por HPLC en fase inversa preparativa modificada base la cual fue repurificada por cromatografía flash en una columna de sílice eluyendo con 2.5–10% metanol/amoniaco en DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo triturado con dietil éter y el sólido resultante secado bajo vacío, a 60 °C, durante 3 horas para proporcionar el compuesto del título como un sólido banco floculento (86 mg, 39%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.67 – 0.70 (2H, m), 0.91 – 0.94 (2H, m), 1.00 (3H, t), 1.48 – 1.99 (14H, m), 2.32 (2H, q), 2.82 – 2.85 (2H, m), 3.18 (3H, s), 3.50 (2H, s), 3.69 – 3.79 (1H, m), 3.93 (3H, s), 4.82 – 4.91 (1H, m), 7.20 (1H, d), 7.76 (1H, s), 7.79 – 7.82 (1H, m), 8.02 (1H, s), 8.34 (1H, d); MS m/z 566 $[M+H]^+$.

Ejemplo 408:

7–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–metil–4–piperidil)benzo[1,3]dioxol–4–carboxamida

A 2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[4,5–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 108 mg, 0.35 mmol) y 7–amino–N–(1–metilpiperidin–4–il)benzo[d][1,3]dioxol–4–carboxamida (Producto intermedio 223; 98 mg, 0.35 mmol) en 4–metil–2–pentanol (3 mL) fue añadido ácido p–toluenosulfónico monohidrato (139 mg, 0.73 mmol) y la mezcla de reacción calentada a 160 °C por irradiación de microondas durante 1 hora.

Después de enfriar la mezcla de reacción fue diluida con MeOH (5 mL) y agua (2 mL). La mezcla fue luego sometida a cromatografía de intercambio iónico, usando una columna SCX–2 (10 g). Después de eluir completamente con metanol (100 mL) el producto crudo fue eluido de la columna usando amoniaco 2M en metanol (50 mL) y evaporado para proporcionar un residuo marrón, el cual fue purificado por HPLC preparativa usando mezclas decrecientemente polares de agua (que contienen 1% NH_3) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar el compuesto del título como un sólido gris (43 mg, 22 %).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.57 – 0.59 (2H, m), 0.81 – 0.83 (2H, m), 1.31 – 1.60 (8H, m), 1.69 – 1.78 (4H, m), 1.92 – 1.97 (2H, m), 2.09 (3H, s), 2.58 – 2.65 (2H, m), 3.09 (3H, s), 3.36 (2H, s), 3.63 – 3.73 (1H, m), 4.71 (1H, quinteto), 6.07 (2H, s), 7.14 (1H, d), 7.22 (1H, d), 7.45 (1H, d), 7.87 (1H, s), 8.51 (1H, s); MS m/z 548 $[M+H]^+$.

Ejemplo 409:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopentano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–metoxi–N–(1–metilpiperidin–4–il)benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclohexano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 255; 80 mg, 0.24 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 63mg, 0.24mmol) y ácido p–toluenosulfónico monohidrato (114 mg, 0.60 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140 °C durante 3 horas. La mezcla fue enfriada y absorbida en una columna SCX, la cual fue luego lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron evaporadas y el residuo purificado en una columna de sílice (2% amoniaco 7N en metanol/DCM) para dar el compuesto del título como un sólido blanco. (70 mg, 52%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.31 – 1.37 (2H, m), 1.50 – 1.80 (14H, m), 1.89 – 2.06 (6H, m), 2.18 (3H, s), 2.79 (2H, d), 3.21 (3H, s), 3.43 (2H, s), 3.71 – 3.79 (1H, m), 3.96 (3H, s), 4.98 – 5.06 (1H, m), 7.47 – 7.51 (2H, m), 7.70 (1H, s), 8.02 (1H, s), 8.07 (1H, d), 8.38 (1H, d); MS m/z 562 $[M+H]^+$.

Ejemplo 410:

3–metoxi–4–[[6–metil–5–oxo–2–(2–oxociclopentil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il]amino]–N–(1–metil–4–piperidil)benzamida

10–cloro–6–metil–2–(2–oxociclopentil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 261; 58 mg, 0.19 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 53 mg, 0.20 mmol) y ácido p–toluenosulfónico monohidrato (80 mg, 0.42 mmol) fueron disueltos en 4–metil–2–pentanol (2 mL) y calentado por irradiación de microondas a 150 °C durante 30 minutos. Después de enfriar, la mezcla de reacción fue disuelta en metanol (5 mL) y agua (5 mL) y vertida directamente en un cartucho SCX–3 (5 g). El cartucho fue lavado con metanol (50 mL), antes de eluir los productos con amoniaco 2M en metanol (50 mL). La fracción amoniacal fue evaporada y el residuo fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido amarillo (11 mg, 7%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.60 (m, 2H), 1.73 – 2.09 (m, 8H), 2.17 (s, 3H), 2.25 (m, 2H), 2.62 (m, 2H), 2.78 (m, 2H), 3.19 (s, 3H), 3.60 (m, 2H), 3.74 (m, 1H), 3.93 (s, 3H), 4.67 (m, 1H), 7.48 (m, 2H), 7.74 (s, 1H), 8.06 (d, 1H), 8.13 (s, 1H), 8.18 (d, 1H); MS m/z 522 $[M+H]^+$.

Ejemplo 411:

2–cloro–4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–5–fluoro–N–(1–metil–4–piperidil)benzamida

2–amino–9–ciclohexil–5–metil–8,9–dihidro–5H–pirimido[5,4–b][1,4]diazepin–6(7H)–ona (Producto intermedio 263; 100 mg, 0.36 mmol), 4–bromo–2–cloro–5–fluoro–N–(1–metilpiperidin–4–il)benzamida (Producto intermedio 262; 133 mg, 0.38 mmol), xantfos (12.61 mg, 0.02 mmol), acetato de paladio(II) (163 mg, 0.73 mmol) y carbonato de cesio (14.20 mg, 0.04 mmol) fueron añadidos a dioxano (10 mL) y calentado a 103 °C toda la noche. La solución resultante fue filtrada y pasada a través de una columna SCX–3 de 5g. La espuma amarilla obtenida fue triturada con etil acetato caliente para proporcionar un sólido amarillo.

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.16 – 1.08 (m, 1H), 1.43 – 1.35 (m, 2H), 1.63 – 1.48 (m, 5H), 1.80 – 1.71 (m, 6H), 2.08 – 1.99 (m, 2H), 2.19 (s, 3H), 2.59 – 2.56 (m, 2H), 2.78 – 2.75 (m, 2H), 3.17 (s, 3H), 3.71 – 3.60 (m, 3H), 4.41 – 4.36 (m, 1H), 7.30 (d, 1H), 8.06 (s, 1H), 8.16 (d, 1H), 8.26 (d, 1H), 8.78 (s, 1H); MS m/z 544 $[M+H]^+$.

Ejemplo 412:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclohexil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 266; 33 mg, 0.113 mmol), 4–amino–2,5–difluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 59; 29 mg, 0.108 mmol) y carbonato de cesio fueron añadidos a dioxano (3 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Tris(dibencilidenoacetona) paladio (II) (4 mg, 0.006 mmol) y XANTFOS (6 mg, 0.1 mmol) fueron añadidos y la mezcla calentada a 100 °C durante 16 horas. La mezcla de reacción fue enfriada a temperatura ambiente y filtrada. La torta del filtro fue lavada con DCM

y el filtrado evaporado. El residuo fue disuelto en DCM y purificado en una columna de sílice eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM sobre 30 volúmenes de columnas. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta un sólido, el cual fue triturado con isohexano luego filtrado y secado para proporcionar el compuesto del título como un sólido amarillo pálido (46 mg, 81%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.18 (m, 1H), 1.57 (m, 6H), 1.78 (m, 1H), 1.91 (m, 4H), 2.06 (m, 2H), 2.17 (m, 2H), 2.30 (s, 3H), 2.68 (m, 2H), 2.80 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 4.01 (m, 1H), 4.48 (m, 1H), 6.58 (m, 1H), 7.29 (m, 1H), 7.82 (m, 1H), 7.94 (s, 1H), 8.38 (m, 1H); MS m/z 528 $[M+H]^+$.

Ejemplo 413:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–2,5–difluoro–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida (Producto intermedio 269; 50 mg, 0.161 mmol) triturando el producto final con dietil éter antes de la filtración y secado, como un sólido blanco (42 mg, 46%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.39 (m, 2H), 0.57 (m, 2H), 1.17 (m, 1H), 1.54 (m, 4H), 1.75 (m, 5H), 1.92 (m, 4H), 2.49 (s, 2H), 2.54 (m, 4H), 2.68 (m, 2H), 3.29 (s, 3H), 3.46 (m, 2H), 3.72 (m, 2H), 4.50 (m, 1H), 7.29 (m, 1H), 7.83 (m, 1H), 7.94 (s, 1H), 8.32 (m, 1H), 8.64 (m, 1H); MS m/z 569 $[M+H]^+$.

Ejemplo 414:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–2,5–difluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio **229**; 41 mg, 0.161 mmol) triturando el producto final con dietil éter antes de la filtración y secado, como un sólido blanco (49 mg, 59%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.18 (m, 1H), 1.54 (m, 4H), 1.76 (m, 2H), 1.91 (m, 4H), 2.29 (m, 1H), 2.42 (m, 4H), 2.68 (m, 4H), 2.90 (m, 1H), 3.29 (s, 3H), 3.72 (m, 2H), 4.48 (m, 1H), 4.66 (m, 1H), 6.94 (m, 1H), 7.29 (m, 1H), 7.81 (m, 1H), 7.94 (s, 1H), 8.37 (m, 1H); MS m/z 514 $[M+H]^+$.

Ejemplo 415:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida (Producto intermedio 235; 46 mg, 0.161 mmol) triturando el producto final con dietil éter antes de la filtración y secado, como un sólido blanco (60 mg, 69%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.10 (t, 3H), 1.18 (m, 1H), 1.55 (m, 6H), 1.78 (m, 1H), 1.91 (m, 4H), 2.11 (m, 4H), 2.43 (q, 2H), 2.68 (m, 2H), 2.89 (m, 2H), 3.29 (s, 3H), 3.71 (m, 2H), 4.04 (m, 1H), 4.48 (m, 1H), 6.59 (m, 1H), 7.28 (m, 1H), 7.82 (m, 1H), 7.94 (s, 1H), 8.38 (m, 1H); MS m/z 542 $[M+H]^+$.

Ejemplo 416:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–2,5–difluoro–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 230; 43 mg, 0.161 mmol) triturando el producto final con dietil éter antes de la filtración y secado, como un sólido blanco (64 mg, 76%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.18 (m, 1H), 1.54 (m, 4H), 1.77 (m, 5H), 1.90 (m, 4H), 2.57 (m, 4H), 2.70 (m, 4H), 3.29 (s, 3H), 3.58 (m, 2H), 3.71 (m, 2H), 4.49 (m, 1H), 7.29 (m, 2H), 7.82 (m, 1H), 7.94 (s, 1H), 8.39 (m, 1H); MS m/z 526 $[M+H]^+$.

Ejemplo 417:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 162; 150 mg, 0.515 mmol), el producto final es tomado en metanol (1 mL) diluida con agua y secado por congelación, como un sólido color crema (201 mg, 71%).

^{1}H NMR (399.902 MHz, $CDCl_3$) d1.06 (m, 2H), 1.18 (m, 1H), 1.33 (m, 2H), 1.52 (m, 4H), 1.77 (m, 1H), 1.95 (m, 8H), 2.52 (m, 5H), 2.67 (m, 2H), 3.11 (m, 2H), 3.29 (s, 3H), 3.70 (m, 2H), 4.49 (m, 2H), 5.75 (d, 1H), 7.24 (m, 1H), 7.52 (m, 2H), 7.92 (s, 1H), 8.56 (m, 1H); MS m/z 550 $[M+H]^+$.

Ejemplo 418:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–[(1R,5S)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida (Producto intermedio 202; 154 mg, 0.509 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (137 mg, 48%).

^{1}H NMR (399.902 MHz, $CDCl_3$) d1.04 (m, 2H), 1.19 (m, 1H), 1.31 (m, 2H), 1.53 (m, 6H), 1.79 (m, 1H), 1.96 (m, 6H), 2.54 (m, 5H), 2.67 (m, 2H), 3.10 (m, 2H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.50 (m, 2H), 5.77 (d, 1H), 7.25 (m, 1H), 7.40 (d, 1H), 7.69 (s, 1H), 7.91 (s, 1H), 8.49 (d, 1H); MS m/z 562 $[M+H]^+$.

Ejemplo 419:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–5–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–2–fluoro–5–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida (Producto intermedio 254; 65 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (4 mg, 3%).

MS m/z 580 $[M+H]^+$. Tiempo de retención 3.69 minutos.

Ejemplo 420:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 182; 55 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (20 mg, 19%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.20 (m, 1H), 1.56 (m, 4H), 1.78 (m, 2H), 1.92 (m, 4H), 2.32 (m, 1H), 2.43 (m, 4H), 2.68 (m, 4H), 2.89 (m, 1H), 3.28 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.52 (m, 1H), 4.67 (m, 1H), 7.00 (m, 1H), 7.56 (m, 1H), 7.76 (s, 1H), 7.92 (s, 1H), 8.31 (d, 1H); MS m/z 526 $[M+H]^+$.

Ejemplo 421:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–3–metoxi–N–(1–metilpirrolidin–3–il)benzamida (Producto intermedio 187; 51 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (37 mg, 36%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.22 (m, 1H), 1.52 (m, 4H), 1.77 (m, 2H), 1.94 (m, 4H), 2.23 (m, 1H), 2.44 (m, 4H), 2.56 (m, 1H), 2.67 (m, 2H), 2.81 (m, 1H), 2.98 (m, 1H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 4.70 (m, 1H), 6.48 (d, 1H), 7.31 (m, 1H), 7.41 (m, 1H), 7.70 (s, 1H), 7.91 (s, 1H), 8.49 (d, 1H); MS m/z 508 $[M+H]^+$.

Ejemplo 422:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida (Producto

intermedio 205; 60 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (27 mg, 24%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.10 (t, 3H), 1.21 (m, 1H), 1.55 (m, 6H), 1.78 (m, 1H), 1.92 (m, 4H), 2.12 (m, 4H), 2.43 (q, 2H), 2.68 (m, 2H), 2.89 (m, 2H), 3.28 (s, 3H), 3.71 (m, 2H), 3.95 (s, 3H), 4.05 (m, 1H), 4.52 (m, 1H), 6.67 (m, 1H), 7.56 (d, 1H), 7.74 (s, 1H), 7.92 (s, 1H), 8.32 (d, 1H); MS m/z 554 $[M+H]^+$.

Ejemplo 423:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(1–etil–4–piperidil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida (Producto intermedio 190; 57 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (61 mg, 56%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.11 (t, 3H), 1.21 (m, 1H), 1.54 (m, 6H), 1.78 (m, 1H), 1.94 (m, 4H), 2.12 (m, 4H), 2.44 (q, 2H), 2.67 (m, 2H), 2.92 (m, 2H), 3.28 (s, 3H), 3.70 (m, 2H), 3.97 (s, 3H), 4.03 (m, 1H), 4.50 (m, 1H), 5.88 (d, 1H), 7.23 (m, 1H), 7.39 (m, 1H), 7.68 (s, 1H), 7.91 (s, 1H), 8.50 (d, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 424:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–N–(3–dimetilaminopropil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4–amino–N–(3–dimetilaminopropil)–3–metoxi–benzamida (Producto intermedio 196; 51 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (50 mg, 48%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.22 (m, 1H), 1.54 (m, 4H), 1.76 (m, 3H), 1.95 (m, 4H), 2.30 (s, 6H), 2.51 (m, 2H), 2.67 (m, 2H), 3.28 (s, 3H), 3.58 (m, 2H), 3.70 (m, 2H), 3.97 (s, 3H), 4.53 (m, 1H), 7.27 (m, 1H), 7.48 (m, 1H), 7.72 (s, 1H), 7.91 (s, 1H), 8.38 (m, 1H), 8.50 (d, 1H); MS m/z 510 $[M+H]^+$.

Ejemplo 425:

4-[(2-ciclohexil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-2-fluoro-5-metoxi-N-(2-pirrolidin-1-iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4-amino-2-fluoro-5-metoxi-N-(2-pirrolidin-1-iletil)benzamida (Producto intermedio 228; 57 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (19 mg, 17%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.20 (m, 1H), 1.56 (m, 4H), 1.77 (m, 5H), 1.91 (m, 4H), 2.58 (m, 4H), 2.70 (m, 4H), 3.28 (s, 3H), 3.60 (m, 2H), 3.71 (m, 2H), 3.95 (s, 3H), 4.53 (m, 1H), 7.32 (m, 1H), 7.57 (d, 1H), 7.73 (s, 1H), 7.92 (s, 1H), 8.33 (d, 1H); MS m/z 540 $[M+H]^+$.

Ejemplo 426:

4-[(2-ciclohexil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-N-(2-dimetilaminoetil)-3-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4-amino-N-(2-dimetilaminoetil)-3-metoxi-benzamida (Producto intermedio 194; 48 mg, 0.204 mmol), el producto final es purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (31 mg, 31%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.22 (m, 1H), 1.54 (m, 4H), 1.76 (m, 1H), 1.94 (m, 4H), 2.29 (s, 6H), 2.54 (m, 2H), 2.67 (m, 2H), 3.28 (s, 3H), 3.53 (m, 2H), 3.70 (m, 2H), 3.97 (s, 3H), 4.51 (m, 1H), 6.74 (m, 1H), 7.32 (m, 1H), 7.43 (m, 1H), 7.67 (s, 1H), 7.91 (s, 1H), 8.50 (d, 1H); MS m/z 496 $[M+H]^+$.

Ejemplo 427:

4-[(2-ciclohexil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-10-il)amino]-2-fluoro-5-metoxi-N-[(1R,5S)-9-metil-9-azabiciclo[3.3.1]non-7-il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 411, utilizando 4-amino-2-fluoro-5-metoxi-N-[(1S,5R)-9-metil-9-azabiciclo[3.3.1]non-7-il]benzamida (Producto intermedio 204; 65 mg, 0.204 mmol), el producto final es

purificado por HPLC en fase inversa preparativa modificada base, como un sólido blanco (52 mg, 44%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.04 (m, 2H), 1.21 (m, 1H), 1.32 (m, 2H), 1.56 (m, 6H), 1.79 (m, 1H), 1.95 (m, 6H), 2.54 (m, 5H), 2.68 (m, 2H), 3.09 (m, 2H), 3.28 (s, 3H), 3.72 (m, 2H), 3.95 (s, 3H), 4.53 (m, 2H), 6.53 (m, 1H), 7.59 (d, 1H), 7.75 (s, 1H), 7.93 (s, 1H), 8.31 (d, 1H); MS m/z 580 $[M+H]^+$.

Ejemplo 428:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–2–fluoro–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclohexil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 267; 89 mg, 0.3 mmol) y 4–amino–3–fluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 61; 76 mg, 0.3 mmol) fueron combinados con ácido p–toluenosulfónico monohidrato (143 mg, 0.75 mmol) en 4–metil–2–pentanol (2 mL) y calentados por irradiación de microondas durante 30 minutos a 160 °C. La mezcla de reacción enfriada fue diluida con metanol (10 mL) y filtrada y el filtrado cargado en un cartucho SCX–3 (5 g) prehumedecido con metanol. El cartucho fue lavado con metanol (2 x 10 mL) y eluido con amoniaco metanólico 7 N (20 mL). La fracción básica fue evaporada para dar un sólido amarillo, el cual fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (55 mg, 37%).

^{1}H NMR (400 MHz, DMSO–d6) δ 1.15 (m, 2H), 1.45 (m, 3H), 1.6 (m, 4H), 1.7 (m, 1H), 1.8 (m, 6H), 1.95 (t, 2H), 2.15 (s, 3H), 2.6 (m, 2H), 2.7 (m, 2H), 3.15 (s, 3H), 3.65 (m, 2H), 3.7 (m, 1H), 4.4 (t, 1H), 7.5 (m, 2H), 7.7 (m, 2H), 8.1 (s, 1H), 9.6 (s, 1H); MS m/z 511 $[M+H]^+$.

Ejemplo 429:

4–[(2–ciclohexil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–fluoro–N–(1–metil–4–piperidil)benzamida

10–cloro–2–ciclohexil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 267; 89 mg, 0.3 mmol) y 4–amino–3–fluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 65; 76 mg, 0.3 mmol) fueron combinados con ácido p–toluenosulfónico monohidrato (143 mg, 0.75 mmol) en 4–metil–2–pentanol (2 mL) y

calentados por irradiación de microondas durante 30 minutos a 160 °C. La mezcla de reacción enfriada fue diluida con metanol (10 mL) y filtrada y el filtrado cargado en un cartucho SCX–3 (5 g) prehumedecido con metanol. El cartucho fue lavado con metanol (2 x 10 mL) y eluido con amoniaco metanólico 7 N (20 mL). La fracción básica fue evaporada para dar una goma amarilla, la cual fue purificada por HPLC en fase inversa preparativa modificada base para dar el compuesto del título como un sólido blanco (56 mg, 37 %).

^{1}H NMR (400 MHz, DMSO–d6) δ 1.1 (m, 1H), 1.3 (q, 2H), 1.55 (m, 5H), 1.75 (m, 6H), 1.95 (t, 2H), 2.2 (s, 3H), 2.6 (m, 2H), 2.75 (d, 2H), 3.2 (s, 3H), 2.6 (m, 2H), 2.75 (d, 2H), 3.2 (s, 3H), 3.6 (m, 2H), 3.7 (m, 1H), 4.3 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 8.0 (s, 1H), 8.1 (m, 2H), 8.7 (s, 1H); MS m/z 511 $[M+H]^+$.

Ejemplo 430:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–metoxi–N–(1–metil–4–piperidil)benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 100 mg, 0.31 mmol), 4–amino–3–metoxi–N–(1–metil–4–piperidil)benzamida (WO06/018220; 83 mg, 0.31 mmol) y ácido p–toluenosulfónico monohidrato (149 mg, 0.78 mmol) fueron calentados a 140 °C en 4–metil–2–pentanol (4 mL) durante 2 horas. La mezcla de reacción fue cargada en una columna SCX–3 fue prehumedecida con metanol y la columna lavada con metanol y eluida con 2% metanol/amoniaco 7N. La fracción amoniacal fue evaporada y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (97 mg, 57%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.68 – 0.71 (2H, t), 0.92 – 0.95 (2H, t), 1.40 – 1.50 (4H, m), 1.59 – 1.63 (2H, m), 1.65 – 1.68 (1H, m), 1.77 (2H, s), 1.79 (4H, t), 1.86 (1H, s), 1.93 – 1.98 (2H, m), 2.18 (3H, s), 2.80 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.70 – 3.76 (1H, m), 3.96 (3H, s), 4.45 (1H, m), 7.46 (1H, m), 7.48 – 7.51 (1H, d), 7.67 (1H, s), 7.96 (1H, s), 8.09 (1H, d), 8.39 (1H, d); MS m/z 547 $[M+H]^+$.

Ejemplo 431:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(3–dimetilaminopropil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 430, utilizando 4–amino–N–(3–dimetilaminopropil)–3–metoxi–benzamida (Producto intermedio 196; 79 mg, 0.31 mmol), como un sólido blanco (96 mg, 58%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.68 – 0.71 (2H, t), 0.92 – 0.95 (2H, t), 1.47 – 1.51 (2H, m), 1.68 (4H, q), 1.76 – 1.78 (4H, m), 1.85 (2H, d), 2.15 (6H, s), 2.28 (2H, t), 3.17 (3H, s), 3.25 (2H, t), 3.51 (2H, s), 3.96 (3H, s), 4.45 (1H, m), 7.45 – 7.47 (1H, m), 7.51 (1H, d), 7.67 (1H, s), 7.96 (1H, s), 8.40 (1H, d), 8.41 (1H, d); MS m/z 537 $[M+H]^+$.

Ejemplo 432:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 430, utilizando 4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida (Producto intermedio 202; 95 mg, 0.31 mmol), como un sólido blanco (111 mg, 61%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.68 – 0.71 (2H, m), 0.93 (2H, d), 0.93 (2H, d), 1.42 (2H, d), 1.45 – 1.47 (3H, m), 1.49 (2H, d), 1.77 (4H, d), 1.85 (4H, d), 1.93 (2H, t), 2.21 (1H, d), 2.42 (3H, s), 2.99 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.98 (3H, s), 4.29 – 4.34 (1H, m), 4.45 (1H, m), 7.47 (1H, d), 7.48 – 7.52 (1H, s), 7.67 (1H, s), 7.92 (1H, d), 7.97 (1H, s), 8.39 – 8.41 (1H, d); MS m/z 589 $[M+H]^+$.

Ejemplo 433:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 430, utilizando 4–amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida (Producto intermedio 190; 87 mg, 0.31 mmol), como un sólido blanco (122 mg, 70%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.68 – 0.71 (2H, t), 0.92 – 0.95 (2H, t), 1.01 (3H, t), 1.45 (3H, t), 1.57 – 1.61 (2H, m), 1.77 (4H, d), 1.82 – 1.86 (3H, m), 1.88 (2H, t), 1.93 (2H, d), 2.33 (2H, q), 2.90 (2H, d), 3.17 (3H, s), 3.51 (2H, s), 3.74 – 3.78 (1H, m), 3.96 (3H, s), 4.41 – 4.45 (1H, m), 7.46 (1H, d), 7.48 – 7.51 (1H, m), 7.67 (1H, s), 7.96 (1H, s), 8.09 (1H, d), 8.39 – 8.41 (1H, m); MS m/z 563 $[M+H]^+$.

Ejemplo 434:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 100 mg, 0.31 mmol), 4–amino–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida (Producto intermedio 235; 98 mg, 0.34 mmol) y carbonato de cesio (204 mg, 0.62 mmol) añadido a dioxano (5 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Tris(dibencilidenoacetona) paladio (II) (18 mg, 0.02 mmol) y XANTFOS (17 mg, 0.03 mmol) añadidos y la mezcla calentada a 110 °C toda la noche. La mezcla fue filtrada y el filtrado cargado en una columna SCX–3 fue prehumedecido con metanol y la columna lavada con metanol y eluida con 2% metanol/amoniaco 7N. La fracción amoniacal fue evaporada y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido cristalino blanco (19 mg, 11%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.69 – 0.72 (2H, t), 0.93 – 0.96 (2H, t), 1.00 (3H, t), 1.42 (2H, t), 1.48 (2H, d), 1.49 – 1.54 (2H, m), 1.63 (2H, d), 1.70 (2H, d), 1.78 (4H, s), 1.95 (2H, d), 2.30 – 2.35 (2H, m), 2.84 (2H, d), 3.17 (3H, s), 3.50 (2H, s), 3.75 (1H, m), 4.46 (1H, m), 7.41 – 7.45 (1H, m), 7.98 (1H, d), 7.99 (1H, s), 8.13 – 8.18 (1H, m), 8.79 (1H, s); MS m/z 589 $[M+H]^+$.

Ejemplo 435:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 97 mg, 0.3 mmol) y 4–amino–3–fluoro–N–(9–metil–9–azabiciclo[3.3.1]non–7–il)benzamida (Producto intermedio 162; 88 mg, 0.3 mmol) fueron combinados con ácido p–toluenosulfónico monohidrato (143 mg, 0.75 mmol) en 4–metil–2–pentanol (2 mL) y calentados por irradiación de microondas durante 30 minutos a 160 °C. La mezcla de reacción enfriada fue diluida con metanol (5 mL) y cargada en un cartucho SCX–3 (5 g) prehumedecido con metanol. El cartucho fue lavado con metanol (2 x 10 mL) y el producto eluido con amoniaco metanólico 7 N (20 mL). Las fracciones que contienen el producto fueron evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (82 mg, 48%).

^{1}H NMR (400 MHz, DMSO–d6) δ 0.7 (m, 2H), 0.95 (m, 4H), 1.15 (m, 1H), 1.35 (m, 2H), 1.45 (m, 4H), 1.7 (m, 4H), 1.8 (d, 2H), 1.95 (m, 2H), 2.05 (m, 1H), 2.15 (m, 2H), 2.9 (s, 3H), 2.95 (d, 2H), 3.15 (s, 3H), 3.45 (s, 2H), 4.35 (m, 2H), 7.65 (m, 1H), 7.7 (m, 1H), 7.9 (s, 1H), 7.95 (m, 1H), 8.2 (t, 1H), 8.55 (s, 1H); MS m/z 576 $[M+H]^+$.

Ejemplo 436:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2,5–difluoro–N–(1–metil–4–piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 434, utilizando 4–amino–2,5–difluoro–N–(1–metil–4–piperidil)benzamida (Producto intermedio 59; 93 mg, 0.34 mmol), como un sólido blanco (76 mg, 44%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.69 – 0.72 (2H, t), 0.93 – 0.96 (2H, t), 1.44 (4H, m), 1.54 – 1.61 (2H, m), 1.71 (2H, d), 1.78 (4H, d), 1.94 – 1.99 (2H, m), 2.17 (3H, s), 2.73 (2H, d), 3.17 (3H, s), 3.29 (2H, d), 3.50 (2H, s), 3.65 – 3.72 (1H,m), 4.46 (1H, m), 7.41 – 7.45 (1H, m), 7.96 (1H, d), 7.98 (1H, s), 8.13 – 8.18 (1H, m), 8.78 (1H, s); MS m/z 554 $[M+H]^+$.

Ejemplo 437:

5–cloro–4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 103 mg, 0.32 mmol), 4–amino–5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida (Producto intermedio 175; 92 mg, 0.29 mmol), y XANTFOS (16 mg, 0.03 mmol) fueron disueltos en 1,4–dioxano (7.5 mL). Carbonato de cesio (210 mg, 0.59 mmol) fue añadido y el sistema purgado con una corriente de nitrógeno durante 15 minutos antes que tris(dibencilidenoacetona) paladio (II) (17 mg, 0.02 mmol) fuera añadido. El aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y luego calentado a 100 °C durante 3 horas. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, y la columna luego lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (49 mg, 28%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.71 (2H, m), 0.94 (2H, m), 1.10 (2H, m), 1.25 – 1.84 (16H, m), 2.09 – 2.19 (7H, m), 3.18 (3H, s), 3.52 (2H, s), 3.63 – 3.70 y 3.88 – 3.94 (each 0.5H, m), 4.43 (1H, m), 7.67 (1H, d), 8.00 – 8.04 (3H, m), 8.27 (1H, d); MS m/z 598 $[M+H]^+$.

Ejemplo 438:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 103 mg, 0.32 mmol), 4–amino–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 182; 87 mg, 0.32 mmol) y ácido p–toluenosulfónico monohidrato (154 mg, 0.81 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140 °C durante 3 horas. La mezcla fue enfriada y absorbida en una columna SCX, la cual fue luego lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas y

purificadas por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (70 mg, 40%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.70 – 0.73 (2H, m), 0.93 – 0.96 (2H, m), 1.10 1.20 (1H, m), 1.40 – 1.54 (4H, m), 1.64 – 1.84 (6H, m), 2.13 – 2.22 (1H, m), 2.26 (3H, s), 2.33 – 2.47 (2H, m), 2.56 – 2.64 (1H, m), 2.66 – 2.71 (1H, m), 3.17 (3H, s), 3.53 (2H, s), 3.94 (3H, s), 4.34 – 4.41 (1H, m), 4.45 – 4.50 (1H, m), 7.22 (1H, d), 7.74 (1H, s), 7.99 (1H, s), 8.01 – 8.03 (1H, m), 8.26 (1H, d); MS m/z 554 $[M+H]^+$.

Ejemplo 439:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 86 mg, 0.27 mmol) y 4–amino–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida (Producto intermedio 22; 75 mg, 0.27 mmol) fueron tomados en 4–metil–2–pentanol (3 mL) y ácido p–toluenosulfónico monohidrato (102 mg, 0.54 mmol) añadido. La mezcla de reacción fue calentada a 160 °C durante 1 hora por irradiación de microondas. Después de enfriar, la mezcla de reacción fue diluida con metanol (5 mL) y agua (5 mL) y la solución resultante cargada en un cartucho SCX–3 (5 g). El cartucho fue lavado con metanol (40 mL) y luego eluido con amoniaco 2M en metanol (25 mL). La evaporación de la solución amoniacal dio una película color crema opaca la cual fue purificada por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como una espuma blanca (83 mg, 55%)

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.69 (m, 2H), 0.90 (s, 6H), 0.93 (m, 2H), 1.16 (m, 1H), 1.44 (m, 4H), 1.62 – 1.88 (m, 5H), 2.22 (s, 2H), 2.28 (s, 6H), 3.17 (s, 3H), 3.21 (d, 2H), 3.50 (s, 2H), 3.96 (s, 3H), 4.45 (m, 1H), 7.40 (m, 1H), 7.47 (d, 1H), 7.68 (s, 1H), 7.96 (s, 1H), 8.40 (d, 1H), 8.50 (t, 1H); MS m/z 564 $[M+H]^+$.

Ejemplo 440:

4-(9'-ciclohexil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-N-(2,2-dimetil-3-pirrolidin-1-il-propil)-3-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 439, en una escala de 0.33 mmol, utilizando 4-amino-N-(2,2-dimetil-3-pirrolidin-1-il-propil)-3-metoxi-benzamida (Producto intermedio 206; 100 mg, 0.33 mmol) calentando térmicamente a 120 °C todo el fin de semana, como un sólido blanco (46 mg, 24%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.57 – 0.54 (m, 2H), 0.93 (s, 6H), 1.12 – 1.02 (m, 4H), 1.46 – 1.25 (m, 4H), 1.74 – 1.64 (m, 4H), 1.82 (d, 4H), 2.48 (s, 2H), 2.64 – 2.58 (m, 4H), 3.20 (s, 3H), 3.33 (d, 2H), 3.39 (s, 2H), 3.90 (s, 3H), 4.53 – 4.47 (m, 1H), 7.19 – 7.17 (m, 1H), 7.43 (s, 1H), 7.58 (s, 1H), 7.77 (s, 1H), 8.38 (d, 1H), 8.92 – 8.88 (m, 1H); MS m/z 590 $[M+H]^+$.

Ejemplo 441:

4-(9'-ciclohexil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-N-[(3R)-1-etilpirrolidin-3-il]-3-metoxi-benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 439, en una escala de 0.24 mmol, utilizando 4-amino-N-[(3R)-1-etilpirrolidin-3-il]-3-metoxi-benzamida (Producto intermedio 245; 70 mg, 0.26 mmol), como un sólido blanco (57 mg, 38%).

^{1}H NMR (400.132 MHz, DMSO-d6) δ 0.69 (m, 2H), 0.93 (m, 2H), 1.04 (t, 3H), 1.15 (m, 1H), 1.45 (m, 4H), 1.76 (m, 6H), 2.15 (m, 1H), 2.43 (m, 4H), 2.66 (m, 1H), 2.72 (m, 1H), 3.16 (s, 3H), 3.50 (s, 2H), 3.96 (s, 3H), 4.42 (m, 2H), 7.50 (m, 1H), 7.54 (d, 1H), 7.66 (s, 1H), 7.96 (s, 1H), 8.31 (d, 1H), 8.40 (d, 1H); MS m/z 548 $[M+H]^+$.

Ejemplo 442:

4-(9'-ciclohexil-5'-metil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-2-fluoro-5-metoxi-N-[(1S,5R)-9-metil-9-azabiciclo[3.3.1]non-3-il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 439, en una escala de 0.17 mmol, utilizando 4-amino-3-metoxi-N-[(1S,5R)-9-metil-9-

azabiciclo[3.3.1]non–3–il]benzamida (Producto intermedio 204; 55 mg, 0.17 mmol), calentando térmicamente a 140 °C durante 2 horas, como un sólido blanco (24 mg, 23%). ^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.70 – 0.73 (2H, m), 0.90 – 0.96 (4H, m), 1.13 – 1.20 (1H, m), 1.40 – 1.55 (7H, m), 1.67 (1H, d), 1.75 – 1.95 (6H, m), 2.01 – 2.11 (1H, m), 2.18 – 2.26 (2H, m), 2.42 (3H, s), 2.98 (2H, d), 3.17 (3H, s), 3.53 (2H, s), 3.94 (3H, s), 4.27 – 4.34 (1H, m), 4.45 – 1.52 (1H, m), 7.22 (1H, d), 7.68 – 7.72 (1H, m), 7.74 (1H, s), 8.00 (1H, s), 8.26 (1H, d); MS m/z 606 $[M+H]^+$.

Ejemplo 443:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 54 mg, 0.17 mmol), 4–amino–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida (Producto intermedio 205; 50 mg, 0.17 mmol), y ácido p–toluenosulfónico monohidrato (81 mg, 0.43 mmol) fueron agitados juntos en 4–metil–2–pentanol (3 mL) y calentados a 110 °C durante 18 horas. La mezcla de reacción enfriada fue cargada en una columna SCX–3 (5 g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volúmenes de columna) y eluida con NH_3 2M/MeOH. La evaporación del solvente de las fracciones amoniacales combinadas dio una goma marrón la cual fue purificada por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (48 mg, 49%)

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.70 (m, 2H), 0.94 (m, 2H), 1.00 (t, 3H), 1.14 (m, 2H), 1.61 (m, 12H), 1.96 (m, 2H), 2.32 (q, 3H), 2.83 (d, 2H), 3.17 (s, 3H), 3.52 (s, 2H), 3.72 (m, 1H), 3.93 (s, 3H), 4.47 (m, 1H), 7.19 (d, 1H), 7.73 (s, 1H), 7.82 (m, 1H), 7.99 (s, 1H), 8.26 (d , 1H); MS m/z 580 $[M+H]^+$.

Ejemplo 444:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–5–metoxi–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 443, en una escala de 0.18 mmol, utilizando 4–amino–2–fluoro–5–metoxi–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 228; 50 mg, 0.18 mmol), como un sólido blanco (58 mg, 57%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.71 (m, 2H), 0.94 (m, 2H), 1.15 (m, 2H), 1.61 (m, 12H), 2.50 (m, 4H), 2.58 (t, 3H), 3.16 (s, 3H), 3.39 (m, 2H), 3.52 (s, 2H), 3.93 (s, 3H), 4.48 (m, 1H), 7.30 (d, 1H), 7.76 (bs, 1H), 7.91 (m, 1H), 7.99 (s, 1H), 8.27 (d, 1H); MS m/z 566 $[M+H]^+$.

Ejemplo 445:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–5–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 443, en una escala de 0.16 mmol, utilizando 4–amino–2–fluoro–5–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida (Producto intermedio 254; 52 mg, 0.16 mmol), como un sólido blanco (53 mg, 55%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.34 (2H, m), 0.51 (2H, m), 0.71 (2H, m), 0.94 (2H, m), 1.16 (1H, m), 1.47 (5H, m), 1.72 (10H, m), 2.44 (2H, s), 2.49 (2H, s), 3.17 (3H, s), 3.37 (2H, d), 3.53 (2H, s), 3.93 (3H, s), 4.48 (1H, m), 7.39 (1H, d), 7.78 (1H, s), 7.99 (1H, s), 8.26 (1H, d), 8.37 (1H, m); MS m/z 606 $[M+H]^+$.

Ejemplo 446:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–3–fluoro–N–(1–metil–4–piperidil)benzamida

2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 200 mg, 0.62 mmol), 4–amino–3–fluoro–N–(1–metilpiperidin–4–il)benzamida (Producto intermedio 65; 157 mg, 0.62 mmol) y ácido p–toluenosulfónico monohidrato (296 mg, 1.56 mmol) fueron suspendidos en 4–Metil–2–pentanol (5 mL) y sellados en un tubo de microondas. La reacción fue calentada a 160 °C

durante 30 minutos en el reactor de microondas y luego se dejó enfriar a temperatura ambiente.

La mezcla de reacción fue purificada por cromatografía de intercambio iónico, usando una columna SCX. El producto deseado fue eluido de la columna usando NH_3 7M /MeOH y las fracciones puras fueron evaporadas hasta secarse para proporcionar un sólido color crema el cual fue purificado por HPLC preparativa usando mezclas decrecientemente polares de agua (que contiene 1% NH_3) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar el compuesto del título como un sólido blanco (125 mg, 37%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.65 (t, 2H), 0.95 (t, 2H), 1.1 (m, 1H), 1.35 (q, 2H), 1.45 (q, 2H), 1.5–1.7 (m, 5H), 1.8 (m, 4H), 1.95 (t, 2H), 2.15 (t, 2H), 2.2 (s, 3H), 2.8 (d, 2H), 3.2 (s, 3H), 3.45 (s, 2H), 3.7 (m, 1H), 4.4 (m, 1H), 7.65 (m, 1H), 7.7 (m, 1H), 7.95 (s 1H), 8.15 (m, 2H), 8.6 (s, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 447:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2,5–difluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

Ácido p–toluenosulfónico monohidrato (338 mg, 1.78 mmol) fue añadido a 4–amino–2,5–difluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 274; 220 mg, 0.71 mmol), y 2–cloro–9–ciclopentil–5–metil–8,9–dihidro–5H–pirimido[5,4–b][1,4]diazepin–6(7H)–ona (Producto intermedio 1; 200 mg, 0.71 mmol) en 4–metil–2–pentanol (4 mL) a 25 °C. La mezcla resultante fue calentada por irradiación de microondas a 150 °C durante 1 hora. El producto crudo fue purificado por cromatografía de intercambio iónico, usando una columna SCX–3 (5g). El producto deseado fue eluido de la columna usando NH_3 2M/MeOH y las fracciones que contienen el producto fueron evaporadas hasta secarse. El residuo fue además purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (91 mg, 23.%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.90 – 0.93 (2H, m), 1.37 – 1.44 (4H, m), 1.57 – 1.71 (6H, m), 1.86 – 2.04 (4H, m), 2.17 – 2.24 (2H, m), 2.41 (3H, s), 2.58 – 2.61 (2H, m), 2.96 – 2.99 (2H, m), 3.18 (3H, s), 3.62 – 3.64 (2H, m), 4.21 – 4.33 (1H, m), 4.78 – 4.86 (1H, m),

7.42 – 7.46 (1H, m), 7.81 (1H, d), 8.11 (1H, s), 8.20 – 8.25 (1H, m), 8.91 (1H, s); MS m/z 555 $[M+H]^+$.

Ejemplo 448:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2,5–difluoro–N–((1R,3r,5S)–9–metil–9–azabiciclo[3.3.1]nonan–3–il)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 446, en una escala de 0.65 mmol, utilizando 2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 200mg, 0.65 mmol), como un sólido blanco (50 mg, 13%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.67 – 0.70 (2H, m), 0.90 – 0.93 (4H, m), 1.36 – 1.60 (7H, m), 1.64 – 1.71 (2H, m), 1.85 – 1.93 (4H, m), 1.97 – 2.04 (1H, m), 2.17 – 2.24 (2H, m), 2.40 (3H, s), 2.96 – 2.98 (2H, m), 3.18 (3H, s), 3.48 (2H, s), 4.21 – 4.32 (1H, m), 4.82 – 4.91 (1H, m), 7.42 – 7.46 (1H, m), 7.79 – 7.82 (1H, m), 8.02 (1H, s), 8.23 – 8.28 (1H, m), 8.85 (1H, s); MS m/z 581 $[M+H]^+$.

Ejemplo 449:

4–(9'–ciclohexil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2,5–difluoro–N–((1R,3r,5S)–9–metil–9–azabiciclo[3.3.1]nonan–3–il)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 446, en una escala de 0.62 mmol, utilizando 2'–cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 270; 200mg, 0.62 mmol), como un sólido blanco (37 mg, 10%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.69 – 0.72 (2H, m), 0.90 – 0.95 (4H, m), 1.09 – 1.16 (1H, m), 1.33 – 1.50 (8H, m), 1.61 – 1.80 (4H, m), 1.86 – 1.92 (2H, m), 1.97 – 2.04 (1H, m), 2.16 – 2.24 (2H, m), 2.41 (3H, s), 2.96 – 2.98 (2H, m), 3.17 (3H, s), 3.50 (2H, s), 4.21 – 4.32 (1H, m), 4.43 – 4.49 (1H, m), 7.42 – 7.47 (1H, m), 7.81 – 7.84 (1H, m), 7.99 (1H, s), 8.13 – 8.18 (1H, m), 8.76 (1H, s); MS m/z 595 $[M+H]^+$.

Ejemplo 450:

4-(9'-ciclohexil-6'-oxo-5',6',8',9'-tetrahidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepina]-2'-ilamino)-3-fluoro-N-((1R,3r,5S)-9-metil-9-azabiciclo[3.3.1]nonan-3-il)benzamida

2'-cloro-9'-ciclohexil-8',9'-dihidroespiro[ciclopropano-1,7'-pirimido[5,4-b][1,4]diazepin]-6'(5'H)-ona (100 mg, 0.33 mmol), 4-amino-3-fluoro-N-((1R,3r,5S)-9-metil-9-azabiciclo[3.3.1]nonan-3-il)benzamida (95 mg, 0.33 mmol) y ácido p-toluenosulfónico. H_2O (155 mg, 0.81 mmol) fueron suspendidos en 4-metil-2-pentanol (2 mL) y sellados en un tubo de microondas. La reacción fue calentada hasta 160 °C durante 25 minutos por irradiación de microondas y luego enfriada a temperatura ambiente. La mezcla de reacción fue filtrada a través de un vaso filtro PTFE para dar un sólido blanco hueso el cual fue purificado por HPLC preparativa usando mezclas decrecientemente polares de agua (que contienen 1% NH_3) y MeCN como eluentes. Las fracciones que contienen el compuesto deseado fueron evaporadas hasta secarse para proporcionar el compuesto del título como un sólido blanco (27 mg, 15 %). ^{1}H NMR (400.132 MHz, DMSO-d_6) δ0.8 (t, 2H), 0.9 (d, 2H), 1.1 (t, 2H), 1.2-1.5 (m, 8H), 1.6 (b, 3H), 1.75 (d, 2H), 1.9 (m,2H), 2.0 (m, 1H), 2.2 (m, 2H), 2.4 (s,3H), 2.95 (d, 2H), 3.4 (s, 2H), 4.3 (m, 1H), 4.5 (m, 1H), 7.55 (d, 1H), 7.6 (d, 1H), 7.85 (s, 1H), 7.95 (d, 1H), 8.15 (t, 1H), 8.5 (s, 1H), 9.5 (s, 1H); MS m/z 563 $[M+H]^+$.

Ejemplo 451:

4-[(2-ciclopentil-6-metil-5-oxo-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-10-il)amino]-3-metoxi-N-[(1R,5S)-9-metil-3-oxa-9-azabiciclo[3.3.1]non-7-il]benzamida

Ácido p-toluenosulfónico monohidrato (143 mg, 0.83 mmol) fue añadido a 10-cloro-2-ciclopentil-6-metil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-8,10,12-trien-5-ona (Producto intermedio 1; 93 mg, 0.33 mmol) y 4-amino-3-metoxi-N-[(1R,5S)-9-metil-3-oxa-9-azabiciclo[3.3.1]non-7-il]benzamida (Producto intermedio 275; 100 mg, 0.33 mmol) en 4-metil-2-pentanol (3 mL) a 25°C. La suspensión resultante fue agitada a 110 °C durante 18 horas. La mezcla de reacción fue enfriada a temperatura ambiente y purificada por cromatografía de intercambio iónico, usando una columna SCX-2 (5g). El producto deseado fue eluido de la columna usando NH_3 2M/MeOH y las fracciones fueron evaporadas hasta secarse para proporcionar el producto crudo como una goma la cual fue purificada por HPLC preparativa usando mezclas decrecientemente polares de agua (que contienen 1% NH_3) y

MeCN como eluente. Las fracciones que contienen el compuesto deseado fueron combinadas y evaporadas hasta secarse para proporcionar el compuesto del título como un sólido blanco (15 mg, 8 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.36 – 1.40 (2H, m), 1.57 – 1.72 (6H, m), 1.89 – 1.95 (2H, m), 2.33 – 2.41 (2H, m), 2.45 (3H, s), 2.57 – 2.63 (4H, m), 3.17 (3H, s), 3.61 – 3.64 (2H, m), 3.71 – 3.74 (2H, m), 3.89 – 3.91 (2H, m), 3.93 (3H, s), 4.39 – 4.45 (1H, m), 4.74 – 4.82 (1H, m), 7.29 (1H, d), 7.38 (1H, s), 7.75 (1H, s), 8.07 (1H, s), 8.37 (1H, d), 8.83 (1H, d); MS m/z 551 $[M+H]^+$.

Ejemplo 452:

N–(azepan–3–il)–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzamida

Una solución de tert–butil 3–[[4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoil]amino]azepan–1–carboxilato (Ejemplo 348; 149 mg, 0.25 mmol) en DCM (2 mL) fue tratada con TFA (1 mL) La solución resultante fue agitada a temperatura ambiente durante 5 horas.

La mezcla de reacción fue diluida con DCM (10 mL) y sometida a cromatografía de intercambio iónico, usando una columna SCX–3. La columna fue eluida con DCM (50 mL) y metanol (50 mL) antes que el producto deseado fuera eluido de la columna usando NH_3 2M/MeOH. La solución amoniacal fue evaporada hasta secarse para proporcionar el compuesto del título como una goma ámbar (95 mg, 76 %).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.41 – 1.92 (16H, m), 2.51 – 2.53 (2H, m), 2.60 – 2.67 (1H, m), 2.73 (1H, t), 2.92 (1H, dd), 3.10 (3H, s), 3.54 – 3.58 (2H, m), 3.88 (3H, s), 3.90 – 3.99 (1H, m), 4.70 – 4.79 (1H, m), 7.38 – 7.43 (2H, m), 7.66 (1H, s), 7.93 (1H, d), 8.01 (1H, s), 8.31 (1H, d); MS m/z 508 $(M+H)^+$

Ejemplo 453:

4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–N–(1–metilazepan–3–il)benzamida

A una solución de N–(azepan–3–il)–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzamida (Ejemplo 453;

88 mg, 0.17 mmol) en formaldehído (1 mL, 13.35 mmol) y ácido acético (100 µL, 1.75 mmol), fue añadido acetato de sodio (142 mg, 1.73 mmol). La mezcla de reacción fue enfriada hasta 0 °C con agitación. Cianoborohidruro de sodio (12 mg, 0.19 mmol) fue añadido y la mezcla de reacción agitada a 0 °C durante 5 minutos antes de eliminar el baño frío. La mezcla de reacción se dejó calentar hasta la temperatura ambiente y fue agitada durante 2 horas y luego sometida a cromatografía de intercambio iónico, usando una columna SCX–3. La columna fue lavada con metanol, antes que los productos crudos fueran eluidos de la columna usando NH_3 2M/MeOH. La evaporación de la solución amoniacal proporcionó el producto crudo como una goma ámbar la cual fue purificada por cromatografía flash en sílice, gradiente en elusión 5 a 10% amoniaco 2M/MeOH en DCM. Las fracciones puras fueron combinados y evaporadas hasta secarse para dar 4–(9–ciclopentil–5–metil–6–oxo–6,7,8,9–tetrahidro–5H–pirimido[5,4–b][1,4]diazepin–2–ilamino)–3–metoxi–N–(1–metilazepan–3–il)benzamida como un vidrio ámbar (44 mg, 49 %).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.53 – 1.86 (12H, m), 1.91 – 1.96 (1H, m), 2.03 – 2.10 (2H, m), 2.45 (3H, s), 2.65 – 2.70 (3H, m), 2.79 – 2.86 (2H, m), 3.30 (3H, s), 3.68 – 3.72 (2H, m), 3.99 (3H, s), 4.25 – 4.33 (1H, m), 4.91 (1H, quinteto), 7.18 – 7.25 (1H, m), 7.31 (1H, d), 7.48 (1H, d), 7.65 (1H, s), 7.95 (1H, s), 8.51 (1H, d); MS m/z 522 $(M+H)^+$

Preparación de los productos intermedios:

Producto intermedio 1:

10–Cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

A una solución fría (0 °C) de 9–cloro–6–ciclopentil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona (Producto intermedio 2; 241 mg, 0.90 mmol) en DMA (20 mL) fue añadido MeI (62 uL, 0.99 mmol) seguido por NaH (39 mg, 0.96 mmol) y la mezcla de reacción agitada a 0 °C durante 30 min luego a temperatura ambiente durante 1 h. La solución fue diluida con etil acetato (20 mL), lavada con agua (2 x 30 mL), salmuera (30 mL), secada ($MgSO_4$) y los volátiles fueron eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 2% MeOH en DCM) proporcionó el compuesto del título (187 mg, 74%) como un sólido.

^{1}H NMR (400 MHz, DMSO–D6) δ_H 1.52 – 1.66 (m, 4H), 1.66 – 1.75 (m, 2H), 1.85 – 1.96 (m, 2H), 2.63 – 2.67 (m, 2H), 3.18 (s, 3H), 3.64 – 3.68 (m, 2H), 4.71 – 4.79 (m, 1H), 8.15 (s, 1H); MS 281, 283 $[M+H]^+$.

Producto intermedio 2:

9–Cloro–6–ciclopentil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–3–ona

A una solución de metil 3–[(2–cloro–5–oxidoazonoil–pirimidin–4–il)–ciclopentil–amino]propanoato (Producto intermedio 3; 1.00 g, 3.04 mmol) en AcOH (50 mL) fue añadido Fe en polvo (1.00 g, 3.04 mmol) y la reacción agitada a 70 °C durante 30 min. La mezcla de reacción fue filtrada caliente a través de una almohadilla de celita, lavado con AcOH (25 mL) y los volátiles eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 0–100% etil acetato en hexano) dio el compuesto del título (480 mg, 43%) como un sólido.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.46 – 1.56 (m, 2H), 1.62 – 1.80 (m, 3H), 1.94 – 2.04 (m, 3H), 2.77 – 2.79 (m, 2H), 3.60 – 3.63 (m, 2H), 5.17 – 5.26 (m, 1H), 7.79 (s, 1H), 7.99 (s, 1H); MS m/z 267, 269 $[M+H]^+$.

Producto intermedio 3:

Metil 3–[(2–cloro–5–oxidoazonoil–pirimidin–4–il)–ciclopentil–amino]propanoato

A una solución de metil 3–(ciclopentilamino)propanoato (2.46 g, 14.37 mmol) en acetona (40 mL) fue añadido K_2CO_3 (2.03 g, 14.65 mmol) y 2,4–dicloro–5–nitropirimidina (3.07 g, 15.80 mmol) y la mezcla de reacción agitada a temperatura ambiente bajo una atmósfera de nitrógeno durante 18 h. Los volátiles fueron eliminados bajo presión reducida y el material crudo fue disuelto en etil acetato (50 mL), lavado con agua (2 x 50 mL), salmuera (50 mL), secado ($MgSO_4$) y los volátiles eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 0–10% etil acetato en hexano) proporcionó el compuesto del título (2.23 g, 53%) como un sólido.

^{1}H NMR (400 MHz, DMSO–d_6): δ_H 1.44 – 1.54 (m, 2H), 1.62 – 1.78 (m, 4H), 1.86 – 1.96 (m, 2H), 2.69 (t, 2H), 3.61 (s, 3H), 3.66 (t, 2H), 3.71 – 3.80 (m, 1H), 8.84 (s, 1H); MS m/z 329, 331 $[M+H]^+$.

Producto intermedio 4:

4–Amino–*N*–(1–metil–4–piperidil)benzamida

Ácido *p*–aminobenzoico (137 mg, 1 mmol), 4–amino–*N*–metilpiperidina (114 mg, 1 mmol) y DIPEA (522 uL, 3 mmol) fueron disueltos en DMA (5 mL). HATU (570 mg, 1.5 mmol) en DMA (5 mL) fue añadido y la reacción agitada a temperatura ambiente durante 2 h. Los volátiles fueron eliminados bajo presión reducida y $NaHCO_3$ (50 mL, sat. ac.) fue añadido. El precipitado resultante fue eliminado por filtración y la fase acuosa neutralizada con HCL (2N). La mezcla de reacción fue luego cargada en un cartucho SCX–2 lavando con cantidades copiosas de agua. El producto crudo fue eluido de un cartucho SCX–2 con NH_3 (60 mL, 7M en MeOH). La purificación por cromatografía en columna (SiO_2, eluente: 10% NH_3 [7M en MeOH] en DCM) proporcionó el compuesto del título (167 mg, 72%) como un sólido.

^{1}H NMR (400 MHz, DMSO–d_6) δ_H 1.50 – 1.60 (2H, m), 1.69 – 1.73 (1H, m), 1.72 (1H, t), 1.89 – 1.96 (2H, m), 2.16 (3H, s), 2.75 (2H, d), 3.65 – 3.71 (1H, m), 5.52 – 5.54 (1H, m), 6.52 – 6.55 (2H, m), 7.56 – 7.59 (2H, m), 7.69 (1H, d); MS m/z 234 $[M+H]^+$.

Producto intermedio 5:

10–cloro–2–ciclopentil–4,6–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

A una solución fría (–78 °C) de 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (90 mg, 0.32 mmol) en THF seco (4 mL) fue añadido LiHMDS (640 µL, 1M en THF, 0.64 mmol) en forma de gotas durante 10 min. MeI (40 µL, 0.64 mmol) en THF (1 mL) fue añadido y la mezcla de reacción fue agitada a –78 °C durante 20 min y luego a 0 °C durante 1 h. La mezcla de reacción fue diluida con DCM (20 mL) y lavada con agua (2 x 20 mL), salmuera (40 mL), secada ($MgSO_4$), filtrada y los volátiles eliminados bajo presión reducida para proporcionar el compuesto del título (106 mg, 100%) como un sólido.

MS m/z 295, 297 $[M+H]^+$.

Producto intermedio 6:

Ácido 4–[(9–ciclopentil–5–metil–6,7,8,9–tetrahidro–5H–pirimido[4,5–b][1,4]diazepin–2–il)amino]–3–metoxibenzoico

Metil 4–[(9–ciclopentil–5–metil–6,7,8,9–tetrahidro–5H–pirimido[4,5–b][1,4]diazepin–2–il)amino]–3–metoxibenzoato (Producto intermedio 7; 250 mg, 0.61 mmol) y HCl (2 mL, concentrado acuoso) fueron suspendidos en agua (4 mL) y calentados a reflujo durante 24 h. La mezcla de reacción fue luego enfriada a temperatura ambiente y los volátiles fueron eliminados bajo presión reducida. El sólido obtenido fue disuelto en MeOH:DCM (1:10, 40 mL) y lavado con $NaHCO_3$ (saturado acuoso, 40 mL). La capa orgánica fue luego secada ($MgSO_4$), filtrada y los volátiles eliminados bajo presión reducida para proporcionar el compuesto del título (240 mg, 99%) como un sólido.

^{1}H NMR (400MHz, DMSO–d_6) δ_H 1.57 (m, 4H), 1.73 (m, 2H), 1.88 (m, 4H), 2.70 (s, 3H), 2.95 (t, 2H), 3.47 (m, 2H), 3.87 (s, 3H), 4.86 (quinteto, 1H), 7.20 (s, 1H), 7.42 (d, 1H), 7.50 (s, 1H), 7.52 (s, 1H), 7.96 (s, 1H), 8.28 (d, 1H); MS m/z 398 $[M+H]^+$.

Producto intermedio 7:

Metil 4–[(9–ciclopentil–5–metil–6,7,8,9–tetrahidro–5H–pirimido[4,5–b][1,4]diazepin–2–il)amino]–3–metoxibenzoato

$BH_3.SMe_2$ (1.36 mL, 5.0 M en Et_2O, 6.8 mmol) fue añadido a una solución de metil 4–[(9–ciclopentil–5–metil–6–oxo–6,7,8,9–tetrahidro–5H–pirimido[4,5–b][1,4]diazepin–2–il)amino]–3–metoxibenzoato (Producto intermedio 8; 290 mg, 0.68 mmol) en THF (4 mL) y agitada durante 5 h a temperatura ambiente bajo una atmósfera de nitrógeno. HCl (10 mL, concentrado acuoso) fue añadido y la solución resultante fue agitada a temperatura ambiente durante 16 h. La solución HCl fue luego diluida con agua (50 mL), y cargada en una columna SCX–2. La columna SCX–2 fue luego lavada con agua (50 mL) y MeOH (50 mL). El producto fue luego eluido de la columna SCX–2 con NH_3 (50 mL, 7M en MeOH). Los volátiles fueron luego eliminados bajo presión reducida para proporcionar el compuesto del título (250 mg, 89%) como un sólido.

^{1}H NMR (400 MHz, DMSO–d_6) δ_H 1.67 (m, 6H), 1.96 (m, 4H), 2.77 (s, 3H), 3.06 (t, 2H), 3.58 (m, 2H), 3.88 (s, 3H), 4.00 (s, 3H), 4.91 (quinteto, 1H), 7.57 (m, 3H), 7.71 (s, 1H), 8.59 (d, 1H); MS m/z 412 $[M+H]^+$.

Producto intermedio 8:

Metil 4-[(9-ciclopentil-5-metil-6-oxo-6,7,8,9-tetrahidro-5H-pirimido[4,5-b][1,4]diazepin-2-il)amino]-3-metoxibenzoato

2-cloro-9-ciclopentil-5-metil-5,7,8,9-tetrahidro-6H-pirimido[4,5-b][1,4]diazepin-6-ona (Producto intermedio 1; 500 mg, 1.78 mmol), metil 4-amino-3-metoxibenzoato (324 mg, 1.78 mmol) y ácido p-toluenosulfónico (847 mg, 4.45 mmol) fueron suspendidos en (2R/S)-4-metil-2-pentanol (10 mL) y calentados a reflujo durante 5 h. La mezcla de reacción fue enfriada y cargada en una columna SCX-2 y lavada con MeOH (20 mL). El producto crudo fue luego eluido de la columna SCX-2 con NH_3 (40 mL, 7M en MeOH) y los volátiles eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente 0-10% MeOH en DCM) proporcionó el compuesto del título (290 mg, 38%) como un sólido.

^{1}H NMR (400.132 MHz, DMSO-d_6) δ_H 1.71 (m, 6H), 2.00 (m, 2H), 2.65 (m, 2H), 3.23 (s, 3H), 3.69 (m, 2H), 3.89 (s, 3H), 4.01 (s, 3H), 4.87 (m, 1H), 7.56 (d, 1H), 7.64 (d, 1H), 7.90 (s, 1H), 8.16 (s, 1H), 8.55 (d, 1H); MS m/z 426 $[M+H]^+$.

Producto intermedio 9:

10-Cloro-2,6-dimetil-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona

3-[(5-Bromo-2-cloro-pirimidin-4-il)-metil-amino]-N-metil-propanamida (Producto intermedio 15; 2.09 g, 6.20 mmol), tris(dibencilidenoacetona)dipaladio(0) (171 mg, 0.19 mmol), (5-difenilfosfanil-9,9-dimetil-xanten-4-il)-difenil-fosfano (288 mg, 0.50 mmol) y Cs_2CO_3 (2930 mg, 8.99 mmol) en 1,4-dioxano (50 mL) fueron calentados a reflujo durante 16 h bajo una atmósfera de nitrógeno. La mezcla de reacción fue evaporada luego suspendida en DCM (20 mL) y filtrado a través de una capa de celita lavando con DCM (40 mL). La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 2-10% MeOH en DCM) proporcionó el compuesto del título (190 mg, 19%) como una espuma.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 2.67 (tr, 2H), 3.08 (s, 3H), 3.20 (s, 3H), 3.72 (tr, 2H), 8.19 (s, 1H); MS m/z 227 $[M+H]^+$.

Producto intermedio 10

10-Cloro-6-metil-2-propan-2-il-2,6,9,11-tetrazabiciclo[5.4.0]undeca-7,9,11-trien-5-ona

Producto intermedio 11:

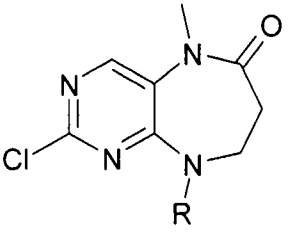
10–Cloro–6–metil–2–(3–metilbutil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

Producto intermedio 12:

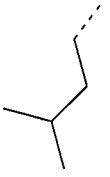
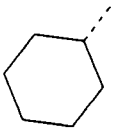
10–Cloro–2–ciclohexil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

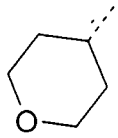
Producto intermedio 13:

10–Cloro–6–metil–2–(oxan–4–il)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona



Productos intermedios 10–13 fueron preparados, usando la amida secundaria apropiada (Productos intermedios 14, 16–18), por un proceso análogo a aquel usado en la preparación del Producto intermedio 9.

Ejemplo	R	**^{1}H NMR (400 MHz, DMSO–d_6)**	**MS m/z $[M+H]^+$**
10		1.18 (d, 6H), 2.65 (tr, 2H), 3.19 (s, 3H), 3.61 (tr, 2H), 8.12 (s, 1H).	225
11		0.99 (d, 6H),1.57 (m, 3H), 2.71 (tr, 2H), 3.22 (s, 3H), 3.63 (tr, 2H), 3.78 (tr, 2H), 8.19 (s, 1H).	283
12		1.14 (m, 1H), 1.32 (m, 2H), 1.60 (m, 3H), 1.78 (m, 4H). 2.61 (tr, 2H), 3.18 (s, 3H), 3.65 (tr, 2H), 4.30 (m, 1H), 8.12 (s, 1H).	295

13		1.68 (m, 2H), 1.83 (m, 2H), 2.63 (tr, 2H), 3.41 (tr, 2H), 3.69 (m, 2H), 3.93 (m, 2H) 4.51 (m, 1H), 8.18 (s, 1H).	297

Producto intermedio 14:

3-[(5-Bromo-2-cloro-pirimidin-4-il)-propan-2-il-amino]-N-metil-propanamida

5-Bromo-2,4-dicloropirimidina (1.83 g, 8.00 mmol), N-metil-3-(propan-2-ilamino)propanamida (Producto intermedio 14, 1.16 g, 8.00 mmol) y Et_3N (1.2 mL, 8.16 mmol) fueron combinados en MeCN (50 mL) y agitado a temperatura ambiente durante 3 días antes que el solvente fuera eliminado bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente 2-10% MeOH para DCM) para proporcionar el compuesto del título (2.08 g, 78%) como una goma.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.16 – 1.20 (6H, m), 2.31 (2H, t), 2.55 – 2.58 (3H, d), 3.65 (2H, t), 4.55 – 4.62 (1H, septet), 7.71 – 7.72 (1H, br s), 8.39 (1H, s); MS m/z 337 $[M+H]^+$.

Producto intermedio 15:

3-[(5-Bromo-2-cloro-pirimidin-4-il)-metil-amino]-N-metil-propanamida

Producto intermedio 16

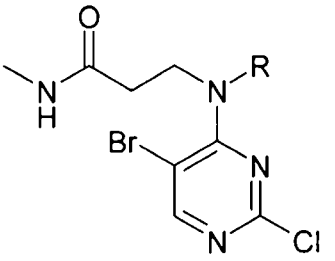
3-[(5-Bromo-2-cloro-pirimidin-4-il)-(3-metilbutil)amino]-N-metil-propanamida

Producto intermedio 17:

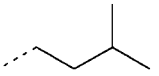
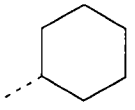
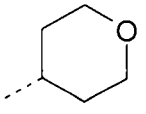
3-[(5-Bromo-2-cloro-pirimidin-4-il)-ciclohexil-amino]-N-metil-propanamida

Producto intermedio 18:

3-[(5-Bromo-2-cloro-pirimidin-4-il)-(oxan-4-il)amino]-N-metil-propanamida



Productos intermedios 15–18 fueron preparados en una manera análoga al Producto intermedio 14 usando **5**–bromo–2,4–dicloropirimidina como el electrófilo y las β–aminoamidas apropiadas conocidas o descritas (Productos intermedios 19 – 21):

Ejemplo	**R**	**^{1}H–NMR (400 MHz, DMSO–d_6)**	**MS m/z $[M+H]^+$**
15	Me	2.46 (2H, t), 2.56 – 2.57 (3H, d), 3.19 (3H, s), 3.86 (2H, t), 7.86 (1H, br s), 8.33 (1H, s)	309
16		0.92 (6H, d), 1.48 – 1.52 (2H, m), 1.59 (1H, m), 2.45 (2H, t), 2.57 (3H, d), 3.63 (2H, m), 3.83 (2H, t), 7.84 (1H, br s), 8.32 (1H, s)	365
17		1.10 – 1.15 (1H, m), 1.27 (2H, q), 1.54 – 1.57 (1H, m), 1.59 (1H, d), 1.62 – 1.63 (1H, m), 1.69 – 1.72 (2H, m), 1.78 (2H, d), 2.31 (2H, t), 2.55 (3H, d), 3.67 (2H, t), 4.14 – 4.20 (1H, m), 7.70 (1H, br s), 8.38 (1H, s)	377
18		1.62 – 1.66 (2H, m), 1.82 – 1.89 (2H, m), 2.32 (2H, t), 2.56 (3H, d), 3.33 (2H, d), 3.69 (2H, t), 3.91 – 3.95 (2H, m), 4.34 – 4.40 (1H, m), 7.72 (1H, br s), 8.43 (1H, s)	379

Producto intermedio 19:

N–Metil–3–(propan–2–ilamino)propanamida

N–Metilacrilamida (851 mg, 10.00 mmol) y isopropilamina (1.71 mL, 1.18 g, 20.00 mmol) en MeOH (10 mL) fueron irradiadas hasta 140 °C durante 30 min en un recipiente de reacción del microondas. La mezcla de reacción fue enfriada y cargada en una columna SCX–2 y lavada con MeOH (100 mL). El producto crudo fue luego eluido de la columna SCX–2 con NH_3 (100 mL, 7M en MeOH) y los volátiles eliminados bajo presión reducida para proporcionar el compuesto del título (1.56 g, Cuant.) como un aceite, el cual fue usado sin purificación adicional.

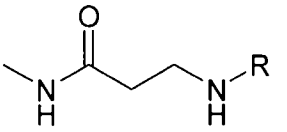
^{1}H NMR (400 MHz, DMSO–d_6) δ_H 0.96 (d, 6H), 2.18 (t, 2H), 2.57 (d, 3H), 2.65 – 2.71 (m, 3H), 7.81 (br s, 1H).

Producto intermedio 20:

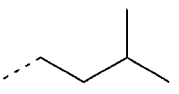
N–Metil–3–(3–metilbutilamino)propanamida

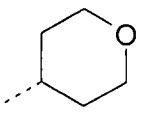
Producto intermedio 21:

N–Metil–3–(oxan–4–ilamino)propanamida



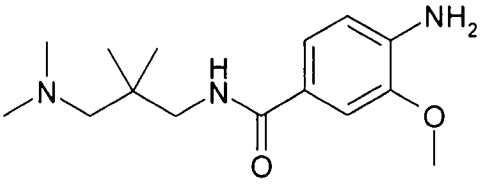
Productos intermedios 20 y 21 fueron preparados en una manera análoga al Producto intermedio 19 usando la N–metilacrilamida como el α,β–no saturada amida y la amina primaria apropiada comercialmente disponible:

Ejemplo	R	^{1}H NMR (400 MHz, DMSO–d_6)
20		0.87 (d, 6H), 1.28 (dt, 2H), 1.60 (septeto, 1H), 2.19 (t, 2H), 2.46 – 2.52 (m, 3H), 2.56 (d, 3H), 2.67 (t, 2H), 7.81 (br s, 1H)

21		1.14 – 1.27 (m, 2H), 1.64 (d, 1H), 1.73 (d, 2H), 2.19 (t, 2H), 2.57 (d, 3H), 2.72 (t, 2H), 3.23 – 3.31 (m, 3H), 3.78 – 3.84 (m, 2H), 7.80 (br s, 1H)

Producto intermedio 22:

4–amino–N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–benzamida



Una suspensión de N–(3–dimetilamino–2,2–dimetil–propil)–3–metoxi–4–nitro–benzamida (Producto intermedio 23; 5.7 g, 18.40 mmol), 5% Pd sobre carbón (569 mg) en EtOH (300 mL) fue agitada a 40 °C bajo una atmósfera de hidrógeno durante 16 h. La mezcla de reacción fue luego filtrada a través de celita, lavada con MeOH copioso y los volátiles eliminados bajo presión reducida para proporcionar el compuesto del título (5.36 g, Cuant.) como una espuma. ^{1}H NMR (400 MHz, DMSO–d_6): δ_H 0.88 (m, 6H), 2.18 (s, 2H), 2.28 (s, 6H), 3.18 (m, 2H), 3.82 (s, 3H), 5.21 (m, 2H), 6.63 (d, 1H), 7.25 m, 2H), 8.11 (m, 1H); MS m/z 280 $[M+H]^+$.

Producto intermedio 23:

N–(3–Dimetilamino–2,2–dimetil–propil)–3–metoxi–4–nitro–benzamida

A una suspensión de ácido 4–nitro–3–metoxibenzoico (Aldrich; 5.0 g, 25.3 mmol), N,N–2–tetrametil–1,3–propanodiamina (Aldrich; 4.64 mL, 27.83 mmol) y DIPEA (8.8 mL, 50.60 mmol) en anhidro DMA (100 mL) bajo nitrógeno a temperatura ambiente fue añadido HATU (10.6 g, 27.83 mmol) y la mezcla de reacción resultante fue agitada a 50 °C durante 3 h y temperatura ambiente durante unas 12 h adicionales. La evaporación eliminó cualquiera de los volátiles y el residuo fue disuelto en DCM (100 mL) y lavado con $NaHCO_3$ (100 mL), salmuera (100 mL), secado ($MgSO_4$) y los volátiles eliminados bajo presión reducida. La purificación por cromatografía en columna (SiO_2, gradiente de eluente: 2–10% MeOH en DCM) proporcionó el compuesto del título (5.7 g, 73%) como un sólido.

^{1}H NMR (400 MHz, DMSO–d_6): δ_H 1.06 (s, 6H), 2.42 (s, 2H), 2.82 (s, 6H), 3.30 (s, 2H), 3.98 (s, 3H), 7.57 (dd, 1H), 7.71 (s, 1H), 8.93 (d, 1H); MS m/z 310 $[M+H]^+$.

Producto intermedio 24:

1–ciclopropilpiperidin–4–amina

N–bencil–1–ciclopropil–piperidin–4–amina (Producto intermedio 25; 2.3 g 10 mmol), 10% paladio sobre carbón (230 mg) y metanol (230 mL) fueron combinados y calentados con agitación a 30°C bajo Hidrógeno a presión de 5 bar durante 16 horas.

La mezcla fue filtrada y concentrada, tomada en DCM, secada ($MgSO_4$) y concentrada para dar el compuesto del título (1.29g, 64%) como un líquido amarillo

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.36 – 0.46 (4H, m), 1.26 – 1.36 (4H, m), 1.52 – 1.58 (1H, m), 1.76 – 1.82 (2H, m), 2.18 – 2.25 (2H, m), 2.63 – 2.70 (1H, m), 2.94 – 2.99 (2H, m); MS m/z 161.90 $[M+H]^+$.

Producto intermedio 25:

N–bencil–1–ciclopropil–piperidin–4–amina

1–ciclopropilpiperidin–4–ona Producto intermedio 26 (3g, 21.55mmol), bencilamina (4.7ml, 43.10mmol) y ácido acético (1.25ml) fueron agitados juntos y triacetoxiborohidruro de sodio (6.86g, 32.33mmol) añadido en forma de porciones. DCM (20ml) fue añadido y la mezcla agitada a temperatura ambiente toda la noche. La mezcla fue concentrada y particionada entre etil acetato y solución de carbonato de potasio 2M. Una capa acuosa fue reextraída con etil acetato y los orgánicos combinados lavados con salmuera, secados ($MgSO_4$) y concentrados. La cromatografía en columna (2% amoniaco 7N en metanol / DCM) dio un líqido marrón el cual contenía Bencilamina y de esta manera fue tomado en DCM y agitado con PS–benzaldehído (NovaBiochem, ≈3.2mmol/g ; ≈1.5 equivalentes comparados a bencilamina) durante 3h. La mezcla fue filtrada y los filtrados combinados concentrados para dar el compuesto del título (2.33g, 47%) como un aceite amarillo.

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.38 – 0.43 (4H, m), 1.33 – 1.40 (2H, m), 1.46 (1H, s), 1.52 – 1.57 (1H, m), 1.86 – 1.90 (2H, m), 2.18 – 2.24 (2H, m), 2.51 – 2.56 (1H, m), 2.96 – 3.01 (2H, m), 3.82 (2H, s), 7.22 – 7.25 (1H, m), 7.29 – 7.33 (4H, m)

Producto intermedio 26:

1–ciclopropilpiperidin–4–ona

1-Etil-1-metil-4-oxopiperidinio yoduro (Journal of the Chemical Society (1949), 708-15; 15 g, 55.74 mmol) fue añadido a ciclopropilamina (Aldrich; 19.3 mL, 278.69 mmol) en tolueno (150 mL). hidrógeno carbonato de sodio (469 mg, 5.57 mmol) en agua (21 mL) fue añadido y la mezcla calentada a 78°C toda la noche. La mezcla fue enfriada y las capas separadas. Una capa acuosa fue extraída (x2) con etil acetato y los orgánicos combinados lavados con salmuera, secados ($MgSO_4$) y concentrados. La cromatografía en columna del residuo (2% MeOH/DCM) dio el compuesto del título (4.1g, 53%) como un líquido marrón pálido.
^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.47 – 0.53 (4H, m), 1.74 (1H, d), 2.40 – 2.44 (4H, m), 2.92 (4H, t)

Producto intermedio 27:

4-amino-2-fluoro-5-metoxi-N-(1-metil-4-piperidil)benzamida

2-fluoro-5-metoxi-N-(1-metil-4-piperidil)-4-nitro-benzamida Producto intermedio 28; 1.3 g, 4.2 mmol) 10% paladio sobre carbón (100 mg) y metanol (50 mL) fueron combinados y agitados a 25°C bajo hidrógeno a presión de 1 bar durante 18 horas.
La mezcla de reacción fue filtrada a través de un tapón de celita, lavando con etanol y concentrado bajo presión reducida para dar el compuesto del título (1.16 g, 100%.) como un sólido amarillo.
^{1}H NMR (399.902 MHz, DMSO-D6) δ 1.54 (qd, 2H), 1.72 – 1.80 (m, 2H), 1.97 (td, 2H), 2.16 (s, 3H), 2.70 (br d, 2H), 3.67 – 3.74 (m, 1H), 3.78 (s, 3H), 5.55 (s, 2H), 6.39 (d, 1H), 7.05 (d, 1H), 7.34 (t, 1H); MS m/z 282.27 $[M+H]^+$.

Producto intermedio 28:

2-fluoro-5-metoxi-N-(1-metil-4-piperidil)-4-nitro-benzamida

A una solución agitada de ácido 2-fluoro-5-metoxi-4-nitro-benzoico (Producto intermedio 29; 861 mg, 4.00 mmol) en DMA (20 mL) fue añadido 4-amino-1-metilpiperidina (Fluorochem; 503 mg, 4.40 mmol) seguido por DIPEA (1.4 mL, 8.00 mmol) y HATU (1.68 g, 4.40 mmol) y la solución amarilla resultante agitada a temperatura ambiente durante 1 h. El solvente fue eliminado bajo presión reducida y el residuo tomado en metanol (aprox. 10 mL) y cargada en un cartucho SCX-2 de 20 g lavando con metanol (50 mL) y eluyendo con amoniaco metanólico 7 N (50 mL) para dar un sólido amarillo, 1.47 g. Esto fue purificado por

cromatografía flash en sílice (Companion, 40 g, 0–5% amoniaco en metanol / DCM) para dar el producto deseado como un sólido amarillo pálido (1.25g, 4.00 mmol, 100%.)

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.54 (qd, 2H), 1.77 – 1.85 (m, 2H), 1.98 (td, 2H), 2.17 (s, 3H), 2.74 (br d, 2H), 3.72 (m, 1H), 3.96 (s, 3H), 7.43 (d, 1H), 7.98 (d, 1H), 8.46 (d, 1H);); MS m/z 161.90 $[M+H]^+$.

Producto intermedio 29:

ácido 2–fluoro–5–metoxi–4–nitro–benzoico

Ácido 2,5–Difluoro–4–nitrobenzoico (Fluorochem; 100 mg, 0.43 mmol) y carbonato de cesio (708 mg, 2.17 mmol) fueron tomados en DMF seco (2 mL) y metanol seco (120 uL, 2.88 mmol) fue añadido y la reacción agitada a temperatura ambiente durante 2 h. La mezcla de reacción fue diluida con etil acetato (50 mL) y agua (50 mL) y acidificada hasta pH1 con solución de HCl 2N. Los orgánicos fueron eliminados y el acuoso adicional extraído con etil acetato (2 x 50 mL). Los orgánicos combinados fueron lavados con agua (50 mL), salmuera (50 mL), secado sobre $MgSO_4$ y concentrado bajo presión reducida para dar el compuesto del título como un sólido amarillo (91 mg, 0.42 mmol, 98%).

^{1}H NMR (399.902 MHz, CDCl3) d 4.00 (s, 3H), 7.63 (d, 1H), 7.70 (d, 1H), 10.78 (br s, 1H); MS m/z 215.27 $[M+H]^+$.

Producto intermedio 30:

Bencil (1R,5S)–6–amino–3–azabiciclo[3.1.0]hexano–3–carboxilato

Bencil (1R,5S)–6–[(2–metilpropan–2–il)oxicarbonilamino]–3–azabiciclo[3.1.0]hexano–3–carboxilato (Bioorganic & Medicinal Chemistry Letters (2004), 14(11), 2773–2776, Compuesto 9; 6.74g, 20.3mmol) fue agitado y disuelto en DCM (90 mL) a temperatura ambiente y TFA (10ml) fue añadido. La solución fue agitada a temperatura ambiente durante 2 horas. Bicarbonato sat. (100ml) fue añadido seguido por carbonato de potasio sólido hasta neutro. La capa DCM fue separada y lavada una vez más con agua. La solución DCM fue secada ($MgSO_4$), filtrada y evaporada hasta una goma.

Rendimiento = 4.05g (86%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.48 (s, 2H), 2.00 (s, 1H), 3.43 (m, 4H), 5.02 (s, 2H), 7.25 (m, 7H).

Producto intermedio 31:

Sal de Metil (1S,3R)–3–aminociclopentano–1–carboxilato hidrocloruro

Ácido (1S,3R)–3–aminociclopentano–1–carboxílico (Acros; 952 mg, 7.37 mmol) fue suspendido en MeOH (15 ml) y enfriado en un baño de acetona/hielo. Cloruro de tionil (1.1 mL, 14.74 mmol) fue añadido en forma de gotas y la solución amarilla pálida resultante agitada en el baño de acetona/hielo durante 30 minutos y luego se dejó calentar a temperatura ambiente, agitada a temperatura ambiente durante 1 h luego calentada a reflujo durante 1 h. Los solventes fueron evaporados para dar el compuesto del título como un sólido color crema después de secar bajo alto vacío. (1.32g 100%).

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.65 (m, 1H), 1.76 (m, 1H), 1.93 (m, 3H), 2.27 (m, 1H), 2.87 (m, 1H), 3.49 (m, 1H), 3.64 (s, 3H), 8.09 (s, 3H)

Producto intermedio 32:

[(2R)–1–(ciclopropilmetil)pirrolidin–2–il]metanamina

Preparación contenida en WO98/39295

Producto intermedio 33:

[1–(pirrolidin–1–ilmetil)ciclopropil]metanamina

A una solución de 1–(pirrolidina–1–carbonil)ciclopropano–1–carboxamida (Producto intermedio 34; 5.0 g, 27.5 mmol) en THF anhidro (150 mL) fue lentamente añadido a THF anhidro 1 M solución de hidruro de aluminio de litio (138 mL, 138 mmol) controlando la temperatura de la reacción a 40°C con un baño de agua/hielo.

La solución clararesulutante fue agitada toda la noche a temperatura ambiente bajo un flujo de gas inerte para dar una suspensión turbia.

Agua (5.24 mL) fue cuidadosamente añadida a la mezcla de reacción manteniendo la temperatura de la reacción a < 30 °C con un baño de agua/hielo para dar lechada blanca espesa. 15% p/v solución de hidróxido de sodio acuoso (5.24 mL) fue cuidadosamente añadida

seguida por agua (15.71 mL). La reacción fue filtrada y el filtrado evaporado hasta secarse para dar el compuesto del título (3.26 g, 77%).

Producto intermedio 34:

1–(pirrolidina–1–Carbonil)ciclopropano–1–carboxamida

A ácido 1–(aminocarbonil)–1–ciclopropano carboxílico (Aldrich; 25 g, 193.6 mmol) en DCM (625 mL) fue añadido HATU (73.61 g, 193.6 mmol) y la suspensión agitada durante 30 minutos. Pirrolidina (Aldrich; 24.25 mL) y base de Huning (67 mL) fue añadida y la reacción agitada a temperatura ambiente todo el fin de semana.

La reacción fue evaporada hasta secarse, DCM añadido y extraído con agua (3x 150 mL). Los extractos acuosos fueron evaporados hasta secarse y el material resultante triturado con etil acetato para dar el compuesto del título como un sólido blanco 11.14 g, 32%).

Producto intermedio 35:

2–metoxi–N'–(2–pirrolidin–1–iletil)benceno–1,4–diamina

A una solución agitada de 4–fluoro–2–metoxi–1–nitro–benceno (Fluorochem; 2.57 g; 15 mmol) en DMA fue añadido 2–pirrolidin–1–iletanamina (Aldrich; 1.88 g, 16.5 mmol) seguido por DIPEA (2.97 mL, 18 mmol). La mezcla fue calentada a 80°C durante 20 horas, luego enfriada hasta temperatura ambiente . La mezcla fue concentrada al vacío, disuelta en DCM y purificada por SCX (columna SCX–2 de 50 g). El producto fue eluido de la columna con amoniaco 7N en metanol, concentrado al vacío para dar el compuesto del título (53 mg) el cual fue disuelto en metanol como una solución de 0.05 mmol y reducida usando un hidrogenador de cuba de H. 10% Catalizador Pd/C, hidrógeno 1 bar (ajuste total de hidrógeno), rango de flujo 3 mL / min a 50°C. La solución resultante fue concentrada al vacío, y el material resultante purificado por cromatografía en columna, eluyendo con 0–10% metanol/amoniaco en DCM, para dar el compuesto del título como un sólido.
MS m/z 236 $[M+H]^+$, Tiempo de retención 1.50 minutos.

En una manera similar los productos intermedios 36–42 fueron preparados a partir de las aminas especificadas.

Producto intermedio 36:

2–metoxi–N'–metil–N'–(1–metil–4–piperidil)benceno–1,4–diamina

Producto intermedio 37:

2–metoxi–4–[4–(2–metoxietil)piperazin–1–il]anilina

Producto intermedio 38:

2–metoxi–4–[4–(1–piperidil)–1–piperidil]anilina

Producto intermedio 39:

N'–(2–dimetilaminoetil)–2–metoxi–benceno–1,4–diamina

Producto intermedio 40:

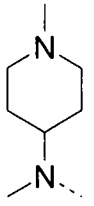
4–(4–ciclohexilpiperazin–1–il)–2–metoxi–anilina

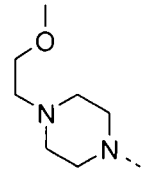
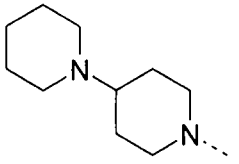
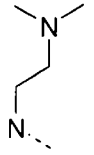
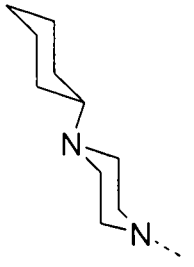
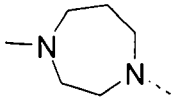
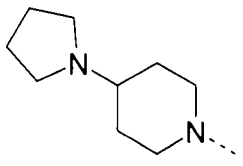
Producto intermedio 41:

2–metoxi–4–(4–metil–1,4–diazepan–1–il)anilina

Producto intermedio 42:

2–metoxi–4–(4–pirrolidin–1–il–1–piperidil)anilina

Producto intermedio	R	Fuente	MS m/z [M+H]+	Tiempo de retención
36		Aldrich	250	1.39

Producto intermedio	R	Fuente	MS m/z [M+H]+	Tiempo de retención
37		Fluorochem	266	1.45
38		Aldrich	290	1.84
39		Aldrich	210	1.26
40		Bulletin of the Chemical Society of Japan (1961), 34 655–9	290	2.02
41		Aldrich	236	1.48
42		Fluorochem	279	1.79

Producto intermedio 43:

2–metoxi–4–[(1–metil–4–piperidil)oxi]anilina

A una solución agitada de 4–(3–metoxi–4–nitro–fenoxi)–1–metil–piperidina (Producto intermedio 44; 12.86 g, 48.34 mmol) en etanol (250 mL) bajo nitrógeno fue añadido en una porción el catalizador Pd/C (10%, 1.29 g). La mezcla resultante fue evacuada y llenada nuevamente con nitrógeno 4 x antes de que gas de hidrógeno fuera introducido mediante un balón. La mezcla de reacción fue agitada a temperatura ambiente durante 18 h. El catalizador fue eliminado por filtración a través de celita y el filtrado concentrado bajo presión reducida para dar un aceite rojo claro (11.1 g, 47.0 mmol, 97%).

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.52 – 1.63 (m, 2H), 1.82 – 1.90 (m, 2H), 2.06 – 2.15 (m, 2H), 2.17 (s, 3H), 2.56 – 2.65 (m, 2H), 3.73 (s, 3H), 4.10 (septeto, 1H), 4.28 (s, 2H), 6.32 (dd, 1H), 6.45 (d, 1H), 6.53 (d, 1H); MS m/z 237.21 $[M+H]^+$.

Producto intermedio 44:

4–(3–metoxi–4–nitro–fenoxi)–1–metil–piperidina

A una solución de 4–Fluoro–2–metoxi–1–nitrobenceno (Apollo Scientific; 10.3 g, 60 mmol) en tolueno (50 mL) y 25% ac. KOH (50 mL), fueron añadidos a temperatura ambiente, 4–hidroxi–1–metilpiperidina (13.8 g, 120 mmol) y tetra–n–butilamonio bromuro (3.87 g, 12 mmol). La mezcla fue calentada a 60 °C durante 18 h. La mezcla de reacción fue enfriada a temperatura ambiente, vertida en hielo–agua (300 mL) y extraida con etil acetato (3 x 150 mL).

La capa orgánica fue extraida con HCl dil (2 M HCl, 300 mL).

La capa acídica acuosa fue tomada hasta pH 4/5 con solución de NaOH 2M y dividida entre 2 x cartuchos SCX–2 de 50 g, lavando con agua y eluyendo con amoniaco metanólico 7 N para dar el compuesto del título como un aceite amarillo, el cual se solidificó lentamente con el paso del tiempo (12.86 g, 80%).

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.64 – 1.72 (m, 2H), 1.93 – 2.00 (m, 2H), 2.17 – 2.24 (m, 5H), 2.59 – 2.64 (m, 2H), 3.92 (s, 3H), 4.60 (septeto, 1H), 6.71 (dd, 1H), 6.78 (d, 1H), 7.94 (d, 1H); MS m/z 267.24 $[M+H]^+$.

Producto intermedio 45:

2–metoxi–4–(1–metilpirrolidin–3–il)oxi–anilina

A una solución agitada de 3–(3–metoxi–4–nitro–fenoxi)–1–metil–pirrolidina (Producto intermedio 46; 5.50 g, 20.68 mmol) en etanol (125 mL) bajo nitrógeno fue añadido en una porción el catalizador Pd/C (10%, 500 mg). La mezcla resultante fue evacuada y llenada nuevamente con nitrógeno (x 4) antes que el gas de hidrógeno fuera introducido mediante un balón. La mezcla de reacción fue agitada a temperatura ambiente durante 18 h. El catalizador fue eliminado por filtración a través de celita y el filtrado concentrado bajo presión reducida para dar a el compuesto del título como un aceite rojo claro (4.74 g, 100%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.94 – 2.02 (m, 1H), 2.22 – 2.30 (m, 1H), 2.36 – 2.45 (m, 1H), 2.38 (s, 3H), 2.73 – 2.83 (m, 3H), 3.50 (s, 2H), 3.81 (s, 3H), 4.74 (octet, 1H), 6.26 (dd, 1H), 6.45 (d, 1H), 6.61 (d, 1H); MS m/z 223.22 $[M+H]^+$.

Producto intermedio 46:

3–(3–metoxi–4–nitro–fenoxi)–1–metil–pirrolidina

A una solución de 4–Fluoro–2–metoxi–1–nitrobenceno (Apollo Scientific; 4.28 g, 25 mmol) en tolueno (20 mL) y 25% Ac. KOH (20 mL), fueron añadidos a temperatura ambiente, 1–metil–3–pirrolidiniol (5.0 g, 50 mmol) y tetra–n–butilamonio bromuro (1.66 g, 5 mmol). La mezcla fue calentada a 60 °C durante 18 h. La mezcla de reacción fue enfriada a temperatura ambiente, vertida en hielo–agua (200 mL) y extraido con etil acetato (3 x 100 mL). La capa orgánica fue lavada con HCl 2M (250 ml) y luego cargada en un cartucho SCX–2 de 50 g, lavando con agua y eluyendo con amoniaco metanólico 7 N para dar el compuesto del título como un aceite amarillo, el cual se solidificó en reposo (5.50 g, 87%).

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.73 – 1.84 (m, 1H), 2.27 (s, 3H), 2.31 – 2.37 (m, 2H), 2.65 (dd, 1H), 2.68 – 2.73 (m, 1H), 2.77 (dd, 1H), 3.92 (s, 3H), 5.02 – 5.07 (m, 1H), 6.62 (dd, 1H), 6.73 (d, 1H), 7.95 (d, 1H); MS m/z 253.23 $[M+H]^+$.

Producto intermedio 47:

2–metoxi–4–(2–morfolin–4–iletoxi)anilina

A 4–[2–(3–metoxi–4–nitro–fenoxi)etil]morfolina (Producto intermedio 48; 16.97 g, 60 mmol, 1eq) en etanol (120 mL) fue añadido 10% paladio sobre carbón (850mg, 5%p). La reacción fue agitada a temperatura ambiente durante 19 horas. Después de filtrar los residuos de

paladio el solvente fue evaporado bajo presión reducida. El producto fue disuelto en etil acetato (100ml) y extraído dos veces con HCl 2M. Las capas acuosas fueron combinadas, lavadas con etil acetato luego basificadas por adición de NaOH 2N. La capa básica fue reacidificada y capturada en resina mp–TsOH. Después de lavar varias veces con metanol el producto fue liberado usando 10% amoniaco en metanol. Después de la evaporación al vacío el compuesto del título fue obtenido como un aceite marrón oscuro. (14.5 g, 89%).
^{1}H NMR (300.132 MHz, DMSO–D6) δ2.49 – 2.51 (4H, m),2.69 (2H, t),3.60 (4H, t),3.74 (3H, s),3.98 (2H, t),4.62 (2H, s),6.30 (1H, dd),6.46 (1H, d),6.54 (1H, d); MS m/z 253 $[M+H]^+$.

Producto intermedio 48:

4–[2–(3–metoxi–4–nitro–fenoxi)etil]morfolina

A una solución de 4–fluoro–2–metoxi–1–nitro–benceno (Apollo Scientific; 10.27 g, 60 mmol) en tolueno (50 mL) y 25% KOH (ac) (50 mL), fue añadido 4–(2–hidroxietil)morfolina (Aldrich; 15.75 g, 120 mmol) y tetra–n–butilamonio bromuro (3.87 g, 12 mmol) a temperatura ambiente. La mezcla fue calentada a 60°C durante 22 horas. La mezcla de reacción fue enfriada a temperatura ambiente, vertida en agua y extraída tres veces con etil acetato. Las capas orgánicas fueron combinadas y lavadas dos veces con hidróxido de sodio 2M luego salmuera. Secadas con sulfato de magnesio, filtradas y evaporadas bajo presión reducida para proporcionar el compuesto del título como un aceite amarillo (16.97 g, 100%).
^{1}H NMR (300.132 MHz, DMSO–D6) δ2.48 (4H, t),2.72 (2H, t),3.58 (4H, t),3.93 (3H, s),4.23 (2H, t),6.68 (1H, dd),6.81 (1H, d),7.94 (1H, d); MS m/z 283 $[M+H]^+$.

Producto intermedio 49:

N–[(4–aminofenil)metil]piridina–2–carboxamida

Piridina–2–carboxilato (Aldrich; 0.35 g, 2.84 mmol), 4–aminobencilamina (Aldrich; 0.51 g, 4.26 mmol) y HATU (1.65g, 4.26mmol) fueron disueltos en DMF (7.5ml). *N,N*–Diisopropiletilamina (1.5ml, 8.53mmol) fue añadido y la mezcla agitada a temperatura ambiente durante 2h. La mezcla fue absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y el residuo purificado por cromatografía en fase normal (2% MeOH/DCM) para

dar un sólido amarillo (440mg). El cual fue suspendido en DCM/Et_2O y filtrado para dar el compuesto del título como un sólido amarillo pálido (235mg, 36%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ4.33 (2H, d), 4.94 (2H, s), 6.50 – 6.53 (2H, m), 7.00 – 7.03 (2H, m), 7.58 – 7.62 (1H, m), 7.98 – 8.07 (2H, m), 8.62 – 8.64 (1H, m), 8.98 (1H, t); MS m/z 228.03 $[M+H]^+$.

Producto intermedio 50:

1–(3–amino–4–metoxi–fenil)–N,N–dimetil–pirrolidin–3–amina

4–metoxi–N–(1–metil–4–piperidil)–3–nitro–benzamida (Producto intermedio 51; 400 mg, 1.4 mmol) 10% paladio sobre carbón (40 mg) y metanol (50 mL) fueron combinados y agitados a 25°C bajo hidrógeno a presión de 5 bar durante 2 horas.

La mezcla de reacción fue filtrada y evaporada hasta secarse. El residuo fue purificado por cromatografía en columna usando 5% amoniaco 7N en MeOH/DCM como el sistema solvente. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido blanco (305mg, 85%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.55 – 1.61 (2H, m), 1.70 – 1.74 (2H, d), 1.89 – 1.96 (2H, t), 2.16 (3H, s), 2.74 – 2.77 (2H, d), 3.68 (1H, m), 3.81 (3H, s), 4.79 (2H, s), 6.81 (1H, d), 7.06 – 7.09 (1H, m), 7.14 (1H, d), 7.86 (1H, d); MS m/z 264.28 $[M+H]^+$.

Producto intermedio 51:

4–metoxi–N–(1–metil–4–piperidil)–3–nitro–benzamida

Ácido 3–Nitro–4–metoxibenzoico (Aldrich; 300mg, 1.52mmol), 1–metil–4–aminopiperidina (Fluorochem; 174mg, 1.52mmol), HATU (868mg, 2.28mmol) y DIPEA (796uL, 4.56mmol) fueron agitados en DMF (6mL) a temperatura ambiente durante 2 horas. La mezcla de reacción fue cargada en una columna SCX–3 prelavada con metanol. La columna fue lavada con metanol y luego eluida con 2% metanol/amoniaco 7N. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido naranja (341mg, 76.4%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.55 – 1.59 (2H, m), 1.75 (2H, d), 1.91 – 1.95 (2H, m), 2.17 (3H, s), 2.70 – 2.79 (2H, d), 3.68 – 3.78 (1H, m), 3.99 (3H, s), 7.46 (1H, d), 8.16 – 8.19 (1H, m), 8.41 (2H, d); MS m/z 294.31 $[M+H]^+$.

Producto intermedio 52:

4–amino–3–cloro–N–(2–morfolin–4–iletil)benzamida

3–cloro–N–(2–morfolin–4–iletil)–4–nitro–benzamida (Producto intermedio 53; 1.2 g, 3.82 mmol), polvo de hierro (1.29 g, 22.95 mmol) y cloruro de amonio (144 mg, 2.68 mmol) fueron calentados en etanol (27 mL) y agua (9 mL a reflujo durante 1h. Unas gotas de ácido acético fueron añadidas y se continuó calentando durante 1h adicional. La mezcla de reacción fue enfriada, filtrada y el filtrado concentrado. El residuo fue particionado entre DCM y $NaHCO_3$ sat . La capa orgánica fue lavada con salmuera, secada ($MgSO_4$) y concentrada. La cromatografía en columna del residuo dio el compuesto del título como un sólido cristalino blanco (650mg, 60%).

^{1}H NMR (399.9 MHz, DMSO–d_6 + D_2O) δ2.38 – 2.46 (6H, m), 3.30 – 3.36 (2H, m), 3.55 – 3.59 (4H, m), 5.83 (1H, NH_2 parcialmente intercambiado), 6.79 (1H, d), 7.53 – 7.55 (1H, m), 7.73 (1H, d), 8.10 (1H, s); MS m/z 284.08 $[M+H]^+$.

Producto intermedio 53:

3–cloro–N–(2–morfolin–4–iletil)–4–nitro–benzamida

3–cloro–4–nitro–benzoil cloruro (Producto intermedio 54; 1.1 g, 5.00 mmol) fue disuelto en DCM (10 mL) y N,N–diisopropiletilamina (1.05 mL, 6.00 mmol) añadido. La mezcla fue enfriada en un baño de hielo/agua y 4–(2–aminoetil)morfolina (Aldrich; 0.66 mL, 5.00 mmol) en DCM (5 mL) añadida en forma de gota. La mezcla se dejó calentar a temperatura ambiente y agitada durante 0.5 h. La mezcla de reacción fue lavada con salmuera, NaOH 2N, secada ($MgSO_4$) y concentrada. La cromatografía en columna del residuo (2% MeoH/DCM) dio el compuesto del título como un sólido amarillo. (1.2 g, 76%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ2.43 (4H, t), 2.48 (2H, t), 3.39 – 3.44 (2H, m), 3.58 (4H, m), 7.98 – 8.01 (1H, m), 8.16 (1H, m), 8.19 (1H, d), 8.78 (1H, t); MS m/z 314.16 $[M+H]^+$.

Producto intermedio 54:

3–cloro–4–nitro–benzoil cloruro

Ácido 3–cloro–4–nitrobenzoico (Apin; 1g, 4.96 mmol) fue suspendido en tolueno (10 mL) y cloruro de tionil (1.1 mL, 14.88 mmol) añadido. La mezcla fue calentada hasta 85°C durante 45min además cloruro de tionil (1.1 mL) fue añadido y la mezcla calentada a reflujo. 0.5 h. La mezcla de reacción se dejó enfriar y reposar toda la noche. La mezcla fue concentrada para dar el compuesto del título como un líquido amarillo (1.15g, 100%).

^{1}H NMR (399.9 MHz, $CDCl_3$) δ7.87 (1H, s), 8.07 – 8.10 (1H, m), 8.23 (1H, d); MS m/z 198.92 $[M+H]^+$.

Producto intermedio 55:

4–amino–3–cloro–N–(1–metil–4–piperidil)benzamida

3–cloro–N–(1–metil–4–piperidil)–4–nitro–benzamida (Producto intermedio 56; 1.8 g, 6 mmol) hidrogenado durante horas con agitación a 298K y presión de 5 bar usando a 5% Catalizador Pt/C y solvente EtOH (50 mL). El catalizador fue filtrado y el filtrado concentrado para dar un sólido cristalino amarillo el cual fue disuelto en DCM y purificado por cromatografía en columna (5% MeOH/DCM) para dar el compuesto del título un sólido cristalino amarillo pálido (1.62 g, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.53 – 1.60 (2H, m), 1.71 – 1.74 (2H, m), 1.90 – 1.95 (2H, m), 2.16 (3H, s), 2.33 – 2.35 (1H, m), 2.67 – 2.69 (1H, m), 2.76 (2H, d), 3.66 – 3.70 (1H, m), 5.82 (2H, d), 6.78 (1H, d), 7.56 – 7.58 (1H, m), 7.76 (1H, d), 7.89 (1H, d); MS m/z 268.14 $[M+H]^+$.

Producto intermedio 56:

3–cloro–N–(1–metil–4–piperidil)–4–nitro–benzamida

3–cloro–4–nitro–benzoil cloruro (Producto intermedio 54; 2.2 g, 10.00 mmol) fue disuelto en DCM (20 mL) y N,N–diisopropiletilamina (2.095 mL, 12.00 mmol) añadido. La mezcla fue enfriada en un baño de hielo/agua y 4–amino–1–metilpiperidina (Fluorochem; 1.14 g, 10.00 mmol) en DCM (10 mL) añadido en forma de gotas. La mezcla se dejó calentar hasta temperatura ambiente y agitada durante 0.5 h. Resultó un precipitado blanco. La mezcla de reacción fue lavada con NaOH 2N, filtrada y la torta del filtro lavada con agua y secada en un sínter todo el fin de semana para dar el compuesto del título como un sólido blanco (1.80g, 60%) como un sólido blanco.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.53 – 1.63 (2H, m), 1.79 (2H, t), 1.92 – 1.99 (2H, m), 2.17 (3H, s), 2.78 (2H, d), 3.70 – 3.77 (1H, m), 7.99 – 8.02 (1H, m), 8.18 (2H, t), 8.60 (1H, d); MS m/z 298.2 $[M+H]^+$.

Producto intermedio 57:

10–amino–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 250 mg; 0.89 mmol), Difenilmetanimina (Fluka; 178 mg, 0.979 mmol) y carbonato de cesio (580 mg, 1.78 mmol) fueron añadidos a dioxano (3 ml y la suspensión burbujeada con nitrógeno durante 10 minutos.

Tris(dibencilidenoacetona)dipaladio(0) (49 mg; 0.053 mmol) y XANTFOS (46 mg, 0.080 mmol) fueron añadidos y la mezcla calentada a 100 °C durante 16 h. La mezcla de reacción fue enfriada a temperatura ambiente filtrada y la torta del filtro lavada con DCM. El filtrado fue evaporado y el material resultante tomado en DCM y purificado en sílice (la columna fue hecha neutral antes de la purificación humedeciendo con iso–hexano, corriendo una solución de 5% trietilamina en iso–hexano completamente seguido por iso–hexano, el material fue luego añadido) eluyendo con un gradiente de 40 – 60% etil acetato / iso–hexano luego 60% etil acetato / iso–hexano. Las fracciones que contienen el Producto intermedio imina fueron combinadas y evaporadas hasta un sólido amarillo (162 mg, 43%), el cual fue disuelto en THF (10 ml). HCl 2M aq (3 mL) fue añadido y la solución agitada a temperatura ambiente durante 20 minutos. La mezcla de reacción fue añadida a una columna SCX–2 de 5g prehumedecida con MeOH (2 volumenes de columna), purgada con MeOH (2 volumenes de columna) y el producto eluido con amoniaco 2M en MeOH. Los solventes fueron evaporados para dar el compuesto del título como un sólido blanco (80 mg, 80% de imina).

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.46 (m, 4H), 1.59 (m, 2H), 1.83 (m, 2H), 3.03 (s, 3H), 3.46 (m, 2H), 4.60 (m, 1H), 5.99 (s, 2H), 7.75 (s, 1H);); MS m/z 262 $[M+H]^+$.

Producto intermedio 58:

4–bromo–2,6–difluoro–N–(1–metil–4–piperidil)benzamida

Ácido 4–bromo–difluorobenzoico (Fluorochem; 3.0 g, 12.66 mol) y HBTU (5.3 g, 13.92 mol) fueron añadidos a DMF (80 mL), a esto fue añadido la 4–amino–1–metilpiperidina requerida (Fluorochem; 1.59 g, 13.93 mol) y DIPEA (5.0 mL, 27.85 mol), la reacción fue agitada durante 48 horas, después de lo cual el solvente fue eliminado al vacío para proporcionar una goma marrón. La goma fue tratada con 2.0 M NaOH (50 mL) y extraída con DCM (3 x 200 ml). Los extractos combinados fueron secados y el solvente eliminado al vacío para proporcionar una goma naranja oscuro el cual fue recristalizado de acetonitrilo caliente para dar el compuesto del título como un sólido blanco (1.9 g, 45%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 8.64 (d, 1H), 7.55 (d, 2H), 3.74 – 3.64 (m, 1H), 2.74 – 2.65 (m, 2H), 2.15 (s, 3H), 1.98 (t, 2H), 1.82 – 1.74 (m, 2H), 1.52 – 1.42 (m, 2H); MS m/z 334 $[M+H]^+$.

Producto intermedio 59:

4–amino–2,5–difluoro–N–(1–metil–4–piperidil)benzamida

2,5–difluoro–N–(1–metil–4–piperidil)–4–nitro–benzamida (Producto intermedio 60; 633 mg 2.1 mmol), 10% paladio sobre carbón (70 mg) y metanol (50 mL) fueron combinados y agitados a 25°C bajo hidrógeno a presión de 3 bar durante 16 horas.

El catalizador fue filtrado y el filtrado evaporado para dar el compuesto del título como un sólido amarillo (554 mg, 97%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.58 (m, 2H), 2.03 (m, 2H), 2.18 (m, 2H), 2.30 (s, 3H), 2.78 (m, 2H), 3.99 (m, 1H), 4.14 (s, 2H), 6.47 (m, 2H), 7.71 (m, 1H); MS m/z 334 $[M+H]^+$.

Producto intermedio 60:

2,5–difluoro–N–(1–metil–4–piperidil)–4–nitro–benzamida

Ácido 1,5–Difluoro–4–nitrobenzoico (Fluorochem; 1 g, 4.92 mmol), 4–Amino–1–metilpiperidina (Fluorochem; 620 mg, 5.41 mmol), HAT (2.05 g, 5.41 mmol), DIPEA (2.57 mL, 14.76 mmol) y DMF (10 mL) fueron combinados y agitados a temperatura ambiente durante 18 h. Los solventes fueron evaporados y el material resultante particionado entre DCM y agua. Ambas fases fueron acidificadas con HCl 2M ac. y añadidas a una columna SCX–2 de 50 g prehumedecida con MeOH (2 volúmenes de columna). La columna fue purgada con MeOH (2 volúmenes de columna) y el producto crudo eluido con amoniaco 2M

ácido p–toluenosulfónico monohidrato (124 mg, 0.65 mmol) fueron combinados en 4–metil–2–pentanol (3 mL) y calentados a 100 °C durante 18 horas. La mezcla de reacción enfriada fue cargada en a una columna SCX–2 (5 g) prehumedecida con MeOH (2 volúmenes de columna), purgada con MeOH (2 volúmenes de columna) luego eluida con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (85 mg, 59%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.62 (m, 2H), 1.11 (m, 2H), 1.46 (m, 2H), 1.72 (m, 4H), 1.79 (m, 4H), 2.03 (m, 2H), 2.58 (m, 4H), 2.72 (m, 2H), 3.29 (s, 3H), 3.47 (s, 2H), 3.60 (m, 2H), 3.95 (s, 3H), 4.96 (m, 1H), 7.31 (m, 1H), 7.56 (d, 1H), 7.70 (s, 1H), 7.87 (s, 1H), 8.41 (d, 1H); MS m/z 552 $[M+H]^+$.

Ejemplo 399:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 100 mg, 0.32 mmol), 4–amino–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida (Producto intermedio 182; 87 mg, 0.32 mmol) y ácido 4–toluenosulfónico monohidrato (154 mg, 0.81 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140 °C durante 3 horas. La mezcla fue enfriada y absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (80 mg, 46%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.67 – 0.72 (2H, m), 0.91 – 0.96 (2H, m), 1.53 – 1.75 (7H, m), 1.87 – 1.96 (2H, m), 2.13 – 2.22 (1H, m), 2.26 (3H, s), 2.34 – 2.45 (2H, m), 2.57 – 2.64 (1H, m), 2.66 – 2.70 (1H, m), 3.18 (3H, s), 3.50 (2H, s), 3.93 (3H, s), 4.35 – 4.43 (1H, m), 4.83 – 4.92 (1H, m), 7.22 (1H, d), 7.77 (1H, s), 7.98 – 8.00 (1H, m), 8.03 (1H, s), 8.35 (1H, d); MS m/z 539 $[M+H]^+$.

Ejemplo 400:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2,5–difluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 109 mg, 0.36 mmol), anilina (Producto intermedio **229**; 83 mg, 0.324 mmol), y carbonato de cesio (211 mg, 0.648 mmol) añadidos a dioxano (3 mL) y la suspensión burbujeada con nitrógeno durante 10 minutos. Tris–dibencilidenoacetonadipaladio (II) (11 mg, 0.02 mmol) y XANTFOS (17 mg, 0.03 mmol) fueron añadidos y la mezcla calentada a 100 °C durante 16 horas. La mezcla de reacción fue enfriada a temperatura ambiente, filtrada, y la torta del filtro lavada con DCM y el filtrado evaporado. El residuo fue disuelto en DCM y purificado en una columna de sílice eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM sobre 30 volumenes de columnas. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (95 mg, 56%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.64 (m, 2H), 1.12 (m, 2H), 1.46 (m, 2H), 1.74 (m, 5H), 2.02 (m, 2H), 2.29 (m, 1H), 2.42 (m, 4H), 2.67 (m, 2H), 2.90 (m, 1H), 3.29 (s, 3H), 3.48 (s, 2H), 4.65 (m, 1H), 4.93 (m, 1H), 6.96 (m, 1H), 7.28 (m, 1H), 7.80 (m, 1H), 7.88 (s, 1H), 8.46 (m, 1H); MS m/z 526 $[M+H]^+$.

Ejemplo 401:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 101 mg, 0.33 mmol), ácido p–toluenosulfónico monohidrato (155 mg, 0.81 mmol) y 4–amino–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida (Producto intermedio 206; 100 mg, 0.33 mmol) fueron añadidos a 4–metil–2–pentanol (7 mL). La reacción fue calentada a 120 °C todo el fin de semana. La muestra fue transferida a un cartucho SCX (10 g) prehumedecido con metanol,

luego lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (34 mg, 18%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.63 – 0.60 (m, 2H), 1.01 (s, 6H), 1.10 – 1.07 (m, 2H), 1.51 – 1.43 (m, 2H), 1.74 – 1.61 (m, 4H), 1.83 – 1.76 (m, 4H), 2.05 – 1.98 (m, 2H), 2.56 (s, 2H), 2.72 – 2.65 (m, 4H), 3.28 (s, 3H), 3.39 (d, 2H), 3.46 (s, 2H), 3.98 (s, 3H), 4.98 (quinteto, 1H), 7.20 (dd, 1H), 7.55 (d, 1H), 7.65 (s, 1H), 7.87 (s, 1H), 8.46 (d, 1H), 9.15 (s, 1H); MS m/z 576 $[M+H]^+$.

Ejemplo 402:

3–cloro–4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

Ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–cloro–benzoico (Producto intermedio 253; 52 mg, 0.12 mmol) fue suspendido en DMF (4 mL). DIPEA (62 ul, 0.35 mmol) fue añadido para dar una solución color paja. Endo–9–metil–9–azabiciclo[3,3,1]–nonan–3–amina (Chempacific; 26 mg, 0.16 mmol) fue añadido, seguido por HATU (67 mg, 0.17 mmol) y la mezcla resultante fue agitada a temperatura ambiente toda la noche.

La mezcla de reacción fue evaporada hasta una goma ámbar, la cual fue particionada entre DCM (5 mL) y solución de bicarbonato de sodio saturada acuosa. (5 mL). La fase orgánica fue separada mediante elusión por gravedad a través de un vaso filtro PTFE y el filtrado evaporado hasta secarse para proporcionar un aceite ámbar el cual fue purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (46 mg, 56%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.68 (m, 2H), 0.92 (m, 4H), 1.39 – 1.70 (m, 9H), 1.80 – 2.08 (m, 5H), 2.19 (m, 2H), 2.41 (s, 3H), 2.98 (m, 2H), 3.18 (s, 3H), 3.47 (s, 2H), 4.31 (m, 1H), 4.78 (m, 1H), 7.80 (m, 1H), 7.99 (s, 1H), 8.00 (d, 1H), 8.05 (d, 1H), 8.08 (s, 1H), 8.32 (d, 1H); MS m/z 578 $[M+H]^+$.

Ejemplo 403:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–N–[(3R)–1–etilpirrolidin–3–il]–3–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Ejemplo 350, utilizando, 2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 75 mg, 0.24 mmol), y 4–amino–N–[(3R)–1–etilpirrolidin–3–il]–3–metoxi–benzamida (Producto intermedio 245; 70 mg, 0.26 mmol) calentando por irradiación de microondas a 160 °C durante 1 hora, como una espuma blanco hueso (50 mg, 39%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.04 (t, 3H), 1.10 (s, 6H), 1.55 – 1.93 (m, 9H), 2.15 (m, 1H), 2.43 (m, 4H), 2.65 (m, 1H), 2.73 (m, 1H), 3.19 (s, 3H), 3.38 (s, 2H), 3.95 (s, 3H), 4.40 (m, 1H), 5.19 (m, 1H), 7.51 (m, 2H), 7.67 (s, 1H), 7.99 (s, 1H), 8.28 (d, 1H), 8.37 (d, 1H); MS m/z 536 $[M+H]^+$.

Ejemplo 404:

4–(9'–ciclopentil–5'–metil–6'–oxo–5',6',8',9'–tetrahidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepina]–2'–ilamino)–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 55 mg, 0.17 mmol), 4–amino–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida (Producto intermedio 204; 53 mg, 0.17 mmol) y ácido p–toluenosulfónico monohidrato (82 mg, 0.43 mmol) fueron calentados en 4–metil–2–pentanol (3 mL) a 140 °C durante 2 horas. La mezcla de reacción fue enfriada y absorbida en una columna SCX, la cual fue luego lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron evaporadas y el residuo purificado por HPLC en fase inversa preparativa modificada base para proporcionar el compuesto del título como un sólido blanco (35mg, 35%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.68 – 0.71 (2H, m), 0.91 – 0.94 (4H, m), 1.40 – 1.46 (3H, m), 1.51 – 1.73 (6H, m), 1.86 – 1.94 (4H, m), 1.99 – 2.09 (1H, m), 2.18 – 2.25 (2H, m), 2.42 (3H, s), 2.98 (2H, d), 3.19 (3H, s), 3.51 (2H, s), 3.94 (3H, s), 4.27 – 4.35 (1H, m), 4.84 –

en MeOH. Las fracciones que contienen el producto fueron evaporadas al vacío y el material resultante tomado en DCM y purificado en sílice eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM luego 5% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido amarillo (635 mg, 43%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.53 (m, 2H), 1.80 (m, 2H), 1.98 (m, 2H), 2.16 (s, 3H), 2.73 (m, 2H), 3.70 (m, 1H), 7.79 (m, 1H), 8.21 (m, 1H), 8.59 (d, 1H); MS m/z 300 $[M+H]^+$.

Producto intermedio 61:

4–amino–2–fluoro–N–(1–metil–4–piperidil)benzamida

2–fluoro–N–(1–metil–4–piperidil)–4–nitro–benzamida (Producto intermedio 62; 1.62 g, 5.8 mmol), 10% paladio sobre carbón (160 mg) y metanol (50 mL) fueron combinados y agitados a 25°C bajo hidrógeno a presión de 5 bar durante 16 horas.

El catalizador fue filtrado y el filtrado evaporado para dar un sólido marrón el cual fue triturado con 5% MeOH / DCM . El precipitado fue recogido por filtración y secado bajo vacío para proporcionar el compuesto del título como un sólido beige (560 mg, 39%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.74 (m, 2H), 1.99 (m, 2H), 2.76 (s, 3H), 3.09 (m, 2H), 3.42 (m, 2H), 3.97 (m, 1H), 5.89 (s, 2H), 6.30 (m, 1H), 6.39 (m, 1H), 7.37 (m, 1H), 7.67 (s, 1H), 9.11 (s, 1H);); MS m/z 252 $[M+H]^+$.

Producto intermedio 62:

2–fluoro–N–(1–metil–4–piperidil)–4–nitro–benzamida

Ácido 2–Fluoro–4–nitrobenzoico (Aldrich; 3 g, 16.21 mmol), 4–Amino–1–metilpiperidina (Fluorochem; 2.03 g, 17.83 mmol), HATU (6.77 g, 17.83 mmol), DIPEA (8.5 mL, 48.63 mmol) y DMF (3 0 mL) fueron combinados y agitados a temperatura ambiente durante 18 h. Los solventes evaporados y particionados entre DCM (200 ml) y agua (100 ml). La fase acuosa fue reextraída con DCM (100 ml). Las fases orgánicas combinadas fueron secadas ($MgSO_4$) y evaporadas. El material resultante fue tomado en DCM y purificado en sílice eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM luego 5% amoniaco 2M en MeOH /

DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido amarillo (2.67 g, 59%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.53 (m, 2H), 1.80 (m, 2H), 2.26 (m, 5H), 2.85 (m, 2H), 3.74 (m, 1H), 7.72 (m, 1H), 8.06 (m, 1H), 8.12 (m, 1H), 8.54 (d, 1H); MS m/z 282 $[M+H]^+$.

Producto intermedio 63:

4–amino–3–metil–N–(1–metil–4– piperidil)benzamida

3–metil–N–(1–metil–4–piperidil)–4–nitro–benzamida (Producto intermedio 64: 3.34 g) 10% paladio sobre carbón (350 mg) y metanol (50 mL) fueron combinados y agitados a 25°C bajo hidrógeno a presión de 5 bar durante 16 horas.

El catalizador fue filtrado y lavado con EtOH. El filtrado fue evaporado para proporcionar un sólido color crema, el cual fue triturado con DCM filtrado y secado bajo vacío para dar el compuesto del título como un sólido blanco (1.2 g).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.75 (m, 2H), 1.96 (m, 2H), 2.08 (s, 3H), 2.74 (s, 3H), 3.04 (m, 2H), 3.38 (m, 2H), 3.96 (m, 1H), 5.36 (s, 2H), 6.58 (d, 1H), 7.47 (m, 2H), 7.86 (d, 1H), 9.13 (s, 1H); MS m/z 248 $[M+H]^+$.

El siguiente Producto intermedio fue preparado de una manera análoga al Producto intermedio 62 utilizando ácido 3–Metil–4–nitrobenzoico, disponible de Aldrich, como el ácido Nitro de partida.

Producto intermedio 64:

3–metil–N–(1–metil–4–piperidil)–4–nitro–benzamida

3–metil–N–(1–metil–4–piperidil)–4–nitro–benzamida fue preparado de una manera análoga al Producto intermedio 62 utilizando ácido 3–Metil–4–nitrobenzoico, disponible de Aldrich, como el ácido Nitro de partida.

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.71 (m, 2H), 1.92 (m, 2H), 3.16 (m, 2H), 3.91 (m, 1H), 7.86 (m, 1H), 7.92 (s, 1H), 8.06 (d, 1H), 8.56 (d, 1H); MS m/z 278 $[M+H]^+$.

Producto intermedio 65:

4–amino–3–fluoro–N–(1–metil–4–piperidil)benzamida

Ácido 4–amino–3–fluorobenzoico (Fluorochem; 1 g, 6.44 mmol), 4–Amino–1–metilpiperidina (Fluorochem; 811 mg, 7.09 mmol), HATU (2.70 g, 7.09 mmol), DIPEA (3.4 mL, 19.32 mmol) y DMF (15 mL) fueron combinados y agitados durante 18 h a temperatura ambiente. El solvente fue evaporado y el material resultante disuelto en DCM (con un poco de MeOH para ayudar a la solubilidad) y cromatografiada en sílice eluyendo con un gradiente de 0 – 10% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar un sólido naranja el cual fue disuelto en MeOH y añadido a una columna SCX–2 de 50 g prehumedecida con MeOH (2 volúmenes de columna). La columna fue purgada con MeOH (2 volúmenes de columna) y el producto eluido con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron evaporadas para proporcionar el compuesto del título como un sólido beige. (1.72 g, 100%).

^{1}H NMR (399.902 MHz, CDCl3) ?1.55 (m, 2H), 2.03 (m, 2H), 2.14 (m, 2H), 2.29 (s, 3H), 2.81 (m, 2H), 3.95 (m, 1H), 4.01 (s, 2H), 5.77 (d, 1H), 6.75 (m, 1H), 7.34 (m, 1H), 7.45 (m, 1H); MS m/z 252 $[M+H]^+$.

Producto intermedio 66:

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–(2–metoxietoxi)benzoico

A una solución agitada de Metil 4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–(2–metoxietoxi)benzoato (Producto intermedio 67; 164 mg, 0.35 mmol) en etanol (3 mL) fue añadido una solución de hidróxido de litio (22 mg, 0.92 mmol) en agua (1 ml). La reacción fue agitada a temperatura ambiente toda la noche. Una adición posterior de hidróxido de litio (20 mg) como una solución en agua (1 ml) fue añadido y se continuó agitando durante 2.5 h y luego calentado hasta 50°C durante 4 h. La mezcla de reacción fue evaporada y el residuo diluido con agua (5 mL). La solución opaca resultante fue tratada con una gotas de HCl 2M (ac.) para ajustar el pH a 2–3. Se formó un precipitado el cual fue recogido mediante filtración por succión, lavando completamente con más agua y secado bajo vacío, a 55°C, durante 3 horas para proporcionar el compuesto del título como un sólido color hueso (113 mg, 71%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.65 (m, 6H), 1.91 (m, 2H), 2.67 (m, 2H), 3.18 (s, 3H), 3.70 (m, 2H), 3.75 (m, 2H), 4.27 (m, 2H), 4.84 (m, 1H), 7.57 – 7.63 (m, 2H), 8.13 (s, 1H), 8.27 (d, 1H), 8.72 (m, 1H); MS m/z 456.4 $[M+H]^+$.

Producto intermedio 67:

Metil 4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–(2–metoxietoxi)benzoato

A 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]u ndeca–8,10,12–trien–5–ona (Producto intermedio 1, 222 mg, 0.79 mmol) fue añadido una solución de metil 4–amino–3–(2–metoxietoxi)benzoato (Producto intermedio 68; 203 mg, 0.90 mmol) en etanol (4 mL). Agua (12 mL) fue añadido seguido por ácido clorhídrico concentrado (36%; 160 µL). La reacción fue calentada hasta 80°C y agitada toda la noche. La reacción se dejó reposar y enfriar toda la noche, antes de la evaporación del etanol. El residuo acuoso fue diluida hasta ~50 mL con agua y la solución basificada hasta pH 9 por adición de una gotas de amoniaco ac..La emulsión resultante fue tratada con un poco de salmuera y extraido con DCM (2 x 50 mL). Los extractos orgánicos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio, filtrados y evaporados para dar una goma ámbar la cual fue purificada por cromatografía flash en sílice (cartucho de Si de 40g; ISCO Companion), eluyendo primero con un gradiente en aumento de 25–75% etil acetato en iso–hexano y luego un gradiente en aumento de 0–10% metanol en DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar un aceite amarillo el cual cristalizó en reposo toda la noche. Este sólido fue triturado con dietil éter, el sólido recogido mediante filtración por succión y secado para proporcionar el compuesto del título como una sólido color crema (173 mg, 47 %).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.59 – 1.81 (m, 6H), 2.04 (m, 2H), 2.67 (m, 2H), 3.29 (s, 3H), 3.48 (s, 3H), 3.70 (m, 2H), 3.81 (m, 2H), 3.90 (s, 3H), 4.27 (m, 2H), 4.89 (m, 1H), 7.58 (m, 1H), 7.69 (m, 1H), 7.87 (s, 1H), 7.95 (s, 1H), 8.56 (d, 1H);); MS m/z 470 $[M+H]^+$.

Producto intermedio 68:

Metil 4–amino–3–(2–metoxietoxi)benzoato

A una solución de Metil 3–hidroxi–4–aminobenzoato (ABCR: 97 mg, 0.58 mmol) en acetona (3 mL), en un tubo de microondas, fue añadido metoxietil bromuro (Aldrich; 85 µL, 0.90 mmol) y carbonato de potasio en polvo (120 mg, 0.87 mmol). La reacción fue calentada en un microondas (150W, CEM explorer) a 100°C y se mantuvo durante 30 minutos. Una adición posterior de metoxietil bromuro (40 µL, 0.43 mmol) fue hecha y la reacción calentada hasta 120°C durante unos 30 minutos adicionales.

La reacción fue repetida en dos lotes como sigue. A una solución de Metil 3–hidroxi–4–aminobenzoato (135 mg, 0.81 mmol) en acetona (4 ml), en un tubo de microondas fue añadido carbonato de potasio (185 mg, 1.34 mmol) y metoxietil bromuro (115 µL, 1.22 mmol) La reacción fue calentada hasta 120°C en un microondas y se mantuvo durante 1 hora. Las reacciones fueron enfriadas, tratada con una alicuota adicional de metoxietil bromuro (58 µL, 0.62 mmol) y recalentado hasta 120°C manteniéndose durante una hora adicional.

Todos los tres lotes fueron combinados y evaporados hasta secarse. El residuo fue particionado entre DCM (25 mL) y agua (25 mL). La fase orgánica fue separada y la fase acuosa reextraída con DCM (20 mL). Las fases orgánicas combinadas fueron lavadas con salmuera, secadas sobre sulfato de magnesio y evaporadas para dar un aceite amarillo el cual fue purificado por cromatografía flash en sílice (cartucho de 40g) eluyendo con un gradiente en aumento de 25–50% etil acetato en iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un aceite oscuro (256 mg, 56%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 3.38 (s, 3H), 3.74 (m, 2H), 3.80 (s, 3H), 4.16 (m, 2H), 5.61 (s, 2H), 6.72 (d, 1H), 7.37 (m, 1H), 7.45 (m, 1H); MS m/z 226 $[M+H]^+$.

Producto intermedio 69:

Ácido 4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–propan–2–iloxi–benzoico

A una solución agitada de Metil 4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–propan–2–iloxi–benzoato (Producto intermedio 70; 128 mg, 0.28 mmol) en Etanol (3 mL) fue añadido una solución de hidróxido de litio (26 mg, 0.92 mmol) en agua (1.5 mL). La reacción se dejó agitar a 70°C

durante 4 horas, enfriada, evaporada y el residuo diluido con agua (10 mL). La solución resultante fue tratada con una gotas de HCl 2M (ac.) hasta un precipitado persistió, pH ~ 3–4. El precipitado fue recogido mediante filtración por succión, lavando completamente con más agua. El sólido fue secado bajo succión toda la noche para proporcionar el compuesto del título como un sólido blanco (108 mg, 88 %).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.36 (d, 6H), 1.57 – 1.77 (m, 6H), 1.95 (m, 2H), 2.61 (m, 2H), 3.18 (s, 3H), 3.65 (m, 2H), 4.69 – 4.85 (m, 2H), 7.52 – 7.56 (m, 2H), 7.83 (s, 1H), 8.10 (s, 1H), 8.46 (d, 1H), 12.62 (s, 1H); MS m/z 440 $[M+H]^+$.

Producto intermedio 70:

Metil 4–[(6–ciclopentil–2–metil–3–oxo–2,6,8,10–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–9–il)amino]–3–propan–2–iloxi–benzoato

A 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]u ndeca–8,10,12–trien–5–ona (Producto intermedio 1, 190 mg, 0.68 mmol) fue añadida una solución de metil 4–amino–3–propan–2–iloxi–benzoato (Producto intermedio 71, 145 mg, 0.69 mmol) en etanol (4 mL), seguido por agua (12 mL). Ácido clorhídrico concentrado (36%; 140 µL) fue añadido y la reacción calentado hasta 80°C, con agitación, toda la noche. La reacción se dejó reposar y enfriar toda la noche, antes de la evaporación del etanol. El residuo acuoso fue diluida hasta ~40 mL con agua y la solución basificada hasta pH9 por adición de una gotas de amoniaco ac., la emulsión resultante fue tratada con un poco de salmuera y extraido con DCM (2 x 30 mL). La mezcla bifásica fue vertida en un vaso PTFE y la fase orgánica se dejó gotear a través de baja gravedad. La evaporación de la fase orgánica proporcionó una goma ámbar, la cual fue purificada por cromatografía flash en sílice (cartucho de Si de 40g; ISCO Companion), eluyendo con un gradiente en aumento de 25–100% etil acetato en iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar un goma incolora la cual fue triturada con a pequeña cantidad de dietil éter y el sólido resultante recogido mediante filtración por succión y secado para proporcionar el compuesto del título como un sólido blanco (132 mg, 43 %).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.36 (d, 6H), 1.58 – 1.77 (m, 6H), 1.95 (m, 2H), 2.60 (m, 2H), 3.18 (s, 3H), 3.64 (m, 2H), 3.83 (s, 3H), 4.77 (m, 2H), 7.53 (m, 1H), 7.57 (m, 1H), 7.78 (s, 1H), 8.10 (s, 1H), 8.51 (d, 1H); MS m/z 452 $[M+H]^+$.

Producto intermedio 71:

Metil 4–amino–3–propan–2–iloxi–benzoato

Metil 3–hidroxi–4–aminobenzoato (ABCR: 100 mg, 0.60 mmol) y carbonato de cesio (396 mg, 1.22 mmol) fueron tomados en acetona (4 mL) y 2–yodopropano (90 µL, 0.90 mmol) añadido y reacción calentada en microondas (CEM discover; 150 W) hasta 120°C y se mantuvo durante 30 min una alicuota adicional de 2–yodopropano (90 µL, 0.90 mmol) fue añadida y la reacción calentada nuevamente hasta 120°C en microondas, manteniéndose durante unos 30 min adicionales la reacción fue repetida dos veces en una escala de 0.89 mmol.

Las mezclas de reacción fueron combinadas y evaporadas hasta secarse y el residuo particionado entre, etil acetato (40 ml) y agua (50 ml). La fase orgánica fue separada y la acuosa reextraída con etil acetato (40 ml). Los extractos orgánicos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio y evaporadas para dar un aceite amarillo el cual fue purificado por cromatografía en columna, en sílice (cartucho de 40 g; ISCO Companion) eluyendo con un gradiente en aumento de 5–50% etil acetato en iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta secarse para proporcionar el producto como un aceite amarillo (301 mg, 60%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.28 (d, 6H), 3.75 (s, 3H), 4.53 (m, 1H), 5.51 (s, 2H), 6.66 (d, 1H), 7.31 (m, 1H), 7.37 (m, 1H); MS m/z 209.4 $[M+H]^+$.

Producto intermedio 72:

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–(2–dimetilaminoetoxi)benzoico

Metil 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–hidroxi–benzoato (Producto intermedio 73: 63 mg, 0.15 mmol) fue disuelto en DMA (2 mL) y tratado secuencialmente con carbonato de potasio en polvo (maya fina; 106 mg, 0.79 mmol) y dimetilaminoetil bromuro hidrobromuro (ASDI; 61 mg, 0.26 mmol). La

mezcla de reacción fue calentada a 100°C, con agitación durante 1 hora y se dejó enfriar toda la noche, antes de verter en agua (40 ml). La mezcla fue extraida con DCM (2 x 30 ml) y los extractos orgánicos lavados con salmuera, secados sobre sulfato de magnesio, filtrados y evaporados para dar un líqido marrón el cual fue tomado en metanol y vertido en un cartucho SCX–3 (2 g). El cartucho fue lavado con metanol (~30 ml) antes de eluir los productos con amoniaco 2M/metanol (~20 ml). El lavado amoniacal fue evaporado para dar el compuesto del título como una goma marrón (41 mg, 57%)

MS m/z 483.4 $[M+H]^+$, Tiempo de retención 2.41 minutos.

Producto intermedio 73:

Metil 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–10–il)amino]–3–hidroxi–benzoato

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 180 mg, 0.64 mmol) y metil 3–hidroxi–4–aminobenzoato (ABCR; 123 mg, 0.73 mmol) fueron tomados en etanol (4 mL) y agua (12 mL). Ácido clorhídrico concentrado (36%; 130 µL) fue añadido y la reacción calentado hasta 80°C y agitada toda la noche. La reacción se dejó reposar y enfriar toda la noche, antes de la evaporación del etanol. El residuo acuoso fue diluida hasta ~30 ml con agua y la solución basificada hasta pH 9 por adición de una gotas de amoniaco acuoso. La mezcla resultante fue extraida con DCM (2 x 50 ml). Un sólido persistió en la fase límite. Este sólido fue recogido mediante filtración por succión y secado para dar el compuesto del título como un sólido púrpura/gris (64 mg, 24%).

Los extractos orgánicos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio, filtrados y evaporados hasta un sólido rosa/marrón (153 mg) el cual fue triturado con DCM (5 mL). El sólido fue luego recogido mediante filtración por succión y secado para dar el compuesto del título como un sólido rosa oscuro (79 mg, 30 %).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.57 – 1.75 (m, 6H), 1.95 (m, 2H), 2.59 (m, 2H), 3.18 (s, 3H), 3.63 (m, 2H), 3.80 (s, 3H), 4.82 (m, 1H), 7.44 (m, 2H), 7.84 (s, 1H), 8.09 (s, 1H), 8.36 (d, 1H); MS m/z 412.3 $[M+H]^+$.

Producto intermedio 74:

4–amino–N–(1–metil–4–piperidil)–3–(trifluorometoxi)benzamida

A una solución de ácido 4–amino–3–(trifluorometoxi)benzoico (Maybridge ; 1.05 g, 4.75 mmol) en DMF (20 ml) fue añadido 4–amino–1–metilpiperidina (Fluorochem; 604 mg, 5.29 mmol) seguido por DIPEA (1.6 ml, 9.19 mmol) y HATU (2.06 g, 5.42 mmol). La mezcla de reacción fue agitada a temperatura ambiente O/N. La mezcla de reacción fue evaporada hasta secarse y el residuo particionado entre DCM (75 mL) y solución de bicarbonato de sodio saturada acuosa. (75 mL). La fase acuosa fue reextraída con DCM (50 ml) y las fases orgánicas combinadas lavadas con salmuera, secadas sobre sulfato de magnesio, filtradas y evaporadas para dar el compuesto del título como una goma ámbar (1.17 g, 78%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.75 (m, 2H), 1.93 (m, 2H), 2.64 (s, 3H), 2.87 (m, 2H), 3.93 (m, 1H), 5.93 (s, 2H), 6.80 (d, 1H), 7.64 (m, 2H), 8.08 (d, 1H); MS m/z 316.4 $[M+H]^+$.

Producto intermedio 75:

Ácido 4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–etoxi–benzoico

A una solución de 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 280 mg, 1 mmol) y ácido 4–amino–3–etoxibenzoico (WO 2001077101; 205 mg, 1.13 mmol) en etanol (5 mL) fue añadido agua (15 mL) y ácido clorhídrico concentrado (0.17 mL, 2 mmol). La mezcla fue calentada bajo reflujo durante 36 horas. La reacción fue enfriada y un sólido marrón precipitó. Esto fue filtrado y secado, triturado bajo acetonitrilo frío y luego secado al vacío. Para proporcionar el compuesto del título como un sólido marrón (190 mg; 45%).

MS m/z 426 $[M+H]^+$. Tiempo de retención 1.58 minutos

Producto intermedio 76:

10–cloro–6–metil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona 3–[(5–bromo–2–cloro–pirimidin–4–il)–propan–2–il–amino]–N–metil–propanamida (Producto intermedio 77; 2.67 g, 7.9 6mmol) fue disuelto en dioxano (80 mL) y tris(dibencilidenoacetona) paladio (II) (146mg, 0.16 mmol), XANTFOS (277 mg, 0.48 mmol) y carbonato de cesio (3.76 g, 11.54 mmol) añadido. El aparato fue evacuado y llenado

nuevamente con nitrógeno (x3) y luego calentado a 100°C durante 24 horas. La mezcla fue filtrada y concentrada y el residuo purificado por cromatografía en columna (1% MeOH/DCM) para dar el compuesto del título como un aceite amarillo viscoso (1.25g, 62%). ^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.18 (6H, d), 2.59 – 2.61 (2H, m), 3.22 (3H, s), 3.59 – 3.62 (2H, m), 4.82 – 4.88 (1H, m), 7.87 (1H, s); MS m/z 255.16 $[M+H]^+$.

Producto intermedio 77:

3–[(5–bromo–2–cloro–pirimidin–4–il)–propan–2–il–amino]–N–metil–propanamida

N–metil–3–(propan–2–ilamino)propanamida (Producto intermedio 78; 2 g, 13.87 mmol), 5–bromo–2,4–dicloropirimidina (Aldrich; 3.8 g, 16.64 mmol) y trietilamina (2.3 mL, 16.64 mmol) fueron calentados en acetonitrilo (85 mL) a 100°C durante 3h. La mezcla fue enfriada y concentrada. El residuo fue disuelto en DCM, lavado con agua, secado ($MgSO_4$) y concentrado. La cromatografía en columna (0.5 – 1 – 2% amoniaco 7N en metanol/DCM) dio: el compuesto del título como un aceite amarillo pálido que cristalizó en reposo (2.67 g, 20%). ^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.20 (6H, d), 2.31 (2H, t), 2.55 (3H, d), 3.65 (2H, t), 4.55 –.4.62 (1H, m), 7.72 (1H, s), 8.39 (1H, s); MS m/z 337.05 $[M+H]^+$.

Producto intermedio 78:

N–metil–3–(propan–2–ilamino)propanamida

Isopropilamina (Aldrich; 1.5ml, 17.62mmol) y metil acrilamida (ABCR; 1.0g, 11.75mmol) fueron combinados en metanol (10ml). La mezcla fue calentada en un microondas a 140°C durante 30min. La reacción fue repetida y las mezclas de reacciones combinadas fueron concentradas para eliminar los excesos de aminas. El residuo fue redisuelto en metanol y absorbida en una columna SCX (50g), lavado con metanol y eluido con metanol/amoniaco. La concentración de las fracciones que contienen el producto dio el compuesto del título como un aceite incoloro (3.2g, 94%) .

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 1.00 (6H, d), 2.27 (2H, t), 2.70 – 2.74 (4H, m), 2.76 – 2.80 (2H, m), 7.50 (1H, s)

Producto intermedio 79:

4–amino–3–cloro–N–(1–metil–4–piperidil)benzamida

3–cloro–N–(1–metil–4–piperidil)–4–nitro–benzamida (Producto intermedio 80; 270 mg, 1 mmol), 10% paladio sobre carbón (30 mg) y metanol (50 mL) fueron combinados y agitados a 25°C bajo hidrógeno a presión de 5 bar durante 16 horas.

El catalizador fue filtrado y los solventes evaporados para dar el compuesto del título como una sólido color crema. (280 mg, 98%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.49 (m, 2H), 1.95 (m, 2H), 2.09 (m, 2H), 2.24 (s, 3H), 2.75 (m, 2H), 3.89 (m, 1H), 4.27 (s, 2H), 5.69 (d, 1H), 6.68 (m, 1H), 7.41 (m, 1H), 7.62 (m, 1H); MS m/z 268 $[M+H]^+$.

Producto intermedio 80:

3–cloro–N–(1–metil–4–piperidil)–4–nitro–benzamida

Los reacctivos combinados y agitados a temperatura ambiente toda la noche. LCMS después de 18 h muestra la reacción completa. Los solventes evaporados y los residuos particionados entre DCM (25 ml) y agua (25 ml) luego filtrados por gravedad a través de un vaso PTFE. Tomado en DCM y purificado en sílice eluyendo con un gradiente de 0 – 5% amoniaco 2M en MeOH / DCM luego 5% amoniaco 2M en MeOH / DCM. El pico correspondiente al producto (el cual solamente era 1 mancha por tlc) fue claramente separado en 2 en la traza cromatográfica. El primer pico (fracciones 6 – 10) fue etiquetado PH17082/048/1 y evaporado hasta una goma marrón. El segundo pico (fracciones 11 – 14) fue etiquetado como PH17082/048/2 y evaporado hasta un sólido blanco. Ambos productos tenían idénticas trazas LCMS y mostraron el ión másico para el producto deseado. NMR mostró un diferencia en la región alifática y un pequeño pico amplio adicional en la región aromática de PH17082/048/1. Fue concluido que PH17082/048/1 fue una sal (posiblemente PF6 de HATU).

PH17082/048/1 fue disuelto en MeOH y añadido a una columna SCX–2 de 2g prehumedecida con MeOH (2 volúmenes de columna). La columna fue luego purgada con MeOH (2 volúmenes de columna) y el producto eluido con amoniaco 2M en MeOH. Esto fue luego combinado con el sólido de PH17082/048/2 y evaporadas a un sólido blanco hueso, 315mg.

^{1}H NMR (500.133 MHz, DMSO–D6) δ 1.66 (m, 2H), 1.85 (m, 2H), 2.14 (m, 2H), 2.25 (s, 3H), 2.83 (m, 2H), 3.78 (m, 1H), 7.97 (m, 1H), 8.09 (m, 1H), 8.12 (m, 1H), 8.26 (d, 1H); MS m/z 298 $[M+H]^+$.

Producto intermedio 81:

10–cloro–2–etil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

Tris(dibencilidenoacetona)dipaladio(0) (52 mg, 0.06 mmol), XANTFOS (98 mg, 0.17 mmol) y carbonato de cesio (1.32 g, 4.06 mmol) fueron añadidos a una solución agitada de 3–[(5–bromo–2–cloro–pirimidin–4–il)–etil–amino]–N–metil–propanamida (Producto intermedio 82; 900 mg, 2.80 mmol) en 1,4–dioxano (28 mL). El aparato fue evacuado y llenado nuevamente con nitrógeno dos veces y luego calentado a 100 °C durante 18 h. La mezcla de reacción fue filtrada a través de una almohadilla de celita y cargada seca en sílice durante la purificación por cromatografía flash en sílice (Companion, 40 g, 0–10% MeOH/DCM) para dar el compuesto del título como un sólido amarillo (638 mg, 2.65 mmol, 95%).

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.17 (t, 3H), 2.66 – 2.69 (m, 2H), 3.19 (s, 3H), 3.57 (q, 2H), 3.72 – 3.74 (m, 2H), 8.13 (s, 1H); MS m/z 241.14 $[M+H]^+$.

Producto intermedio 82:

3–[(5–bromo–2–cloro–pirimidin–4–il)–etil–amino]–N–metil–propanamida

5–Bromo–2,4–dicloropirimidina (Aldrich; 1.14 g, 5.00 mmol), 3–etilamino–N–metil–propanamida (Producto intermedio 83; 0.642 g, 5.00 mmol) y trietilamina (0.71 mL, 5.10 mmol) fueron combinados en acetonitrilo (25 mL) y calentados a 100 °C durante 4 h. El solvente fue eliminado bajo presión reducida y el residuo tomado en etil acetato, lavado con agua y purificado por cromatografía flash en sílice (Companion, 40 g, 0–10% metanol/DCM) para dar el compuesto del título como un sólido blanco (1.06 g, 3.3 mmol, 66%).

^{1}H NMR (399.902 MHz, DMSO–D6) δ 1.18 (t, 3H), 2.46 (t, 2H), 2.58 (d, 3H), 3.67 (q, 2H), 3.81 (t, 2H), 7.85 (m, 1H), 8.31 (s, 1H); MS m/z 320.95 $[M+H]^+$.

Producto intermedio 83:

3–etilamino–N–metil–propanamida

N–metilacrilamida (ABCR: 851 mg, 10.00 mmol) y etilamina (2 M en metanol, 10 mL, 20.00 mmol) fueron combinados en un recipiente de reacción del microondas, el cual fue sellado e irradiado a 140 °C durante 30 min. La mezcla de reacción se dejó enfriar y luego fue cargada directamente en un cartucho SCX–2 de 50 g, lavando con metanol (100 mL) y eluyendo el producto deseado con amoniaco metanólico 7 N (100 mL). La concentración bajo presión

reducida de las fracciones que contienen el producto dio el compuesto del título como un aceite claro (1.285 g; 99%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.93 – 0.99 (3H, m), 2.19 (2H, t), 2.52 – 2.52 (2H, m), 2.54 – 2.59 (3H, d), 2.68 (2H, t), 7.80 (1H, br s)

Producto intermedio 84:

10–cloro–6–metil–2–(2–metilpropil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

3–[(5–bromo–2–cloro–pirimidin–4–il)–(2–metilpropil)amino]–N–metil–propanamida (Producto intermedio 85; 3.26 g, 9.32 mmol)) fue suspendido en dioxano (70 mL), carbonato de cesio (6 g, 18,64 mmol) fue añadido y la mezcla burbujeada con nitrógeno durante 10 minutos. Tris(dibencilidenoacetona)dipaladio(0) (512 mg, 0.56 mmol) y XANTFOS (485 mg, 0.839 mmol) fueron añadidos y la mezcla calentada a 100 °C durante 24 h. La mezcla de reacción fue enfriada a temperatura ambiente, los solventes evaporados y el residuo particionado entre DCM (250 mL) y agua (250 mL). La fase acuosa fue reextraída con DCM (200 mL) y las fases orgánicas combinadas secadas sobre $MgSO_4$ y evaporadas hasta una goma marrón oscuro la cual fue tomada en DCM y purificada en sílice, eluyendo con un gradiente de 30 – 50% etil acetato / iso–hexano luego 50% etil acetato / iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta un sólido amarillo, el cual fue calentado a reflujo en iso–hexano (50 mL) durante 15 minutos y se dejó enfriar a temperatura ambiente toda la noche. El sólido resultante fue filtrado y secado para dar el compuesto del título como un sólido amarillo pálido (1.02 g, 41%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.85 (d, 6H), 2.03 (m, 1H), 2.65 (m, 2H), 3.23 (s, 3H), 3.45 (d, 2H), 3.69 (m, 2H), 7.89 (s, 1H); MS m/z 269 $[M+H]^+$.

Producto intermedio 85:

3–[(5–bromo–2–cloro–pirimidin–4–il)–(2–metilpropil)amino]–N–metil–propanamida

5–Bromo–2,4–dicloropirimidina (Aldrich; 2.82 g, 12.37 mmol), N–metil–3–(2–metilpropilamino)propanamida (Producto intermedio 86; 1.78 g; 11.25 mmol), trietilamina (1.65 mL, 11.81 mmol) y DCM (40 mL) fueron combinados y agitados todo el fin de semana a temperatura ambiente. La mezcla de reacción fue lavada con solución de bicarbonato de

sodio saturada acuosa y filtrada por gravedad a través de un vaso PTFE y los solventes evaporados. El residuo fue disuelto en DCM y pasado a través de una columna de sílice eluyendo con un gradiente de 30 – 50% etil acetato / iso–hexano durante 10 volúmenes de columnas luego 50% etil acetato / iso–hexano. Las fracciones que contienen el producto combinadas y evaporadas para dar el compuesto del título como un sólido blanco. (3.26 g, 83%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.84 (d, 6H), 1.98 (m, 1H), 2.44 (m, 2H), 2.75 (d, 3H), 3.58 (m, 2H), 3.91 (m, 2H), 5.57 (s, 1H), 8.11 (s, 1H); MS m/z 351 $[M+H]^+$.

Producto intermedio 86:

N–metil–3–(2–metilpropilamino)propanamida

N–metilacrilamida (ABCR; 1 g, 11.75 mmol) fue disuelto en EtOH (5 mL). Isobutilamina (Aldrich; 2.33 mL, 23.5 mmol) fue añadida y agitada a temperatura ambiente en un frasco taponeado todo el fin de semana. La reacción fue luego transferida a un recipiente del reactor de microondas y calentado en un microondas durante 10 minutos a 140 °C. Los solventes fueron evaporados al vacío para dar el compuesto del título como un líquido incoloro. (1.78 g, 96%).

^{1}H NMR (400.132 MHz, CDCl3)δ 0.93 (d, 6H), 1.74 (m, 1H), 2.35 (m, 2H), 2.43 (d, 2H), 2.78 (d, 3H), 2.85 (m, 2H), 7.88 (s, 1H)

Producto intermedio 87:

2–butan–2–il–10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución de 3–[(5–bromo–2–cloro–pirimidin–4–il)–butan–2–il–amino]–N–metil–propanamida (Producto intermedio 88; 559 mg, 1.60 mmol) en 1,4–dioxano anhidro(15 mL) fue añadido carbonato de cesio (1.04 g, 3.19 mmol). Nitrógeno fue burbujeado a través de la mezcla de reacción durante 10 minutos, antes de la adición de tris(dibencilidenoacetona) dipaladio(0) (87 mg, 0.095 mmol) y XANTFOS (88 mg, 0.152 mmol). La reacción fue calentada a 100°C y agitada bajo nitrógeno durante 18 h. La mezcla de reacción fue enfriada y diluida hasta ~40 ml con DCM. La mezcla de reacción fue filtrada para eliminar el material insoluble, lavando completamente la torta del filtro con DCM. El filtrado fue evaporado para dar una goma marrón la cual fue purificada por cromatografía flash en sílice (cartucho de 40g;

ISCO Companion) eluyendo con un gradiente 25–75% de etil acetato en iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar un sólido ceroso blanco hueso el cual mediante trituración con iso–hexano caliente proporcionó, al enfriarse y recogerse mediante filtración por succión el compuesto del título como un sólido amarillo pálido (121 mg, 28%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 0.83 (t, 3H), 1.16 (d, 3H), 1.57 (m, 2H), 2.65 (m, 2H), 3.18 (s, 3H), 3.49 – 3.66 (m, 2H), 4.57 (m, 1H), 8.12 (s, 1H); MS m/z 269 $[M+H]^+$.

Producto intermedio 88:

3–[(5–bromo–2–cloro–pirimidin–4–il)–butan–2–il–amino]–N–metil–propanamida

A una solución de 3–(butan–2–ilamino)–N–metil–propanamida (Producto intermedio 89; 563 mg, 3.56 mmol) en DCM (7 mL) fue añadido trietilamina (550 µL, 3.94 mmol) y, como un sólido, 5–bromo–2,4–dicloropirimidina (Aldrich; 890 mg, 3.90 mmol). La reacción fue agitada a temperatura ambiente toda la noche.

La solución de bicarbonato de sodio saturada acuosa (10 mL) fue añadido y la mezcla agitada. La fase orgánica fue recogida mediante elusión por gravedad a través de un vaso filtro PTFE. La solución DCM fue inyectada directamente en el cartucho de Si de 40g y eluida con un gradiente 25–75% de etil acetato en hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido cristalino incoloro (565 mg; 45%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.83 (t, 3H), 1.28 (d, 3H), 1.58 (m, 1H), 1.72 (m, 1H), 2.44 (m, 2H), 2.83 (d, 3H), 3.64 (m, 1H), 3.85 (m, 1H), 4.58 (m, 1H), 5.78 (m, 1H), 8.23 (s, 1H); MS m/z 351 $[M+H]^+$.

Producto intermedio 89:

3–(butan–2–ilamino)–N–metil–propanamida

Una mezcla de N–metilacrilamida (ABCR; 500 mg, 5.87 mmol), sec–butilamina (Aldrich; 530 mL, 5.22 mmol) y etanol (4 mL) fue calentado en un microondas hasta 140°C durante 45 minutos y luego a 150°C durante 30 minutos. La mezcla de reacción fue enfriada y vertida en un cartucho SCX–2 (5g) y el cartucho lavado completamente con metanol (~50 mL). Los

productos fueron luego eluidos con amoniaco 2M en metanol (~50 mL) y evaporados para proporcionar el compuesto del título como un aceite color paja (563 mg; 61%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.92 (t, 3H), 1.06 (d, 3H), 1.31 – 1.53 (m, 2H), 2.34 (m, 2H), 2.57 (m, 1H), 2.78 – 2.94 (m, 5H), 7.77 (s, 1H)

Producto intermedio 90:

10–cloro–2–ciclobutil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución de 3–[(5–bromo–2–cloro–pirimidin–4–il)–ciclobutil–amino]–N–metil–propanamida (Producto intermedio 91; 600 mg, 1.73 mmol) en 1,4–dioxano anhidro(15 mL) fue añadido carbonato de cesio (1.1 g, 3.38 mmol). Nitrógeno fue burbujeado a través de la mezcla de reacción durante 10 minutos, antes de la adición de tris(dibencilidenoacetona)dipaladio(0) (99 mg, 0.11 mmol) y XANTFOS (95 mg, 0.16 mmol). La reacción fue calentada a 100°C y agitada bajo nitrógeno toda la noche.

La mezcla de reacción fue enfriada y diluida hasta ~40 ml con DCM, filtrada para eliminar el material insoluble, la torta del filtro completamente lavada con DCM y evaporada para dar un sólido marrón/verde el cual fue purificado por cromatografía flash en sílice (120g cartucho; ISCO Companion) eluyendo con un gradiente 25–100% de etil acetato en iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar un sólido ceroso blanco hueso el cual mediante trituración con iso–hexano caliente proporcionó, al enfriarse y recogerse mediante filtración por succión el compuesto del título como un sólido amarillo pálido (216 mg, 47%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.68 (m, 2H), 2.09 (m, 2H), 2.21 (m, 2H), 2.63 (m, 2H), 3.19 (s, 3H), 3.69 (m, 2H), 4.43 (m, 1H), 8.19 (s, 1H); MS m/z 267.4 $[M+H]^+$.

Producto intermedio 91:

3–[(5–bromo–2–cloro–pirimidin–4–il)–ciclobutil–amino]–N–metil–propanamida

Usando 3–(ciclobutilamino)–N–metil–propanamida – Producto intermedio 92 y condiciones análogas al Producto intermedio 88 el compuesto del título fue obtenido como un sólido blanco (609 mg).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.62 – 1.79 (m, 2H), 2.16 – 2.34 (m, 4H), 2.45 (m, 2H), 2.81 (d, 3H), 3.95 (m, 2H), 4.72 (m, 1H), 5.72 (m, 1H), 8.24 (s, 1H)

Producto intermedio 92:

3–(ciclobutilamino)–N–metil–propanamida

Usando ciclobutanamina – Aldrich y condiciones análogas al Producto intermedio 89 el compuesto del título fue obtenido como un aceite amarillo pálido (541 mg).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.64 – 1.75 (m, 4H), 2.23 (m, 2H), 2.33 (m, 2H), 2.77 – 2.81 (m, 5H), 3.26 (m, 1H), 7.32 (m, 1H)

Producto intermedio 93:

10–cloro–2–(ciclopropilmetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución parcial de 3–[(5–bromo–2–cloro–pirimidin–4–il)–(ciclopropilmetil)amino]–N–metil–propanamida (Producto intermedio 94; 426 mg, 1.18 mmol) en 1,4–dioxano anhidro (15 mL) fue añadido carbonato de cesio (790 mg, 2.42 mmol). Nitrógeno fue burbujeado a través de la mezcla de reacción durante 10 minutos, antes de la adición de tris(dibencilidenoacetona)dipaladio(0) (69 mg, 0.075 mmol) y XANTFOS (62 mg, 0.107 mmol). La reacción fue calentada a 100°C y agitada bajo nitrógeno durante 18 h.

La mezcla de reacción fue enfriada y diluida hasta ~40 ml con DCM, filtrada para eliminar el material insoluble, la torta del filtro completamente lavada con DCM, y evaporada para dar una goma marrón la cual fue purificada por cromatografía flash en sílice (cartucho de 40g; ISCO Companion) eluyendo con un gradiente 25–75% de etil acetato en iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar un sólido traslúcido cristalino amarillo. La trituración con iso–hexano caliente proporcionó, al enfriarse y recogerse mediante filtración por succión el compuesto del título como un sólido amarillo pálido (165 mg, 50%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 0.00 (m, 2H), 0.33 (m, 2H), 0.59 (m, 1H), 1.44 (q, 2H), 2.60 (m, 2H), 3.11 (s, 3H), 3.55 (m, 2H), 3.68 (m, 2H), 8.05 (s, 1H)

MS m/z 281.4 $[M+H]^+$.

Producto intermedio 94:

3–[(5–bromo–2–cloro–pirimidin–4–il)–(ciclopropilmetil)amino]–N–metil–propanamida

Usando 3–(ciclopropilmetilamino)–N–metil–propanamida– Producto intermedio 95 y condiciones análogas al Producto intermedio 88 el compuesto del título fue obtenido como un sólido blanco (431 mg).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.35 (m, 2H), 0.60 (m, 2H), 1.14 (m, 1H), 2.57 (m, 2H), 2.84 (d, 3H), 3.66 (d, 2H), 4.03 (m, 2H), 5.79 (m, 1H), 8.21 (s, 1H); MS m/z 349.0 $[M+H]^+$.

Producto intermedio 95:

3–(ciclopropilmetilamino)–N–metil–propanamida

Usando 2–ciclopropiletanamina– Aldrich y condiciones análogas al Producto intermedio 89 el compuesto del título fue obtenido como un aceite amarillo pálido (590 mg).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.13 (m, 3H), 0.51 (m, 2H), 0.94 (m, 1H), 2.36 (m, 2H), 2.49 (d, 2H), 2.81 (d, 3H), 2.90 (m, 2H), 7.59 (s, 1H).

Producto intermedio 96:

10–cloro–2–[(2,4–dimetoxifenil)metil]–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución de 3–[(5–bromo–2–cloro–pirimidin–4–il)–[(3,5–dimetoxifenil)metil]amino]–N–metil–propanamida (Producto intermedio 97; 2.1 g, 4.73 mmol) en 1,4–dioxano (50 mL) fue añadido carbonato de cesio (3.4 g, 10.44 mmol) y la mezcla de reacción burbujeada con argón durante 20 minutos. Tris(dibencilidenoacetona)dipaladio(0) (260 mg, 0.28 mmol) y XANTFOS (248 mg, 0.43 mmol) fueron añadidos y mezcla de reacción calentada a 100°C y se dejó agitar bajo nitrógeno toda la noche.

La mezcla de reacción fue enfriada y diluida hasta ~100 ml con DCM, filtrada para eliminar el material insoluble, la torta del filtro completamente lavada con DCM y evaporada para dar un aceite amarillo oscuro con algún sólido el cual fue tomado en DCM (~20 ml) y el material insoluble eliminado por filtración. El filtrado fue purificado por cromatografía flash en sílice (120g cartucho) eluyendo con un gradiente en aumento de 25–100% etil acetato en hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido amarillo pálido (690 mg).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 2.71 (m, 2H), 3.20 (s, 3H), 3.63 (m, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 4.68 (s, 2H), 6.48 (m, 1H), 6.59 (d, 1H), 7.06 (d, 1H), 8.17 (s, 1H); MS m/z 363.3 $[M+H]^+$.

Producto intermedio 97:

3–[(5–bromo–2–cloro–pirimidin–4–il)–[(3,5–dimetoxifenil)metil]amino]–N–metil–propanamida

3–[(3,5–dimetoxifenil)metilamino]–N–metil–propanamida (Producto intermedio 98; 1 g, 3.96 mmol) fue disuelto en DCM (10 mL) y trietilamina (0.68 mL, 4.36 mmol). 5–bromo–2,4–dicloropirimidina (Aldrich; 993 mg, 4.36 mmol) fue añadido y la mezcla agitada a temperatura ambiente durante 18 horas. La mezcla fue diluida con DCM y lavada con agua, salmuera, secada ($MgSO_4$), filtrada y evaporada para dar una goma amarilla la cual fue purificada en un ISCO Companion 40g eluyendo con 50–70% etil acetato en iso–hexano para dar el compuesto del título como un sólido blanco (461mg, 26%).

1H NMR (400.13MHz; DMSO–d_6) δ2.5 (m, 2H) bajo DMSO, 2.55 (d, 3H), 3.72 (s, 6H), 3.8 (t, 2H), 4.85 (s, 2H), 6.41 (s, 3H), 7.84 (bm, 1H), 8.38 (s, 1H); MS m/z 443/445 $[M+H]^+$.

Producto intermedio 98:

3–[(3,5–dimetoxifenil)metilamino]–N–metil–propanamida

N–metilacrilamida (ABCR; 500mg, 5.87 mmol) y 3.5–dimetoxibencilamina (Aldrich; 0.98 mL, 6.46 mmol) fueron disueltos en etanol (4 mL) y calentados en un microondas a 140°C durante 45 minutos. La mezcla fue vertida en una columna SCX–2 de 20g, lavada con metanol y eluida con 3.5N NH_3 en metanol. Las fracciones del producto fueron evaporadas hasta el compuesto del título como un aceite amarillo (1.3 g, 88%).

1H NMR (CDCl3) 2.36 (t, 2H), 2.78 (d, 3H), 2.88 (t, 2H), 3.72 (s, 2H), 3.79 (s, 6H), 6.36 (m, 1H), 6.45 (m, 2H), 7.31 (bs, 1H); MS m/z 253 $[M+H]^+$.

Producto intermedio 99:

2–bencil–10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una suspensión enfriada (baño de hielo/agua) de hidruro de sodio (60% dispersión en aceite mineral; 6.5 mg, 0.16 mmol) en DMA (0.5 mL) fue añadida una solución de 10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 100; 32 mg, 0.15 mmol) en DMA (1.0 mL). La mezcla de reacción se dejó agitar, bajo nitrógeno, en un baño de hielo durante 15 minutos antes de la adición de bencil bromuro (Aldrich; 20 µL, 0.17 mmol). La mezcla de reacción fue agitada en un baño de hielo durante 15 minutos y luego a temperatura ambiente durante 3 h.

Una adición posterior de hidruro de sodio (2 mg) fue hecha y se continuó agitando durante 6 h.

Cloruro de amonio saturado (0.5 ml) fue añadido y la mezcla de reacción vertida directamente en un cartucho SCX–3 (2g). El cartucho fue lavado con metanol (~30 mL) antes de eluir los productos con amoniaco 2M en metanol (~30 mL). Las fracciones que contienen el producto fueron evaporadas hasta secarse para dar un goma incolora, la cual fue combinada con el cartucho de metanol prelavado y esta solución evaporada hasta secarse. El material resultante fue particionado entre DCM (10 mL) y agua (10 mL). La fase orgánica fue recogida mediante elusión por gravedad a través de un vaso filtro PTFE y evaporada para dar el compuesto del título como una goma opaca amarillo pálido (46 mg, 89%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 2.71 (m, 2H), 3.22 (s, 3H), 3.66 (m, 2H), 4.82 (s, 2H), 7.27 – 7.38 (m, 5H), 8.21 (s, 1H); MS m/z 303.3 $[M+H]^+$.

Producto intermedio 100:

10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

3–[(5–bromo–2–cloro–pirimidin–4–il)–[(3,5–dimetoxifenil)metil]amino]–N–metil–propanamida (Producto intermedio 97; 83 mg, 0.23 mmol) fue tomado en DCM (1 mL) y TFA (1 mL) y agitado durante 30 minutos. Una adición posterior de TFA (1 mL) fue hecha y se continuó agitando toda la noche. La mezcla de reacción fue diluida con DCM (25 m L) y vertida directamente en un cartucho SCX–3 (2g). El cartucho fue lavado completamente con metanol (~50 mL). Los productos fueron eluidos con amoniaco 2M en metanol y el eluente amoniacal evaporado hasta secarse para proporcionar el compuesto del título como un sólido color hueso (34 mg, 70%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 2.66 (m, 2H), 3.21 (s, 3H), 3.52 (m, 2H), 8.14 (m, 1H), 8.28 (m, 1H); MS m/z 213.4 $[M+H]^+$.

Producto intermedio 101:

10–cloro–6–metil–2–[(2–metil–1,3–thiazol–4–il)metil]–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una suspensión enfriada (baño de hielo/agua) de hidruro de sodio (60% dispersión en aceite mineral; 13 mg, 0.38 mmol) en DMA (0.5 mL) fue añadida una solución de 10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 100; 63 mg, 0.30 mmol) en DMA (1 mL). La mezcla de reacción se dejó agitar, bajo nitrógeno, en baño de hielo durante 10 minutos antes de la adición de 4–clorometil–2–metiltiazol (ASDI; 75 mg, 0.51 mmol). La mezcla de reacción fue agitada en un baño de hielo durante 20 minutos y luego calentada hasta la temperatura ambiente durante 1 hora.

La mezcla de reacción fue apagada por adición cuidadosa de cloruro de amonio saturado acuoso (0.5 ml) y la mezcla de reacción fue particionada entre DCM(10 mL) y agua (10 mL). La fase orgánica fue separada mediante filtración por gravedad a través de un vaso filtro PTFE y evaporada hasta secarse para dar el compuesto del título como una goma color paja (61 mg; 63%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 2.64 (s, 3H), 2.74 (m, 2H), 3.21 (s, 3H), 3.78 (m, 2H), 4.82 (m, 2H), 7.31 (m, 1H), 8.20 (s, 1H); MS m/z 324.3 $[M+H]^+$.

Producto intermedio 102:

10–cloro–2–(ciclobutilmetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una suspensión enfriada (baño de hielo/agua) de hidruro de sodio (60% dispersión en aceite mineral; 13 mg, 0.38 mmol) en DMA (0.5 ml) fue añadida una solución de (Producto intermedio 100; 63 mg, 0.30 mmol) en DMA (1 mL). La mezcla de reacción se dejó agitar, bajo nitrógeno, en un baño de hielo durante 10 minutos antes de la adición de bromometil ciclobutano (Aldrich; 40 µL, 0.36 mmol). La mezcla de reacción fue agitada en un baño de hielo durante 20 minutos y luego calentada a temperatura ambiente durante 1 hora.

Una adición posterior de hidruro de sodio (2 mg) y bromometil ciclobutano (20 µL, 0.18 mmol fue hecha y la reacción agitada durante una hora adicional.

La mezcla de reacción fue apagada por adición cuidadosa de cloruro de amonio saturado acuoso (0.5 ml) y la mezcla de reacción particionada entre DCM(10 mL) y agua (10 mL). La fase orgánica fue separada mediante filtración por gravedad a través de un vaso filtro PTFE y la evaporación hasta secarse dio el compuesto del título como una goma amarillo pálido (71 mg, 84%).

^{1}H NMR (400.132 MHz, DMSO–D6) δ 1.71 – 1.86 (m, 4H), 2.01 (m, 2H), 2.66 (m, 3H), 3.17 (s, 3H), 3.63 (d, 2H), 3.70 (m, 2H), 8.12 (s, 1H); MS m/z 281.3 $[M+H]^+$.

Producto intermedio 103:

10–cloro–6–metil–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución de 10–cloro–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 104; 1.185 g, 4.31 mmol) en DMA (100 mL) a 0°C, fue añadido metil yoduro (282 µL, 4.53 mmol) seguido por hidruro de sodio (60% dispersión de aceite, 182 mg, 4.53 mmol) en una porción. La mezcla fue agitada a 0°C durante 4 h y hielo fue luego añadido, resultando en un precipitado pegajoso marrón, el cual fue filtrado y lavado con agua. Un sólido blanco precipitado del filtrado, fue filtrado y triturado con dietiléter para dar el compuesto del título (494mg).

El precipitado pegajoso marrón fue disuelto en DCM y pasado por una columna de succión en 2– 5% metanol/diclorometano para dar un aceite amarillo.

El filtrado acuoso fue extraido con DCM y metanol, lavado con salmuera saturada acuosa y evaporado para dar un aceite amarillo el cual fue purificado mediante una columna de succión como anteriormente para dar un aceite amarillo.

Ambos aceites amarillos fueron combinados y triturados con dietiléter para dar el compuesto del título como un sólido blanco (401mg).

^{1}H NMR (399.9 MHz, DMSO–D6) : δ_H : 2.89 (m, 2H), 3.29 (s, 3H), 4.06 (m, 2H), 7.30 (m, 3H), 7.42 (m, 2H), 8.38 (s, 1H); MS m/z 289 $[M+H]^+$.

Producto intermedio 104:

10–cloro–2–fenil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

Metil 3-[(2-cloro-5-nitro-pirimidin-4-il)-fenil-amino]propanoato (Producto intermedio 105; 21.855 g, 64.9 mmol), polvo de hierro (5.44 g, 97.35 mmol) y ácido acético (200 mL) fueron calentados a 80°C durante 2h y luego agitados a temperatura ambiente toda la noche. La mezcla de reacción fue filtrada a través de celita y la torta del filtro lavada con diclorometano. El solvente fue evaporado y el material resultante fue preabsorbido en sílice con metanol/diclorometano y luego purificado mediante cromatografía de filtración al vacío eluyendo con diclorometano, dietiléter, etilacetato y finalmente 20% metanol/diclorometano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar un sólido marrón el cual fue triturado con dietiléter y luego metanol y un pequeño % de diclorometano para dar el compuesto del título como un sólido color hueso (2.29 g). La columna de filtración de sílice fue suspendida en 20% metanol/diclorometano y filtrada y lavada con una porción adicional de 20% metanol/diclorometano. La evaporación proporcionó un sólido amarillo el cual fue triturado con metanol y un pequeño % de diclorometano para dar el compuesto del título como un sólido color hueso (1.35g).

^{1}H NMR (399.9 MHz, DMSO-D6) : δ_H : 2.89 (m, 2H), 3.98 (m, 2H), 7.32 (m, 3H), 7.42 (m, 2H), 8.01 (s, 1H), 9.90 (s, 1H); MS m/z 275 $[M+H]^+$.

Producto intermedio 105:

Metil 3-[(2-cloro-5-nitro-pirimidin-4-il)-fenil-amino]propanoato

A una solución de; 3,4-dicloro-5-nitropirimidina (Aldrich; 12.59 g, 64.9 mmol) en THF anhidro (300 mL) a temperatura ambiente bajo una atmósfera de nitrógeno fue añadido en forma de gotas durante 6 h una solución de metil 3-anilinopropanoato (Producto intermedio 106; 12.795 g, 71.39 mmol) y Base Hunigs (13.54 mL, 77.88 mmol) en THF anhidro (300 mL). La mezcla de reacción fue agitada toda la noche a temperatura ambiente. El solvente fue evaporado a 40°C y el residuo disuelto en DCM y lavado con agua y salmuera saturada. La fase orgánica resultante fue secada sobre sulfato de sodio anhidro luego preabsorbida en sílice y purificada mediante cromatografía de filtración al vacío eluyendo con diclorometano. La evaporación de las fracciones que contienen el producto proporcionó el compuesto del título como un aceite rojo oscuro (24.25g, >100%).

MS m/z 275 $[M+H]^+$. Tiempo de retención 2.32 min.

Producto intermedio 106:

Metil 3–anilinopropanoato

Anilina (Acros; 59.89 mL, 657 mmol) , Metilacrilato (Acros; 62.54 mL, 690 mmol) y ácido acético glacial (15 mL) fueron combinados y calentados a 79°C toda la noche

La mezcla de reacción fue enfriada a temperatura ambiente y añadido a hielo agua, un sólido precipitado y fue filtrado y disuelto en alicuota de diclorometano tomada y pre–absorbida en sílice y purificado mediante cromatografía de filtración al vacío eluyendo con DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido pegajoso amarillo pálido (14.33 g, 12%) .

^{1}H NMR (399.9 MHz, DMSO–D6) : δ_H : 2.57 (tr, 2H), 3.29 (tr, 2H), 3.61 (s, 3H), 5.57 (tr, 1H), 6.55 (m, 3H), 7.08 (m, 1H); MS m/z 180 $[M+H]^+$.

Producto intermedio 107:

4–amino–3–cloro–N–(3–dimetilamino–2,2–dimetil–propil)benzamida

3–cloro–N–(3–dimetilamino–2,2–dimetil–propil)–4–nitro–benzamida (2.29 g, 7.67 mmol), polvo de hierro (2.45 g, 43.79 mmol) y cloruro de amonio (781 mg, 14.60 mmol) fueron calentados en etanol (50 mL) y agua (18 mL) a reflujo durante una hora. Unas gotas de ácido acético fueron añadidas y se continuó calentando durante una hora adicional. La mezcla de reacción fue enfriada, filtrada y el filtrado concentrado. Este residuo fue particionado entre $NaHCO_3$ saturado (ac.) y DCM. La fase orgánica fue lavada con salmuera, secada con $MgSO_4$ y concentrada. La cromatografía en columna dio el compuesto del título como un sólido cristalino naranja. (850mg, 39%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.86 (6H, s), 2.16 (2H, s), 2.26 (6H, s), 3.14 (2H, d), 5.83 (2H, s), 6.80 (1H, d), 7.52 – 7.54 (1H, m), 7.72 (1H, d), 8.15 (1H, t); MS m/z 286.16 $[M+H]^+$.

Producto intermedio 108:

3–cloro–N–(3–dimetilamino–2,2–dimetil–propil)–4–nitro–benzamida

3–cloro–4–nitro–benzoil cloruro (Producto intermedio 54; 2.2 g, 10.00 mmol) fue disuelto en DCM (20 mL) y N,N–diisopropiletilamina (2.095 mL, 12.00 mmol) añadido. La mezcla fue enfriada en un baño de hielo/agua y N,N,2,2–tetrametil–1,3–propanodiamina (3.652 mL, 10.00 mmol) en DCM (10 mL) añadido en forma de gotas. La mezcla se dejó calentar a

temperatura ambiente y se agitó durante 0.5h. La mezcla fue lavada con salmuera, NaOH 2N (ac.), secada ($MgSO_4$) y concentrada. La cromatografía en columna del residuo (2% MeOH/DCM) dio el compuesto del título como un aceite amarillo 17171/2/1 (2.29g, 77%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.89 (6H, s), 2.17 (2H, s), 2.26 (6H, s), 3.21 (2H, d), 7.96 – 7.98 (1H, m), 8.13 (1H, d), 8.18 (1H, d), 8.73 (1H, t); MS m/z 314.21 $[M+H]^+$.

Producto intermedio 109:

10–cloro–2–(2–metoxietil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

3–[(5–bromo–2–cloro–pirimidin–4–il)–(2–metoxietil)amino]–N–metil–propanamida (Producto intermedio 110; 1.12 g, 3.185 mmol) fue suspendido en dioxano (70 mL), carbonato de cesio (2.08 g, 6.37 mmol) añadido y la mezcla burbujeada con nitrógeno durante 10 minutos. Tris(dibencilidenoacetona)dipaladio(0) (175 mg, 0.151 mmol) y XANTFOS (166 mg, 0.287 mmol) fueron añadidos y la mezcla calentada a 100 °C durante 20 h. Un equivalente 0.06 adicional de tris(dibencilidenoacetona)dipaladio(0) y 0.09 equivalente de XANTFOS fueron añadidos y se continuó calentando durante unas 2 h adicionales. La mezcla de reacción fue enfriada a temperatura ambiente filtrada y la torta del filtro lavada con DCM. El filtrado fue evaporado y disuelto en DCM y purificado en sílice eluyendo con un gradiente de 40 – 55% etil acetato / iso–hexano luego 55% etil acetato / iso–hexano y finalmente 70% etil acetato / iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta un sólido amarillo. El cual fue purificado por HPLC en fase inversa modificada base para proporcionar el compuesto del título como un sólido blanco (157 mg, 18%).

^{1}H NMR (399.902 MHz, CDCl3) δ2.73 (m, 2H), 3.29 (s, 3H), 3.35 (s, 3H), 3.68 (m, 2H), 3.84 (m, 2H), 3.90 (m, 2H), 7.95 (s, 1H); MS m/z 271 $[M+H]^+$.

Producto intermedio 110:

3–[(5–bromo–2–cloro–pirimidin–4–il)–(2–metoxietil)amino]–N–metil–propanamida

3–(2–metoxietilamino)–N–metil–propanamida (Producto intermedio 111; 608 mg, 3.79 mmol) 5–Bromo–2,4–dicloropirimidina (Aldrich; 950 mg, 4.17 mmol), trietilamina (555 µL, 3.98 mmol), y DCM (5 mL) fueron combinados y agitados todo el fin de semana a

temperatura ambiente. La mezcla de reacción fue lavada con solución de bicarbonato de sodio saturada acuosa, luego filtrada por gravedad a través de un vaso PTFE y los solventes orgánicos evaporados. El residuo fue disuelto en DCM y pasado a través de una columna de sílice, eluyendo con 50% etil acetato / iso–hexano luego 60% etil acetato / iso–hexano y finalmente 70% etil acetato / iso–hexano. Las fracciones que contienen el producto combinadas y evaporadas hasta un líquido incoloro el cual cristalizó bajo alto vacío para dar el compuesto del título como un sólido blanco (1.12 g, 84%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ2.57 (m, 2H), 2.82 (d, 3H), 3.35 (s, 3H), 3.63 (m, 2H), 3.95 (m, 2H), 4.01 (m, 2H), 5.80 (s, 1H), 8.20 (s, 1H); MS m/z 353 $[M+H]^+$.

Producto intermedio 111:

3–(2–metoxietilamino)–N–metil–propanamida

N–metilacrilamida (ABCR; 500 mg, 5.87 mmol), 2–metoxietilamina (Aldrich; 441 mg, 5.87 mmol), y EtOH (2 mL) fueron combinados y calentados en un microondas a 140 °C durante 40 minutos. La mezcla de reacción fue enfriada y añadida a una columna SCX–2 de 5g prehumedecida con MeOH (2 volúmenes de columna), purgada con MeOH (2 volúmenes de columna), luego el producto eluido con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron evaporadas al vacío para dar el compuesto del título como un aceite claro (608 mg, 65%).

^{1}H NMR (399.902 MHz, CDCl3) δ2.35 (m, 2H), 2.79 (m, 5H), 2.88 (m, 2H), 3.37 (s, 3H), 3.49 (m, 2H), 7.55 (s, 1H)

Producto intermedio 112:

10–cloro–2–(1–metoxipropan–2–il)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

N–(2,4–dicloropirimidin–5–il)–N–metil–prop–2–enamida (Producto intermedio 113; 318 mg, 1.37 mmol), 2–amino–1–metoxipropano (152 µL, 1.44 mmol), trietilamina (382 µL, 2.74 mmol), tetraetóxido de titanio (29 µL, 0.137 mmol) y DCM (5 mL) fueron combinados y agitados a temperatura ambiente durante 1h, calentados hasta 40 °C durante 3h, enfriados a temperatura ambiente, lavados con agua y filtrados por gravedad a través de un PTFE. La solución orgánica fue purificada por separación cromatográfica en sílice eluyendo con un

gradiente superficial (25 volúmenes de columna) de 10 – 50% etil acetato / iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como una goma clara (54 mg, 18%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.25 (m, 3H), 2.69 (m, 2H), 3.29 (s, 3H), 3.34 (s, 3H), 3.53 (m, 2H), 3.75 (m, 2H), 4.99 (m, 1H), 7.94 (s, 1H); MS m/z 285 $[M+H]^+$.

Producto intermedio 113:

N–(2,4–dicloropirimidin–5–il)–N–metil–prop–2–enamida

5–Metilamino–2,4–dicloropirimidina (800 mg, 4.5 mmol) fue disuelto en THF (18 mL) y trietilamina (1.88 mL, 13.5 mmol) fue añadida. Una solución de 3–cloropropionil cloruro (644 µL, 6.55 mmol) en DCM (2 mL) fue añadido en forma de gotas dando un precipitado instantáneo la reacción fue agitada a temperatura ambiente durante 30 minutos. El precipitado fue filtrado y el filtrado evaporado y el material resultante disuelto en DCM, lavado con agua, solución de bicarbonato de sodio saturada acuosa y luego filtrado por gravedad a través de un vaso PTFE. El solvente orgánico fue evaporado para dar el producto crudo como una goma amarilla la cual fue disuelta en THF (18 mL). Trietilamina (1.8 mL) fue añadida y una porción adicional de 3–cloropropionil cloruro (215 µL, 2.25 mmol). La reacción fue agitada a temperatura ambiente durante 1 h y luego se le aplicó el tratamiento final como anteriormente para dar el compuesto del título como una goma marrón (624 mg, 60%).

MS m/z 232 $[M+H]^+$. Tiempo de retención 1.39 min.

Producto intermedio 114:

5–Metilamino–2,4–Dicloropirimidina

A metilamino–5–uracil (Producto intermedio 115; 6.81 g, 48.25 mmol) fue añadida trietilamina (13.45 mL, 96.51 mmol) seguido por oxicloruro de fósforo (67.5 mL, 723 mmol) muy lentamente. La reacción fue calentada hasta reflujo durante 3 h enfriada a temperatura ambiente y el $POCl_3$ evaporado y los residuos azeotropizados con tolueno. El residuo fue diluido con tolueno (100 mL). Hielo (200 mL) fue añadido y la mezcla agitada durante 5 minutos. La mezcla fue luego neutralizada hasta pH 8 con solución de bicarbonato de sodio saturada acuosa y extraida con tolueno (300 mL). La fase acuosa fue reextraída con DCM (5 x 300 mL). La solución de tolueno fue lavada con agua (100 mL), secada ($MgSO_4$) y evaporada.

Las soluciones de DCM combinadas fueron también lavadas con agua (300 mL), secadas ($MgSO_4$), combinadas con la solución de tolueno y evaporadas hasta una goma marrón la cual fue disuelta en DCM con un poco de MeOH y cromatografiada en sílice eluyendo con un gradiente de 0 – 10% etil acetato / iso–hexano seguido por 10% etil acetato / iso–hexano luego 15% etil acetato / iso–hexano. Las fracciones que contienen el producto impuro fueron recromatografiadas eluyendo con 10% etil acetato / iso–hexano hasta que la impureza fue desprendida y luego 15% etil acetato / iso–hexano. Las fracciones que contienen el producto fueron evaporadas para dar el compuesto del título como una sólido color crema (2.58 g, 30%).

^{1}H NMR (399.902 MHz, CDCl3) δ2.98 (d, 3H), 4.35 (s, 1H), 7.90 (s, 1H); MS m/z 175 [M–H]$^-$.

Producto intermedio 115:

Metilamino–5–uracil

5 Bromo uracil (Aldrich; 49.66 g, 260 mmol) y 25% metilamina en etanol (Aldrich; 200 mL) fueron combinados y calentados en un autoclave a 160 °C durante 6 horas.
La solución fue enfriada y evaporada y el residuo lavado con agua, acetona y dietiléter para dar el compuesto del título como un sólido blanco (28 g, 70%).

Producto intermedio 116:

10–cloro–2–(3–furilmetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

3–Furilmetilamina (Maybridge; 175 mg, 1.8 mmol), N–(2,4–dicloropirimidin–5–il)–N–metil–prop–2–enamida (Producto intermedio 113; 347 mg, 1.5 mmol), trietilamina (420 µL, 3 mmol), tetraetóxido de titanio (157 µL, 0.75 mmol) y DCM (5 mL) fueron combinados y agitados a temperatura ambiente durante 1 h, calentados a 40 °C toda la noche luego enfriados a temperatura ambiente. La mezcla de reacción fue lavada con agua luego filtrada por gravedad a través de un vaso PTFE, una capa acuosa que contiene la emulsión de titanio fue lavada con DCM adicional (3 x 10 mL) y las soluciones orgánicas combinadas filtradas por gravedad a través de un vaso PTFE y los solventes evaporados. El residuo fue disuelto en

DCM y purificado por separación cromatográfica en sílice eluyendo con un gradiente superficial (25 volúmenes de columna) de 10 – 50% etil acetato / iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como una goma amarilla (67 mg, 15%).

^{1}H NMR (399.902 MHz, CDCl3) δ2.63 (m, 2H), 3.31 (s, 3H), 3.75 (m, 2H), 4.60 (s, 2H), 6.49 (m, 1H), 7.41 (m, 1H), 7.50 (m, 1H), 8.00 (s, 1H); MS m/z 293 $[M+H]^+$.

Producto intermedio 117:

10–cloro–2–ciclopropil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

Ciclopropilamina (Aldrich; 150 µL, 2.18 mmol), N–(2,4–dicloropirimidin–5–il)–N–metil–prop–2–enamida (Producto intermedio 113; 337 mg, 1.45 mmol) trietilamina (404 µL, 2.9 mmol), tetraetóxido de titanio (152 µL, 0.725 mmol) y DCM (5 mL) fueron combinados y agitados a temperatura ambiente durante 1 h, calentados a 40 °C durante 4 h y luego enfriados a temperatura ambiente. La mezcla de reacción fue lavada con agua luego filtrada por gravedad a través de un vaso PTFE, una capa acuosa que contiene la emulsión de titanio fue lavada con DCM adicional (3 x 10 mL) y las soluciones orgánicas combinadas filtradas por gravedad a través de un vaso PTFE y los solventes evaporados. El residuo fue disuelto en DCM y purificado por separación cromatográfica en sílice eluyendo con un gradiente superficial (25 volúmenes de columna) de 10 – 50% etil acetato / iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido color crema (42 mg, 11%).

^{1}H NMR (399.902 MHz, CDCl3) δ 0.58 (m, 2H), 0.91 (m, 2H), 2.68 (m, 2H), 2.85 (m, 1H), 3:28 (s, 3H), 3.84 (m, 2H), 8.02 (s, 1H); MS m/z 253 $[M+H]^+$.

Producto intermedio 118:

10–cloro–6–metil–2–(1–metil–4–piperidil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

4–Amino–1–metilpiperidina (Fluorochem; 200 mg, 1.74 mmol), N–(2,4–dicloropirimidin–5–il)–N–metil–prop–2–enamida (Producto intermedio 113; 337 mg, 1.45 mmol) trietilamina (404 µL, 2.9 mmol), tetraetóxido de titanio (152 µL, 0.725 mmol) y DCM (5 mL) fueron combinados y agitados a temperatura ambiente durante 1 h, calentados a 40 °C durante 3 h y

luego enfriados a temperatura ambiente. La mezcla de reacción fue lavada con agua, luego filtrada por gravedad a través de un vaso PTFE, una capa acuosa que contiene la emulsión de titanio fue lavada con DCM adicional (3 x 10 mL) y las soluciones orgánicas combinadas filtradas por gravedad a través de un vaso PTFE y los solventes evaporados. El residuo fue disuelto en DCM y purificado por separación cromatográfica en sílice eluyendo con un gradiente superficial (25 volumenes de columna) de 0 – 5% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido amarillo (39 mg).

Producto intermedio 119:

4–amino–N–ciclohexil–3–metoxi–benzamida

EDAC(7.46 g, 3.90 mmol) fue añadido a una solución agitada de ácido 4–amino–3–metoxi (Aldrich; 5 g, 2.9 mmol), ciclohexilamina (Aldrich; 5.13mL, 4.49 mmol) y DMAP (11 g, 9 mmol) en DCM (200 mL) y la mezcla de reacción fue agitada durante unas 18 h bajo una atmósfera de nitrógeno. La mezcla fue lavada con solución (x3) de ácido cítrico 1M, solución de bicarbonato de sodio saturado y secada. El solvente fue evaporado y el residuo triturado con dietiléter para dar el compuesto del título como un sólido rosa (5.3 g, 71%).
MS m/z 293 $[M+H]^+$.

Producto intermedio 120:

10–cloro–2–ciclopentil–3,6–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona.

3–[(5–bromo–2–cloro–pirimidin–4–il)–ciclopentil–amino]–N–metil–butanamida (Producto intermedio 121; 196 mg, 0.52 mmol) fue disuelto en 1,4–dioxano (5 mL) y tris(dibencilidenoacetona)dipaladio(0) 10 mg, 0.02 mmol), XANTFOS (20 mg, 0.02 mmol) y carbonato de cesio (247 m, 0.76 mmol) fueron añadidos a un recipiente de reacción del microondas el cual fue sellado e irradiado a 150 °C durante 30 min. Una adición posterior de tris(dibencilidenoacetona)dipaladio(0) (10 mg, 0.02 mmol) y XANTFOS (20 mg, 0.02 mmol) fue hecha y la mezcla de reacción irradiada a 150 °C durante 2 h. La mezcla de reacción enfriada fue filtrada a través de una almohadilla de celita y el filtrado concentrado en sílice y purificado por cromatografía flash en sílice (Companion, 12 g, 0–5% metanol/DCM). Las

fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido amarillo (126 mg, 82%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.34 (d, 3H), 1.44 – 1.95 (m, 8H), 2.63 (dd, 1H), 2.77 (dd, 1H), 3.32 (s, 3H), 3.98 (ddq, 1H), 4.56 (quinteto, 1H), 7.94 (s, 1H); MS m/z 295.2 $[M+H]^+$.

Producto intermedio 121:

3–[(5–bromo–2–cloro–pirimidin–4–il)–ciclopentil–amino]–N–metil–butanamida

Una solución agitada de 3–(ciclopentilamino)–N–metil–butanamida (Producto intermedio 122; 887 mg, 4.80 mmol), 5–bromo–2,4–dicloropirimidina (1.15 g, 5.04 mmol) y carbonato de potasio (1.34 g, 9.60 mmol) en acetona (20 mL) fueron calentados bajo condiciones de reflujo hasta 65 °C durante 3 días y luego a 75 °C durante unas 16 h adicionales. El solvente fue evaporado y el residuo tomado en etil acetato (200 mL) y agua (200 mL). La fase acuosa fue separada y la fase orgánica adicional lavada con agua (200 mL) y salmuera (200 mL). La fase orgánica fue evaporada y el residuo purificado por cromatografía flash en sílice (Companion, 40 g, 0–10% MeOH/DCM) seguido por HPLC preparativa modificada base (30–50% gradiente) para dar el compuesto del título como un sólido amarillo (117 mg, 6%).

^{1}H NMR (399.902 MHz, DMSO–d_6) δ 1.29 (d, 3H), 1.36 – 1.51 (m, 2H), 1.65 – 1.93 (m, 6H), 4.03 (quinteto, 1H), 4.48 (sexteto, 1H), 7.69 (q, 1H), 8.26 (s, 1H), 5 protones oscurecidos en la señal DMSO. MS m/z 375.17 $[M+H]^+$.

Producto intermedio 122:

3–(ciclopentilamino)–N–metil–butanamida

Metilamida del ácido but–2–enoico (Journal of Organic Chemistry (1981), 46(1), 27–34; 1 g, 10.0 mmol) y ciclopentilamina (Aldrich; 1.49 mL, 15.0 mmol) fueron combinadas en metanol (6 mL) en un recipiente de reacción del microondas de 10mL y la solución resultante calentada hasta 140 °C durante 60 minutos. La mezcla de reacción fue concentrada bajo presión reducida redisuelta en metanol (6 mL) y reintroducida en un recipiente de reacción del microondas con ciclopentilamina (1.49 mL, 15.0 mmol) y el recipiente de reacción sellado calentados hasta 140 °C durante unos 60 min adicionales.

El proceso fue repetido con ciclopentilamina (3.0 mL, 30 mmol) añadida y el recipiente de reacción sellado irradiado hasta 140 °C durante 2 h. El solvente fue eliminado bajo presión

reducida y el residuo disuelto en metanol (aprox. 10 mL) y cargado directamente en un cartucho SCX–2 de 50 g, lavando con metanol (100 mL) y eluyendo el producto deseado con amoniaco metanólico 7 N (100 mL). Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un aceite amarillo (1.65 g, 90%).

^{1}H NMR (399.902 MHz, DMSO–d_6) δ 0.96 (d, 3H), 1.17 – 1.81 (m, 8H), 1.99 (dd, 1H), 2.16 (dd, 1H), 2.56 (d, 3H), 2.93 (m, 1H), 3.09 (quinteto, 1H), 3.31 (br s, 1H), 7.87 (br s, 1H)

Producto intermedio 123:

10–cloro–2–ciclopentil–4–etil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5– ona

A una solución de 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 1 g, 3.56 mmol) en THF anhidro (50 mL) a 0°C fue añadido en forma de gotas una solución de sodio bis (trimetilsilil)amida 2N en THF (1.96 mL, 3.92 mmol). La solución resultante fue agitada a 0°C durante 10 minutos. Etil yoduro (314 µL, 3.92 mmol) fue añadido en forma de gotas a través de una jeringuilla y la reacción agitada a 0°C durante 2 h y luego a temperatura ambiente toda la noche.

La mezcla de reacción fue evaporada, tomado en agua y extraida con DCM. La fase orgánica fue lavada con salmuera saturada y secado sobre sulfato de magnesio. La evaporación proporcionó una goma, la cual fue disuelta en DCM y purificada mediante cromatografía de filtración al vacío, eluyendo con DCM y luego 2. 2–5% metanol / DCM.

Las fracciones que contienen el producto fueron evaporadas para dar el compuesto del título como una espuma blanca (483 mg, 44%).

^{1}H NMR (399.9 MHz, DMSO–D6) : δ_H : 0.81 (tr, 3H), 1.21–2.01 (m, 10H), 2.60 (m, 1H), 3.15 (s, 3H), 3.39 (m, 2H), 4.68 (m, 1H), 8.11 (s, 1H); MS m/z 309 $[M+H]^+$.

Producto intermedio 124:

10–cloro–2–ciclopentil–6–metil–4–propil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

A una solución de 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 1 g, 3.56 mmol) en THF anhidro (50 mL) a 0°C

fue añadido en forma de gotas una solución de sodio bis (trimetilsilil)amida 2N en THF (1.96 mL, 3.92 mmol). La solución resultante fue agitada a 0°C durante 10 minutos. 1–Yodopropano (Aldrich; 382 µL, 3.92 mmol) fue añadido en forma de gotas a través de una jeringuilla y la reacción agitada a 0°C durante 2 h y luego a temperatura ambiente toda la noche.

La mezcla de reacción fue evaporada, tomada en agua y extraida con DCM. La fase orgánica fue lavada con salmuera saturada y secada sobre sulfato de magnesio.

La evaporación proporcionó una goma, la cual fue disuelta en DCM y purificada mediante cromatografía de filtración al vacío, eluyendo con DCM y luego 2. 2–5% metanol / DCM. Las fracciones que contienen el producto fueron evaporadas para dar el compuesto del título como una espuma amarilla (467 mg, 41%).

^{1}H NMR (399.9 MHz, DMSO–d_6) : δ_H : 0.81 (tr, 3H), 1.21–2.1 (m, 12H), 2.70 (m, 1H), 3.20 (s, 3H), 3.40 (m, 2H), 4.71 (m, 1H), 8.13 (s, 1H).; MS m/z 323 $[M+H]^+$.

Producto intermedio 125:

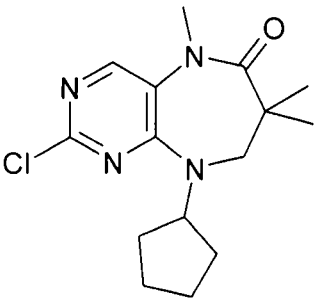
10–cloro–2–ciclopentil–4,6–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

A una solución fría (–78°C) magnéticamente agitada de 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 801 mg, 2.85 mmol) en THF seco (15 mL) fue añadido LHMDS en forma de gotas (1 M en THF, 5.71 mL, 5.70 mmol). Después de 10 minutos a esta temperatura una solución de metil yoduro (356 uL, 5.70 mmol) en THF (3 mL) fue añadida. La mezcla de reacción fue agitada a –78 °C durante 20 minutos y luego a 0 °C una hora. La mezcla de reacción fue diluida con DCM y lavada con agua, seguido por salmuera. La fase orgánica separada fue secada sobre $MgSO_4$, filtrada y concentrada al vacío. El material crudo fue cargado seco en sílice y purificado a través de cromatografía en columna (0–50% etil acetato en hexano) para proporcionar el compuesto del título como un sólido blanco. (613 mg, 73%).

MS m/z 323 $[M+H]^+$.

Producto intermedio 126:

10–cloro–2–ciclopentil–4,4,6–trimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona



A una solución agitada de 10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 127; 9.67 g, 32.8 mmol) en DMA (710 mL) bajo nitrógeno fue añadido metil yoduro (2.25 mL, 36.08 mmol). La mezcla fue enfriada en hielo/agua hasta 2.5°C. Hidruro de sodio (60% dispersión en aceite mineral, 1.45 g, 36.08 mmol) fue añadido en una porción. Una pequeña exoterma hasta 4°C fue observada. La mezcla de reacción fue agitada en un baño de hielo/agua durante 1 hora, y luego agitada a temperatura ambiente toda la noche. El solvente fue eliminado al vacío y el residuo líquido marrón claro fue tratado con agua. Esto proporcionó un sólido, el cual fue filtrado y lavado con agua. El material sólido fue disuelto en DCM (200 mL) y la solución secada usando $MgSO_4$, filtrada y evaporada para dar un sólido blanco hueso el cual fue purificado en columna de Si de 330g (Companion) cargando como una solución en DCM (60 mL). La columna habiendo sido equilibrada con 30% etil acetato en isohexano, y eluida con 30% etil acetato en isohexano durante los primeros 5 minutos y luego con un gradiente lineal lentamente creciente a 100% etil acetato. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta secarse para dar el compuesto del título como un sólido blanco (9.29 g, 92%).

1H NMR (400.13 MHz, $CDCl_3$) δ 1.20 (6H, s), 1.47 – 1.56 (2H, m), 1.64 – 1.80 (4H, m), 1.94 – 2.02 (2H, m), 3.29 (3H, s), 3.40 (2H, s), 5.25 – 5.34 (1H, m), 7.86 (1H, s); MS m/z 309 $[M+H]^+$.

Producto intermedio 127:

10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

Etil 3–[(2–cloro–5–nitro–pirimidin–4–il)–ciclopentil–amino]–2,2–dimetil–propanoato (Producto intermedio 127; 23.73 g, 64 mmol) fue disuelto en ácido acético (512 mL) calentando hasta 70–75°C bajo nitrógeno en un baño de aceite. Polvo de hierro (9.6 g) fue añadido en porciones durante 10 minutos y la reacción agitada a 70°C durante 3 horas. La mezcla de reacción fue filtrada mientras todavía estaba caliente a través de una cama de celita y la cama lavada con DCM. El filtrado combinado y lavado fue evaporado hasta secarse y el residuo azeotropizado resultante tres veces con tolueno. El residuo fue tomado en DCM y celita añadida antes de filtrar a través de una pequeña cama de celita. El volumen de DCM fue reducido y la solución purificada en dos lotes cargando directamente en Biotage Flash 75 y un cartucho de Si de 400g preacondicionado con 50% etil acetato en isohexano. El cartucho fue eluido con ~500 ml de 50% etil acetato en isohexano seguido por etil acetato. Las fracciones que contienen el producto fueron combinadas y evaporadas y el sólido amarillo resultante triturado bajo isohexano. El material sólido fue recogido por filtración, lavado con isohexano y secado desecando bajo alto vacío a temperatura ambiente hasta peso constante para dar el compuesto del título como un sólido color hueso (9.67 g , 51%).

1H NMR (400.13 MHz, DMSO–d_6) δ 1.14 (6H, s), 1.51 – 1.62 (4H, m), 1.69 – 1.74 (2H, m), 1.75 – 1.85 (2H, m), 3.32 (2H, s), 5.02 – 5.11 (1H, m), 7.93 (1H, s), 9.72 (1H, s); MS m/z 295.3 $[M+H]^+$.

Producto intermedio 128:

Etil 3–[(2–cloro–5–nitro–pirimidin–4–il)–ciclopentil–amino]–2,2–dimetil–propanoato

A una solución agitada clara inclora de etil 3–(ciclopentilamino)–2,2–dimetil–propanoato (US 2004/0176380 A1; 29.8 g, 139.7 mmol) en la acetona (700 mL) a temperatura ambiente fue añadido carbonato de potasio (21.3 g, 153.7 mmol) seguido por 2,4–dicloro–5–nitropirimidina (Aldrich; 29.81g, 153.7 mmol). La mezcla de reacción fue agitada vigorosamente a temperatura ambiente toda la noche. Carbonato de potasio (7.75 g, 56 mmol) fue añadido se continuó agitando unas 4 horas adicionales. La mezcla de reacción fue concentrada al vacío para disminuir el volumen y particionada entre etil acetato (600 mL) y agua (400 mL). Las fases fueron separadas y la fase acuosa reextraída con etil acetato (1x200 ml, 1x100 ml). Los extractos orgánicos combinados fueron secados usando $MgSO_4$ y evaporados hasta secarse. El residuo fue disuelto en DCM (150 mL) y purificado en dos lotes usando un sistema Biotage

Flash 75 con columna de Si de 400g, acondicionado con 10% etil acetato en isohexano y eluido con 10% etil acetato en isohexano. Las fracciones que contienen el producto fueron combinadas y evaporadas dando el compuesto del título como un aceite amarillo el cual se solidificó en reposo en un congelador (27.90 g, 54%).

1H NMR (399.9 MHz, $CDCl_3$) δ 1.22 (6H, s), 1.24 (3H, t), 1.50 – 1.62 (4H, m), 1.70 – 1.75 (2H, m), 1.89 – 1.95 (2H, m), 3.50 – 3.55 (1H, m), 3.82 (2H, s), 4.13 (2H, q), 8.74 (1H, s);); MS m/z 371 $[M+H]^+$.

Producto intermedio 129:

Ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzoico

A una solución de 10–cloro–2–ciclopentil–4,4,6–trimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 126; 308 mg, 1 mmol) y ácido 4–amino–3–metoxibenzoico (Aldrich; 155 mg, 1.13 mmol) en etanol (5 mL) fue añadida agua (15 mL) y ácido clorhídrico concentrado (0.17 mL, 2 mmol). La mezcla fue calentada bajo reflujo durante 36 horas. La reacción fue enfriada y se formó un precipitado. Esto fue filtrado, secado y triturado bajo acetonitrilo frío, refiltrado y secado al vacío. Para dar el compuesto del título como un sólido marrón (394 mg, 96%).

MS m/z 410 $[M+H]^+$.

Producto intermedio 130:

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona

A una solución agitada de 2'–cloro–9'–ciclopentil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[4,5–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 131; 15 g, 51.24 mmol) en DMA (1 L) bajo nitrógeno fue añadido metil yoduro 3.51 mL, 56.36 mL). La mezcla fue enfriada en hielo/agua hasta 4°C. Hidruro de sodio (60% dispersión en aceite mineral; 2.26 g, 56.36 mmol) fue añadido en una porción. Una pequeña exoterma hasta 6°C fue observada. La mezcla de reacción fue agitada en un baño de hielo/agua durante 1 hora, el baño frío fue eliminado y la reacción agitada a temperatura ambiente toda la noche. El solvente fue evaporado al vacío y el residuo tratado con agua. Esto proporcionó un sólido, el cual fue

filtrado y lavado con agua para dar un sólido blanco hueso, el cual fue cristalizado a partir de IPA (100 mL) con filtración caliente a través de papel de filtro plegado para eliminar una pequeña cantidad de materia insoluble. El material cristalizado fue filtrado, lavado con IPA fría, y secada por desecación bajo alto vacío a temperatura ambiente todo el fin de semana para dar el compuesto del título como un sólido cristalino blanco (12.78 g, 81%). ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.56 – 0.59 (2H, m), 1.04 – 1.07 (2H, m), 1.28 – 1.37 (2H, m), 1.57 – 1.63 (4H, m), 1.88 – 1.96 (2H, m), 3.20 (3H, s), 3.40 (2H, s), 4.82 – 4.91 (1H, m), 7.79 (1H, s); MS m/z 307.09 $[M+H]^+$.

Producto intermedio 131:

2'–cloro–9'–ciclopentil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[4,5–b][1,4]diazepin]–6'(5'H)–ona

Etil 1–[[(2–cloro–5–nitro–pirimidin–4–il)–ciclopentil–amino]metil]ciclopropano–1–carboxilato (Producto intermedio 132; 35.92 g, 97.4 mmol) fue disuelto en el ácido acético (750 mL) y la solución agitada y calentada hasta 70 °C bajo nitrógeno. Polvo de hierro (14.61 g) fue añadido en porciones durante 10 minutos. Durante los próximos 10–15 minutos la exoterma resultante alcanzó la temperatura de la mezcla de reacción hasta un máximo de 92 °C. La temperatura luego lentamente cayó hasta 75 °C. La mezcla de reacción oscura fue luego agitada a 75 °C durante 3 horas. La mezcla de reacción fue filtrada mientras todavía estaba caliente a través de una cama de celita y la cama lavada completamente con DCM. El ácido acético/DCM filtrado fue evaporado hasta secarse y el residuo azeotropizado resultante tres veces con tolueno. El residuo fue dejado bajo alto vacío a temperatura ambiente toda la noche, tomado en DCM y filtrado a través de una pequeña cama de celita. La celita fue lavada con DCM y el filtrado concentrado hasta 250 mL y cargado en una columna seca de sílice preacondicionada con DCM. La columna fue eluida con un gradiente 5–10% de NH_3 7N/MeOH en DCM y las fracciones que contienen el producto fueron combinadas y evaporadas. El material resultante fue recristalizado de isopropanol. El sólido precipitado fue recogido por filtración, lavado con isopropanol frío y secado desecando bajo alto vacío a temperatura ambiente hasta un peso constante para proporcionar el compuesto del título como un sólido gris (17.1 g)

^{1}H NMR (399.9 MHz, $CDCl_3$) δ 0.79 – 0.84 (2H, m), 1.19 – 1.29 (2H, m), 1.36 – 1.41 (2H, m), 1.56 – 1.67 (4H, m), 1.85 – 1.95 (2H, m), 3.25 (2H, s), 4.95 – 5.04 (1H, m), 7.75 (1H, s), 8.56 (1H, s); MS m/z 292.97 $[M+H]^+$.

Producto intermedio 132:

Etil 1–[[(2–cloro–5–nitro–pirimidin–4–il)–ciclopentil–amino]metil]ciclopropano–1–carboxilato

A una solución agitada de Etil 1–[(ciclopentilamino)metil]ciclopropano–1–carboxilato en acetona (700 mL) a temperatura ambiente fue añadido carbonato de potasio (29.0 g, 209.6 mmol) seguido por la 2,4–dicloro–5–nitropirimidina (Frontier Scientific; 29.81 g, 153.7 mmol). La mezcla de reacción fue agitada vigorosamente a temperatura ambiente toda la noche, concentrado al vacío para disminuir el volumen y el residuo marrón particionado entre etil acetato (600 mL) y agua (400 mL). Las fases fueron separadas y la acuosa reextraída con etil acetato (1 x 200 mL, 1x100 mL). Los extractos orgánicos combinados fueron secados usando $MgSO_4$ y evaporados hasta secarse dando un aceite marrón claro el cual se solidificó en reposo. El material resultante fue recristalizado a partir de IPA. El sólido fue recogido por filtración, lavado con IPA fría, succionado tan seco como sea posible luego secado hasta un peso constante desecando bajo alto vacío a temperatura ambiente para proporcionar el compuesto del título como un sólido marrón claro (35.92 g, 70%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.88 – 0.91 (2H, m), 1.07 (3H, t), 1.26 – 1.29 (2H, m), 1.44 – 1.53 (2H, m), 1.71 – 1.88 (6H, m), 3.65 (2H, s), 3.65 – 3.71 (1H, m), 4.01 (2H, q), 8.65 (1H, s); MS m/z 369.03 $[M+H]^+$.

Producto intermedio 133:

Etil 1–[(ciclopentilamino)metil]ciclopropano–1–carboxilato

A una solución claraagitada de etil 1–(aminometil)ciclopropano–1–carboxilato (Producto intermedio 134; 74.15 g, 191.6 mmol) en DCM (900 mL) bajo nitrógeno a temperatura ambiente fue añadida ciclopentanona (Aldrich; 17.5 mL, 195.4 mmol). La reacción fue agitada a temperatura ambiente durante 1.25 horas. Acetato de sodio (Aldrich; 16.03 g, 195.4 mmol) fue añadido, seguido por triacetoxiborohidruro de sodio (Aldrich; 60.93 g, 287.4 mmol). La suspensión resultante fue agitada a temperatura ambiente toda la noche.

La mezcla de reacción fue tratada con solución de bicarbonato de sodio saturada acuosa (1 L) seguido por una lenta adición de NaOH (ac.) 2M hasta pH 8–9. La fase acuosa fue separada reextraída con DCM (3 x 250 mL). Las soluciones orgánicas combinadas fueron combinadas, secadas con $MgSO_4$ y evaporadas para dar el compuesto del título como un aceite poco espeso amarillo claro (39.39 g, 97%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.79 – 0.81 (2H, m), 1.23 (3H, t), 1.24 – 1.28 (2H, m), 1.30 – 1.33 (2H, m), 1.46 – 1.57 (2H, m), 1.63 – 1.73 (2H, m), 1.77 – 1.86 (2H, m), 1.91 (1H, s), 2.69 (2H, s), 3.03 – 3.10 (1H, m), 4.11 (2H, q).

Producto intermedio 134:

Etil 1–(aminometil)ciclopropano–1–carboxilato

Etil 1–cianociclopropano–1–carboxilato (Aldrich; 76.45 g, 550 mmol), óxido de platino (7.5 g) y ácido acético (1 L) fueron combinados luego agitados a temperatura ambiente bajo hidrógeno a presión de 4 bar durante 8 horas. La mezcla de reacción fue filtrada y el filtrado concentrado al vacío para dar el compuesto del título como un aceite incoloro que contiene 4.5 equivalentes de ácido acético. (115 g, 51%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.81 – 0.84 (2H, m), 1.01 (3H, t), 1.12 – 1.15 (2H, m), 1.77 (13.5H, s – AcOH), 2.89 (2H, s), 3.92 (2H, q), 10.12 (6.5H, br s – AcOH + NH_2).

Producto intermedio 135:

4–amino–3–metoxi–N–(2–morfolin–4–iletil)benzamida

Ácido 4–amino–3–metoxibenzoico (Aldrich; 5 g, 29.9 mmol) fue agitado y disuelto en DMF (100 mL) a temperatura ambiente. 4–(2–Aminoetil)morfolina (Aldrich; 4.7 mL, 35.8 mmol) fue añadido seguido por DIPEA (15.6 mL, 89.7 mmol) y HATU (13.7 g, 36.0 mmol) provocando una isoterma ligera. La solución marrón fue agitada durante 24 h y el solvente evaporado hasta una goma marrón.

Una muestra (1.2 g) fue disuelta en metanol y purificada cargando en una columna SCX–2 (20 g) prehumedecida con metanol y eluida con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como una goma (726 mg).

El producto restante fue purificado en la misma manera que en columnas SCX–2 (5 g per columna de 50 g). Para dar el compuesto del título como un sólido naranja (9.55 g).
^{1}H NMR (400.132 MHz, DMSO–D_6) δ 2.43 (4H, m), 3.18 (2H, m), 3.34 (2H, m), 3.57 (4H, m), 3.80 (3H, s), 5.20 (2H, s), 6.61 (1H, d), 7.27 (2H, m), 7.96 (1H, t); MS m/z 280 $[M+H]^+$.

Producto intermedio 136:

4–amino–N–(3–dimetilamino–2,2–dimetil–propil)benzamida

A una solución de ácido 4–aminobenzoico (Aldrich; 4.0 g, 29.17 mmol) en DMF (100 mL) fue añadido *N,N,2,2*–tetrametil–*1,3*–diaminopropano (Aldrich; 5 mL, 31.38 mmol). Se formó un precipitado sólido inmediato. DIPEA (15 ml, 86.11 mmol) fue añadida y la suspensión resultante agitada. HATU (13g, 34.18 mmol) fue añadido en forma de porciones a una tasa y un intervalo de tiempo tal como para mantener la temperatura de reacción interna <30°C. La solución resultante amarilla fue agitada a temperatura ambiente, toda la noche.
El solvente fue eliminado al vacío, y el residuo particionado entre solución de bicarbonato de sodio saturada acuosa (250 mL) y DCM (250 mL). La fase orgánica fue separada y la fase acuosa reextraída con DCM (250 mL). Los extractos orgánicos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio, filtrados y evaporados hasta un jarabe viscoso naranja el cual fue purificado por cromatografía flash en sílice eluyendo con 0–10% amoniaco metanólico 0.2M en DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como una goma color paja pálido (1.134 g, 15%).
^{1}H NMR (400.132 MHz, DMSO–d_6) δ 0.90 (m, 6H), 2.07 – 2.40 (m, 6H), 2.67 – 2.95 (m, 2H), 3.15 – 3.20 (m, 2H), 5.57 (s, 2H), 6.56 (m, 2H), 7.55 (m, 2H), 7.97 – 8.17 (m, 1H); MS m/z 250.5 $[M+H]^+$.

Producto intermedio 137:

10–cloro–2–(1–metoxipropan–2–il)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución de N–(2,4–dicloropirimidin–5–il)prop–2–enamida (Producto intermedio 138; 104 mg, 0.477 mmol) en THF (2 mL) fue añadido trietilamina (73 µL, 0.525 mmol) seguido

por 2–amino–1–metoxipropano (Aldrich; 50 µL, 0.477 mmol) y la reacción agitada a temperatura ambiente durante 90 minutos.

La mezcla de reacción fue calentada en un microondas a 150 °C durante 30 minutos y luego a 160 °C durante unos 90 minutos adicionales. Los solventes fueron evaporados y el residuo cromatografiado en sílice eluyendo con un gradiente de 30 – 100% etil acetato / iso–hexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido color hueso (35 mg, 29%).

MS m/z 250.5 $[M+H]^+$.

Producto intermedio 138:

N–(2,4–dicloropirimidin–5–il)prop–2–enamida

A una solución de 5–amino–2,4–dicloropirimidina (Chempacific; 100 mg, 0.610 mmol) en THF (2 mL) fue añadido trietilamina (170 µL, 1.22 mmol) seguido por 3–cloropropionil cloruro (Aldrich; 64 mL, 0.671 mmol). La reacción fue agitada a temperatura ambiente durante 18 h.

La reacción fue filtrada y el solvente evaporado. El residuo fue disuelto en DCM y lavado con agua, luego filtrado por gravedad a través de un vaso PTFE y el filtrado orgánico evaporado para dar el compuesto del título como una goma amarilla (104 mg).

MS m/z 218 $[M+H]^+$.

Producto intermedio 139:

10–cloro–2–ciclopentil–6–etil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

Tris(dibencilidenoacetona)dipaladio(0) (81 mg, 0.09 mmol), XANTFOS (153 mg, 0.26 mmol) y carbonato de cesio (2.08 g, 6.37 mmol) fueron añadidos a una solución agitada de 3–[(5–bromo–2–cloro–pirimidin–4–il)–ciclopentil–amino]–N–etil–propanamida (Producto intermedio 140; 1.65 g, 4.39 mmol) en 1,4–dioxano (44 mL). El aparato fue evacuado y llenado nuevamente con nitrógeno dos veces y luego calentado a 100 °C durante 18 h. La mezcla de reacción fue filtrada a través de una almohadilla de celita y cargada seca en sílice durante la purificación por cromatografía flash en sílice (Companion, 40 g, 0–10% MeOH/DCM) para dar el compuesto del título como una goma amarilla (1.26 g, 4.27 mmol, 97%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 1.02 (t, 3H), 1.50 – 1.76 (m, 6H), 1.85 – 1.95 (m, 2H), 2.58 – 2.61 (m, 2H), 3.64 – 3.66 (m, 2H), 3.74 (q, 2H), 4.69 (quinteto, 1H), 8.21 (s, 1H); MS m/z 295.15 $[M+H]^+$.

Producto intermedio 140:

3-[(5-bromo-2-cloro-pirimidin-4-il)-ciclopentil-amino]-N-etil-propanamida

5-Bromo-2,4-dicloropirimidina (Aldrich; 1.825 g, 8.00 mmol), 3-(ciclopentilamino)-N-etil-propanamida (Producto intermedio 141; 1.48 g, 8.00 mmol) y trietilamina (1.2 mL, 8.16 mmol) fueron combinados en acetonitrilo (50 mL) y calentados a 100 °C durante 4 horas. El solvente fue eliminado bajo presión reducida y el residuo tomado en etil acetato, lavado con agua y purificado por cromatografía flash en sílice (Companion, 40 g, 0–10% metanol/DCM) para dar el compuesto del título como un aceite amarillo, (2.14 g, 71%).

^{1}H NMR (399.902 MHz, DMSO-d_6) δ 0.99 (t, 3H), 1.45 – 1.58 (m, 2H), 1.60 – 1.77 (m, 4H), 1.78 – 1.90 (m, 2H), 2.33 (t, 2H), 3.03 (qd, 2H), 3.66 (t, 2H), 4.57 (quinteto, 1H), 7.79 (t, 1H), 8.39 (s, 1H); MS m/z 376.78 $[M+H]^+$.

Producto intermedio 141:

3-(ciclopentilamino)-N-etil-propanamida

N-etilacrilamida (ABCR: 1.045 g, 10.50 mmol) y ciclopentilamina (Aldrich; 987 uL, 10.00 mmol) en metanol (10 mL) fueron combinados en un recipiente de reacción del microondas, el cual fue sellado e irradiado hasta 140 °C durante 30 minutos. La mezcla de reacción se dejó enfriar y se cargó directamente en un cartucho SCX-2 de 50 g, lavando con metanol (100 mL) y eluyendo el producto deseado con amoniaco metanólico 7 N (100 mL). La concentración bajo presión reducida de las fracciones combinadas que contienen el producto proporcionó el compuesto del título como un aceite amarillo (1.48 g, 80%).

^{1}H NMR (399.9 MHz, DMSO-d_6) δ 1.01 (3H, t), 1.27 – 1.32 (2H, m), 1.41 – 1.53 (2H, m), 1.55 – 1.64 (2H, m), 1.65 – 1.69 (2H, m), 2.18 (2H, t), 2.67 (2H, t), 2.94 – 3.01 (1H, m), 3.03 – 3.09 (2H, m), 7.89 (1H, br s)

Producto intermedio 142:

10–cloro–2–ciclopentil–6–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

Tris(dibencilidenoacetona)dipaladio(0) (47 mg, 0.05 mmol), XANTFOS (90 mg, 0.15 mmol) y carbonato de cesio (2.425 g, 7.44 mmol) fueron añadidos a una solución agitada de PH17075–018 (mezcla de reacción purificada, 2.00 g, 5.13 mmol) en 1,4–dioxano (50 mL). El aparato fue evacuado y llenado nuevamente con nitrógeno dos veces y luego calentado a 100 °C durante 1.5 h. Tris(dibencilidenoacetona)dipaladio(0) (47 mg, 0.05 mmol) y XANTFOS (90 mg, 0.15 mmol) fueron añadidos y se continuó calentando durante unas 18 h adicionales. Tris(dibencilidenoacetona)dipaladio(0) (47 mg, 0.05 mmol) fue añadido y la temperatura aumentó hasta 120 °C durante 18 h. La mezcla de reacción fue transferida a un recipiente de microondas e irradiado a 150 °C durante 30 minutos.

La mezcla de reacción fue filtrada a través de una almohadilla de celita, concentrada en sílice y purificada por cromatografía flash en sílice (Companion, 40 g, 0–5% MeOH/DCM). Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un aceite amarillo (532 mg, 33%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.24 (d, 6H), 1.50 – 1.80 (m, 6H), 1.97 – 2.07 (m, 2H), 2.57 – 2.60 (m, 2H), 3.66 – 3.69 (m, 2H), 4.52 (septeto, 1H), 4.73 (quinteto, 1H), 8.03 (s, 1H); MS m/z 309 [M+H]+.

Producto intermedio 143:

3–[(5–bromo–2–cloro–pirimidin–4–il)–ciclopentil–amino]–N–propan–2–il–propanamida

A una solución agitada de 3–(ciclopentilamino)–N–propan–2–il–propanamida (Producto intermedio 144; 1.90 g, 9.58 mmol) y trietilamina (1.36 mL, 9.77 mmol) en acetonitrilo (100 mL) fue añadido 5–bromo–2,4–dicloropirimidina (Aldrich; 2.30 g, 10.06 mmol) y la solución resultante calentada a 100 °C durante 18 h. El solvente fue eliminado bajo presión reducida y el residuo fue tomado en etil acetato (200 mL) y agua (200 mL). La fase acuosa fue eliminada y la fase orgánica lavada con agua (200 mL). La solución orgánica fue cargada en un cartucho SCX–2 de 50 g, lavando con metanol (50 mL), y etil acetato (50 mL), antes de eluir con amoniaco metanólico 7 N. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado por cromatografía flash en sílice (Companion, 120 g, 0–

10% MeOH/DCM) para dar el compuesto del título claro como un sólido blanco (1.17 g, 31%).

^{1}H NMR (399.902 MHz, DMSO–d_6) δ 1.06 (d, 6H), 1.53 – 1.62 (m, 2H), 1.66 – 1.80 (m, 4H), 1.84 – 1.94 (m, 2H), 2.35 (t, 2H), 3.69 (t, 2H), 3.84 (sexteto, 1H), 4.60 (quinteto, 1H), 7.71 (d, 1H), 8.44 (s, 1H); MS m/z 391 [M+H]+.

Producto intermedio 144:

3–(ciclopentilamino)–N–propan–2–il–propanamida

N–Isopropilacrilamida (Aldrich; 1.19 g, 10.50 mmol) y ciclopentilamina (Aldrich; 0.98 mL, 10.0 mmol) fueron combinados en metanol (6 mL) en un recipiente de reacción de microondas de 10 mL y la solución resultante calentada hasta 140 °C durante 30 min. La mezcla de reacción fue cargada directamente en un cartucho SCX–2 de 50 g, lavando con metanol (100 mL) y eluyendo el producto deseado con amoniaco metanólico 7 N (100 mL). El producto eluido fue concentrado bajo presión reducida para dar el compuesto del título como un aceite marrón claro (1.90 g, 96%).

^{1}H NMR (399.902 MHz, DMSO–d_6) δ 1.04 (d, 6H), 1.22 – 1.32 (m, 2H), 1.41 – 1.53 (m, 2H), 1.54 – 1.74 (m, 4H), 2.16 (t, 2H), 2.65 (t, 2H), 2.97 (quinteto, 1H), 3.76 – 3.88 (m, 1H), 7.83 (br d, 1H); MS m/z 199 [M+H]+.

Producto intermedio 145:

2–amino–N–(1–metil–4–piperidil)–1,3–tiazol–4–carboxamida

Sal de 2–Aminotiazol–4–carboxilato hidrobromuro (Chempacific; 1.13 g, 5.02 mmol), HATU (2.87 g, 7.53 mmol) y 4–amino–1–metilpiperidina (0.86 g, 7.53 mmol) fueron agitados en DMF (5 mL) y DIPEA (5.2 mL, 30.12 mmol) añadido. La mezcla fue agitada a temperatura ambiente toda la noche. La mezcla de reacción fue concentrada y el residuo tomado en metanol, absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas, evaporadas y el residuo purificado adicionalmente por cromatografía en columna (5% NH_3 7N en MeOH/DCM). Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un sólido amarillo (635mg, 53%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.49 – 1.59 (2H, m), 1.72 – 1.76 (2H, m), 1.98 (2H, t), 2.16 (3H, s), 2.67 – 2.70 (2H, m), 3.60 – 3.69 (1H, m), 7.09 (2H, s), 7.17 (1H, s), 7.38 – 7.40 (1H, m); MS m/z 241.44 $[M+H]^+$.

Producto intermedio 146:

2–amino–4–metil–N–(1–metil–4–piperidil)–1,3–tiazol–5–carboxamida

Utilizando ácido 2–amino–4–metil–1,3–tiazol–5–carboxílico – Buttpark y un método análogo al Producto intermedio 145 el compuesto del título fue obtenido.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.49 – 1.59 (2H, m), 1.67 – 1.70 (2H, m), 1.88 – 1.94 (2H, m), 2.15 (3H, s), 2.31 (3H, s), 2.72 (2H, m), 3.56 – 3.62 (1H, m), 7.22 – 7.26 (3H, m); MS m/z 255.45 $[M+H]^+$.

Producto intermedio 147:

2–amino–N–(1–metil–4–piperidil)–1,3–tiazol–5–carboxamida

Utilizando ácido 2–amino–1,3–tiazol–5–carboxílico, Journal of Medicinal Chemistry (1972), 15(12), 1310–12, compuesto 1, y un método análogo al Producto intermedio 145 el compuesto del título fue obtenido.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.47 – 1.57 (2H, m), 1.71 (2H, d), 1.94 (2H, t), 2.17 (3H, s), 2.75 (2H, d), 3.59 – 3.65 (1H, m), 7.08 (2H, s), 7.36 (1H, s), 7.68 (1H, d). MS m/z 241.06 $[M+H]^+$.

Producto intermedio 148:

2–amino–N–(1–metil–4–piperidil)–1,3–oxazol–5–carboxamida

Utilizando ácido 2–amino–1,3–oxazol–5–carboxílico – Producto intermedio 149 y un método análogo al Producto intermedio 145 el compuesto del título fue obtenido.

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.46 – 1.56 (2H, m), 1.70 – 1.74 (2H, m), 1.89 – 1.96 (2H, m), 2.16 (3H, s), 2.76 (2H, d), 3.59 – 3.63 (1H, m), 7.38 (2H, s), 7.63 (1H, s), 7.82 (1H, d)); MS m/z 225.14 $[M+H]^+$.

Producto intermedio 149:

ácido 2–amino–1,3–oxazol–5–carboxílico

Etil 2–aminooxazol–4–carboxilato (Apollo Scientific; 1.175 g, 7.50 mmol) fue disuelto en THF (15 mL) y agua (8 mL). Hidróxido de litio monohidrato (1.58 g, 37.52 mmol) fue añadido y la mezcla agitada toda la noche a temperatura ambiente. La mezcla fue neutralizada con $HCl_{(ac)}$ 2N y concentrada. El residuo fue suspendido en agua y filtrado y el sólido recogido disuelto en $NaOH_{(ac)}$ 2N, filtrado y luego acidificado con ácido acético hasta aproximadamente pH 4. La mezcla se dejó reposar en un baño de hielo durante 10 minutos y luego se filtró. El sólido fue secado en el filtro y luego en un desecador toda la noche para dar el compuesto del título como un sólido amarillo (194mg, 20%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ7.37 (2H, s), 7.45 (1H, s), 12.60 (1H, brS).

Producto intermedio 150:

Ácido 2–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–1,3–oxazol–4–carboxílico

Etil 2–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–1,3–oxazol–4–carboxilato (Producto intermedio 151; 160 mg, 0.40 mmol) fue disuelto en THF (1 mL) y agua (0.5 mL). Hidróxido de litio monohidrato (84 mg, 2.0 mmol) fue añadido y unas gotas de metanol y la mezcla agitada a temperatura ambiente toda la noche. La mezcla fue neutralizada con $HCl_{(ac)}$ 2N y concentrada. El residuo fue tomado en MeOH/Agua y absorbido en una columna SCX, lavado con metanol/agua y eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas, el residuo tomado en DCM, secado ($MgSO_4$) y concentrado para dar el compuesto del título como un sólido blanco (90mg, 60%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.54 – 1.66 (6H, m), 1.92 (2H, s), 2.57 – 2.60 (2H, m), 3.17 (3H, s), 3.61 (2H, t), 4.77 (1H, t), 7.96 (1H, s), 8.06 (1H, s); MS m/z 373.20 $[M+H]^+$.

Producto intermedio 151:

Etil 2–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–1,3–oxazol–4–carboxilato

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 248 mg, 0.88 mmol), etil 2–aminooxazol–4–carboxilato (Fluorochem; 125 mg, 0.80 mmol) y XANTFOS (42 mg, 0.07 mmol) fueron disueltos en 1,4–

dioxano (7.5 ml). Carbonato de cesio (522 mg, 1.60 mmol) fue añadido y la mezcla purgada con una corriente de nitrógeno durante 5 minutos. Tris(dibencilidenoacetona) paladio (II) (44 mg, 0.05 mmol) fue añadido y el aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y la reacción calentada a 100°C toda la noche. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, lavado con metanol y el producto eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en fase normal (5% metanol/DCM) para dar el compuesto del título como un sólido blanco (165mg, 51%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.29 (3H, t), 1.59 (6H, m), 1.95 (2H, m), 2.54 – 2.60 (2H, m), 3.18 (3H, s), 3.60 – 3.63 (2H, m), 4.27 (2H, q), 4.83 (1H, t), 8.08 (1H, s), 8.50 (1H, s), 10.65 (1H, s); MS m/z 401.24 $[M+H]^+$.

Producto intermedio 152:

6–amino–N–(1–metil–4–piperidil)piridina–3–carboxamida

Ácido 6–aminonicotínico (Aldrich; 2 g, 14.48 mmol) y 4–amino–1–metilpiperdina (Fluorochem; 1.82 g, 15.92 g) fueron suspendidos en DMF (20 mL), DIPEA (7.5 mL, 43.44 mmol) y HATU (6.05 g, 15.92 mmol) fueron añadidos y la reacción agitada a temperatura ambiente durante 18 h. El solvente fue evaporado y los residuos agitados con agua (50 mL durante 1 h, filtrado, acidificado con HCl ac 2M y añadido a una columna SCX–2 de 50 g prehumedecida con MeOH (2 volumenes de columna). Purgado con MeOH (2 volumenes de columna) y luego el producto crudo eluido con amoniaco 2M en MeOH y evaporado. El residuo fue disuelto en DCM con un poco de MeOH para ayudar a la solubilidad y purificado en sílice eluyendo con un gradiente de 10 – 20% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto combinado y evaporado para dar el compuesto del título como una sólido color crema (1.75 g, 52%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.47 (m, 2H), 1.65 (m, 2H), 1.85 (m, 2H), 2.09 (s, 3H), 2.68 (m, 2H), 3.61 (m, 1H), 6.33 (m, 3H), 7.73 (m, 1H), 7.78 (d, 1H), 8.36 (m, 1H); MS m/z 235 $[M+H]^+$.

Producto intermedio 153:

5–amino–N–(1–metil–4–piperidil)piridina–2–carboxamida

Utilizando ácido 5–aminopiridina–2–carboxílico – Chempacific y un método análogo al Producto intermedio 152, el compuesto del título fue obtenido como un sólido color crema (1.29 g, 31%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.60 (m, 2H), 1.72 (m, 2H), 1.97 (m, 2H), 2.16 (s, 3H), 2.71 (m, 2H), 3.69 (m, 1H), 5.89 (s, 2H), 6.97 (m, 1H), 7.69 (d, 1H), 7.91 (m, 1H), 7.97 (d, 1H); MS m/z 235 $[M+H]^+$.

Producto intermedio 154:

9–cloro–2–metil–6–prop–2–inil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–3–ona

A una suspensión enfriada (baño de hielo/agua) de hidruro de sodio (60% dispersión en aceite mineral; 15 mg, 0.38 mmol) en DMA (1 mL) fue cuidadosamente añadida una solución de 10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 100; 65 mg, 0.31 mmol) en DMA (1.5 mL). La mezcla de reacción se dejó agitar, bajo nitrógeno, en un baño de hielo durante 1 hora antes de la adición de propargil cloruro (34 mg, 0.47 mmol). La mezcla de reacción se dejó agitar a temperatura ambiente toda la noche y luego fue apagada por adición de solución de cloruro de amonio saturado acuoso (0.5 mL) y agitada durante 15 minutos. La mezcla resultante fue particionada entre DCM (10 mL) y agua (10 mL). La fase orgánica fue separada por filtración a través de un vaso filtro PTFE. La fase acuosa fue reextraída con DCM (5 mL) y las soluciones orgánicas combinadas evaporadas hasta secarse para proporcionar el compuesto del título como un sólido color beige (52 mg, 67%).

^{1}H NMR (400.132 MHz, DMSO) δ 2.70 (m, 2H), 3.20 (s, 3H), 3.26 (t, 1H), 3.80 (m, 2H), 4.33 (d, 2H), 8.25 (s, 1H); MS m/z 251 $[M+H]^+$.

Producto intermedio 155:

2–(10–cloro–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–2–il)acetonitrilo

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 154, en una escala de 0.31 mmol, utilizando bromoacetonitrilo (Aldrich; 33 ∝Λ, 0.47 mmol), como una goma ámbar que contiene 0.6 equivalentes de DMF (97 mg, 100%).

^{1}H NMR (400.132 MHz, DMSO) δ 2.74 (m, 2H), 3.21 (s, 3H), 3.81 (m, 2H), 4.53 (s, 2H), 8.36 (s, 1H); MS m/z 252 $[M+H]^+$.

Producto intermedio 156:

9–cloro–6–[(3,5–dimetil–1,2–oxazol–4–il)metil]–2–metil–2,6,8,10–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–3–ona

A una solución agitada de 10–cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 100; 64 mg, 0.3 mmol) en DMF (2 mL) fue añadido hidruro de sodio (60% dispersión en aceite mineral; 18 mg, 0.36 mmol) y la solución agitada a temperatura ambiente hasta que la efervecencia hubo cesado. 3 Clorometil–2,4–dimetilisoxazol (Aldrich; 52 mg, 0.36 mmol) fue añadido y la reacción calentada a 50 °C con agitación toda la noche. El solvente fue evaporado y el residuo disuelto en metanol, tranferido a un cartucho SCX prehumedecido con metanol, lavado con metanol y eluido con amoniaco metanólico. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido color hueso (82 mg, 85%).

Producto intermedio 157:

10–cloro–2–(2–fluoroetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 154, en una escala de 0.31 mmol, utilizando 1–bromo–2–fluoroetano (Apollo Scientific; 235 mg, 1.44 mmol), como un sólido cristalino blanco que contiene 0.6 equivalentes de DMF (86 mg, 100%).

1H NMR (400.132 MHz, DMSO) d 2.71 (m, 2H), 3.19 (s, 3H), 3.81 (m, 2H), 3.88 – 3.97 (m, 2H), 4.62 – 4.77 (m, 2H), 8.18 (s, 1H); MS m/z 259 $[M+H]^+$.

Producto intermedio 158:

10–cloro–2–(2–dimetilaminoetil)–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 156, en una escala de 0.3 mmol, utilizando 2 cloroetildimetilamina hidrocloruro

(Aldrich; 52 mg, 0.36 mmol) e hidruro de sodio (60% dispersión en aceite mineral; 36 mg, 0.75 mmol), como un sólido (84 mg, 98%).

Producto intermedio 159:

10–cloro–6–metil–2–[2–(1–piperidil)etil]–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 156, en una escala de 0.3 mmol, utilizando 2–cloroetilpiperidina hidrocloruro (Aldrich; 55 mg, 0.36 mmol) e hidruro de sodio (60% dispersión en aceite mineral; 36 mg, 0.75 mmol), como un sólido (90 mg, 93%).

Producto intermedio 160:

10–cloro–6–metil–2–(2–morfolin–4–iletil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 156, en una escala de 0.3 mmol, utilizando N–(2–cloroetil)morfolina hidrocloruro (Aldrich; 67 mg, 0.36 mmol) e hidruro de sodio (60% dispersión en aceite mineral; 36 mg, 0.75 mmol), como un sólido (95 mg, 97%).

Producto intermedio 161:

4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

Una mezcla de ácido 4–amino–3–metoxibenzoico (Aldrich; 5.015 g, 30 mmol) y endo–9–metil–9–azabiciclo[3,3,1]nonano–3–ona (Chempacific; 5.095 g, 33 mol) fueron disueltos en DMF (150 mL), y a la solución fue añadido DIPEA (10.4 mL, 60 mmol). La reacción fue enfriada en un baño de hielo, y a la reacción fue añadido, en forma de porciones, HATU (12.55 g, 33 mmol). La mezcla de reacción fue agitada a temperatura ambiente durante 18 horas. El solvente fue eliminado por evaporación, y el residuo fue particionado entre etil acetato (200 mL), y solución de carbonato de sodio saturada acuosa (3 x 50 mL), lavado con salmuera (3 x 50 mL), secado sobre sulfato de magnesio anhidro, filtrado, y el solvente eliminado por evaporación para dar el producto crudo como un aceite (14g), el cual fue purificado en columnas SCX–2 (4 x 50 g), desarrollando y eluyendo con : 1) agua ; 2) MeOH

; y 3) NH_3–MeOH 3.5M. El solvente fue eliminado por evaporación para dar el producto como un semi sólido, el cual fue triturado con dietiléter y filtrado para proporcionar el compuesto del título como un sólido color canela (4.84 g, 53%).

^{1}H NMR (400.1MHz ; DMSO–d_6) δ 0.88–0.96 (1H, d), 1.38–1.50 (3H, m), 1.86–1.96 (2H, m), 2.00–2.10 (1H, m), 2.10–2.20 (2H, m), 2.42 (3H, s), 2.92–3.00 (2H, d), 3.82 (3H, s), 4.22–4.38 (1H, m), 5.17 (2H, s), 6.58–6.62 (1H, d), 7.28 (1H, s), 7.30 (1H, s), 7.60–7.64 (1H, d). MS m/z 292 $[M+H]^+$.

Producto intermedio 162:

4–amino–3–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

Ácido 4–amino–3–fluorobenzoico (Fluorochem; 5.0 g, 32.2 mmol), HATU (13.5 g, 35.4 mmol) y DIPEA (18.5 mL, 106 mmol) fueron agitados juntos en anhidro DMA (100 mL) durante 25 minutos. Endo–9–metil–9–azabiciclo[3,3,1]nonano–3–ona (Chempacific; 5.5 g, 35.4 mmol) fue añadido y la solución agitada a temperatura ambiente toda la noche. El solvente fue evaporado y el residuo disuelto en MeOH y cargado en una columna SCX–2 (50g x 4) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volumenes de columna) y el producto eluido con NH_3/MeOH (2 volumenes de columna). La solución amoniacal fue evaporada y el material resultante purificado en una columna de sílice eluido con 0–10% $2NH_3$/MeOH/DCM. Las fracciones que contienen el producto fueron evaporadas para proporcionar el compuesto del título como un sólido blanco después de la trituración con etil acetato (5.7 g, 61%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.91 (m, 2H), 1.42 (m, 3H), 1.90 (m, 4H), 2.03 (m, 1H), 2.14 (m, 3H), 2.40 (s, 3H), 2.96 (m, 2H), 4.27 (m, 1H), 5.60 (bs, 2H), 6.74 (m, 1H), 7.46 (m, 1H), 7.53 (m, 1H), 7.70 (d, 1H); MS m/z 292 $[M+H]^+$.

Producto intermedio 163:

Ácido 3–etoxi–4–[(6–metil–5–oxo–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]benzoico

10–cloro–6–metil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 10; 625 mg, 2.45 mmol), ácido 4–amino–3–etoxibenzoico (Producto intermedio 164; 509 mg, 2.82 mmol) y ácido 4–toluenosulfónico mono hidrato (1.17 g, 6.13

mmol) fueron calentados a 140 °C en 4–metil–2–pentanol (15 mL) durante 1.5 horas. La mezcla fue enfriada y filtrada para proporcionar el compuesto del título como un sólido blanco (135 mg, 14 %). El filtrado fue absorbido en una columna SCX, lavado con metanol y eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (1% – 3% MeOH/DCM) para proporcionar el compuesto del título como un sólido blanco (115 mg, 12%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.26 (6H, d), 1.44 (3H, t), 2.74 (2H, m), 3.18 (3H, s), 3.73 (2H, m), 4.22 (2H, q), 4.85 – 4.92 (1H, m), 7.57 (1H, d), 7.63 – 7.66 (1H, m), 8.20 (2H, m), 9.41 (1H, brs), 12.90 (1H, brs); MS m/z 400 [M+H]+.

Producto intermedio 164:

Ácido 4–amino–3–etoxibenzoico

Una solución de ácido 3–etoxi–4–nitrobenzoico (Producto intermedio 165; 1.0 g, 4.74 mmol) etanol:DMF (50 mL : 5 mL) sobre 5% catalizador Pd/C (100 mg) fue hidrogenado con agitación a temperatura ambiente durante 4 horas. La mezcla fue filtrada y el catalizador lavado con etanol y el solvente evaporado y el residuo al triturar con dietil éter produjo el compuesto del título como un sólido color hueso (688 mg, 81%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.36 (t, 3H), 4.04 (q, 2H), 5.45 (bs, 2H), 6.63 (d, 1H), 7.28 (s, 1H), 7.35 (d, 1H), 12.03 (bs, 1H).

Producto intermedio 165:

Ácido 3–etoxi–4–nitrobenzoico

ácido 3–fluoro–4–nitrobenzoico (Apollo Scientific; 15 g, 81 mmol) e hidróxido de potasio (10.5 g, 186.3 mmol) fueron agitados juntos en etanol (150 mL) a temperatura ambiente. La mezcla de reacción fue lentamente calentada hasta el reflujo durante 10 minutos. La reacción fue refluida vigorosamente y se formó un precipitado sólido. La reacción fue enfriada, diluida con agua (100 mL) y acidificada con HCl 2N para dar un precipitado el cual fue filtrado, lavado con agua y secado con aire para proporcionar el compuesto del título como un sólido marrón pálido (16.88 g, 99%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.35 (t, 3H), 4.29 (q, 2H), 7.63 (d, 1H), 7.75 (s, 1H), 7.95 (d, 1H), 13.58 (s, 1H); MS m/z 210 [M+H]+.

Producto intermedio 166:

4–amino–3–etoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

Ácido 4–amino–3–etoxibenzoico (Producto intermedio 164; 400 mg, 2.21 mmol), HATU (1.26 g, 3.31 mmol) y (3R)–1–metilpirrolidin–3–amina dihidrocloruro (Producto intermedio 184; 453 mg, 3.31 mmol) fueron agitados en DMF (5 mL) y diisopropiletilamina (1.7 ml, 9.95 mmol) añadido. La mezcla fue agitada durante 2 horas y luego absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (2.5% amoniaco en metanol/DCM) para proporcionar el compuesto del título como una espuma amarilla (396 mg, 68%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.37 (3H, t), 1.70 – 1.78 (1H, m), 2.09 – 2.17 (1H, m), 2.25 (3H, s), 2.35 – 2.42 (2H, m), 2.56 – 2.62 (1H, m), 2.65 – 2.69 (1H, m), 4.05 (2H, q), 4.33 – 4.41 (1H, m), 5.16 (2H, s), 6.61 (1H, d), 7.30 – 7.54 (2H, m), 7.98 (1H, d); MS m/z 264 [M+H]+.

Producto intermedio 167:

4–amino–N–((1s,4s)–4–(dimetilamino)ciclohexil)–3–etoxibenzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 166, en una escala de 2.21 mmol, utilizando 1–amino–4–dimetilaminociclohexano (ABChem Inc.; 472 mg, 3.31 mmol) y diisopropiletilamina 1.15 mL, 6.62 mmol), después de la separación del cis isómero por cromatografía en columna, como una espuma amarilla (162 mg, 24%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.35 – 1.50 (7H, m), 1.68 – 1.78 (2H, m), 1.83 – 1.86 (2H, m), 2.00 (1H, m), 2.18 (6H, s), 3.87 (1H, m), 4.05 (2H, q), 5.13 (2H, s), 6.60 (1H, d), 7.31 (2H, m), 7.70 (1H, d); MS m/z 306 [M+H]+.

Producto intermedio 168:

4–amino–N–((1r,4r)–4–(dimetilamino)ciclohexil)–3–etoxibenzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 166, en una escala de 2.21 mmol, utilizando 1–amino–4–dimetilaminociclohexano

(ABChem Inc.; 472 mg, 3.31 mmol) y diisopropiletilamina 1.15 mL, 6.62 mmol), después de la separación del trans isómero por cromatografía en columna, como un sólido blanco (164 mg, 24%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.20 – 1.39 (7H, m), 1.81 – 1.88 (4H, m), 2.12 (1H, t), 2.18 (6H, m), 3.64 – 3.70 (1H, m), 4.04 (2H, q), 5.14 (2H, s), 6.60 – 6.62 (1H, d), 7.28 (2H, m), 7.71 (1H, d) ; MS m/z 306 [M+H]+.

Producto intermedio 169:

4–amino–5–etoxi–2–fluoro–N–(1–metil–4–piperidil)benzamida

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Ácido 4–amino–5–etoxi–2–fluorobenzoico (Producto intermedio 171; 190 mg, 0.95 mmol), HATU (545 mg, 1.43 mmol) y 4–amino–1–metilpiperidina (Fluorochem; 164 mg, 1.43 mmol) fueron agitados en DMF (3 mL) y diisopropiletilamina (0.58 ml, 2.86 mmol) añadido. La mezcla fue agitada toda la noche y luego absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (3% amoniaco en metanol/DCM) para proporcionar el compuesto del título como un sólido cristalino blanco (245mg, 86%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.35 (3H, t), 1.50 – 1.55 (2H, m), 1.71 – 1.79 (2H, m), 1.94 – 1.99 (2H, m), 2.16 (3H, s), 2.68 – 2.71 (2H, m), 3.65 – 3.73 (1H, m), 4.00 (2H, q), 5.50 (2H, s), 6.40 (1H, d), 7.04 (1H, d), 7.33 (1H, t); MS m/z 296 [M+H]+.

Producto intermedio 170:

4–amino–5–etoxi–2–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 169, en una escala de 0.5 mmol, utilizando endo–9–metil–9–azabiciclo[3,3,1]nonano–3–ona (Chempacific; 111 mg, 0.75 mmol), como un sólido blanco (171 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.91 (2H, d), 1.32 – 1.44 (6H, m), 1.86 – 1.92 (2H, m), 1.99 – 2.10 (1H, m), 2.14 – 2.22 (2H, m), 2.40 (3H, s), 2.96 (2H, d), 4.01 (2H, q), 4.21 – 4.30 (1H, m), 5.48 (2H, s), 6.40 (1H, d), 7.05 (1H, d), 7.24 (1H, t); MS m/z 336 [M+H]+.

Producto intermedio 171:

Ácido 4–amino–5–etoxi–2–fluorobenzoico

Ácido 5–etoxi–2–fluoro–4–nitrobenzoico (Producto intermedio 172; 1.24 g, 5.40 mmol) fue agitado y disuelto en etanol:DMF (50 mL : 5 mL) sobre 5% Pd/C (125mg) e hidrogenado a temperatura ambiente durante 4 horas. El catalizador fue filtrado y lavado con etanol y el solvente evaporado. El material resultante fue purificado en una columna de sílice, eluyendo con 0 – 5% MeOH/DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido marrón pálido (433 mg, 40%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.33 (3H, t), 4.25 (2H, q), 7.66 (1H, d), 7.99 (1H, m), 13.99 (1H, s).

Producto intermedio 172:

Ácido 5–etoxi–2–fluoro–4–nitrobenzoico

Ácido 2,5–difluoro–4–nitrobenzoico (Fluorochem; 1g, 4.92 mmol) fue agitado y disuelto en DMF (10 mL) y carbonato de cesio (4.8 g, 14.7 mmol) fue añadido seguido por etanol (2.3 g, 49.9 mmol). La mezcla blanca resultante fue agitada a temperatura ambiente durante 3 horas, diluida con agua, acidificada hasta pH 1 con HCl (ac) 2N, extraido con EtOAc (x3). Los extractos combinados fueron lavados con agua, secados ($MgSO_4$), filtrados y evaporados para proporcionar el compuesto del título como un sólido amarillo (1.24 g, 100%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ 1.34 (3H, t), 4.00 (2H, q), 5.79 (2H, s), 6.38 (1H, d), 7.14 (1H, d), 12.32 (1H, s).

Producto intermedio 173:

4–amino–5–cloro–2–fluoro–N–(1–metil–4–piperidil)benzamida

Ácido 4–amino–5–cloro–2–fluorobenzoico (Producto intermedio 176; 500 mg, 2.64 mmol), 4–amino–1–metilpiperidina (452 mg, 3.96 mmol) y diisopropiletilamina (1.38 ml, 7.91 mmol) fueron agitados en DMF (5 mL) y HATU (1.50 g, 3.96 mmol) añadido. La mezcla de reacción fue agitada durante 3 horas a temperatura ambiente. La mezcla fue absorbida en una columna SCX, la cual fue lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas para dar un sólido cristalino que fue suspendido en

dietil éter y filtradas para proporcionar el compuesto del título como un sólido marrón pálido (572 mg, 76%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.47 – 1.58 (2H, m), 1.71 – 1.76 (2H, m), 1.95 (2H, t), 2.15 (3H, s), 2.69 – 2.72 (2H, m), 3.67 (1H, m), 6.09 (2H, s), 6.55 (1H, d), 7.49 (1H, d), 7.61 (1H, d); MS m/z 286 [M+H]+.

Producto intermedio 174:

4–amino–5–cloro–N–(1–etil–4–piperidil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 173, en una escala de 2.64 mmol, utilizando 4–amino–1–metilpiperidina (Fluorochem; 508 mg, 3.96 mmol) después de la purificación en una columna de sílice (gradiente (3–4% amoniaco en metanol/DCM), como una espuma marrón pálido (647 mg, 82%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.99 (3H, t), 1.46 – 1.55 (2H, m), 1.75 – 1.78 (2H, m), 1.92 – 1.97 (2H, m), 2.31 (2H, q), 2.81 (2H, d), 3.67 – 3.71 (1H, m), 6.09 (2H, s), 6.53 – 6.57 (1H, m), 7.48 (1H, d), 7.59 – 7.62 (1H, m); MS m/z 300 [M+H]+.

Producto intermedio 175:

4–amino–5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 173, en una escala de 2.64 mmol, utilizando 1–amino–4–dimetilaminociclohexano (ABChem Inc.; 472 mg, 3.31 mmol) después de la purificación en una columna de sílice (gradiente (3–4% amoniaco en metanol/DCM), como una espuma marrón pálido (716 mg, 86%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.19 – 1.35 (2H, m), 1.47 – 1.54 (2H, m), 1.62 – 1.91 (4H, m), 2.03 – 2.13 (1H, m), 2.17 (6H, s), 3.59 – 3.68 y 3.85 – 3.90 (both 0.5H, m), 6.08 (2H, s), 6.53 – 6.57 (1H, m), 7.47 – 7.49 (1H, m), 7.52 – 7.56 (1H, m); MS m/z 314 [M+H]+.

Producto intermedio 176:

Ácido 4–amino–5–cloro–2–fluorobenzoico

Ácido 4–amino–5–cloro–2–fluorobenzoico *tert*–butil éster (Producto intermedio 177; 3.0 g, 12.21 mmol) fue disuelto en DCM (75 mL) y ácido trifluoro acético (25 mL) añadido. La mezcla fue agitada durante 1 hora a temperatura ambiente y luego concentrada para proporcionar el compuesto del título como un sólido amarillo pálido (2.45 g, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ6.40 (2H, s), 6.53 – 6.56 (1H, m), 7.67 (1H, d), 12.56 (1H, s).

Producto intermedio 177:

***tert*–Butil éster del ácido 4–Amino–5–cloro–2–fluorobenzoico**

tert–butil éster del ácido 4–amino–2–fluorobenzoico (ABChem Inc.; 1 g, 4.73 mmol) en DMF (15 mL) fue añadido en forma de gotas a N–clorosuccinimida (633 mg, 4.73 mmol) en DMF (20 mL). La mezcla fue agitada a temperatura ambiente durante 72 horas. La mezcla de reacción fue vertida en agua (130 mL) y extraida con etil acetato (2 x 50 mL). Los extractos combinados fueron lavados con agua, salmuera, secados ($MgSO_4$) y concentrados. La cromatografía en columna (5% etil acetato/isohexano) produjo el compuesto del título como un sólido cristalino amarillo pálido (321 mg, 27.5%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.50 (9H, s), 6.41 (2H, s), 6.54 (1H, d), 7.61 (1H, d)

Producto intermedio 178:

10–cloro–4,4,6–trimetil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

A una solución agitada de 10–cloro–4,4–dimetil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 179; 2.96 g, 11.01 mmol) en DMA (240 mL), bajo nitrógeno, fue añadido metil yoduro (0.754 mL, 12.12 mmol). La mezcla fue enfriada en un baño de hielo/agua hasta 3 °C. Hidruro de sodio (60% dispersión en aceite mineral; 485 mg, 12.12 mmol) fue añadido en una porción. La mezcla de reacción fue agitada en un baño de hielo/agua durante 1 hora y luego a temperatura ambiente toda la noche. El solvente fue eliminado al vacío y agua fue añadida al residuo resultante para proporcionar un sólido blanco, el cual fue filtrado y lavado bien con agua y disuelto en DCM (125 mL). La solución fue secada usando $MgSO_4$, filtrada y evaporada y el sólido resultante, disuelto en DCM (25 mL), purificado en una columna de sílice, equilibrado con 30% EtOAc

en isohexano, y eluido con 30% –100% EtOAc en isohexano gradiente. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido blanco (2.7 g, 87%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.12 (6H, s), 1.13 (6H, d), 3.21 (3H, s), 3.29 (2H, s), 5.15 – 5.22 (1H, m), 7.78 (1H, s); MS m/z 283 [M+H]+.

Producto intermedio 179:

10–Cloro–4,4–dimetil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona

4–Amino–5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida (Producto intermedio 180; 6.7 g, 19.43 mmol) fue agitado y disuelto en ácido acético (155 mL) calentando hasta 70 °C bajo nitrógeno. Polvo de hierro (2.92 g) fue añadido en una porción y la mezcla de reacción agitada a 70°C durante 2.5 horas. La mezcla de reacción fue filtrada mientras estaba caliente a través de una cama de celita y la cama lavada con DCM. El filtrado fue evaporado hasta secarse y el residuo resultante azeotropizado tres veces con tolueno. El residuo resultante fue purificado en una columna de sílice preacondicionada la columna con 50% EtOAc en isohexano, cargado como una solución en DCM a la cual había sido añadido celita y la mezcla resultante filtrada a través de una pequeña cama de celita. La columna fue eluida con un gradiente 50% – 100% EtOAc en isohexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido blanco (2.96 g, 57%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.13 (6H, d), 1.19 (6H, s), 3.21 (2H, s), 5.23 – 5.30 (1H, m), 7.75 (1H, s), 8.39 (1H, s); MS m/z 269 [M+H]+.

Producto intermedio 180:

4–amino–5–cloro–N–(4–dimetilaminociclohexil)–2–fluoro–benzamida

A una solución agitada del Nombre (Producto intermedio 181; 10 g; 53.4 mmol)) en acetona (250 mL) a temperatura ambiente fue añadido carbonato de potasio (11.07 g, 80.1 mmol) seguido por la 2,4–dicloro–5–nitropirimidina (Apollo Scientific; 10.35 g, 53.4 mmol). La suspensión amarilla resultante fue agitada vigorosamente a temperatura ambiente todo el fin de semana.

La mezcla de reacción fue evaporada hasta secarse y el residuo particionado entre EtOAc (250 mL) y agua (150 mL). Las fases fueron separadas después de la filtración a través de una almohadilla de celita, y la fase acuosa fue reextraída con EtOAc (2 x 100 mL, 1 x 75 mL). Los extractos orgánicos combinados fueron secados usando $MgSO_4$ y evaporados hasta secarse. El aceite marrón resultante fue purificado en una columna de sílice pre–condicionado con 10% EtOAc en isohexano y eluido con 10% EtOAc en isohexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido cristalino amarillo (6.71 g, 36%).

MS m/z 350 [M+H]+. Tiempo de retención 2.72 minutos.

Producto intermedio 181:

Etil 2,2–dimetil–3–(propan–2–ilamino)propanoato

A una solución agitada de etil, 3–amino–2,2–dimetilpropanoato (Macromolecules (1976), 9(2), 227–30; 30.85 g, 150.3 mmol) en DCM (500 mL) bajo nitrógeno a temperatura ambiente fue añadida acetona (13.25 mL, 180.36 mmol). Después de agitar a temperatura ambiente durante 1 hora acetato de sodio (12.57 g, 153.31 mmol) fue añadido, seguido por triacetoxiborohidruro de sodio (47.8 g, 225.45 mmol). La suspensión resultante fue agitada a temperatura ambiente toda la noche.

Acetona (7 mL, 90 mmol), acetato de sodio (7 g, 75 mmol) y triacetoxiborohidruro de sodio (24 g, 112 mmol) fueron añadidos y la reacción agitada nuevamente a temperatura ambiente toda la noche.

Este proceso de adicionar reactivos adicionales fue repetido.

Hidrógeno carbonato de sodio saturado acuoso (1.1 L) fue cautelosamente añadido a la mezcla de reacción agitada seguido por hidróxido de sodio 2N hasta pH = 8. Las fases fueron separadas y la fase acuosa reextraída con DCM (2x500,1x400 ml). Los extractos orgánicos combinados fueron secados usando $MgSO_4$ y luego evaporados *a no menos de 350 mbar!* Esto proporcionó el compuesto del título como un líquido claro casi incoloro (27.50 g, 98%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 1.02 (6H, d), 1.18 (6H, s), 1.24 (3H, t), 2.65 (2H, s), 4.08 – 4.16 (2H, m).

Producto intermedio 182:

4–Amino–2–fluoro–5–metoxi–N–[(3R)–1–metilpirrolidin–3–il]benzamida

Ácido 4–amino–2–fluoro–5–metoxibenzoico (Producto intermedio 183; 500 mg, 2.70 mmol), HATU (1.55 g, 4.05 mmol) y (3R)–1–metilpirrolidin–3–amina dihidrocloruro (Producto intermedio 184; 631 mg, 3.31 mmol) fueron agitados en DMF (7.5 mL) y diisopropiletilamina (2.36 ml, 13.50 mmol) añadido. La mezcla de reacción fue agitada durante 2 horas y luego absorbida en una columna SCX, la cual fue luego lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (2.5% amoniaco en metanol/DCM) para proporcionar el compuesto del título como un aceite viscoso marrón. (662 mg, 92%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.62 – 1.70 (1H, m), 2.11 – 2.20 (1H, m), 2.25 (3H, s), 2.32 – 2.46 (2H, m), 2.54 – 2.67 (2H, m), 3.78 (3H, s), 4.34 – 4.39 (1H, m), 5.57 (2H, s), 6.39 (1H, d), 7.07 (1H, d), 7.51 (1H, t); MS m/z 268 [M+H]+.

Producto intermedio 183:

Ácido 4–amino–2–fluoro–5–metoxi–benzoico

Ácido 2–fluoro–5–metoxi–4–nitrobenzoico (Producto intermedio 12; 7.76g, 36.1mmol) fue agitada y disuelto en etanol (200 mL) sobre 5% Pd/C (770mg) e hidrogenado a temperatura ambiente durante 4 horas. Durante este tiempo el producto precipitó en la reacción. DMF (20 mL) fue añadido para dar una solución. El catalizador fue filtrado y lavado con EtOH y el solvente evaporado. El residuo fue triturado con dietil éter para proporcionar el compuesto del título como un sólido marrón oscuro (3.06 g, 46%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 3.78 (s, 3H), 5.84 (bs, 2H), 6.37 (d, 1H), 7.14 (d, 1H), 12.25 (bs, 1H).

Producto intermedio 184:

(3R)–1–metilpirrolidin–3–amina dihidrocloruro

tert–butil N–[(3R)–1–metilpirrolidin–3–il]carbamato (Producto intermedio 185; 1.18 g, 5.67 mmol) fue disuelto en 1,4–dioxano (10 mL) y 4M HCl en dioxano (10 mL) añadido. La mezcla fue agitada a temperatura ambiente durante 1 hora y luego concentrado para proporcionar el compuesto del título como un sólido higroscópico blanco (810 mg, 100%).

^{1}H NMR (399.9 MHz, D_2O) 2.19 – 2.29 (1H, m), 2.60 – 2.71 (1H, m), 3.10 (3H, M), 3.48 – 3.67 (3H, m), 3.85 – 3.93 (1H, m), 4.18 – 4.26 (1H, m).

Producto intermedio 185

tert–Butil N–[(3R)–1–metilpirrolidin–3–il]carbamato

(3R)–3–(Bocamino)pirrolidina (Fluorochem; 2.5 g, 13.42 mmol) fue disuelto en 37% formaldehído acuoso (78 mL) y ácido acético (8.5 mL, 134.23 mmol). Acetato de sodio (11.0 g, 134.23 mmol) fue añadido y la mezcla enfriada en un baño de hielo/agua. Cianoborohidruro de sodio (844 mg, 13.42 mmol) fue añadido y la mezcla se dejó agitar durante 3 horas. Hidrógeno carbonato de sodio saturado acuoso fue añadido hasta que la mezcla fue básica. La mezcla fue extraida con DCM (x2) y los extractos combinados secados ($MgSO_4$) y concentrados. La cromatografía en columna (2.5 – 5% amoniaco 7N en metanol) produjo el compuesto del título como un líquido incoloro que cristalizó en reposo (1.20 g, 45%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.38 (9H, s), 1.51 – 1.59 (1H, m), 1.97 – 2.06 (1H, m), 2.20 (4H, m), 2.34 – 2.47 (2H, m), 2.61 – 2.65 (1H, m), 3.89 (1H, m), 6.90 (1H, d).

Producto intermedio 186:

4–Amino–5–etoxi–2–fluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 169, en una escala de 0.5 mmol, utilizando (3R)–1–metilpirrolidin–3–amina dihidrocloruro (Producto intermedio 184; 129 mg, 0.75 mmol), como un sólido blanco (95 mg, 68%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.35 (3H, t), 1.62 – 1.70 (1H, m), 2.13 – 2.18 (1H, m), 2.25 (3H, s), 2.32 – 2.46 (2H, m), 2.59 – 2.68 (2H, m), 4.00 (2H, q), 4.30 – 4.38 (1H, m), 5.53 (2H, s), 6.40 (1H, d), 7.06 (1H, d), 7.50 (1H, t); MS m/z 282 [M+H]+.

Producto intermedio 187:

4–Amino–3–metoxi–N–(1–metilpirrolidin–3–il)benzamida

Una solución de 3–metoxi–N–[(3R)–1–metilpirrolidin–3–il]–4–nitro–benzamida (Producto intermedio 188; 227 mg, 0.81 mmol) en metanol (25 mL) fue hidrogenado usando 10%

catalizador Pd/C. El catalizador fue filtrado y los solventes evaporados para proporcionar el compuesto del título como una goma amarilla (200 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.76 (1H, m), 2.12 (1H, m), 2.28 (3H, s), 2.41 (2H, m), 2.61 (1H, m), 2.69 (1H, m), 3.80 (3H, s), 4.36 (1H, m), 5.18 (2H, s), 6.60 (1H, d), 7.29 (1H, s), 7.31 (1H, s), 7.99 (1H, d); MS m/z 250 [M+H]+.

Producto intermedio 188:

3–Metoxi–N–[(3R)–1–metilpirrolidin–3–il]–4–nitro–benzamida

3–Metoxi–4–nitro–benzoil cloruro (Producto intermedio 189; 374 mg, 1.73 mmol) fue disuelto en DCM (20 mL) y N,N–diisopropiletilamina (0.96 mL, 5.54 mmol) añadido. La mezcla fue enfriada en un baño de hielo/agua y (3R)–1–metilpirrolidin–3–amina dihidrocloruro (Producto intermedio 184; 300 mg, 1.73 mmol) en DCM (10 mL) añadido en forma de gotas. La mezcla se dejó calentar a temperatura ambiente y agitada durante 0.5 horas. La mezcla fue lavada con salmuera, NaOH $_{(ac)}$ 2N, secada con $MgSO_4$ y evaporada para proporcionar el compuesto del título como un sólido marrón (227 mg, 46.9%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.78 (1H, m), 2.19 (2H, s), 2.26 (3H, s), 2.38 (1H, m), 2.65 (1H, m), 4.05 (3H, s), 4.41 (1H, m), 7.57 (1H, d), 7.72 (1H, s), 7.93 (1H, d), 8.70 (1H, d); MS m/z 280 [M+H]+.

Producto intermedio 189:

3–Metoxi–4–nitro–benzoil cloruro

Ácido 3–metoxi–4–nitrobenzoico (Aldrich; 9 g, 45.65 mmol) fue suspendido en tolueno (90 mL) y cloruro de tionil (9.99 mL, 136.95 mmol) añadido y la mezcla calentada hasta reflujo durante 1 hora. La reacción fue evaporada para proporcionar el compuesto del título como un sólido marrón (9.84 g, 100%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ4.00 (3H, s), 7.64 – 7.67 (1H, m), 7.78 (1H, d), 7.97 (1H, m).

Producto intermedio 190:

4–Amino–N–(1–etil–4–piperidil)–3–metoxi–benzamida

El compuesto del título fue preparado con rendimiento cuantitativo por un método análogo a la preparación del Producto intermedio 187, en una escala de 2g utilizando N–(1–etil–4–piperidil)–3–metoxi–4–nitro–benzamida (Producto intermedio 191).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.99 – 1.02 (3H, t), 1.49 – 1.59 (2H, m), 1.75 (2H, d), 1.92 (2H, t), 2.32 (2H, q), 2.87 (2H, d), 3.68 – 3.76 (1H, m), 3.81 (3H, s), 5.19 (2H, s), 6.59 – 6.62 (1H, m), 7.28 – 7.30 (2H, m), 7.77 (1H, d); MS m/z 280 [M+H]+.

Producto intermedio 191:

N–(1–etil–4–piperidil)–3–metoxi–4–nitro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 188, en una escala de 9.28 mmol utilizando 1–etilpiperidin–4–amina (Fluorochem; 1.19 g, 9.28 mmol), como un sólido marrón (3.3 g, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.01 (3H, t), 1.56 – 1.63 (2H, m), 1.82 (2H, m), 1.92 – 1.98 (2H, m), 2.34 (2H, q), 2.89 (2H, d), 3.75 – 3.79 (1H, m), 4.00 (3H, s), 7.54 – 7.57 (1H, m), 7.70 (1H, d), 7.96 (1H, d), 8.49 (1H, d); MS m/z 308 [M+H]+.

Producto intermedio 192:

4–Amino–3–metoxi–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado con rendimiento cuantitativo por un método análogo a la preparación del Producto intermedio 187, en una escala de 2g utilizando 3–metoxi–4–nitro–N–(2–pirrolidin–1–iletil)benzamida (Producto intermedio 193).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.68 (4H, t), 2.49 (4H, s), 2.55 (2H, t), 3.36 (2H, d), 3.81 (3H, s), 5.20 (2H, s), 6.59 – 6.62 (1H, m), 7.26 – 7.29 (1H, m), 7.31 (1H, s), 8.00 (1H, s); MS m/z 280 [M+H]+.

Producto intermedio 193:

3–Metoxi–4–nitro–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 188, en una escala de 9.28 mmol utilizando 2–pirrolidin–1–iletanamina (Aldrich; 1.06 g, 9.28 mmol), como un sólido marrón (2.3 g, 85%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.67 – 1.72 (4H, m), 2.47 – 2.54 (4H, m), 2.60 (2H, t), 3.39 – 3.44 (2H, m), 3.99 (3H, s), 7.54 – 7.56 (1H, m), 7.72 (1H, d), 7.96 (1H, d), 8.71 (1H, t); MS m/z 294 [M+H]+.

Producto intermedio 194:

4–Amino–N–(2–dimetilaminoetil)–3–metoxi–benzamida

El compuesto del título fue preparado en rendimiento cuantitativo por un método análogo a la preparación del Producto intermedio 187, en una escala de 2g utilizando N–(2–dimetilaminoetil)–3–metoxi–4–nitro–benzamida (Producto intermedio 195).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ2.19 (6H, s), 2.38 (2H, t), 3.38 (2H, m), 3.81 (3H, s), 5.20 (2H, s), 6.61 (1H, d), 7.25 – 7.28 (1H, m), 7.30 (1H, s), 7.96 (1H, t); MS m/z 238 [M+H]+.

Producto intermedio 195:

N–(2–dimetilaminoetil)–3–metoxi–4–nitro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 188, en una escala de 9.28 mmol utilizando N,N–dimetiletano–1,2–diamina (Aldrich; 818 mg, 9.28 mmol), como un sólido marrón (2.5 g, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 2.24 (6H, s), 2.47 – 2.49 (2H, m), 3.37 – 3.41 (2H, m), 4.00 (3H, s), 7.55 – 7.57 (1H, m), 7.74 (1H, d), 7.96 (1H, d), 8.73 (1H, t); MS m/z 268 [M+H]+.

Producto intermedio 196:

4–Amino–N–(3–dimetilaminopropil)–3–metoxi–benzamida

El compuesto del título fue preparado con rendimiento cuantitativo por un método análogo a la preparación del Producto intermedio 187, en una escala de 2g utilizando N–(2–dimetilaminoetil)–3–metoxi–4–nitro–benzamida (Producto intermedio 197).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.60 – 1.67 (2H, m), 2.14 (6H, s), 2.25 (2H, t), 3.21 – 3.26 (2H, m), 3.81 (3H, s), 5.19 (2H, s), 6.61 (1H, d), 7.25 – 7.30 (2H, m), 8.09 (1H, t); MS m/z 252 [M+H]+.

Producto intermedio 197:

N–(3–dimetilaminopropil)–3–metoxi–4–nitro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 188, en una escala de 9.28 mmol utilizando N,N–dimetilpropano–1,3–diamina (Aldrich; 948 mg, 9.28 mmol), como un sólido marrón (2.33 g, 90%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.65 – 1.72 (2H, m), 2.16 (6H, s), 2.29 (2H, t), 3.34 (2H, m), 4.00 (3H, s), 7.53 – 7.56 (1H, m), 7.72 (1H, d), 7.96 (1H, d), 8.77 (1H, t); MS m/z 282 [M+H]+.

Producto intermedio 198:

10–cloro–4,4–dietil–6–metil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución agitada de 10–cloro–4,4–dietil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 197; 2.7 g, 9.1 mmol) en DMA (50 mL) bajo nitrógeno fue añadido metil yoduro (0.627 mL, 10.0 mmol). La mezcla fue enfriada en un baño de hielo/agua hasta 3°C, e hidruro de sodio (60% dispersión en aceite mineral; 0.567 g, 11.8 mmol) añadido en una porción. La reacción fue agitada toda la noche. La reacción fue evaporada hasta secarse para proporcionar un sólido amarillo, esta fue apagada con $NH_4Cl_{(ac)}$ (50 mL) saturado, extraída con DCM (3 X 100 mL), secada ($MgSO_4$) y evaporada para proporcionar un sólido amarillo. Esto fue disuelto en una mínima cantidad de DCM, dietil éter fue añadido y el sistema fue sonicado para proporcionar un sólido blanco hueso. (2.24 g, 80%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.84 (t, 6H), 1.20 (d, 6H), 1.68 – 1.50 (m, 4H), 3.27 (s, 3H), 3.41 (s, 2H), 5.31 (septeto, 1H), 7.83 (s, 1H); MS m/z 311 [M+H]+.

Producto intermedio 199:

10–cloro–4,4–dietil–2–propan–2–il–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución de 2,4–dicloro–5–nitropirimidina (Aldrich; 5.1 g, 26.4 mmol) y K_2CO_3 (4.4 g, 31.6 mmol) en acetona (150 mL) fue lentamente añadido metil 2–etil–2–[(propan–2–ilamino)metil]butanoato (Producto intermedio 200; 5.3 g, 26.4 mmol) en acetona (30 mL). La mezcla fue agitada a temperatura ambiente durante 18 horas. La reacción fue filtrada y el

solvente evaporado. El residuo y hierro (4.4 g, 79.2 mmol) fueron añadidos al ácido acético (175 mL) y calentados a 80 °C toda la noche. La solución resultante fue filtrada y el solvente evaporado y el residuo apagado con $NaOH_{(ac)}$ 2.0 N (75 mL), a la emulsión resultante, fue añadido 10%MeOH/DCM (100 ml) y la suspensión filtrada a través de una almohadilla de celita. El filtrado obtenido fue extraído con 10%MeOH/DCM (3 X 150 mL, secado y el solvente eliminado. El material resultante fue disuelto en DCM y filtrado. Acetonitrilo fue añadido al DCM y el DCM fue lentamente eliminado al vacío para dar un precipitado, el cual fue filtrado y secado para proporcionar el compuesto del título como un sólido blanco. (3.1 g, 33%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.90 (t, 6H), 1.21 (d, 6H), 1.68 – 1.60 (m, 4H), 3.35 (s, 2H), 5.36 (septeto, 1H), 7.83 (s, 1H), 8.65 (brs, 1H); MS m/z 297 [M+H]+.

Producto intermedio 200:

Metil 2–etil–2–[(propan–2–ilamino)metil]butanoato

Metil 2–(aminometil)–2–etil–butanoato (Producto intermedio 201; 8 g, 50 mmol) y acetona (4.35 g, 75 mmol) fueron añadidos a metanol (230 mL) y agitados durante 10 minutos antes de la adición rápida de triacetoxiborohidruro de sodio (15.9 g, 75 mmol). La reacción fue agitada toda la noche antes de ser evaporada hasta secarse. El residuo fue apagado con $K_2CO_{3(ac)}$ saturado (100 mL), extraído con DCM (3 x 150 mL), secado y los solventes evaporados para proporcionar un líquido oscuro. La purificación fue lograda mediante la destilación (65°C @ 0.18 mbar) para proporcionar el compuesto del título como un aceite claro (5.3 g, 53%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 0.79 (t, 6H), 1.02 – 0.98 (m, 7H), 1.62 (q, 4H), 2.74 – 2.67 (m, 3H), 3.67 (s, 3H)

Producto intermedio 201:

Metil 2–(aminometil)–2–etil–butanoato

Metilcianoacetato (Aldrich; 20 g, 0.201 mol) fue disuelto en THF (250 mL), a esto fue añadido DBU (75 mL, 0.505 mol) y etil bromuro (40 mL, 0.606 mol). La reacción fue agitada a 50 °C durante 2 horas antes de ser enfriada y apagada con $NH_4Cl_{(ac)}$ sat. La capa orgánica fue separada y el acuoso restante fue extraído con dietil éter (2 x 100 mL), secado y el

solvente eliminado al vacío para proporcionar aceite amarillo. La purificación fue lograda mediante la destilación a 70 °C a 0.5 mbar para proporcionar metil 2–ciano–2–etil–butanoato como un aceite claro (20 g, 0.129 mol) el cual fue reducido con hidrógeno bajo presión usando un catalizador de níquel Raney (2 g). La mezcla de reacción fue filtrada y el solvente evaporado al compuesto del título como un aceite ligeramente oscuro. (16 g, 50%).

Producto intermedio 202:

4–amino–3–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]benzamida

El compuesto del título fue preparado con rendimiento cuantitativo por un método análogo a la preparación del Producto intermedio 187, en una escala de 2g utilizando (Producto intermedio 203).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.92 (2H, d), 1.39 – 1.46 (3H, m), 1.88 – 1.95 (1H, m), 1.92 (1H, d), 2.06 (1H, s), 2.12 – 2.20 (2H, m), 2.41 (3H, s), 2.97 (2H, d), 3.82 (3H, s), 4.30 (1H, d), 5.18 (2H, s), 6.61 (1H, d), 7.29 – 7.31 (2H, m), 7.63 (1H, d); MS m/z 304 [M+H]+.

Producto intermedio 203:

3–Metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–3–il]–4–nitro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 188, en una escala de 9.28 mmol utilizando endo–9–metil–9–azabiciclo[3,3,1]–nonan–3–amina (Chempacific; 1.435 g, 9.28 mmol), como un sólido marrón (1.6 g, 52%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.93 (2H, d), 1.45 (3H, m), 1.89 – 1.95 (1H, m), 1.94 (1H, d), 2.03 (1H, t), 2.18 – 2.23 (2H, m), 2.42 (3H, s), 3.00 (2H, d), 4.00 (3H, d), 4.31 – 4.35 (1H, m), 7.56 – 7.59 (1H, m), 7.72 (1H, d), 7.96 (1H, d), 8.37 (1H, d); MS m/z 332 [M–H]+.

Producto intermedio 204:

4–Amino–2–fluoro–5–metoxi–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

Ácido 4–amino–2–fluoro–5–metoxibenzoico (Producto intermedio 183; 0.75 g, 4.07 mmol), HATU (1.70 g, 4.48 mmol) y DIPEA (2.1 mL, 12.21 mmol) fueron agitados juntos en DMF (10 mL) durante 10 minutos. Endo–9–metil–9–azabiciclo[3,3,1]–nonan–3–amina (Chempacific; 0.69 g, 4.48 mmol) en DMF (1 mL) fue añadido y la solución marrón agitada a

temperatura ambiente durante 2 horas. El solvente fue evaporado y el residuo disuelto en MeOH y cargado en una columna SCX–2 (20 g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volúmenes de columna) y el producto eluido con NH_3 2M/MeOH (2 volúmenes de columna). Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante purificado en una columna de sílice eluyendo con 0–10% NH_3 2M /MeOH/DCM). Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como una goma marrón oscuro (897 mg, 69%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.91 (m, 2H), 1.39 (m, 3H), 2.04 (m, 5H), 2.40 (s, 3H), 2.96 (m, 2H), 3.78 (s, 3H), 4.27 (m, 1H), 5.53 (s, 2H), 6.39 (d, 1H), 7.06 (d, 1H), 7.24 (m, 1H); MS m/z 322 [M+H]+.

Producto intermedio 205:

4–amino–N–(1–etil–4–piperidil)–2–fluoro–5–metoxi–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 188, en una escala de 5.43 utilizando 1–etilpiperidin–4–amina (Fluorochem; 0.77 g, 5.97 mmol), como una goma (1.21 g, 76%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.99 (t, 3H), 1.52 (m, 2H), 1.78 (m, 2H), 1.97 (m, 2H), 2.31 (q, 2H), 2.80 (m, 2H), 3.72 (m, 1H), 3.77 (s, 3H), 5.54 (bs, 2H), 6.39 (d, 1H), 7.05 (d, 1H), 7.33 (m, 1H); MS m/z 296 [M+H]+.

Producto intermedio 206:

4–amino–N–(2,2–dimetil–3–pirrolidin–1–il–propil)–3–metoxi–benzamida

Una mezcla del ácido 4–amino–3–metoxi–benzoico (Aldrich; 2 g, 12 mmol) y 2,2–dimetil–3–pirrolidin–1–il–propan–1–amina (WO 2004033419; 2.1 g, 13.2 mmol) fueron disueltos en DMF (50 mL), y a la solución fue añadido DIPEA (3.1 g, 4.2 mL). La reacción fue enfriada con un baño de hielo, y a esta fue añadido, en forma de porciones, HATU (5.02 g, 13.2 mmol). La mezcla de reacción fue agitada a temperatura ambiente durante 18 horas. El solvente fue evaporado, y el residuo fue particionado entre etil acetato (100 mL), y solución de carbonato de sodio saturada acuosa (3 x 40 mL), lavado con salmuera (3 x 40 mL), secado sobre sulfato de magnesio anhidro, filtrado, y el solvente evaporado. El residuo fue purificado

por cromatografía en una columna de sílice preacondicionado con etil acetato y eluido con 10% MeOH–DCM +1% NH_3. Esas fracciones que contiene el producto deseado fueron combinadas y el solvente fue evaporado para proporcionar el compuesto del título como una goma marrón pálido, la cual cristalizó en reposo. (500mgs ; 14%).

^{1}H NMR (400.132 MHz, CDCl3) : δ1.00 (6H,s), 1.75–1.85 (4H,m), 2.55 (2H,s), 2.63–2.75 (4H,m), 3.35–3.39 (2H,d), 3.90 (3H,s), 6.61–6.65 (1H,d), 7.06–7.11 (1H,d), 7.47 (1H,s), 9.05 (1H,bs). MS m/z 306 [M+H]+.

Producto intermedio 207:

4–Amino–5–cloro–2–fluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida

Ácido 4–amino–5–cloro–2–fluorobenzoico (Producto intermedio 176; 300 mg, 1.58 mmol), HATU (903 mg, 2.37 mmol) y (3R)–1–metilpirrolidin–3–amina dihidrocloruro (Producto intermedio 184; 325 mg, 2.37 mmol) fueron agitados en DMF (5 mL) y diisopropiletilamina (1.2 mL, 7.12 mmol) añadido. La mezcla fue agitada durante 2 horas a temperatura ambiente y luego absorbida en una columna SCX, lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y purificadas por cromatografía en columna (5% amoniaco en metanol/DCM) para proporcionar el compuesto del título como un sólido naranja oscuro (333 mg, 77%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.63 – 1.71 (1H, m), 2.09 – 2.18 (1H, m), 2.25 (3H, s), 2.33 – 2.41 (2H, m), 2.55 – 2.61 (1H, m), 2.64 – 2.69 (1H, m), 4.30 – 4.35 (1H, m), 6.10 (2H, s), 6.55 (1H, d), 7.50 (1H, d), 7.76 – 7.79 (1H, m)

Producto intermedio 208:

2'–cloro–9'–isopropil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona

A una solución de 2'–cloro–9'–isopropil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 209; 5.055 g, 19 mmol) en DMA (300 mL) fue añadido metil yoduro (1.305 mL, 20.9 mmol), seguido por hidruro de sodio (60% dispersión en aceite mineral; 814 mg, 20.33 mmol). La mezcla fue agitada a temperatura ambiente durante 30 minutos. El DMA fue eliminado al vacío, luego agua (50 mL) fue añadida. El producto precipitó como una goma pegajosa, la cual se tornó en un sólido con la

sonicación. El sólido fue recogido por filtración para dar un polvo marrón. Este material fue disuelto en DCM y secado sobre sulfato de sodio, luego purificado por cromatografía en columna, eluyendo con 25% etil acetato en hexano, para proporcionar el compuesto del título como un sólido blanco (3.73 g, 70%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.63 – 0.66 (2H, m), 1.11 – 1.16 (8H, m), 3.26 (3H, s), 3.44 (2H, s), 4.91 – 4.98 (1H, m), 7.84 (1H, s) ; MS m/z 281 [M+H]+.

Producto intermedio 209:

2'–Cloro–9'–isopropil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona

Etil 1–[[(2–cloro–5–nitro–pirimidin–4–il)–propan–2–il–amino]metil]ciclopropano–1–carboxilato (Producto intermedio 208; 10.26 g, 30 mmol) fue disuelto en ácido acético (500 mL) y calentado hasta 70 °C. Polvo de hierro (6 g) fue añadido en porciones durante 10 minutos. La mezcla fue agitada a 70 °C durante 3 horas. La mezcla de reacción fue filtrada caliente a través de celita, y la almohadilla lavada con DCM. El filtrado fue evaporado hasta secarse luego sonicado en solución de hidrógeno carbonato de sodio saturada acuosa para dar una suspensión marrón. Esto fue filtrado, y el sólido resultante lavado con agua. El sólido fue luego succionado seco en un filtro, y suspendido en una pequeña cantidad de metanol con sonicación. La suspensión de metanol fue luego diluida con DCM (10 x excesos), y filtrada para dar una solución amarilla, la cual fue secada sobre sulfato de sodio, luego concentrada al vacío para dar un sólido amarillo/verde. El sólido fue triturado bajo metanol frío para proporcionar el compuesto del título como un polvo blanco (5 g, 63%).

MS m/z 267 [M–H]+. Tiempo de retención 1.81 minutos.

Producto intermedio 210:

Etil 1–[[(2–cloro–5–nitro–pirimidin–4–il)–propan–2–il–amino]metil]ciclopropano–1–carboxilato

A una solución de etil 1–[(propan–2–ilamino)metil]ciclopropano–1–carboxilato (Producto intermedio 211; 9.55 g, 50 mmol) en acetona (300 mL) fue añadido carbonato de potasio (7.05 g, 51 mmol) seguido por 2,4–dicloro–5–nitropirimidina (Aldrich; 10.675 g, 55 mmol). La mezcla fue agitada toda la noche a temperatura ambiente, concentrada al vacío y particionada

entre EtOAc y agua. La capa EtOAc fue separada, secada sobre sulfato de sodio, luego purificada por cromatografía en columna (EtOAc / isohexano 10:90), para proporcionar el compuesto del título como un aceite amarillo. (11 g, 64%).

^{1}H NMR (400.13 MHz, CDCl3) δ 0.75 – 0.78 (2H, m), 0.96 (3H, t), 1.10 – 1.14 (8H, m), 3.42 – 3.48 (1H, m), 3.59 (2H, s), 3.87 – 3.93 (2H, m), 8.48 (1H, s); MS m/z 343 [M+H]+.

Producto intermedio 211:

Etil 1–[(propan–2–ilamino)metil]ciclopropano–1–carboxilato

A una solución de etil 1–(aminometil)ciclopropano–1–carboxilato (Producto intermedio 114; 20.65 g, 250 mmol) en DCM (200 mL) fue añadida acetona (3.74 mL, 51 mmol). Después de agitar a temperatura ambiente durante 15 minutos, acetato de sodio (4.185 g, 51 mmol) fue añadido, seguido por triacetoxiborohidruro de sodio (15.905 g, 75 mmol). La suspensión fue agitada a temperatura ambiente durante 2 días luego particionada entre DCM y una solución acuosa de hidrógeno carbonato de sodio saturada. La capa orgánica fue separada, luego secada sobre sulfato de sodio, evaporada para proporcionar el compuesto del título como un aceite claro (9.2 g, 100%).

^{1}H NMR (400.13 MHz, CDCl3) δ 0.60 – 0.63 (2H, m), 0.86 (6H, d), 1.02 – 1.09 (5H, m), 1.69 (1H, br s), 2.50 (2H, s), 2.58 – 2.64 (1H, m), 3.93 (2H, q).

Producto intermedio 212:

4–Amino–3–cloro–N–(1–etil–4–piperidil)benzamida

A una mezcla de ácido 4–amino–3–cloro–benzoico (Fluorochem; 2.575 g, 15 mmol) y 1–etilpiperidin–4–amina (Fluorochem; 2.12 g, 16.5 mmol) en DMF (50 mL), fue añadido DIPEA (5.2 mL, 30 mmol). La mezcla fue enfriada con un baño de hielo. HATU (6.27g) añadido y la mezcla de reacción agitada a temperatura ambiente durante 18 horas. El solvente fue evaporado y el residuo particionado entre una solución de bicarbonato de sodio saturada acuosa (100 mL), y etil acetato (4 x 50 mL). Los extractos orgánicos fueron lavados con salmuera (2 x 75 ml), secados sobre sulfato de magnesio anhidro, filtrados, y el solvente evaporado para dar el producto crudo como una goma, la cual fue triturada con éter para proporcionar el compuesto del título como un sólido color canela (3.54 g, 84%).

^{1}H NMR ;400.1MHz (DMSO–d6) δ1.20–1.26 (3H,t), 1.65–1.85 (2H,bm), 1.92–2.10 (2H,bm), 2.90–3.20 (4H,m), 3.30 (3H,s), 3.40–3.60 (2H,bm), 3.90–4.05 (1H,m), 5.98 (2H,s), 6.77–6.81 (1H,d), 7.554–7.60(1H,dd), 7.88 (1H,s), 8.10 (1H,bs); MS m/z 282 [M+H]+.

Producto intermedio 213:

4–Amino–3–cloro–N–(2–dimetilaminoetil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 212, en una escala de 15 mmol utilizando 2,2–dimetiaminoetilamina (Aldrich; 1.455 g, 16.5 mmol), como un sólido blanco (1.45 g, 40%).

^{1}H NMR ;400.1MHz (DMSO–d6) δ 2.83 (6H,s), 3.18–3.24 (2H,t), 3.50–3.58 (2H, cuarteto), 5.95 (2H,s), 6.80–6.83 (1H,d), 7.55–7.60 (1H,d), 7.76 (1H,s), 8.30–8.38 (1H,t); MS m/z 242 [M+H]+.

Producto intermedio 214:

4–Amino–3–cloro–N–(3–dimetilaminopropil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 212, en una escala de 15 mmol utilizando 3–dimetilamino–1–propilamina (Aldrich; 1.685 g, 16.5 mmol), como un sólido color canela (3.25 g, 85%).

^{1}H NMR 400.1MHz,(DMSO–d6) δ 1.80–1.90 (2H,m), 2.77 (6H,s), 3.00–3.08 (2H,m), 3.25–3.50 (2H,m), 5.88 (2H,s), 6.78–6.82 (1H,d), 7.53–7.59 (1H,dd), 7.75 (1H,s), 8.24–8.30 (1H,t); MS m/z 256 [M+H]+.

Producto intermedio 215:

4–Amino–3–cloro–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 212, en una escala de 15 mmol utilizando 2–pirrolidin–1–iletanamina (Aldrich; 1.885 g, 16.5 mmol), como un sólido color canela (2.67 g, 66%).

^{1}H NMR ; 400.1MHz, (DMSO–d6) δ 1.80–2.05 (4H,m), 3.20–3.45 (6H,m), 3.48–3.58 (2H,q), 5.92 (2H,s), 6.78–6.82 (1H,d), 7.55–7.60 (1H,dd), 7.77 (1H,s), 8.30–8.40 (1H,t);); MS m/z 268 [M+H]+.

Producto intermedio 216:

4–Amino–2–cloro–5–metoxi–N–(1–metil–4–piperidil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 212, en una escala de 3.06 mmol utilizando ácido 4–amino–2–cloro–5–metoxi–benzoico (Producto intermedio 217; 617 mg, 3.06 mmol) y 1–metilpiperidin–4–amina (Fluorochem; 385 mg, 3.37 mmol), como un sólido color hueso (845 mg, 93%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.61 (m, 2H), 2.05 (m, 2H), 2.20 (m, 2H), 2.30 (s, 3H), 2.76 (m, 2H), 3.88 (s, 3H), 4.03 (m, 3H), 6.57 (d, 1H), 6.63 (s, 1H), 7.34 (s, 1H); MS m/z 298 [M+H]+.

Producto intermedio 217:

Ácido 4–amino–2–cloro–5–metoxi–benzoico

Ácido 2–cloro–5–metoxi–4–nitro–benzoico (Producto intermedio 218; 762 mg, 3.8 mmol) fue disuelto en EtOH (20 mL) y una cantidad catalítica de 5% Pt en carbón añadida bajo una atmósfera inerte. La solución fue desgasificada y agitada bajo una atmósfera de hidrógeno a temperatura ambiente toda la noche. El catalizador fue filtrado y lavado con EtOH y el solvente evaporado y el material resultante secado bajo vacío para proporcionar el compuesto del título como un sólido color hueso. (617 mg, 98%).

^{1}H NMR (399.902 MHz, DMSO–d6) δ3.72 (s, 3H), 5.65 (br s, 2H), 6.59 (s, 1H), 7.21 (s, 1H), 12.30 (br s, 1H); MS m/z 201 [M+H]+.

Producto intermedio 218:

Ácido 2–cloro–5–metoxi–4–nitro–benzoico

1–cloro–4–metoxi–2–metil–5–nitro–benceno (APIN; 1 g, 4.96 mmol) fue suspendido en agua (100 mL), permanganato de potasio (3.14 g, 19.84 mmol) fue añadido y la mezcla diluida además con agua (140 mL). La mezcla fue calentada muy lentamente hasta reflujo durante un periodo de 2 horas y luego agitada a reflujo durante 4 horas, luego se dejó enfriar a temperatura ambiente toda la noche con agitación. Después de 18 horas la mezcla fue recalentada hasta 80 °C y filtrada caliente, la torta del filtro de manganeso fue lavada con agua hirviendo (100 mL), luego el filtrado acuoso fue tratado con un par de gotas de solución de metabisulfito de sodio y el color del permanganato fue eliminado para dar una solución

amarilla. La solución fue acidificada hasta pH 2 con ácido clorhídrico concentrado y parcialmente evaporada hasta un volumen de (200 mL) y extraído con EtOAc (2 x 100 mL). Los extractos orgánicos combinados fueron lavados con salmuera, secados ($MgSO_4$) y evaporados para proporcionar el compuesto del título como un sólido amarillo. (752 mg, 65%).

^{1}H NMR (399.902 MHz, DMSO–d6) δ3.98 (s, 3H), 7.67 (s, 1H), 8.14 (s, 1H), 14.03 (br s, 1H); MS m/z 229 [M–H]+.

Producto intermedio 219:

Ácido 5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoico

tert–Butil 5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoato (Producto intermedio 220; 220 mg, 0.45 mmol) fue disuelto en DCM (7.5 mL) y ácido trifluoroacético (2.5 mL) añadido. La mezcla fue agitada a temperatura ambiente durante 2 horas. La mezcla de reacción fue evaporada, el residuo disuelto en metanol/DCM y absorbido en una columna SCX, la cual fue posteriormente lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido blanco (195 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.54 – 1.73 (6H, m), 1.88 – 1.95 (2H, m), 2.58 – 2.63 (2H, m), 3.18 (3H, s), 3.61 – 3.65 (2H, m), 4.74 – 4.79 (1H, m), 7.70 (2H, brs), 7.70 (1H, d), 8.06 – 8.11 (2H, m); MS m/z 434 [M+H]+.

Producto intermedio 220:

tert–Butil 5–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoato

tert–Butil éster del ácido 4–amino–5–cloro–2–fluorobenzoico (Producto intermedio 177; 123 mg, 0.5 mmol) fue disuelto en dioxano (7.5 mL). 10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 155 mg, 0.55 mmol), XANTFOS (27 mg, 0.05 mmol) y carbonato de cesio (327 mg, 1.0 mmol) fueron añadidos. El sistema fue purgado con una corriente de nitrógeno durante 15 minutos y luego

tris(dibencilidenoacetona) paladio (II) (28 mg, 0.03 mmol) añadido. El aparato fue evacuado y llenado nuevamente con nitrógeno (x3) y luego calentado a 100 °C durante 3 horas. La mezcla fue enfriada, filtrada y el filtrado absorbido en una columna SCX, la cual fue posteriormente lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron evaporadas y el residuo purificado por cromatografía en columna (2% MeOH/DCM) para proporcionar el compuesto del título como una espuma amarillo pálido (225mg, 92%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.53 – 1.74 (15H, m), 1.92 – 1.95 (2H, m), 2.62 (2H, t), 3.19 (3H, s), 3.65 (2H, t), 4.73 – 4.84 (1H, m), 7.85 (1H, d), 8.15 (1H, s), 8.24 (1H, s), 8.41 (1H, d); MS m/z 490 [M+H]+.

Producto intermedio 221:

3,5–dicloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoico ácido

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 219, utilizando tert–butil 3,5–dicloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoato (Producto intermedio 222; 236 mg, 0.45mmol), como un sólido color hueso (180 mg, 87%).

^{1}H NMR (399.9 MHz, DMSO–d_6 + d_4 AcOH) δ 1.30 – 1.63 (8H, m), 2.55 (2H + DMSO, m), 3.15 (3H, s), 3.51 – 3.54 (2H, m), 4.31 (1H, m), 7.75 (1H, d), 7.97 (1H, s); MS m/z 468 [M+H]+.

Producto intermedio 222:

tert–Butil 3,5–dicloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–2–fluoro–benzoato

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 220, utilizando tert–butil 4–amino–3,5–dicloro–2–fluoro–benzoato (Aislado como un subproducto durante la preparación del Producto intermedio 177; 236 mg, 0.45mmol), como un sólido color hueso (180 mg, 87%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.30 – 1.63 (17H, m), 2.55 (2H + DMSO–d6, m), 3.16 (3H, s), 3.52 – 3.54 (2H, m), 4.25 (1H, m), 7.89 (1H, d), 8.00 (1H, s), 9.18 (1H, s); MS m/z 524 [M+H]+.

Producto intermedio 223:

7–amino–N–(1–metil–4–piperidil)benzo[1,3]dioxol–4–carboxamida

N–(1–metil–4–piperidil)–7–nitro–benzo[1,3]dioxol–4–carboxamida (Producto intermedio 224; 290 mg, 0.94 mmol) fue suspendido en metanol (50 mL) y el sistema purgado con nitrógeno. 10% Pd/C (30 mg) fue añadido y la mezcla agitada bajo una atmósfera de hidrógeno durante 2 horas. El catalizador fue filtrado y el filtrado evaporado para dar el compuesto del título como un sólido blanco (249mg, 96%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.43 – 1.53 (2H, m), 1.78 – 1.82 (2H, m), 1.98 – 2.05 (2H, m), 2.12 (3H, s), 2.67 (2H, d), 3.69 – 3.73 (1H, m), 5.48 (2H, d), 6.06 (2H, s), 6.32 (1H, d), 6.95 (1H, d), 7.11 (1H, d); MS m/z 278 [M+H]+.

Producto intermedio 224:

N–(1–metil–4–piperidil)–7–nitro–benzo[1,3]dioxol–4–carboxamida

4–Amino–1–metilpiperidina (Fluorochem; 325 mg, 2.84 mmol), HATU (1.09 g, 2.84 mmol) y ácido 7–nitrobenzo[1,3]dioxol–4–carboxílico (WO 2003082827; 400 mg, 1.89m mol) fueron agitados en DMF (5 mL) y diisopropiletilamina (0.99 ml, 5.68 mmol) añadido. La mezcla fue agitada durante 2 horas a temperatura ambiente. La mezcla de reacción fue cargada en una columna SCX, la cual fue posteriormente lavada con metanol y eluida con amoniaco en metanol. Las fracciones que contienen el producto fueron concentradas y el sólido suspendido en metanol y filtrado para proporcionar el compuesto del título como un sólido amarillo (295mg, 51%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.50 – 1.60 (2H, m), 1.78 – 1.82 (2H, m), 1.96 – 2.03 (2H, m), 2.17 (3H, s), 2.72 (2H, d), 3.72 – 3.76 (1H, m), 6.42 (2H, s), 7.28 (1H, d), 7.62 (1H, d), 7.94 (1H, d); MS m/z 308 [M+H]+.

Producto intermedio 225:

4–Amino–N–(1–etil–4–piperidil)–3–fluoro–benzamida

Ácido 4–amino–3–fluorobenzoico (2.115 g, 13.6 mmol), 4–amino–1–etil piperidina (Fluorochem; 1.923 g, 15 mmol), HATU (5.7 g, 15 mmol) y DIPEA (7.1 mL, 40.8 mmol) fueron combinados en DMA (60 mL) y la solución amarilla resultante agitada a temperatura ambiente durante 20 minutos. La reacción se dejó todo el fin de semana a temperatura ambiente, los solventes evaporados y el residuo disuelto en metanol (10 mL) y cargados en una columna SCX–2 (50 g) la cual prehumedecida con MeOH (40 mL), purgada con MeOH (4 x 30 ml) y eluida con amoniaco 7N en MeOH (4 x 30 mL). Las fracciones amoniacales que contienen el producto fueron combinadas para proporcionar el compuesto del título como un sólido marrón (0.819 g, 22%).

MS m/z 266 [M+H]+. Tiempo de retención 1.5 minutos.

Producto intermedio 226:

4–(azetidin–1–il)ciclohexan–1–amina

tert–Butil N–[4–(azetidin–1–il)ciclohexil]carbamato (Producto intermedio 227; 260 mg, 1.01 mmol) fue tomado en DCM (3 mL) y TFA (2 mL) y agitada a temperatura ambiente durante 3 horas.

La mezcla de reacción fue vertida directamente en un cartucho SCX–3 (5 g). El cartucho fue lavado completamente con DCM (30 mL), seguido por metanol (30 mL) y luego eluido con amoniaco 2M en metanol (25 mL). Las fracción amoniacales fueron combinadas y evaporadas para proporcionar el compuesto del título como un aceite incoloro (124 mg, 80%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.04 (m, 2H), 1.36 – 1.56 (m, 4H), 1.80 (m, 2H), 1.87 – 2.10 (m, 3H), 2.63 & 2.79 (2 x m, 1H), 3.16 (m, 4H).

Producto intermedio 227:

tert–Butil N–[4–(azetidin–1–il)ciclohexil]carbamato

A una solución agitada de N–4–boc–aminociclohexanona (500 mg, 2.34 mmol) en DCM (7 mL) fue añadido azetidina (220 ul, 3.26 mmol) y la mezcla agitada durante 15 minutos. Acetato de sodio (193 mg, 2.34 mmol) fue añadido, seguido por adición cuidadosa de triacetoxiborohidruro de sodio (746 mg, 3.52 mmol) la mezcla de reacción fue agitada a temperatura ambiente bajo nitrógeno durante 3 horas, diluida con DCM a un volumen total de 25 mL y filtrado. El filtrado fue vertida en y SCX–2 (10 g) cartucho y el cartucho lavado con

metanol (75 mL) luego eluido con amoniaco 2M en metanol (75 mL). La solución amoniacal fue evaporada, para dar un sólido ceroso blanco hueso (200 mg). El cartucho SCX lavado fue resometido a un segundo cartucho SCX–2 (10 g) y el cartucho nuevamente lavado con metanol (75 mL) y eluido con amoniaco 2M/metanol (75 mL). La solución amoniacal fue evaporada a un goma incolora. Los productossólidos fueron combinados y triturados con isohexano. El sólido cristalino resultante fue recogido mediante filtración por succión y secado para proporcionar el compuesto del título como un sólido blanco (104 mg). Un segundo cultivo cristalizó del filtrado. Esto fue nuevamente recogido y secado para dar el compuesto del título como una aguja blanca fina (260 mg).

Rendimiento total (364 mg, 61%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.80 – 0.90 (1H, m), 1.05 – 1.16 (1H, m), 1.21 – 1.30 (1H, m), 1.37 (9H, s), 1.41 – 2.09 (8H, m), 3.01 (4H, q), 3.06 – 3.26 (1H, m), 6.57 – 6.66 (1H, m).

Producto intermedio 228:

4–amino–2–fluoro–5–metoxi–N–(2–pirrolidin–1–iletil)benzamida

ácido 4–amino–2–fluoro–5–metoxibenzoico (Producto intermedio 183; 0.75 g, 4.07 mmol), HATU (1.70 g, 4.48 mmol) y DIPEA (2.1 mL, 12.21 mmol) fueron agitados juntos en DMF (10 mL) durante 25 min. N–(2–aminoetil)pirrolidina (Aldrich; 0.51 g, 4.48 mmol) en DMF (2 mL) fue añadido y la solución agitada a temperatura ambiente durante 2 horas.

El solvente fue evaporado y el residuo disuelto en MeOH y cargado en una columna SCX–2 (20 g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volumenes de columna) y eluida con NH_3 2M/MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma marrón, la cual fue purificada en una columna de sílice eluyendo con 0–10% NH_3 2M/MeOH/DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido marrón pálido (948 mg, 83%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ1.69 (m, 4H), 2.48 (m, 4H), 2.56 (t, 2H), 3.36 (m, 4H), 3.77 (s, 3H), 5.59 (s, 2H), 6.40 (d, 1H), 7.13 (d, 1H), 7.51 (m, 1H); MS m/z 282 [M+H]+.

Producto intermedio 229:

4–Amino–2,5–difluoro–N–[(3R)–1–metilpirrolidin–3–il]benzamida

Ácido 4–amino–2,5–difluoro–benzoico (Rare Chemicals GmbH; 450 mg, 2.6 mmol), (3R)–1–metilpirrolidin–3–amina dihidrocloruro (Producto intermedio 184; 473 mg, 2.73 mmol), HATU (1.08 g2.86 mmol) y DIPEA (2.25 mL, 13 mmol) fueron combinados en DMF (10 mL) y agitados a temperatura ambiente durante 4 horas. El solvente fue evaporado y el residuo disuelto en MeOH y añadido a una columna SCX–2 (20 g), prehumedecida con MeOH (2 volúmenes de columna). La columna fue purgada con MeOH (2 volúmenes de columna) y eluida con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas y el material resultante disuelto en DCM y purificado en una columna de sílice eluyendo con 5% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas hasta una goma amarilla. Dietiléter fue añadido y reevaporado y secado bajo alto vacío para proporcionar el compuesto del título como una goma amarilla, la cual cristalizó lentamente hasta un sólido color crema (550 mg, 83%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.71 (m, 1H), 2.26 – 2.42 (m, 5H), 2.64 (m, 2H), 2.86 (m, 1H), 4.13 (s, 2H), 4.62 (m, 1H), 6.43 (m, 1H), 6.87 (m, 1H), 7.70 (m, 1H); MS m/z 256 [M+H]+.

Producto intermedio 230:

4–Amino–2,5–difluoro–N–(2–pirrolidin–1–iletil)benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 229, en una escala 5.77 mmol utilizando 2–pirrolidin–1–iletanamina (Aldrich; 725 mg, 6.35 mmol), como un sólido beige (648 mg, 42%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.78 (m, 4H), 2.56 (m, 4H), 2.69 (m, 2H), 3.55 (m, 2H), 4.12 (s, 2H), 6.43 (m, 1H), 7.16 (m, 1H), 7.72 (m, 1H); MS m/z 270 [M+H]+.

Producto intermedio 231:

Ácido 2–cloro–4–[(2–ciclopentil–6–metil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–5–metoxi–benzoico

10–cloro–2–ciclopentil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 1; 1 g, 3.56 mmol) y ácido 2–cloro–3–metoxi–4–amino–benzoico (Producto intermedio 223;) fueron suspendidos en agua / EtOH (3:1) mezcla (40 mL). Ácido clorhídrico concentrado (712 µL, 7.12 mmol) fue añadido y la reacción calentada a 80 °C toda la noche. La mezcla de reacción fue enfriada a temperatura ambiente y el sólido resultante filtrado y secado para dar el compuesto del título como un sólido beige (951 mg, 60%).
^{1}H NMR (399.902 MHz, DMSO–d6) δ 1.61 (m, 6H), 1.91 (m, 2H), 2.63 (m, 2H), 3.10 (s, 3H), 3.66 (m, 2H), 3.88 (s, 3H), 4.86 (m, 1H), 7.42 (s, 1H), 8.12 (s, 1H), 8.35 (s, 1H), 8.91 (br s, 1H), 13.10 (br s, 1H); MS m/z 446 [M+H]+.

Producto intermedio 232:

Ácido 2–cloro–3–metoxi–4–Amino–benzoico

Ácido 2–cloro–5–metoxi–4–nitro–benzoico (Producto intermedio 233; 5.87 g, 26.3 mmol) fue disuelto en EtOH (100 mL) y una cantidad catalítica de 5% Pt en carbón añadido bajo una atmósfera inerte. La solución fue desgasificada y luego agitada bajo una atmósfera de hidrógeno a temperatura ambiente durante 6 horas. El catalizador fue filtrado y lavado con EtOH y el filtrado evaporado y el residuo triturado con dietiléter y el sólido filtrado y secado para proporcionar el compuesto del título como un sólido amarillo (4.53 g, 89%).
^{1}H NMR (399.902 MHz, DMSO–d6) δ3.80 (s, 3H), 5.73 (s, 2H), 6.67 (s, 1H), 7.29 (s, 1H), 12.42 (s, 1H); MS m/z 201 [M+H]+.

Producto intermedio 233:

Ácido 2–cloro–5–metoxi–4–nitro–benzoico

1–cloro–4–metoxi–2–metil–5–nitro–benceno (APIN Chemicals; 12.58 g, 62.4 mmol) fue suspendido en agua (600 mL) y calentado hasta 90 °C bajo nitrógeno. Permanganato de potasio (2 eq, 19.74 g, 125 mmol) en agua (500 mL) fue añadido durante un período de 25 minutos y luego la mezcla fue calentada a reflujo durante 2 horas. Una adición posterior de permanganato de potasio (19.74 g, 125 mmol) en agua (500 mL) fue hecha durante 15 minutos con la temperatura de la reacción reducida hasta 91 °C y luego continuó calentando a

reflujo durante 3 horas y luego enfriada a temperatura ambiente y se dejó reposar toda la noche.

La reacción fue recalentada hasta reflujo y adición posterior de permanganato de potasio (9.86 g 62.5 mmol) en agua (200 mL) hecha durante 5 minutos y la reacción calentada a reflujo durante 2 horas durante unas 2 horas adicionanales.

La mezcla de reacción fue enfriada hasta 80 °C y filtrada caliente a través de una almohadilla de celita. El recipiente reactor fue lavado con agua (500 mL) y la torta del filtro de manganeso fue lavada con agua hirviendo (1200 mL). Los lavados acuosos combinados fueron enfriados a temperatura ambiente y cualquier exceso de color de permanganato fue eliminado por adición de una solución de metabisulfito de sodio acuosa. La solución amarilla resultante fue acidificada hasta pH 1 con ácido clorhídrico concentrado acuoso y el volumen reducido de aproximadamente 4000 mL a 3000 mL al vacío. Una capa acuosa fue extraida con EtOAc (2 x 1000 mL) y los extractos orgánicos combinados lavados con salmuera (500 mL), secados sobre $MgSO_4$ y evaporados para proporcionar el compuesto del título como un sólido amarillo. (8.45 g, 58%).

^{1}H NMR (399.902 MHz, DMSO–d6) δ 3.98 (s, 3H), 7.67 (s, 1H), 8.14 (s, 1H), 14.02 (br s, 1H); MS m/z 229 $[M–H]^+$.

Producto intermedio 234:

tert–Butil 4–[(4–amino–3–metoxi–benzoil)amino]piperidina–1–carboxilato

A una solución de ácido 4–amino–3–metoxibenzoico (Aldrich; 2.4 g, 14.36 mmol) en DMF (100 mL) fue añadido 4–amino–1–bocpiperidina (Aldrich; 3.15 g, 15.72 mmol) y DIPEA (7.5 mL, 43.06 mmol). La solución resultante fue cuidadosamente tratada en forma de porciones (2–3 porciones) con HATU (6.88 g, 18.09 mmol) y la mezcla resultante fue agitada, bajo nitrógeno, a temperatura ambiente toda la noche.

El solvente fue eliminado al vacío y el residuo particionado entre una solución de bicarbonato de sodio saturada acuosa (100 mL) y etil acetato (100 mL). La fase orgánica fue separada y lavada con agua (150 mL) y salmuera (150 mL), secada sobre sulfato de magnesio, filtrada y evaporada. El residuo fue purificado por cromatografía flash en un cartucho de sílice eluyendo con un gradiente en aumento de 0–10% metanol en DCM. Las fracciones que contienen el

producto fueron combinadas y evaporadas para proporcionar el compuesto del título como una espuma color durazno (2.88 g, 57%).

1H NMR (400.132 MHz, DMSO) δ 1.35 – 1.47 (11H, m), 1.72 – 1.80 (2H, m), 2.76 – 2.90 (2H, m), 3.81 (3H, s), 3.91 – 4.00 (3H, m), 5.20 (2H, s), 6.61 (1H, d), 7.28 – 7.30 (2H, m), 7.80 (1H, d); MS m/z 348 $[M-H]^+$.

Producto intermedio 235:

4–Amino–N–(1–etil–4–piperidil)–2,5–difluoro–benzamida

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 229, en una escala 5.77 mmol utilizando 4–amino–1–etilpiperidina (Fluorochem; 815 mg, 6.35 mmol), como un sólido naranja (1.23 g, 75%).

^{1}H NMR (399.902 MHz, CDCl3) δ 1.09 (t, 3H), 1.57 (m, 2H), 2.04 (m, 2H), 2.14 (m, 2H), 2.42 (q, 2H), 2.86 (m, 2H), 4.02 (m, 1H), 4.13 (s, 2H), 6.43 (m, 1H), 6.51 (m, 1H), 7.72 (m, 1H); MS m/z 284 $[M+H]^+$.

Producto intermedio 236:

Ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–metoxi–benzoico

10–cloro–2–ciclopentil–4,4–dimetil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–8,10,12–trien–5–ona (Producto intermedio 127; 200 mg, 0.65 mmol) y ácido 4–amino–3metoxibenzoico (Aldrich; 130 mg, 0.78 mmol) fueron tomados en agua /etanol (3:1 v/v; 4 mL). Ácido clorhídrico concentrado (130 ul, 1.30 mmol) fue añadido y la reacción calentada por irradiación de microondas a 120°C durante 30 minutos.

La mezcla de reacción fue sumergida en agua (20 mL) y un sólido precipitado recogido mediante filtración por succión y secado en un horno al vacío, a 55°C durante 90 minutos, para dar un sólido cristalino rosa oscuro (180 mg).

El filtrado fue evaporado hasta secarse para dar un sólido adicional, el cual fue combinado con el primer lote y triturado con un mezcla de MeCN/agua dio un sólido rosa el cual fue nuevamente recogido mediante filtración por succión (160 mg).

El filtrado fue evaporado y combinado con el sólido purificado por cromatografía flash en un cartucho de sílice eluyendo con 0–5% MeOH en DCM para dar el compuesto del título como un sólido color hueso (85 mg, 30%).

^{1}H NMR (400.132 MHz, DMSO–d6)δ1.16 (s, 6H), 1.56 – 1.93 (m, 8H), 3.20 (s, 3H), 3.52 (s, 2H), 3.96 (s, 3H), 5.14 (m, 1H), 7.60 (m, 2H), 8.08 (s, 1H), 8.19 (d, 1H), 9.18 (br s, 1H) OH solamente visible a 12.84 (br s, 1H); MS m/z 440 $[M+H]^+$.

Producto intermedio 237:

4–Pirrolidin–1–ilciclohexan–1–amina

tert–Butil N–(4–pirrolidin–1–ilciclohexil)carbamato (Producto intermedio 238; 222 mg, 0.83 mmol) fue tomado en DCM (1.5 mL) y TFA (1 mL). La mezcla de reacción fue agitada a temperatura ambiente durante 3 horas, vertida directamente en un cartucho SCX–3 (2 g), prehumedecido con DCM. El cartucho fue lavado completamente con DCM (10 mL), seguido por metanol (30 mL) y luego eluido con amoniaco 2M en metanol (25 mL). La evaporación hasta secarse de la solución amoniacal produjo el compuesto del título como un aceite color ámbar (103 mg, 74%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.94 – 1.20 (m, 4H), 1.63 (m, 4H), 1.73 (m, 2H), 1.87 (m, 3H), 2.45 (m, 4H), 3.29 (br m, 1H)

Producto intermedio 238:

tert–Butil N–(4–pirrolidin–1–ilciclohexil)carbamato

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 227, en una escala de 2.34 mmol utilizando pirrolidina (Aldrich; 250 µL, 3.04 mmol), como un sólido blanco (175 mg, 44%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 1.15 (m, 4H), 1.38 (s, 9H), 1.64 (m, 4H), 1.75 (m, 2H), 1.88 (m, 3H), 2.45 (m, 4H), 3.15 (m, 1H), 6.64 (m, 1H).

Producto intermedio 239:

4–Amino–N–(4–dimetilaminociclohexil)–3–metoxi–benzamida

4–Amino–N–(4–dimetilaminociclohexil)–3–metoxi–benzamida (Producto intermedio 240; 500 mg, 1.56 mmol) fue reducida con 10% Pd/C (60 mg) e hidrógeno para proporcionar el compuesto del título (454 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.25 – 1.30 (2H, m), 1.40 – 1.44 (2H, m), 1.71 – 1.74 (1H, m), 1.80 (2H, m), 1.82 (2H, m), 2.19 (6H, d debido a la mezcla racémica), 3.82 (3H, s), 3.65 y 3.85 (0.5H cada uno debido a la mezcla racémica), 5.16 (2H, s), 7.26 (1H, dd), 7.30 (1H, d), 7.71 (1H, t); MS m/z 292 $[M+H]^+$.

Producto intermedio 240:

4–Amino–N–(4–dimetilaminociclohexil)–3–metoxi–benzamida

3–Metoxi–4–nitro–benzoil cloruro (Producto intermedio 189; 1.0 g, 4.64 mmol) fue disuelto en DCM (20 mL) y enfriado en un baño de hielo. DIPEA (970 uL) fue añadido en forma de gotas. 1–Amino–4–dimetilaminociclohexano (ABChem Inc.; 660 mg, 4.64 mmol) fue disuelto en DCM (10 mL) y añadido a la solución de la reacción. La mezcla de reacción fue llevada nuevamente a la temperatura ambiente y agitada durante 2 horas. La mezcla de reacción fue lavada con salmuera y NaOH $_{(ac)}$. La capa orgánica fue extraída filtrando a través de un vaso PTFE y evaporada para proporcionar el compuesto del título como un sólido naranja (1.54 g, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 1.29 – 1.35 (2H, m), 1.45 – 1.48 (1H, m), 1.52 – 1.56 (1H, m), 1.75 (1H, m), 1.85 – 1.87 (2H, d), 1.95 (2H, d), 2.20 (6H, d debido a N–dimetil debe ser singlete pero es doblete debido a los estereoisómeros), 3.71 y 3.91 (dos x 0.5H debido a los estereoisómeros), 3.99 (3H, s), 7.51 (1H, t), 7.60 (1H, d), 7.92 (1H, t), 844 (1H, t); MS m/z 332 $[M+H]^+$.

Producto intermedio 241:

4–Amino–2–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

2–fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]–4–nitro–benzamida (Producto intermedio 242; 500 mg, 1.56 mmol) fue reducido usando 10% Pd/C (50mg) e hidrógeno agitando a temperatura ambiente durante 3 horas. El catalizador fue eliminado por filtración y el filtrado evaporado para proporcionar el compuesto del título (454 mg, 100%).

^{1}H NMR (399.9 MHz, DMSO–d_6) δ 0.90 (2H, d), 1.38 – 1.40 (3H, m), 1.85 – 1.95 (2H, m), 1.99 – 2.05 (1H, m), 2.14 – 2.22 (2H, m), 2.40 (3H, s), 2.96 (2H, d), 4.20 – 4.28 (1H, m), 5.81 – 5.85 (2H, s), 6.28 – 6.32 (1H, d), 6.38 – 6.43 (1H, m), 7.20 – 7.24 (1H, t), 7.38 – 7.41 (1H, t); MS m/z 292 $[M+H]^+$.

Producto intermedio 242:

2–Fluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]–4–nitro–benzamida

2–Fluoro–4–nitro–benzoil cloruro (Producto intermedio 243; 2.40 g, 11.79 mmol) fue disuelto en DCM (20 mL) y enfriado en un baño de hielo. DIPEA (2.46 mL, 14.15 mmol) fue añadido en forma de gotas seguido por endo–9–metil–9–azabiciclo[3,3,1]–nonan–3–amina (Chempacific; 1.82 g, 11.79 mmol) disuelto en DCM (10 mL). La mezcla de reacción se dejó retornar a temperatura ambiente y agitada durante 2 horas y luego lavada con salmuera y $NaOH_{(ac)}$. La capa orgánica fue evaporada para proporcionar el compuesto del título como un sólido naranja (3 g, 79%).

1H NMR (399.9 MHz, DMSO–d_6) δ 0.93 (2H, d), 1.34 – 1.41 (2H, m), 1.46 (1H, t), 1.90 (1H, t), 1.94 (2H, d), 2.21 – 2.29 (2H, m), 2.41 (3H, s), 2.98 – 3.00 (2H, m), 4.23 – 4.34 (1H, m), 7.79 – 7.83 (1H, m), 8.08 – 8.16 (1H, m), 8.18 – 8.24 (1H, m), 8.41 (1H, d); MS m/z 292 $[M+H]^+$.

Producto intermedio 243:

2–Fluoro–4–nitro–benzoil cloruro

Ácido 2–fluoro–4–nitrobenzoico (Fluorochem; 2.5 g, 13.51 mmol) fue suspendido en tolueno (25 mL) y cloruro de tionil (2.96 mL, 40.52 mmol) añadido. La mezcla de reacción fue calentada a reflujo durante 1.5 horas, se dejó enfriar y evaporada para dar el compuesto del título como un líquido amarillo el cual gradualmente se solidificó en reposo (2.74 g, 100%). ^{1}H NMR (399.9 MHz, DMSO–d_6) δ7.90 – 8.10 (3H, m).

Producto intermedio 244:

4–Amino–3–cloro–N–(2,2–dimetil–3–pirrolidin–1–il–propil)benzamida

Una mezcla del ácido 4–amino–3–cloro–benzoico (Fluorochem; 2.49 g, 14.5 mmol) y 2,2–dimetil–3–pirrolidin–1–il–propan–1–amina (Chemstep; 2.49 g, 15.95 mmol) fueron disueltos

en DMF (50 mL), y a la solución fue añadida DIPEA (5.1 mL, 29.0 mmol).La mezcla de reacción fue enfriada con un baño de hielo, y HATU (6.06 g, 15.95 mmol) añadido, en forma de porciones. La mezcla de reacción fue agitada a temperatura ambiente durante 18 horas. El solvente fue evaporado y el residuo particionado entre etil acetato (100 mL), y solución de carbonato de sodio saturada acuosa (3 x 40 mL), lavado con salmuera (3 x 40 mL), secada sobre sulfato de magnesio anhidro, filtrado, y el solvente evaporado para dar el producto crudo como un semisólido aceitoso, el cual fue triturado con dietil éter y filtrado para proporcionar el compuesto del título un sólido cristalino amarillo pálido (850 mg, 19%). Los licores madre a partir de la trituración fueron purificados en una columna de sílice, etil acetato preequilibrado y eluyendo con 10% MeOH–DCM + 1%NH_3. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar el compuesto del título como un aceite amarillo viscoso (1.72 g, 38%).

^{1}H NMR (400.1MHz , $CDCl_3$) δ 1.00 (6H,s), 1.82–1.88 (4H,m), 2.56 (2H,s), 2.65–2.72 (4H,bs), 3.33–3.36 (2H,d), 4.30 (2H,s), 6.73–6.77 (1H,d), 7.55–7.60 (1H,dd), 7.65 (1H,s), 9.38 (1H,s). MS m/z 310 $[M+H]^+$.

Producto intermedio 245:

4–Amino–N–[(3R)–1–etilpirrolidin–3–il]–3–metoxi–benzamida

A una solución de ácido 4–amino–3–metoxibenzoico (Aldrich; 424 mg , 2.54 mmol) y (3R)–1–etilpirrolidin–3–amina (Producto intermedio 246; 312 mg, 2.73 mmol) en DMF (10 mL) fue añadido DIPEA (1.4 ml, 8.04 mmol). La solución resultante fue tratada con HATU (1.21 g, 3.18 mmol) y agitada, bajo nitrógeno, a temperatura ambiente toda la noche.

La mezcla de reacción fue evaporada a un aceite marrón viscoso, el cual fue particionado entre DCM (20 mL) y la solución de bicarbonato de sodio saturada acuosa (20 mL). La fase orgánica fue separada y la fase acuosa reextraída con DCM (20 mL). Las soluciones orgánicas combinadas fueron evaporadas hasta secarse y el residuo purificado en una columna de sílice, eluyendo con un gradiente de 0–10% metanol en DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas. El material resultante fue disuelto en metanol y cargado en un cartucho SCX–2 (10 g). El cartucho fue lavado con metanol (75 mL) y luego eluido con amoniaco 2M/metanol. La solución amoniacal fue evaporada para proporcionar el compuesto del título como una goma naranja (210 mg, 31%).

Producto intermedio 246:

(3R)–1–etilpirrolidin–3–amina

tert–Butil N–[(3R)–1–etilpirrolidin–3–il]carbamato (Producto intermedio 247; 945 mg, 4.41 mmol) fue tomado en DCM (8 mL) y TFA (4 mL) y agitado a temperatura ambiente durante 3 horas.

La mezcla de reacción fue cargada en un cartucho SCX–3 (5 g), prehumedecido con DCM. El cartucho fue lavado con DCM (30 mL), seguido por metanol (30 mL), luego eluido con amoniaco 2M en metanol (30 mL). La solución amoniacal fue evaporada hasta secarse para proporcionar el compuesto del título como un aceite ámbar (152 mg).

El prelavado del cartucho SCX, el cual fue altamente coloreado, fue vertido en un cartucho SCX–3 (20 g) y el cartucho purgado con metanol (150 mL) y luego eluido con amoniaco 2M en metanol (100 mL). La evaporación de la fracción amoniacal proporcionó un lote adicional del compuesto del título como un aceite ámbar (165 mg).

Rendimiento combinado (317 mg, 63%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.99 (3H, t), 1.28 – 1.36 (1H, m), 1.93 – 2.02 (1H, m), 2.08 (1H, dd), 2.32 – 2.42 (3H, m), 2.46 – 2.49 (1H, m), 2.60 – 2.65 (1H, m), 3.26 – 3.33 (1H, m).

Producto intermedio 247:

tert–Butil N–[(3R)–1–etilpirrolidin–3–il]carbamato

A una solución de (3R)–(+)–3–(t–butioxicarbonilamino)pirrolidina (Fluka; 1.54 g, 8.27 mmol) en DMF (25 mL) fue añadida trietilamina (2.3 mL, 16.50 mmol) y etil bromuro (Aldrich; 1 mL, 13.40 mmol). La mezcla de reacción fue calentada por irradiación de microondas a 100 °C en durante 1 hora.

La mezcla de reacción fue vertida en agua (400 mL) y la mezcla extraida con dietil éter (2 x 300 mL). Los extractos orgánicos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio, filtrados y evaporados hasta secarse para proporcionar el compuesto del título como un aceite color ámbar (825 mg, 47%).

^{1}H NMR (400.132 MHz, DMSO–d6) δ 0.99 (t, 3H), 1.38 (s, 9H), 1.53 (m, 1H), 1.99 (m, 1H), 2.20 (m, 1H), 2.32 – 2.48 (m, 4H), 2.67 (m, 1H), 3.88 (m, 1H), 6.87 (m, 1H).

Producto intermedio 248:

4–Amino–N–(4–dimetilaminociclohexil)–2–fluoro–5–metoxi–benzamida

Ácido 4–amino–2–fluoro–5–metoxi–benzoico (Producto intermedio 183; 0.75 g, 4.07 mmol), HATU (1.70 g, 4.48 mmol) y DIPEA (2.1 ml, 12.21 mmol) fueron agitados juntos en DMF (10 mL) durante 10 minutos a temperatura ambiente. 1–Amino–4–dimetilaminociclohexano (ABChem Inc.; 0.637 g, 4.48 mmol) en DMF (2 mL) fue añadido y la mezcla de reacción agitada a temperatura ambiente toda la noche.

El solvente fue evaporado y el residuo disuelto en MeOH y cargado en una coumna SCX–2 (20 g) prehumedecida con MeOH. La columna fue lavada con MeOH (2 volumenes de columna) y eluida con NH_3 2M /MeOH. Las fracciones que contienen el producto fueron combinadas y evaporadas para dar una goma marrón la cual fue purificada en una columna de sílice eluyendo con 0–10% NH_3 2M/MeOH/DCM para dar una isoforma no asignada simple del compuesto del título como una goma marrón pálido (250 mg, 20%).

^{1}H NMR (400.132 MHz, DMSO–d_6) δ1.63 (m, 8H), 2.08 (m, 1H), 2.18 (s, 6H), 3.77 (s, 3H), 3.91 (m, 1H), 5.54 (bs, 2H), 6.40 (d, 1H), 7.06 (d, 1H), 7.24 (m, 1H); MS m/z 310 $[M+H]^+$.

Una segunda isoforma no asignada fue también aislada y designada Producto intermedio 249 (394 mg, 31%).

Producto intermedio 249:

4–amino–N–(4–dimetilaminociclohexil)–2–fluoro–5–metoxi–benzamida

El compuesto del título fue obtenido como una isoforma no asignada simple descrita anteriormente en la preparación del Producto intermedio 248 como un sólido blanco (394 mg, 31%).

^{1}H NMR (400.132 MHz, DMSO–d_6)δ1.28 (m, 4H), 1.85 (m, 4H), 2.11 (m, 1H), 2.18 (s, 6H), 3.66 (m, 1H), 3.77 (s, 3H), 5.53 (bs, 2H), 6.38 (d, 1H), 7.04 (d, 1H), 7.26 (m, 1H); MS m/z 310 $[M+H]^+$.

Producto intermedio 250:

10–Cloro–2–ciclopentil–4,4–dietil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución agitada de 10–cloro–2–ciclopentil–4,4–dietil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 251; 2.5 g, 7.76 mmol) en DMA (50 mL) bajo nitrógeno fue añadido metil yoduro (0.627 mL, 10.0 mmol). La mezcla fue enfriada en un baño de hielo/agua hasta 3°C, e hidruro de sodio (60% dispersión en aceite mineral; 0.567 g, 11.8 mmol) añadido en una porción. La mezcla de reacción fue agitada en el baño de hielo/agua durante 1 hora antes de calentar a temperatura ambiente y la reacción agitada durante 4 horas. La mezcla de reacción fue evaporada hasta secarse para proporcionar un sólido negro, el cual fue apagado con solución de NH_4Cl saturada acuosa (50 mL), extraído con DCM (3 X 100 mL), secado y el solvente eliminado al vacío para proporcionar un sólido negro el cual fue purificado en una columna de sílice eluyendo con DCM. El sólido obtenido fue añadido a dietil éter y sonicado y el material resultante filtrado y secado para proporcionar el compuesto del título como un sólido color hueso (2.1 g, 80%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.83 (t, 6H), 1.77 – 1.48 (m, 10H), 1.99 – 1.91 (m, 2H), 3.27 (s, 3H), 3.43 (s, 2H), 5.34 (quinteto, 1H), 7.82 (s, 1H); MS m/z 337 $[M+H]^+$.

Producto intermedio 251:

10–Cloro–2–ciclopentil–4,4–dietil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

A una solución de metil 2–[(ciclopentilamino)metil]–2–etil–butanoato (Producto intermedio 252; 7.1 g, 31.3 mmol) en acetona (150 mL) fue añadido carbonato de potasio (5.3 g, 38.0 mmol) seguido por 2,4–dicloro–5–nitropirimidina (Aldrich; 6.1 g, 31.3 mmol). La mezcla negra fue agitada a temperatura ambiente durante 18 horas. La reacción fue filtrada y el solvente eliminado al vacío para proporcionar una goma negra, la cual fue disuelto en ácido acético (175 mL) y hierro (7.0 g, 125 mmol) añadido y la reacción calentada a 80 °C toda la noche. La solución resultante fue filtrada y el solvente eliminado al vacío, el sólido negro/goma fue apagado con agua (75 mL) y a esto fue añadido carbonato de sodio hasta hacerse básica, la emulsión negra resultante fue filtrada a través de una almohadilla de celita. La mezcla obtenida fue extraída con DCM (3 X 150 mL), secada y el solvente eliminado al vacío para proporcionar un sólido negro. Esto fue pasado a través de una columna de elusión unida (50 g) eluyendo con 0–1% MeOH en DCM para proporcionar un sólido marrón, el cual

fue triturado con dietil éter para proporcionar el compuesto del título como un sólido blanco (3.05 g, 30%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.90 (t, 6H), 1.57 – 1.48 (m, 2H), 1.81 – 1.61 (m, 6H), 1.98 – 1.91 (m, 2H), 3.36 (s, 2H), 5.31 (quinteto, 1H), 7.80 (s, 1H), 8.40 (s, 1H); MS m/z 323 $[M+H]^+$.

Producto intermedio 252:

Metil 2–[(ciclopentilamino)metil]–2–etil–butanoato

El compuesto del título fue preparado por un método análogo a la preparación del Producto intermedio 200, en una escala de 50 mmol utilizando Ciclopetanona (Aldrich; 6.33 g, 75 mmol), y destilación a 50 °C y presión de 0.53 mbar, como un aceite claro (7.5 g, 65%).

^{1}H NMR (400.132 MHz, CDCl3) δ 0.79 (t, 6H), 1.32 – 1.24 (m, 2H), 1.53 – 1.46 (m, 2H), 1.68 – 1.57 (m, 6H), 1.83 – 1.72 (m, 2H), 2.67 (s, 2H), 2.99 (quinteto, 1H), 3.66 (s, 3H).

Producto intermedio 253:

Ácido 4–[(2–ciclopentil–4,4,6–trimetil–5–oxo–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–10–il)amino]–3–cloro–benzoico

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 130; 496 mg, 1.62 mmol) y ácido 4–amino–3–clorobenzoico (Fluorochem; 278 mg, 1.62 mmol) fueron tomados en agua /etanol (3:1 v/v; 12 mL). Ácido clorhídrico concentrado (330 uL, 3.30 mmol) fue añadido y la reacción calentada a reflujo toda la noche.

La mezcla de reacción fue enfriada y luego vertida en $NaOH_{(ac)}$ 1M (75 mL), y DCM (50 mL) añadido. La fase acuosa fue separada y lavada con DCM (50 mL) luego acidificada hasta que se formó un precipitado (~pH 2–3) el cual fue recogido mediante filtración por succión y secado, bajo vacío, a 70°C, durante 2 horas para proporcionar un sólido rosa pálido. El material fue tomado en 10% MeOH en DCM (10 mL) y resultó una suspensión fina. La mezcla fue filtrada y el sólido recogido secado para proporcionar el compuesto del título como un sólido rosa, (58 mg, 8%).

MS m/z 442 $[M+H]^+$. Tiempo de retención 1.26 minutos

Producto intermedio 254:

4–Amino–2–fluoro–5–metoxi–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida

Ácido 4–amino–2–fluoro–5–metoxi–benzoico (Producto intermedio 183; 500 mg, 2.70 mmol), [1–(pirrolidin–1–ilmetil)ciclopropil]metanamina (Producto intermedio 33; 417 mg, 2.70 mmol), HATU (1.545 g, 4.05 mmol) y DIPEA (1.415 mL, 8.10 mmol) fueron disueltos en DMF (8 mL) y se dejó agitar durante 3 horas a temperatura ambiente. La mezcla de reacción fue cargada en una columna SCX–3 prelavada con metanol. La columna fue lavada con metanol eluido con 2% metanol/amoniaco 7N. Las fracciones que contienen el producto fueron combinadas y evaporadas y el residuo purificado en una columna de sílice (elusión en gradiente 5–12% MeOH amoniaco/DCM) para proporcionar el compuesto del título como un sólido marrón naranja (200 mg, 23%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 0.29 (2H, amplio s), 0.50 (2H, amplio s), 1.70 (4H, amplio s), 2.45 (4H, s), 2.50 (2H, s), 3.30 (2H, d), 3.75 (3H, s), 5.60 (2H, s), 6.40 (1H, d), 7.15 (1H, d), 8.05 (1H, t); MS m/z 322 $[M+H]^+$.

Producto intermedio 255:

2'–cloro–9'–ciclopentil–5'–metil–8',9'–dihidroespiro[ciclohexano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona

2'–cloro–9'–ciclopentil–8',9'–dihidroespiro[ciclohexano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 256; 300 mg, 0.94 mmol) fue disuelto en N,N–dimetilacetamida (10 mL) y metil yoduro (65 mL, 1.03 mmol) añadido seguido por hidruro de sodio (41 mg de una dispersión en aceite mineral al 60%, 1.00 mmol). La mezcla de reacción fue agitada durante 30 minutos. Una gota de agua fue añadida y luego la mezcla de reacción fue diluida con agua y extraída con etil acetato (x2). Los extractos orgánicos combinados fueron secados ($MgSO_4$) y concentrados y el residuo purificado por cromatografía en columna (1% MeOH/DCM) para dar un sólido blanco pegajoso (Nota 4) que fue suspendido en dietil éter y filtrado para proporcionar el compuesto del título como un sólido cristalino blanco (242 mg, 77%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.30 – 1.37 (2H, m), 1.51 – 1.62 (8H, m), 1.68 – 1.74 (2H, m), 1.84 – 1.91 (2H, m), 1.96 – 2.04 (2H, m), 3.21 (3H, s), 3.47 (2H, s), 4.88 – 4.96 (1H, m), 8.09 (1H, s); MS m/z 335 $[M+H]^+$.

Producto intermedio 256:

2'–Cloro–9'–ciclopentil–8',9'–dihidroespiro[ciclohexano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona

Metil 1–(aminometil)ciclopentano–1–carboxilato (Producto intermedio 257; 940 mg, 2.46 mmol) fue disuelto en ácido acético (40 mL) y la mezcla calentada hasta 70 °C. Polvo de hierro (412 mg, 7.37 mmol) fue añadido y la mezcla calentada durante 4 horas, filtrada mientras aún estaba caliente y concentrada. El residuo fue suspendido entre DCM y solución de hidrógeno carbonato de sodio saturada acuosa y la mezcla fue filtrada. Las capas fueron luego separadas y la capa orgánica secada ($MgSO_4$) y concentrada para dar un aceite verde viscoso. Además de metanol un sólido blanco se formó el cual fue filtrado para proporcionar el compuesto del título (300mg, 38%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.45 – 1.63 (10H, m), 1.68 – 1.75 (2H, m), 1.79 – 1.86 (2H, m), 1.96 – 2.01 (2H, m), 3.42 (2H, s), 5.06 – 5.15 (1H, m), 7.87 (1H, s), 9.70 (1H, s); MS m/z 321 $[M+H]^+$.

Producto intermedio 257:

Metil 1–(aminometil)ciclopentano–1–carboxilato

Metil 1–[(ciclopentilamino)metil]ciclopentano–1–carboxilato (Producto intermedio 258; 1.60 g, 7.10 mmol), 2,4–dicloro–5–nitropirimidina (Aldrich; 1.66 g, 8.52 mmol) y trietilamina (1.2 mL, 8.52 mmol) fueron agitados en acetonitrilo (50 mL) durante 4 horas. La mezcla de reacción fue evaporada y el residuo disuelto en DCM, lavado con agua, secado ($MgSO_4$) y evaporado. El residuo fue purificado en una columna de sílice eluyendo con 1% metanol/DCM para proporcionar el compuesto del título como un aceite amarillo que cristalizó en reposo (945 mg, 35%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.43 – 1.70 (12H, m), 1.80 – 1.87 (2H, m), 1.97 – 2.01 (2H, m), 3.46 – 3.55 (1H, m), 3.58 (3H, s), 3.77 (2H, s), 8.90 (1H, s); MS m/z 383 $[M+H]^+$.

Producto intermedio 258:

Metil 1–[(ciclopentilamino)metil]ciclopentano–1–carboxilato

Metil 1–(aminometil)ciclopentano–1–carboxilato (Producto intermedio 259; 1.5 g, 9.54 mmol) y ciclopentanona (1.0 mL, 11.45 mmol) fueron agitados en DCM (40 mL). Acetato de sodio (940 mg, 11.45 mmol) y triacetoxiborohidruro de sodio (3.04 g, 14.31 mmol) fueron añadidos. La mezcla fue agitada a temperatura ambiente durante 48 horas. La mezcla de reacción fue filtrada y el filtrado concentrado. El residuo fue disuelto en metanol y absorbido en una columna SCX, el cual fue luego lavado con metanol y eluido con amoniaco en metanol. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un aceite incoloro (1.64g, 81%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.21 – 1.34 (2H, m), 1.39 – 1.70 (13H, m), 1.88 – 1.94 (2H, m), 2.63 (2H, s), 2.90 – 2.96 (1H, m), 3.59 (3H, s).

Producto intermedio 259:

Metil 1–(aminometil)ciclopentano–1–carboxilato

17328/13 Reacción llevada en RSL (P Walker – No.009/07, 09/01/2007)

Metil 1–cianociclopentano–1–carboxilato (Producto intermedio 260; 6 g, 39.2 mmol) en ácido acético (70 mL) fue hidrógenado usando Pt O_2 (600 mg) como un catalizador a temperatura ambiente bajo presión de 4 bar durante 4 horas. La mezcla de reacción fue filtrada y concentrada. El residuo fue tomado en metanol y absorbido en una columna SCX (3x 50g), la cual fue luego lavada con metanol y eluida con amoniaco en metanol. La concentración de las fracciones que contienen el producto proporcionaron el compuesto del título como un líquido amarillo pálido (6.18g, 100%).

^{1}H NMR (399.9 MHz, DMSO–d6) δ 1.38 (2H, s), 1.52 – 1.58 (6H, m), 1.87 – 1.93 (2H, m), 2.67 (2H, s), 3.61 (3H, s).

Producto intermedio 260:

Metil 1–cianociclopentano–1–carboxilato

Metil cianoacetato (Fluka ; 25 g, 252.3 mmol) y carbonato de potasio (83.7 g, 605.5 mmol) fueron agitados en DMF (250 mL). 1,4–Dibromobutano (Aldrich; 30.1 mL, 252.3 mmol) fue lentamente añadido. Esto provocó una exoterma que continuó después que la adición fue completada y un baño de agua fue usado para prevenir que la temperatura exceda 90 °C. La mezcla lentamente enfriada a temperatura ambiente y fue agitada toda la noche y luego

calentado a 75°C durante 3 horas. La mezcla de reacción fue enfriada y filtrado y el filtrado concentrado a alrededor de la mitad del volumen. La mezcla fue diluida con agua (250 mL) y extraida con dietil éter (2 x 65 mL). Los extractos orgánicos combinados fueron lavados con ácido clohídrico 1N, salmuera, secados ($MgSO_4$) y evaporados para proporcionar el compuesto del título como un líquido amarillo pálido (31.73 g, 82%).

^{1}H NMR (399.9 MHz, CDCl3) δ 1.86 – 1.91 (4H, m), 2.25 – 2.29 (4H, m), 3.83 (3H, s).

Producto intermedio 261:

10–Cloro–6–metil–2–(2–oxociclopentil)–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

10–Cloro–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 100; 256 mg, 1.20 mmol) fue tomado en DMA (10 mL) y enfriado en un baño de hielo, con agitación, bajo nitrógeno. Hidruro de sodio (60% en aceite mineral; 232 mg, 5.8 mmol) fue cuidadosamente añadido en forma de porciones y la mezcla de reacción se dejó agitar durante 5 minutos, antes de eliminar del baño frío y agitar durante unos 30 minutos adicionales. Una solución de 2–clorociclopentanona (Aldrich; 600 uL, 6.00 mmol) en DMA (5 mL) fue luego añadida. La mezcla de reacción fue calentada a 100 °C y agitada durante 3.5 horas y luego se dejó enfriar, antes de la adición de la solución de cloruro de amonio saturada acuosa (1 mL). La mezcla fue particionada entre DCM (40 mL) y agua (40 mL). Las fases fueron separadas y la fase acuosa reextraída con DCM (40 mL). Los extractos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio, filtrados y evaporados. El residuo fue purificado en una columna de sílice eluyendo con etil acetato. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como una goma marrón pegajosa (211 mg, 60%).

MS m/z 295 $[M+H]^+$.

Producto intermedio 262:

4–Bromo–2–cloro–5–fluoro–N–(1–metil–4–piperidil)benzamida

Ácido 4–bromo–2–cloro–5–fluoro–benzoico (Apollo Scientific; 5.0 g, 19.8 mmol) fue añadido a DMF (250 mL), a esto fue añadido HBTU (9.8 g, 25.7 mmol), N–metil–4–

aminopiperidina (Fluorochem; 2.5 g, 21.8 mmol) y DIPEA (7.0 mL, 39.5 mmol). La reacción fue agitada toda la noche, evaporada hasta secarse, apagada con NaOH 2.0 N (100 mL), extraída con DCM (3 x 100 mL), secada y el solvente eliminado al vacío. El residuo fue disuelto en acetonitrilo caliente, se dejó enfriar filtrado, y el filtrado pasado a través de una columna SCX y el residuo, después de la evaporación de las fracciones que contienen el producto, recristalizado a partir de acetonitrilo caliente para proporcionar el compuesto del título como un sólido blanco (5.0 g, 82%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.64 – 1.55 (m, 2H), 2.07 – 2.03 (m, 2H), 2.19 – 2.14 (m, 2H), 2.29 (s, 3H), 2.79 – 2.76 (m, 2H), 4.04 – 3.95 (m, 1H), 6.13 (brd, 1H), 7.48 (d, 1H), 7.62 (d, 1H); MS m/z 350 $[M+H]^+$.

Producto intermedio 263:

10–Amino–2–ciclohexil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

10–Amino–2–ciclohexil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 264; 1.0 g, 3.83 mmol) fue disuelto en DMF (65 ml), a esto fue añadido hidruro de sodio (60% dispersión en aceite mineral; 0.37 g, 7.66 mmol) en una porción. La reacción fue agitada bajo nitrógeno durante 30 minutos antes de ser enfriada a 0 °C. Metil yoduro (0.238 mL, 3.83 mmol) en DMF (10 mL) fue lentamente añadido a la reacción y la reacción agitada a 0 °C durante 2 horas. La reacción fue apagada con MeOH y el solvente eliminado al vacío. La lechada resultante fue apagada con solución de NH_4Cl saturada acuosa (50 mL), extraída con DCM (3 x 50 mL), secada y el solvente evaporado para proporcionar una goma amarilla la cual fue purificada en una columna de sílice eluyendo con 0–5% MeOH en DCM. Con la evaporación de las fracciones que contienen el producto el residuo fue disuelto en una pequeña cantidad de DCM, a esto fue añadido dietil éter (50 mL), y la solución lentamente evaporada hasta que se formó un precipitado. La solución fue luego sonicada y el precipitado filtrado y secado para proporcionar el compuesto del título como un sólido blanco. (0.55g, 52%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.18 – 1.07 (m, 1H), 1.52 – 1.34 (m, 4H), 1.74 – 1.68 (m, 1H), 1.85 – 1.80 (m, 4H), 2.63 – 2.61 (m, 2H), 3.24 (s, 3H), 3.64 – 3.61 (m, 2H), 4.41 – 4.35 (m, 1H), 4.66 (brs, 2H), 7.77 (s, 1H); MS m/z 276 $[M+H]^+$.

Producto intermedio 264:

10–Amino–2–ciclohexil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

2,4–Dicloro–5–nitropirimidina (Aldrich; 10 g, 0.052 mol) fue disuelto en THF (250 mL). A esto fue añadido DIPEA (11 mL, 0.062 mol) y la reacción enfriada hasta 0 °C. Metil 3–(ciclohexilamino)propanoato (9.5 g, 0.052 mol) en THF (30 mL) fue lentamente añadido. El baño frío fue eliminado y la reacción fue agitada a temperatura ambiente durante 1 hora. A la mezcla de reacción fue añadido $NH_4OH_{(ac)}$ saturado (100 mL), y la reacción calentada a 55 °C durante 4 horas usando un condensador de hielo seco. La mezcla de reacción fue extraída con DCM (3 x 100 ml), y los extractos orgánicos combinados secados y evaporados. El residuo fue disuelto en metanol (200 mL). Formato de amonio (33 g, 0.52 mol) y 10% paladio (1.5 g) fueron añadidos. La reacción fue calentada a reflujo durante 5 horas, filtrada y el metanol evaporado para proporcionar un sólido naranja oscuro, el cual fue apagado con $NaOH_{(ac)}$ 2.0 N (100 mL), extraído con DCM (3 x 150 mL), y los extractos combinados secados y evaporados para proporcionar un sólido naranja. Acetonitrilo caliente fue añadido, esto fue agitado y luego sonicado para dar un precipitado que fue filtrado y secado para proporcionar el compuesto del título como un sólido amarillo (7.5 g, 55%).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.18 – 1.05 (m, 1H), 1.48 – 1.37 (m, 4H), 1.84 – 1.68 (m, 5H), 2.68 – 2.66 (m, 2H), 3.62 – 3.59 (m, 2H), 4.74 – 4.65 (m, 1H), 5.34 (brs, 2H), 7.59 (s, 1H), 9.57 (s, 1H); MS m/z 262 $[M+H]^+$.

Producto intermedio 265:

Metil 3–(ciclohexilamino)propanoato

Ciclohexilamina (Aldrich; 17 g, 0.174 mol) fue disuelto en THF (300 mL). A esto fue añadido metil acrilato (Aldrich; 15 g, 0.174 mol) en una porción. La mezcla de reacción fue agitada todo el fin de semana. El solvente fue evaporado con cuidado debido a la volatilidad del producto y el residuo destilado a 72 °C a 0.30 mbar para proporcionar el compuesto del título como un aceite claro (23.7 g, 74%).

^{1}H NMR (400.132 MHz, CDCl3) δ 1.31 – 1.01 (m, 6H), 1.63 – 1.57 (m, 1H), 1.75 – 1.70 (m, 2H), 1.89 – 1.85 (m, 2H), 2.46 – 2.39 (m, 1H), 2.50 (t, 2H), 2.90 (t, 2H), 3.68 (s, 3H).

Producto intermedio 266:

10–Cloro–2–ciclohexil–6–metil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

10–Cloro–2–ciclohexil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona (Producto intermedio 267; 5.87 g, 20.91 mmol) fue suspendido en DMA (450 mL) bajo nitrógeno. Metil yoduro (3.26 g, 23 mmol) fue añadido y la suspensión enfriada hasta 5 °C en un baño de hielo–agua. Hidruro de sodio (60% dispersión en aceite mineral; 920 mg, 23 mmol) fue añadido en una porción simple y la mezcla resultante agitada en el baño de hielo–agua durante 30 minutos se dejó calentar a temperatura ambiente y fue agitada durante 16 horas. La mezcla de reacción fue apagada con solución de cloruro de amonio saturada acuosa (10 mL) y el solvente evaporado. El residuo fue particionado entre DCM (200 mL) y agua (300 mL) y la fase acuosa reextraída con DCM (100 mL). Las fases orgánicas combinadas fueron secadas ($MgSO_4$) y evaporadas. El residuo fue tomado en DCM y purificado en una columna de sílice eluyendo con un gradiente de 10 – 50% EtOAc / isohexano durante 10 volúmenes de columnas. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como una sólido color crema (5.02 g, 81%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.13 (m, 1H), 1.47 (m, 4H), 1.72 (m, 1H), 1.85 (m, 4H), 2:66 (m, 2H), 3.28 (s, 3H), 3.69 (m, 2H), 4.47 (m, 1H), 7.93 (s, 1H); MS m/z 295 $[M+H]^+$.

Producto intermedio 267:

10–Cloro–2–ciclohexil–2,6,9,11–tetrazabiciclo[5.4.0]undeca–7,9,11–trien–5–ona

Metil 3–[(2–cloro–5–nitro–pirimidin–4–il)–ciclohexil–amino]propanoato (Producto intermedio 238; 19.03 g, 55.52 mmol) fue disuelto en ácido acético (440 mL) y calentado hasta 70 °C bajo una atmósfera de nitrógeno. Polvo de hierro (8.37 g, 150 mmol) fue añadido cautelosamente, dando una exoterma lenta hasta 82 °C, y la mezcla agitada a 70 °C durante 2 horas. La mezcla de reacción fue enfriada hasta aproximadamente 60 °C y filtrada a través de una almohadilla de celita. La celita fue lavada completamente con DCM (500 mL) y el filtrado evaporado y el residuo azeotropizado con tolueno. El material resultante fue disuelto en DCM y diluido con EtOAc para dar un precipitado el cual fue filtrado. El filtrado fue añadido a una almohadilla muy corta de sílice y eluido con EtOAc y el eluente evaporado para dar un sólido naranja, el cual fue disuelto en DCM (500 mL) y lavado con solución de bicarbonato de sodio saturada acuosa. (300 mL). La fase orgánica contenía algún material insoluble el cual fue

filtrado para dar un sólido color crema. El filtrado fue evaporado hasta secarse y la goma marrón oscuro resultante triturada con DCM (20 mL) y filtrada para dar un sólido color crema. Los dos sólidos fueron combinados y lavados con una pequeña cantidad de DCM luego secados bajo alto vacío para proporcionar el compuesto del título como una sólido color crema (5.87 g, 38%).

^{1}H NMR (399.902 MHz, DMSO–d6) δ 1.13 (m, 1H), 1.34 (m, 2H), 1.52 (m, 2H), 1.66 (m, 3H), 1.80 (m, 2H), 2.66 (m, 2H), 3.60 (m, 2H), 4.53 (m, 1H), 7.84 (s, 1H), 9.68 (s, 1H); MS m/z 281 $[M+H]^+$.

Producto intermedio 268:

Metil 3–[(2–cloro–5–nitro–pirimidin–4–il)–ciclohexil–amino]propanoato

A metil 3–(ciclohexilamino)propanoato (Producto intermedio 265; 15 g, 80.96 mmol) en acetona (300 mL) a temperatura ambiente fue añadido carbonato de potasio en polvo (16.8 g, 121 mmol). 2,4–Dicloro–5–nitropirimidina (Frontier Scientific; 17.27 g, 89.06 mmol) en acetona (100 mL) fue añadida durante 10 minutos y la mezcla amarilla resultante agitada a temperatura ambiente durante 16 horas. El solvente fue evaporado y el residuo particionado entre EtOAc (500 mL) y agua (500 mL). La fase acuosa fue reextraída con EtOAc (2 x 200 mL). Las soluciones orgánicas combinadas fueron evaporadas hasta aprox. medio volumen, lavadas con salmuera (200 mL) y evaporadas. El residuo fue tomado en DCM y purificado en una columna de sílice, eluyendo con 10% EtOAc / isohexano. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como un sólido amarillo (19.03 g, 62%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 1.27 (m, 2H), 1.49 – 1.68 (m, 4H), 1.85 (m, 4H), 2.70 (m, 2H), 3.20 (m, 1H), 3.71 (s, 3H), 3.82 (m, 2H), 8.63 (s, 1H); MS m/z 343 $[M+H]^+$.

Producto intermedio 269:

4–Amino–2,5–difluoro–N–[[1–(pirrolidin–1–ilmetil)ciclopropil]metil]benzamida

Ácido 4–amino–2,5–difluoro–benzoico (Rare Chemicals GmbH; 700 mg, 4.04 mmol), [1–(pirrolidin–1–ilmetil)ciclopropil]metanamina (Producto intermedio 33; 655 mg, 4.25 mmol), HATU (1.69 g, 4.44 mmol) y DIPEA (2.1 mL, 12.12 mmol) fueron combinados en DMF (10 mL) y agitados a temperatura ambiente durante 2 horas. La mezcla de reacción dividida en dos

porciones y cada una cargada en una columna SCX–2 (20 g) prehumedecida con MeOH (2 volúmenes de columna), purgada con MeOH (2 volúmenes de columna) y eluida con amoniaco 2M en MeOH. Las fracciones que contienen el producto fueron evaporadas y el residuo tomado en DCM y purificado en una columna de sílice eluyendo con un gradiente de amoniaco 0 – 5% 2M en MeOH / DCM luego 5% amoniaco 2M en MeOH / DCM. Las fracciones que contienen el producto fueron combinadas y evaporadas para proporcionar el compuesto del título como una goma naranja la cual se solidificó en reposo hasta un sólido naranja (472 mg, 38%).

^{1}H NMR (399.902 MHz, $CDCl_3$) δ 0.37 (m, 2H), 0.55 (m, 2H), 1.75 (m, 4H), 2.50 (m, 6H), 3.42 (m, 2H), 4.08 (s, 2H), 6.43 (m, 1H), 7.70 (m, 1H), 8.53 (m, 1H); MS m/z 310 $[M+H]^+$.

Producto intermedio 270:

2'–Cloro–9'–ciclohexil–5'–metil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona

A una solución agitada de 2'–cloro–9'–ciclohexil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona (Producto intermedio 271; 849 mg, 2.767 mmol) en DMA (60 mL) bajo nitrógeno fue añadido metil yoduro (190 µL, 3.044 mmol). La mezcla fue enfriada en un baño de hielo/agua e hidruro de sodio (60% dispersión en aceite mineral; 122 mg, 3.044 mmol) añadido en una porción. La mezcla de reacción fue agitada en el baño de hielo/agua durante 1 hora, el baño frío eliminado y se dejó calentar a temperatura ambiente. Depués de 1.5 horas el solvente fue evaporado y el residuo tratado con un exceso de agua. Esto proporcionó un sólido, el cual fue filtrado y lavado bien con agua y luego secado por desecación bajo alto vacío sobre P_2O_5 toda la noche. Para proporcionar el compuesto del título como un sólido color hueso (887 mg, 100%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.57 – 0.60 (2H, m), 0.97 – 1.04 (1H, m), 1.05 – 1.08 (2H, m), 1.18 – 1.28 (2H, m), 1.34 – 1.44 (2H, m), 1.60 – 1.67 (1H, m), 1.71 – 1.78 (4H, m), 3.19 (3H, s), 3.40 (2H, s), 4.42 – 4.50 (1H, m), 7.77 (1H, s); MS m/z 321 $[M+H]^+$.

Producto intermedio 271:

2'–Cloro–9'–ciclohexil–8',9'–dihidroespiro[ciclopropano–1,7'–pirimido[5,4–b][1,4]diazepin]–6'(5'H)–ona

Etil 1–[[(2–cloro–5–nitro–pirimidin–4–il)–ciclohexil–amino]metil]ciclopropano–1–carboxilato (Producto intermedio 272; 3.89 g, 10.16 mmol) fue disuelto en el ácido acético (75 mL) y la solución calentada con agitación hasta 72 °C bajo nitrógeno en un baño de aceite. Polvo de hierro (1.5 g) fue añadido en una porción dando una pequeña exoterma hasta 75 °C en los posteriores 15 minutos. La temperatura de la reacción cayó hasta 72 °C y la reacción fue mantenida a esta temperatura durante 3 horas y luego se dejó enfriar a temperatura ambiente toda la noche.

La mezcla de reacción fue recalentada y filtrada caliente a través de celita, y la almohadilla lavada con más ácido acético. El filtrado fue concentrado al vacío, luego sonicado en solución de hidrógeno carbonato de sodio saturado acuoso para dar una suspensión marrón. Esto fue filtrado, y el sólido resultante lavado con agua. El sólido fue succionado seco, y suspendido en metanol con sonicación. La suspensión fue luego diluida con DCM, y sulfato de sodio añadido. Esta mezcla fue filtrada para dar una solución amarilla, la cual fue concentrada al vacío para dar un sólido amarillo, el cual fue triturado bajo metanol frío para dar el producto como un polvo blanco. Los licores madre fueron purificados en una columna de sílice, para dar un producto más claro, el cual fue combinado con el primer lote para proporcionar el compuesto del título como un sólido blanco (850 mg, 27%).

^{1}H NMR (400.13 MHz, DMSO–d_6) δ 0.88 – 0.91 (2H, m), 1.05 – 1.15 (1H, m), 1.15 – 1.18 (2H, m), 1.31 – 1.42 (4H, m), 1.61 – 1.63 (3H, m), 1.74 – 1.81 (2H, m), 3.44 (2H, s), 4.44 (1H, s), 7.93 (1H, s), 9.77 (1H, s); MS m/z 307 $[M+H]^+$.

Producto intermedio 272:

Etil 1–[[(2–cloro–5–nitro–pirimidin–4–il)–ciclohexil–amino]metil]ciclopropano–1–carboxilato

A una solución de etil 1–[(ciclohexilamino)metil]ciclopropano–1–carboxilato (Producto intermedio 273; 7.175 g, 34 mmol) en acetona (200 mL) fue añadido carbonato de potasio 7.05 g, 51 mmol) seguido por 2,4–dicloro–5–nitropirimidina (Aldrich; 9.235 g, 47.6 mmol). La mezcla de reacción fue agitada a temperatura ambiente durante 5 horas. Una adición posterior de 2,4–dicloro–5–nitropirimidina (4.62 g, 23.8 mmol) y carbonato de potasio (3.5 g, 25.5 mmol) fue hecha y la reacción agitada toda la noche a temperatura ambiente. La mezcla de reacción fue luego concentrada al vacío y particionada entre EtOAc y agua. La capa EtOAc

fue separada, secada sobre sulfato de sodio y purificada en una columna de sílice eluyendo con EtOAc / isohexano 10:90, para proporcionar el compuesto del título como un aceite amarillo (12 g, 92%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.76 – 0.83 (2H, m), 0.90 – 0.97 (1H, m), 1.00 (4H, s), 1.04 – 1.10 (2H, m), 1.13 – 1.15 (2H, m), 1.56 (6H, m), 2.93 – 2.99 (1H, m), 3.69 (2H, s), 3.94 (2H, q), 8.49 (1H, s); MS m/z 383 $[M+H]^+$.

Producto intermedio 273:

Etil 1–[(ciclohexilamino)metil]ciclopropano–1–carboxilato

A una solución de etil 1–(aminometil)ciclopropano–1–carboxilato (Producto intermedio 114; 20.65 g, 50 mmol) en DCM (200 mL) fue añadido ciclohexanona (Aldrich; 5.28 mL, 51 mmol). Después de agitar a temperatura ambiente durante 15 minutos, acetato de sodio (4.185 g, 75 mmol) fue añadido, seguido por triacetoxiborohidruro de sodio (15.905 g, 75 mmol). La suspensión fue agitada a temperatura ambiente durante 2 días, luego particionada entre DCM y solución de hidrógeno carbonato de sodio saturada acuosa. La solución orgánica fue secada sobre sulfato de sodio y evaporada para proporcionar el compuesto del título como un aceite incoloro (7.2 g, 64%).

^{1}H NMR (400.13 MHz, $CDCl_3$) δ 0.55 – 0.58 (2H, m), 0.81 – 0.97 (4H, m), 0.99 – 1.08 (7H, m), 1.34 – 1.39 (1H, m), 1.47 – 1.51 (2H, m), 1.57 – 1.65 (2H, m), 2.14 – 2.21 (1H, m), 2.49 (2H, s), 3.88 (2H, q).

Producto intermedio 274:

4–Amino–2,5–difluoro–N–[(1S,5R)–9–metil–9–azabiciclo[3.3.1]non–7–il]benzamida

Una mezcla del ácido 4–amino–2,5–difluorobenzoico (Rarechem; 2.4 g, 13.87 mmol) y endo–9–metil–9–azabiciclo[3,3,1]–nonan–3–amina (Chempacific; 2.355 g, 15.26 mmol) fue disuelto en DMF (150 mL), y a la solución fue añadido DIPEA (5.3 mL, 27.74 mmol). La reacción fue enfriada en un baño de hielo, y HATU (5.805 g, 15.26 mmol) fue añadido, en forma de porciones. La mezcla de reacción fue luego agitada a temperatura ambiente durante 18 horas, y el solvente evaporado, y el residuo particionado entre etil acetato (200 mL), y solución de carbonato de sodio saturada acuosa (3 x 50 mL), lavado con salmuera (3 x 50 mL), secado sobre anhidro sulfato de magnesio, filtrado, y el solvente evaporado. El residuo

fue purificado en una columna SCX–2 (50 g), desarrollando y eluyendo con 1) agua ; 2) MeOH ; y 3) 3.5M NH_3–MeOH. El solvente fue evaporado para proporcionar el compuesto del título como un sólido cristalino color canela (2.58 g, 60%).

^{1}H NMR (400.1MHz; $CDCl_3$) δ 1.00–1.10 (2H,d), 1.23–1.33 (2h,dt), 1.48–1.58 (1H,m), 1.85–2.03 (4H,d+m), 2.50 (3H,s), 2.44–2.56 (2H,m), 3.04–3.12 (2H,d), 4.20 (2H,s), 4.42–4.56 (1H,m), 6.33–6.50 (1H,m), 6.42–6.50 (1H,dd),7.70–7.77 (1H,dd). MS m/z 310 $[M+H]^+$.

Producto intermedio 275:

4–Amino–3–metoxi–N–[(1R,5S)–9–metil–3–oxa–9–azabiciclo[3.3.1]non–7–il]benzamida

N–Etildiisopropilamina (0.119 mL, 0.68 mmol) fue añadido a ácido 4–amino–3–metoxibenzoico (Aldrich; 114 mg, 0.68 mmol), (1R,5S,7s)–9–metil–3–oxa–9–azabiciclo[3.3.1]nonan–7–amina (Bioorganic & Medicinal Chemistry Letters (1992), 2(6), 519–22, 107 mg, 0.68 mmol) y HATU (260 mg, 0.68 mmol) en DMF (5 mL) a 25°C. La solución resultante fue agitada a temperatura ambiente durante 6 horas. El DMF fue evaporado para dar una goma marrón como residuo, el cual fue purificado por cromatografía de intercambio iónico, usando una columna SCX–2 (5g) prehumedecida con metanol. El producto deseado fue eluido de la columna usando NH_3 2M/MeOH y las fracciones purificadas fueron evaporadas hasta secarse para proporcionar una goma marrón la cual fue purificada por cromatografía flash en sílice, gradiente en elusión 0 a 100% 5% MeOH/DCM en DCM. Las fracciones puras fueron combinadas y evaporadas hasta secarse para proporcionar el compuesto del título como una goma color beige (205 mg, 98 %).

^{1}H NMR (400.132 MHz, $CDCl_3$) δ 1.38 (2H, d), 2.39 – 2.45 (2H, m), 2.53 (3H, s), 2.58 – 2.68 (4H, m), 3.64 (2H, d), 3.83 (3H, s), 4.58 – 4.64 (1H, m), 5.60 (2H, s), 6.59 (1H, d), 7.09 (1H, d), 7.33 (1H, d), 8.80 (1H, d); MS m/z 306 $[M+H]^+$.

Detalles de los Suministradores

Apin Chemicals Ltd

43d Milton Park

Abingdon

Oxon

OX14 4RU

Reino Unido

ABChem Inc
5785 Chemin St–Francois
Ville St–Laurent
Quebec H4S 1B6, Canadá

ABCR GmbH & Co. KG
Im Schlehert 10
D–76187 Karlsruhe
Alemania

Activate Scientific GMBH
Eichenstrasse 36
D–93161 Regensburg
Alemania

Sigma–Aldrich Company Ltd.
The Old Brickyard
New Road
Gillingham
Dorset
SP8 4XT
Reino Unido

Apollo Scientific Ltd.
Whitefield Rd.
Bredbury,
Stockport,
Cheshire,
SK6 2QR

Reino Unido

ASDI Inc
601 Interchange Blvd.
Newark,
DE, 19711
EUA

Asinex Ltd.
6 Schukinskaya Street
Moscú
123182
Rusia

CBI Building Blocks
40–144 Leninsky Prospect,
Moscú, 119334
Rusia

ChemBridge Corporation
16981 Via Tazon
Suite G
San Diego
CA 92127
EUA

ChemPacific Corporation
6200 Freeport Center
Baltimore
MD 21224
EUA

Chembasics Pty Ltd
5 Blamey St
Unit 1
O'Connor
WA 6163
Australia

Chemstep
20 Avenue Victor Hugo
Carbon Blanc
33560
Francia

Enamina Ltd.
23 Alexandra Matrosova Street
Kiev
01103
Ucrania

Maybridge
Treville
Tintagel
Cornwall
PL34 OHW
Reino Unido

Fluka Chemie AG
Industriestrasse 25
9471 Buchs
Suiza

Fluorochem Ltd
Wesley Street
Glossop
Derbyshire
SK13 7RY
Reino Unido

Frinton Laboratories, Inc.
P.O. Box 2428
NJ, 08362
EUA

Matrix Marketing GMBH
Bahnweg Nord 35
CH–9475 Sevelen
Suiza

Suzhou ChonTech PharmaChem Technology Company Ltd
77 Jinfeng Rd.
Suzhou
Jiang
China

TimTec LLC
Harmony Business Park Building 301–A
Newark
DE
EUA
19711

Zelinsky Institute of Organic Chemistry
47 Leninsky Prospect
Moscú, 117913
Rusia

Ensayos Biológicos para la Inhibición de la PLK

El siguiente ensayo fue usado para medir los efectos de los compuestos de la presente invención comos Inhibidores de Plk quinasa.

Ensayo de la Enzima Plk1 In Vitro

El ensayo usa Tecnología de Ensayo de Proximidad de Centelleo (SPA) (Antonsson y otros, Analytical Biochemistry, 1999, 267: 294–299) para determinar la capacidad de los compuestos de prueba para inhibir la fosforilación por Plk1 recombinante. La proteína Plk1 en toda la longitud es expresada en células de insectos como una fusión de la etiqueta 6His al terminal N y purificada por técnicas de purificación de quelato de Níquel estándares usando la etiqueta His.

El fragmento amino terminal de Cdc25C (que codifica los residuos 1–165) es expresado en E.coli como una fusión GST y purificado usando la etiqueta GST por técnicas de purificación estándares.

Los compuestos de prueba fueron preparados como soluciones madre de 10mM en dimetil sulfóxido (DMSO) y diluidas en agua como se requiera para dar un rango de concentraciones de ensayo final. Alícuotas (5µL) de cada dilución del compuesto fueron dispensados en un pocillo de una placa de poliestireno de fondo plano de 384–pocillos (Matrix, Catálogo No. 4316). Una mezcla de 35µL de la enzima Plk1 purificada recombinante (12ng/pocillo), GST–Cdc25C purificado (150ng/pocillo), trifosfato de adenosina (ATP; 64nM), trifosfato de adenosina marcado ^{33}P (^{33}P–ATP; 60 nCi/pocillo) en una solución buffer [comprendiendo 50mM HEPES pH7.5 buffer, 10mM cloruro de manganeso ($MnCl_2$), 1mM ditiotreitol (DTT), 1mg/ml albúmina de suero bovino (BSA), 100µM vanadato de sodio (Na_3VO_4), 100µM fluoro de sodio (NaF) y 10mM glicerofosfato de sodio] fue añadido y las reacciones incubadas a temperatura ambiente durante 90 minutos.

Las reacciones fueron detenidas por adición de EDTA (110mM) y el sustrato Cdc25C capturado a través de su etiqueta GST para las perlas SPA PVT de Proteína A recubiertas con el anticuerpo anti–GST (Molecular Probes, Cat No A–5800) (Amersham Biosciences, Catálogo No. RPQ0019; 250µg/pocillo) en 50mM HEPES pH 7.5 buffer que contiene 0.05% (p/v) de azida de sodio e incubado por hasta 2 horas, seguido por la adición de 20µL de cloruro de cesio 4M (concentración ensayo final de 1M). Las placas fueron luego dejadas en la oscuridad toda la noche antes del conteo en un Packard TopCount NXT.

El sustrato fosforilado radiomarcado es formado in *situ* como resultado de la fosforilación mediada por la Plk1. Las perlas SPA contienen un centelleo que puede ser estimulado para emitir luz. Esta estimulación solamente ocurre cuando un sustrato fosforilado radiomarcado es enlazado a la superficie de la perla SPA recubierta provocando la emisión de luz azul que puede ser medida en un contador de centelleo. En correspondencia, la extensión de la fosforilación de Cdc25C mediada por Plk1 fue evaluada. Los datos del ensayo en bruto fueron luego analizados por análisis de regresión no lineal y la inhibición de la enzima Plk1 para un compuesto de prueba dado es expresada como un valor IC50.

Los siguientes ejemplos fueron probados en este ensayo y fueron medidos para tener valores de IC50 menores de 100 uM.

4, 50, 51, 53, 54, 74, 77, 88, 94, 96, 99, 116,
117, 118, 120, 121, 122, 123, 125, 133, 134, 135, 136, 137,
140, 141, 144, 145, 146, 147, 148, 149, 151, 153, 154, 155,
156, 157, 158, 159, 160, 163, 164, 166, 168, 169, 172, 174,
175, 177, 180, 183, 187, 199, 205, 239, 247, 248, 249, 251,
253, 254, 255, 256, 257, 258, 260, 261, 263, 264, 265, 266,
268, 273, 275, 276, 277, 433,

con los siguientes ejemplos teniendo valores IC50 menores de 1uM

7, 8, 12, 24, 31, 32, 35, 36, 37, 38, 52, 65,
67, 70, 76, 80, 81, 89, 90, 93, 95, 98, 105, 107,
109, 112, 113, 115, 124, 128, 129, 130, 131, 132, 138, 139,
143, 150, 161, 162, 165, 173, 178, 179, 182, 184, 191, 195,
196, 197, 200, 212, 215, 216, 220, 223, 225, 226, 227, 228,

230, 233, 238, 243, 244, 250, 259, 262, 267, 272, 282, 323, 383, 410,

con los siguientes ejemplos teniendo valores IC50 menores de 0.3 uM

1, 2, 5, 6, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 33, 34, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 69, 71, 72, 73, 75, 78, 82, 83, 84, 85, 86, 87, 91, 92, 100, 102, 104, 111, 114, 119, 142, 170, 176, 181, 185, 186, 188, 189, 193, 194, 201, 202, 203, 206, 207, 208, 209, 210, 211, 212, 213, 217, 218, 219, 221, 222, 224, 229, 231, 232, 234, 235, 236, 237, 240, 241, 245, 246, 269, 270, 281, 283, 314, 315, 316, 317, 318, 319, 320, 321, 322, 325, 326, 327, 328, 382, 385, 386, 387, 430, 431, 432.

Por ejemplo, el Ejemplo 14 fue medido para tener un IC50 de 110nM, IC50 célula 92 nM.

Ensayo Celular

La condensación del cromosoma en mitosis está acompañada por la fosforilación de la histona H3 en serina 10. La defosforilación comienza en anafase y termina en una telofase temprana, de esta manera la fosforilación de la histona H3 en serina 10 actúa como un marcador mitótico excelente y es usada para determinar la capacidad de los compuestos de la presente invención para bloquear las células en la mitosis.

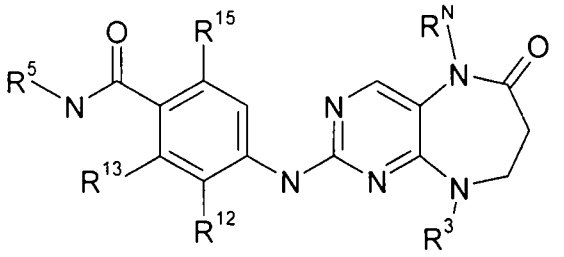
Las células de la línea celular del tumor de colon humano HT29 fueron sembradas en placas negras de 96 pocillos (Costar, Catálogo No 3904) en Medio Eagles Modificado de Dulbecco (DMEM) libre de fenol rojo suplementado con 10% (v/v) FCS y 1% (v/v) L–Glutamina e incubadas toda la noche a 37°C. Los compuestos de prueba fueron solubilizados en DMSO, diluidos para dar un rango de concentraciones de ensayo final, añadidos a las células e incubados durante 24 h a 37°C. Después de 24 horas, las células fueron fijadas en 3.7% (v/v) formaldehído luego permeabilizadas y bloqueadas durante 10 minutos en 100µl 0.5% (v/v) Triton X–100, 1% (p/v) albúmina de suero bovino (BSA) en fosfato de buffer salino (PBS). Después de lavar con PBS, 50µl de anticuerpo primario (1:500 dilución de anti–

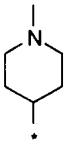
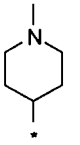
fosfohistona H3 de conejo (Upstate Catálogo No 06–570) en 1% BSA, 0.05% Tween 20) fueron añadidos a las células que fueron dejadas durante 1 hora a temperatura ambiente. Las células fueron nuevamente lavadas con PBS e incubadas con 50µl anticuerpo secundario (1:1000 Alexa Fluor 488 cabra anti–conejo (Molecular Probes Cat No A–11008) y Hoechst (1:10000) diluidas en PBS 0.05% (v/v) Tween 20 y dejadas durante 1 hora a temperatura ambiente en la oscuridad. Las células fueron lavadas con PBS luego cubiertas con PBS fresco y almacenadas a 4°C hasta el análisis. Las imágenes son adquiridas y analizadas de manera automatizada usando el Cellomics ArrayScan II o VTi. En este ensayo son medidos tanto el teñido con Hoechst y con fosfohistona H3. El teñido con Hoechst genera un conteo de células válido mientras que el teñido con fosfohistona H3 determina el número de células mitóticas. La inhibición de las perlas Plk para un aumento en la población de células de histona H3 Ser10 positivas, que indican la inhibición de la proliferación es producida fundamentalmente por la detención de las células en la fase mitótica del ciclo celular. Los datos del ensayo en bruto fueron analizados por análisis de regresión no lineal y usados para determinar un valor IC50 para cada compuesto.

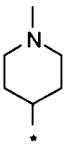
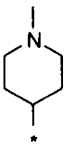
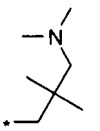
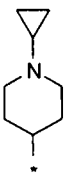
Los siguientes compuestos ejemplos cuando fueron probados en este ensayo tuvieron un valor IC50 menor de 30uM 5, 23, 24, 40, 42, 89, 103, 105, 107, 112, 115, 122, 123, 124, 125, 126, 127, 128, 129, 131, 132, 133, 138, 143, 159, 165, 167, 170, 171, 173, 177, 178, 179, 180, 186, 187, 192, 195, 212, 215, 218, 220, 221, 223, 224, 228, 229, 230, 231, 232, 233, 248, 253, 256, 257, 263, 264, 265, 270, 271, 272, 275, 277, 284, 286, 287, 296, 297, 332, 410 con los siguientes ejemplos teniendo un IC50 menor de 1uM 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451 con el siguiente ejemplo teniendo un IC50 menor de 0.3 uM 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345,

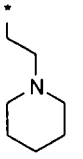
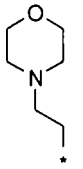
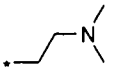
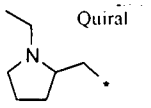
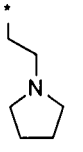
346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 y 453.

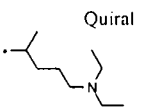
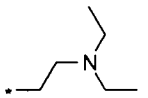
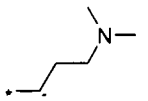
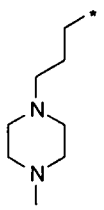
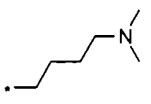
Por ejemplo, el Ejemplo 14 fue medido para tener un IC50 de 92 nM.

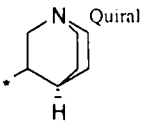
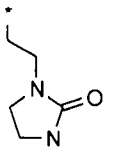
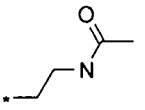
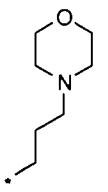


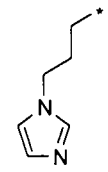
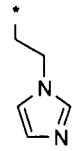
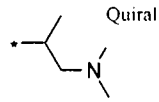
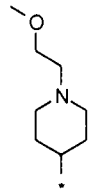
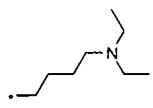
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 1:	Ciclopentil	Me	OMe	H	H	
Ejemplo 2:	Ciclopentil	Me	H	H	H	

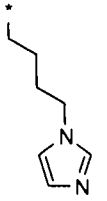
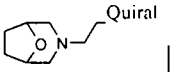
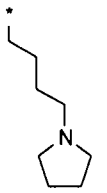
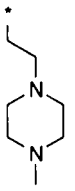
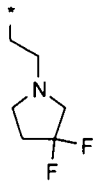
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 6:	^{i}Pr	Me	OMe	H	H	
Ejemplo 8:	Ciclohexil	Me	OMe	H	H	
Ejemplo 10:	Ciclopentil	Me	OMe	H	H	
Ejemplo 11:	Ciclopentil	Me	OMe	H	H	

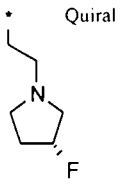
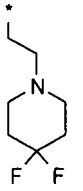
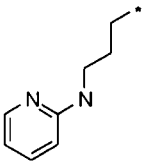
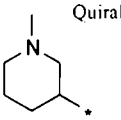
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 12:	Ciclopentil	Me	OMe	H	H	
Ejemplo 13:	Ciclopentil	Me	OMe	H	H	
Ejemplo 14:	Ciclopentil	Me	OMe	H	H	
Ejemplo 15:	Ciclopentil	Me	OMe	H	H	 Quiral
Ejemplo 16:	Ciclopentil	Me	OMe	H	H	

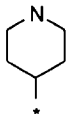
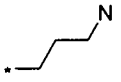
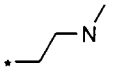
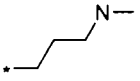
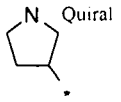
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 17:	Ciclopentil	Me	OMe	H	H	
Ejemplo 18:	Ciclopentil	Me	OMe	H	H	
Ejemplo 19:	Ciclopentil	Me	OMe	H	H	
Ejemplo 20:	Ciclopentil	Me	OMe	H	H	
Ejemplo 21:	Ciclopentil	Me	OMe	H	H	

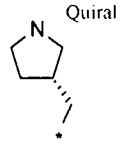
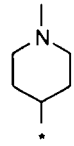
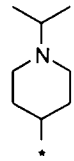
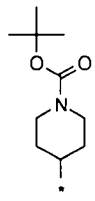
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 22:	Ciclopentil	Me	OMe	H	H	
Ejemplo 23:	Ciclopentil	Me	OMe	H	H	
Ejemplo 24:	Ciclopentil	Me	OMe	H	H	
Ejemplo 25:	Ciclopentil	Me	OMe	H	H	

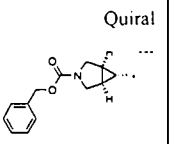
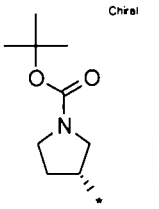
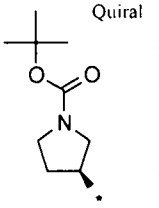
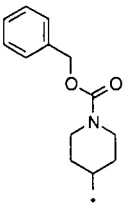
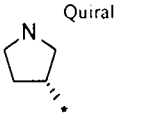
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 26:	Ciclopentil	Me	OMe	H	H	
Ejemplo 27:	Ciclopentil	Me	OMe	H	H	
Ejemplo 28:	Ciclopentil	Me	OMe	H	H	
Ejemplo 29:	Ciclopentil	Me	OMe	H	H	
Ejemplo 30:	Ciclopentil	Me	OMe	H	H	

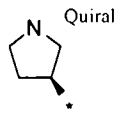
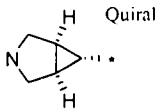
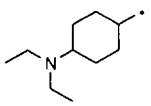
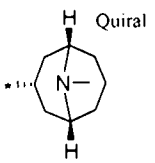
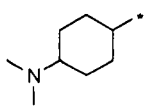
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 31:	Ciclopentil	Me	OMe	H	H	
Ejemplo 32:	Ciclopentil	Me	OMe	H	H	
Ejemplo 33:	Ciclopentil	Me	OMe	H	H	
Ejemplo 34:	Ciclopentil	Me	OMe	H	H	
Ejemplo 35:	Ciclopentil	Me	OMe	H	H	

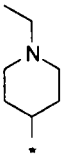
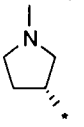
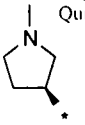
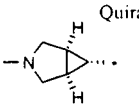
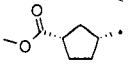
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 36:	Ciclopentil	Me	OMe	H	H	
Ejemplo 37:	Ciclopentil	Me	OMe	H	H	
Ejemplo 38:	Ciclopentil	Me	OMe	H	H	
Ejemplo 39:	Ciclopentil	Me	OMe	H	H	
Ejemplo 40:	Ciclopentil	Me	OMe	H	H	

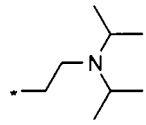
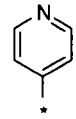
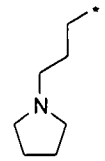
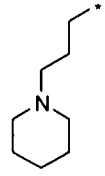
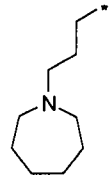
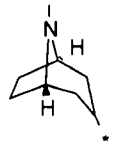
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 41:	Ciclopentil	Me	OMe	H	H	
Ejemplo 42:	Ciclopentil	Me	OMe	H	H	
Ejemplo 43:	Ciclopentil	Me	OMe	H	H	
Ejemplo 44:	Ciclopentil	Me	OMe	H	H	
Ejemplo 45:	Ciclopentil	Me	OMe	H	H	

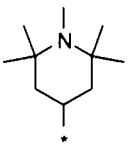
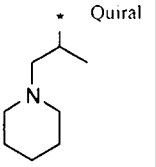
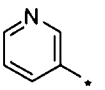
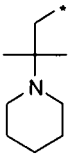
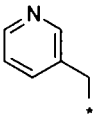
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 46:	Ciclopentil	Me	OMe	H	H	
Ejemplo 47:	Ciclopentil	Me	OMe	H	H	
Ejemplo 48:	Ciclopentil	Me	OMe	H	F	
Ejemplo 49:	Ciclopentil	Me	OMe	H	H	
Ejemplo 50:	Ciclopentil	Me	OMe	H	H	

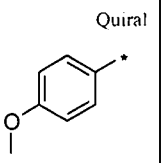
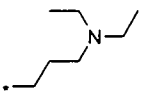
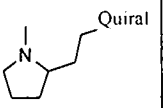
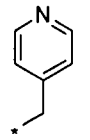
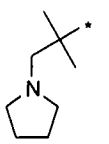
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 51:	Ciclopentil	Me	OMe	H	H	
Ejemplo 52:	Ciclopentil	Me	OMe	H	H	
Ejemplo 53:	Ciclopentil	Me	OMe	H	H	
Ejemplo 54:	Ciclopentil	Me	OMe	H	H	
Ejemplo 55:	Ciclopentil	Me	OMe	H	H	

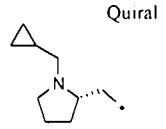
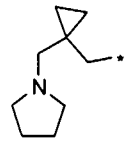
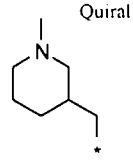
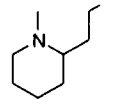
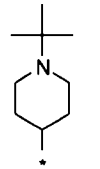
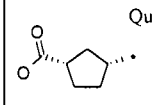
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 56:	Ciclopentil	Me	OMe	H	H	
Ejemplo 57:	Ciclopentil	Me	OMe	H	H	
Ejemplo 58:	Ciclopentil	Me	OMe	H	H	
Ejemplo 59:	Ciclopentil	Me	OMe	H	H	
Ejemplo 60:	Ciclopentil	Me	OMe	H	H	

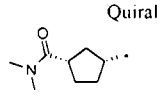
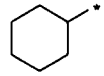
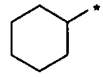
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 61:	Ciclopentil	Me	OMe	H	H	
Ejemplo 62:	Ciclopentil	Me	OMe	H	H	Quiral 
Ejemplo 63:	Ciclopentil	Me	OMe	H	H	Quiral 
Ejemplo 64:	Ciclopentil	Me	OMe	H	H	Quiral 
Ejemplo 65:	Ciclopentil	Me	OMe	H	H	Quiral 

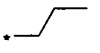
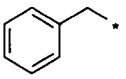
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 66:	Ciclopentil	Me	OMe	H	H	
Ejemplo 67:	Ciclopentil	Me	OMe	H	H	
Ejemplo 68:	Ciclopentil	Me	OMe	H	H	
Ejemplo 69:	Ciclopentil	Me	OMe	H	H	
Ejemplo 70:	Ciclopentil	Me	OMe	H	H	
Ejemplo 71:	Ciclopentil	Me	OMe	H	H	Quiral 

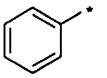
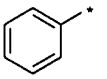
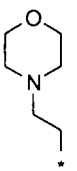
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 72:	Ciclopentil	Me	OMe	H	H	
Ejemplo 73:	Ciclopentil	Me	OMe	H	H	
Ejemplo 74:	Ciclopentil	Me	OMe	H	H	
Ejemplo 75:	Ciclopentil	Me	OMe	H	H	
Ejemplo 76:	Ciclopentil	Me	OMe	H	H	

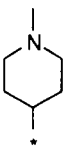
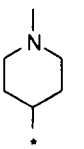
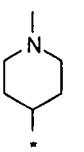
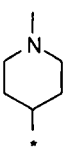
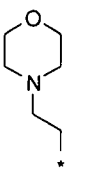
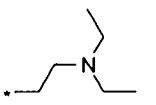
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 77:	Ciclopentil	Me	OMe	H	H	
Ejemplo 78:	Ciclopentil	Me	OMe	H	H	
Ejemplo 79:	Ciclopentil	Me	OMe	H	H	
Ejemplo 80:	Ciclopentil	Me	OMe	H	H	
Ejemplo 81:	Ciclopentil	Me	OMe	H	H	

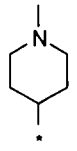
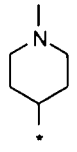
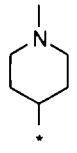
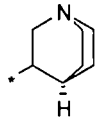
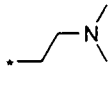
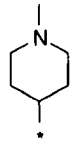
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 82:	Ciclopentil	Me	OMe	H	H	
Ejemplo 83:	Ciclopentil	Me	OMe	H	H	
Ejemplo 84:	Ciclopentil	Me	OMe	H	H	
Ejemplo 85:	Ciclopentil	Me	OMe	H	H	
Ejemplo 86:	Ciclopentil	Me	OMe	H	H	
Ejemplo 87:	Ciclopentil	Me	OMe	H	H	

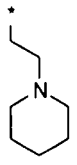
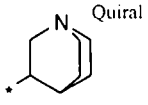
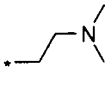
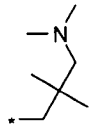
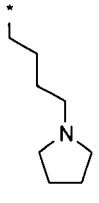
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 88:	Ciclopentil	Me	OMe	H	H	Quiral 
Ejemplo 89:	Ciclopentil	Me	H	H	H	
Ejemplo 90:	Ciclopentil	Me	OMe	H	H	
Ejemplo 91:	Ciclopentil	Me	OMe	H	H	
Ejemplo 92:	Ciclopentil	Me	OMe	H	H	H

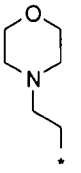
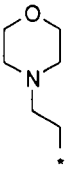
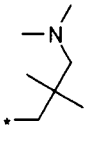
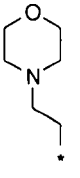
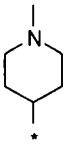
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 93:	Ciclopentil	Me	OMe	H	H	
Ejemplo 94:	Ciclopentil	Me	OMe	H	H	
Ejemplo 95:	Ciclopentil	Me	OMe	H	H	
Ejemplo 96:	Ciclopentil	Me	OMe	H	H	
Ejemplo 97:	Ciclopentil	Me	H	H	H	H
Ejemplo 98:	Ciclopentil	Me	OMe	H	H	

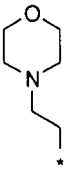
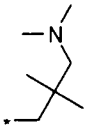
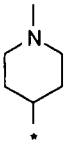
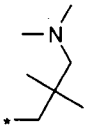
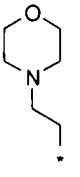
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 99:	Ciclopentil	Me	OMe	H	H	
Ejemplo 100:	Ciclopentil	Me	H	H	H	
Ejemplo 101:	Ciclopentil	Me	H	H	H	
Ejemplo 102:	Ciclopentil	Me	H	H	H	
Ejemplo 184:	Ciclopentil	Me	Cl	H	H	

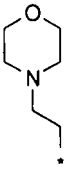
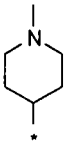
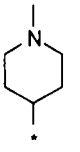
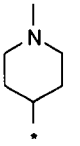
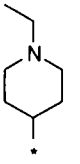
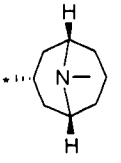
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 185:	Ciclopentil	Me	Cl	H	H	
Ejemplo 187:	Ciclopentil	Me	H	H	F	
Ejemplo 188:	Ciclopentil	Me	F	H	F	
Ejemplo 189:	Ciclopentil	Me	H	H	H	
Ejemplo 191:	Ciclopentil	Me	H	H	H	
Ejemplo 192:	Ciclopentil	Me	H	H	H	

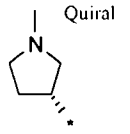
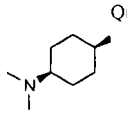
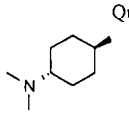
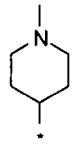
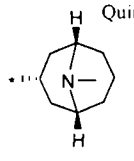
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 193:	Ciclopentil	Me	Me	H	H	
Ejemplo 194:	Ciclopentil	Me	F	H	H	
Ejemplo 200:	Ciclopentil	Me	OEt	H	H	
Ejemplo 201:	Ciclopentil	Me	OEt	H	H	Quiral 
Ejemplo 202:	Ciclopentil	Me	OEt	H	H	
Ejemplo 203:	^{i}Pr	Me	Cl	H	H	

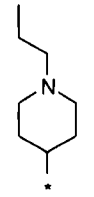
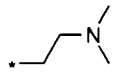
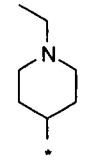
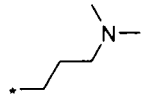
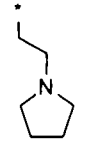
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 205:	^{i}Pr	Me	OMe	H	H	
Ejemplo 206:	^{i}Pr	Me	OMe	H	H	 Quiral
Ejemplo 207:	^{i}Pr	Me	OMe	H	H	
Ejemplo 208:	^{i}Pr	Me	OMe	H	H	
Ejemplo 209:	^{i}Pr	Me	OMe	H	H	

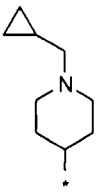
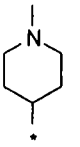
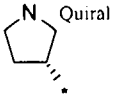
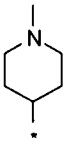
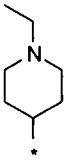
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 218:	^{i}Pr	Me	H	H	H	
Ejemplo 219:	^{i}Pr	Me	OMe	H	H	
Ejemplo 222:	^{i}Pr	Me	H	H	H	
Ejemplo 228:	^{i}Pr	Me	Cl	H	H	
Ejemplo 234:	Ciclopentil	Me	OMe	H	H	

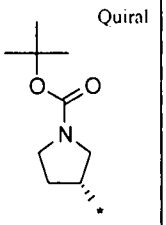
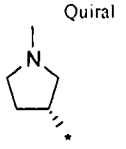
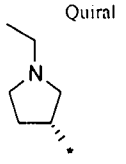
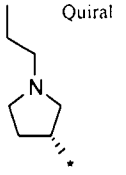
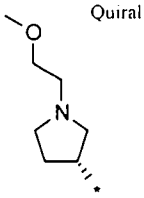
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 250:	Ciclopentil	H	OMe	H	H	
Ejemplo 253:	Ciclopentil	H	H	H	H	
Ejemplo 254:	Ciclopentil	H	H	H	H	
Ejemplo 255:	Ciclopentil	H	Cl	H	H	
Ejemplo 256:	Ciclopentil	H	H	H	H	

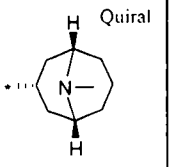
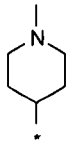
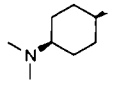
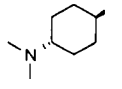
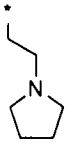
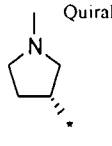
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 257:	Ciclopentil	H	Cl	H	H	
Ejemplo 259:	Ciclopentil	Me	OMe	H	H	
Ejemplo 260:	Ciclopentil	Me	OMe	H	H	
Ejemplo 281:	^{i}Pr	Me	OEt	H	H	
Ejemplo 282:	^{i}Pr	Me	OEt	H	H	
Ejemplo 283:	^{i}Pr	Me	OEt	H	H	Quiral 

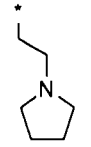
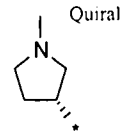
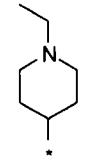
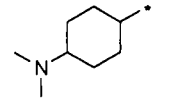
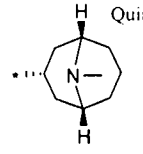
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 284:	^{i}Pr	Me	OEt	H	H	
Ejemplo 285:	^{i}Pr	Me	OEt	H	H	
Ejemplo 286:	^{i}Pr	Me	OEt	H	H	
Ejemplo 287:	^{i}Pr	Me	OEt	H	F	
Ejemplo 288:	^{i}Pr	Me	OEt	H	F	

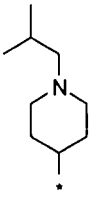
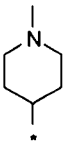
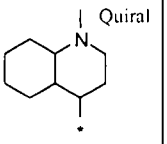
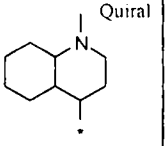
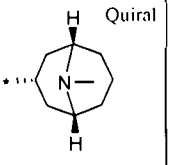
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 314:	Ciclopentil	Me	OMe	H	H	
Ejemplo 315:	Ciclopentil	Me	Cl	H	H	
Ejemplo 316:	Ciclopentil	Me	Cl	H	H	
Ejemplo 317:	Ciclopentil	Me	Cl	H	H	
Ejemplo 318:	Ciclopentil	Me	Cl	H	H	

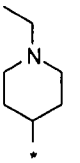
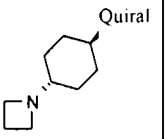
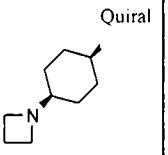
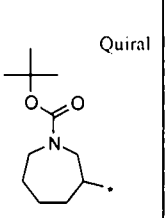
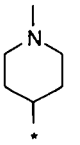
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 319:	Ciclopentil	Me	OMe	H	H	
Ejemplo 320:	Ciclopentil	Me	OMe	H	Cl	
Ejemplo 321:	Ciclopentil	Me	Cl	H	F	
Ejemplo 322:	Ciclopentil	Me	Cl	H	F	
Ejemplo 323:	Ciclopentil	Me	Cl	H	F	

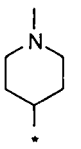
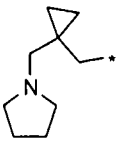
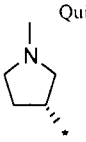
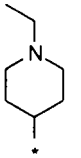
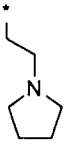
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 324:	Ciclopentil	Me	Cl	H	F	
Ejemplo 325:	Ciclopentil	Me	Cl	H	F	
Ejemplo 326:	Ciclopentil	Me	OMe	H	H	
Ejemplo 327:	Ciclopentil	Me	OMe	H	H	
Ejemplo 328:	Ciclopentil	Me	OMe	H	H	

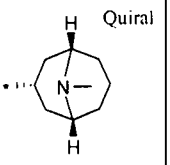
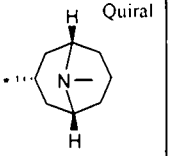
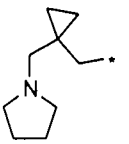
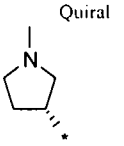
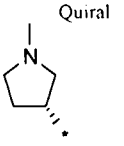
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 329:	Ciclopentil	Me	F	H	H	 Quiral
Ejemplo 330:	Ciclopentil	Me	Cl	H	H	
Ejemplo 331:	Ciclopentil	Me	Cl	H	H	 Quiral
Ejemplo 332:	Ciclopentil	Me	Cl	H	H	 Quiral
Ejemplo 333:	Ciclopentil	Me	OMe	H	F	
Ejemplo 334:	Ciclopentil	Me	F	H	F	 Quiral

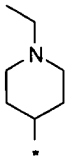
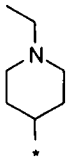
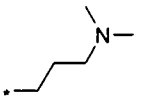
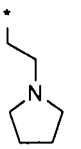
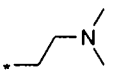
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 335:	Ciclopentil	Me	F	H	F	
Ejemplo 336:	Ciclopentil	Me	OMe	H	Cl	 Quiral
Ejemplo 337:	Ciclopentil	Me	OMe	H	Cl	
Ejemplo 338:	Ciclopentil	Me	OMe	H	Cl	
Ejemplo 339:	Ciclopentil	Me	OMe	H	Cl	 Quiral

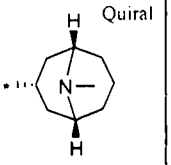
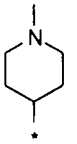
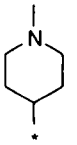
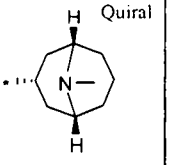
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 340:	Ciclopentil	Me	OMe	H	H	
Ejemplo 341:	Ciclopentil	Me	OCH2O		H	
Ejemplo 342:	Ciclopentil	Me	OMe	H	H	
Ejemplo 343:	Ciclopentil	Me	OMe	H	H	
Ejemplo 344:	Ciclopentil	Me	OMe	H	F	

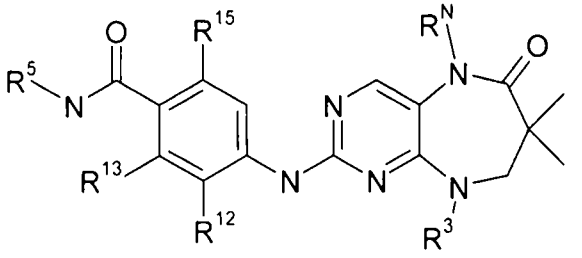
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 345:	Ciclopentil	Me	F	H	H	
Ejemplo 346:	Ciclopentil	Me	OMe	H	H	
Ejemplo 347:	Ciclopentil	Me	OMe	H	H	
Ejemplo 348:	Ciclopentil	Me	OMe	H	H	
Ejemplo 411:	Ciclohexil	Me	F	H	Cl	

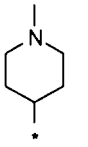
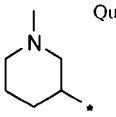
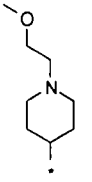
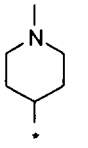
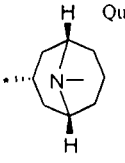
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 412:	Ciclohexil	Me	F	H	F	
Ejemplo 413:	Ciclohexil	Me	F	H	F	
Ejemplo 414:	Ciclohexil	Me	F	H	F	Quiral 
Ejemplo 415:	Ciclohexil	Me	F	H	F	
Ejemplo 416:	Ciclohexil	Me	F	H	F	

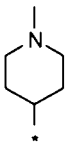
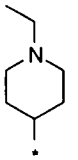
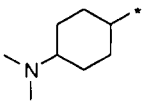
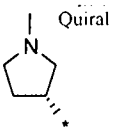
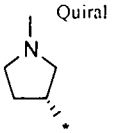
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 417:	Ciclohexil	Me	F	H	H	
Ejemplo 418:	Ciclohexil	Me	OMe	H	H	
Ejemplo 419:	Ciclohexil	Me	OMe	H	F	
Ejemplo 420:	Ciclohexil	Me	OMe	H	F	
Ejemplo 421:	Ciclohexil	Me	OMe	H	H	

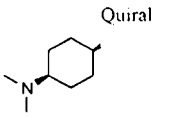
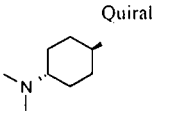
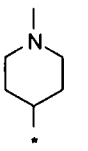
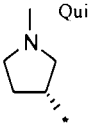
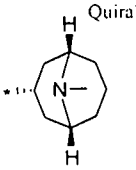
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 422:	Ciclohexil	Me	OMe	H	F	
Ejemplo 423:	Ciclohexil	Me	OMe	H	H	
Ejemplo 424:	Ciclohexil	Me	OMe	H	H	
Ejemplo 425:	Ciclohexil	Me	OMe	H	F	
Ejemplo 426:	Ciclohexil	Me	OMe	H	H	

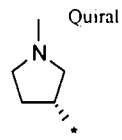
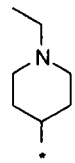
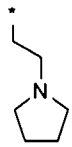
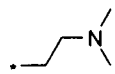
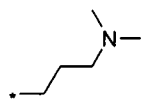
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 427:	Ciclohexil	Me	OMe	H	F	 Quiral
Ejemplo 428:	Ciclohexil	Me	H	H	H	
Ejemplo 429:	Ciclohexil	Me	F	H	H	
Ejemplo 447:	Ciclopentil	Me	F	H	F	 Quiral

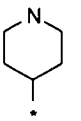
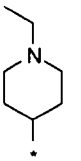
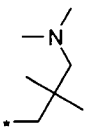
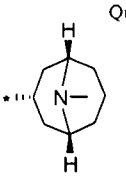
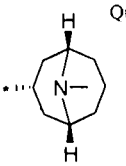


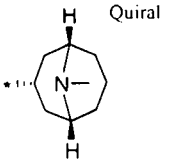
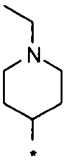
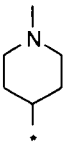
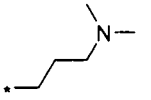
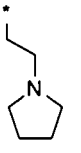
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 235:	Ciclopentil	Me	OMe	H	H	
Ejemplo 243:	Ciclopentil	Me	OMe	H	H	 Quiral
Ejemplo 244:	Ciclopentil	Me	OMe	H	H	
Ejemplo 245:	Ciclopentil	Me	H	H	H	
Ejemplo 278:	Ciclopentil	H	OMe	H	H	 Quiral

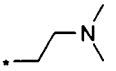
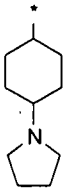
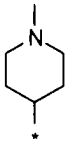
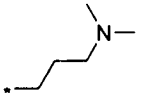
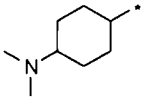
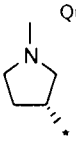
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 289:	^{i}Pr	Me	Cl	H	F	
Ejemplo 290:	^{i}Pr	Me	Cl	H	F	
Ejemplo 291:	^{i}Pr	Me	Cl	H	F	
Ejemplo 292:	^{i}Pr	Me	OMe	H	F	 Quiral
Ejemplo 293:	^{i}Pr	Me	OEt	H	H	 Quiral

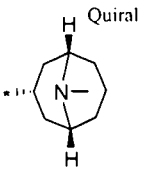
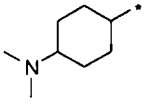
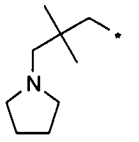
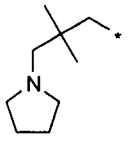
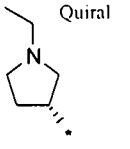
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 294:	^{i}Pr	Me	OEt	H	H	 Quiral
Ejemplo 295:	^{i}Pr	Me	OEt	H	H	 Quiral
Ejemplo 296:	^{i}Pr	Me	OEt	H	F	
Ejemplo 297:	^{i}Pr	Me	OEt	H	F	 Quiral
Ejemplo 298:	^{i}Pr	Me	F	H	H	 Quiral

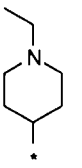
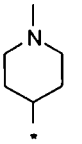
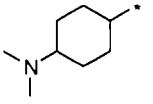
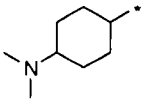
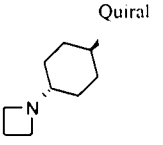
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 299:	^{i}Pr	Me	OMe	H	H	
Ejemplo 300:	^{i}Pr	Me	OMe	H	H	
Ejemplo 301:	^{i}Pr	Me	OMe	H	H	
Ejemplo 302:	^{i}Pr	Me	OMe	H	H	
Ejemplo 303:	^{i}Pr	Me	OMe	H	H	

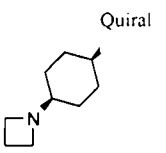
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 349:	Ciclopentil	Me	OMe	H	H	
Ejemplo 350:	Ciclopentil	Me	OMe	H	H	
Ejemplo 351:	Ciclopentil	Me	OMe	H	H	
Ejemplo 352:	Ciclopentil	Me	OMe	H	F	Quiral 
Ejemplo 353:	Ciclopentil	Me	F	H	H	Quiral 

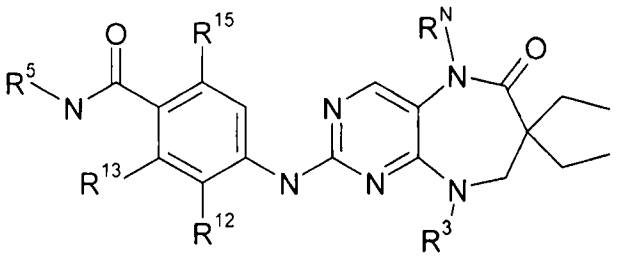
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 354:	Ciclopentil	Me	OMe	H	H	 Quiral
Ejemplo 355:	Ciclopentil	Me	F	H	F	
Ejemplo 356:	Ciclopentil	Me	F	H	F	
Ejemplo 357:	Ciclopentil	Me	OMe	H	H	
Ejemplo 358:	Ciclopentil	Me	OMe	H	H	

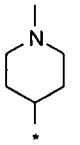
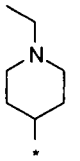
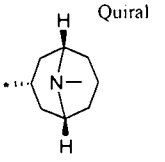
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 359:	Ciclopentil	Me	OMe	H	H	
Ejemplo 360:	Ciclopentil	Me	OMe	H	H	
Ejemplo 361:	Ciclopentil	Me	OMe	H	F	
Ejemplo 362:	Ciclopentil	Me	Cl	H	H	
Ejemplo 363:	Ciclopentil	Me	OMe	H	H	
Ejemplo 364:	Ciclopentil	Me	OMe	H	F	Quiral 

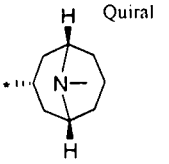
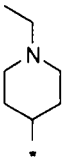
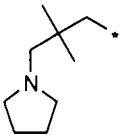
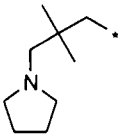
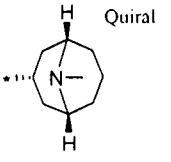
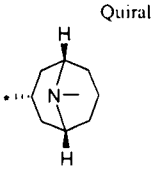
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 365:	Ciclopentil	Me	H	H	H	
Ejemplo 366:	Ciclopentil	Me	Cl	H	F	
Ejemplo 367:	Ciclopentil	Me	Cl	H	H	
Ejemplo 368:	Ciclopentil	Me	OMe	H	H	
Ejemplo 369:	Ciclopentil	Me	OMe	H	H	

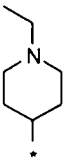
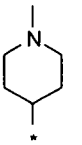
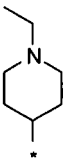
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 370:	Ciclopentil	Me	OMe	H	F	
Ejemplo 371:	Ciclopentil	Me	F	H	H	
Ejemplo 372:	Ciclopentil	Me	OMe	H	F	
Ejemplo 373:	Ciclopentil	Me	OMe	H	F	
Ejemplo 374:	Ciclopentil	Me	OMe	H	H	

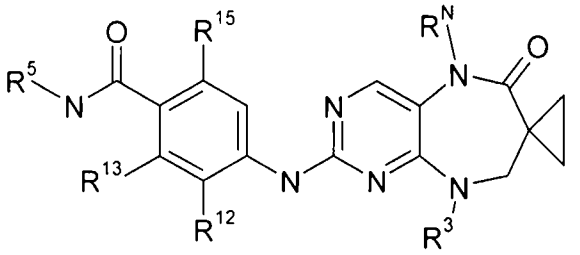
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 375:	Ciclopentil	Me	OMe	H	H	

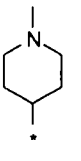


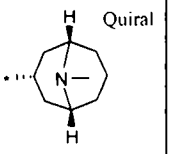
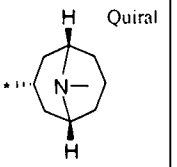
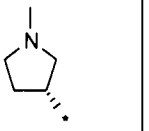
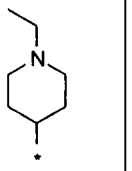
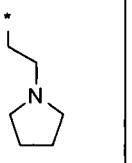
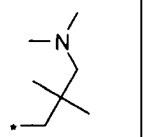
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 304:	^{i}Pr	Me	OMe	H	H	
Ejemplo 305:	^{i}Pr	Me	OMe	H	H	
Ejemplo 306:	^{i}Pr	Me	OMe	H	H	

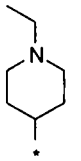
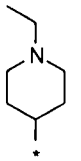
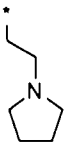
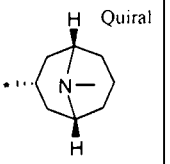
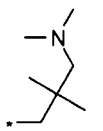
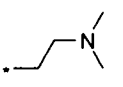
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 307:	^{i}Pr	Me	OMe	H	F	
Ejemplo 308:	^{i}Pr	Me	OMe	H	F	
Ejemplo 309:	^{i}Pr	Me	OMe	H	H	
Ejemplo 376:	Ciclopentil	Me	OMe	H	H	
Ejemplo 377:	Ciclopentil	Me	OMe	H	H	
Ejemplo 378:	Ciclopentil	Me	OMe	H	F	

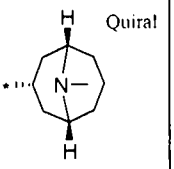
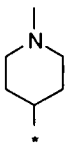
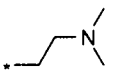
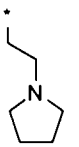
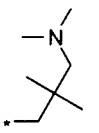
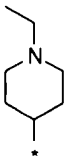
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 379:	Ciclopentil	Me	OMe	H	F	
Ejemplo 380:	Ciclopentil	Me	OMe	H	H	
Ejemplo 381:	Ciclopentil	Me	OMe	H	H	

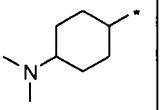
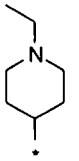
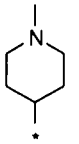
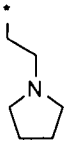
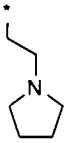
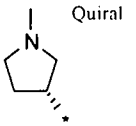


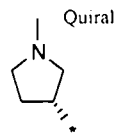
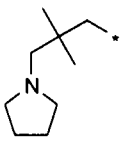
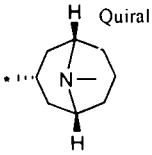
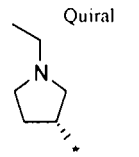
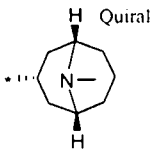
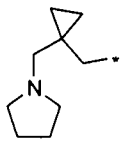
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 246:	Ciclopentil	Me	OMe	H	H	

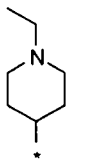
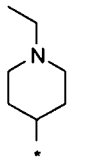
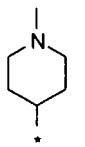
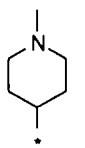
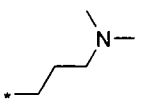
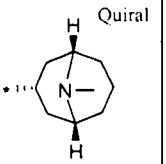
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 279:	Ciclopentil	H	F	H	H	
Ejemplo 280:	Ciclopentil	H	OMe	H	H	
Ejemplo 310:	^{i}Pr	Me	Cl	H	F	
Ejemplo 311:	^{i}Pr	Me	Cl	H	F	
Ejemplo 312:	^{i}Pr	Me	OMe	H	H	
Ejemplo 313:	^{i}Pr	Me	OMe	H	H	

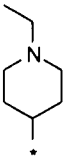
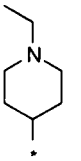
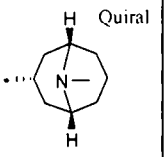
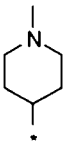
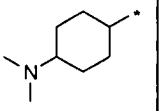
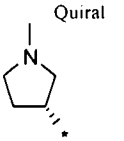
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 382:	Ciclopentil	Me	Cl	H	H	
Ejemplo 383:	Ciclopentil	Me	OMe	H	H	
Ejemplo 384:	Ciclopentil	Me	OMe	H	H	
Ejemplo 385:	Ciclopentil	Me	OMe	H	H	 Quiral
Ejemplo 386:	Ciclopentil	Me	OMe	H	H	
Ejemplo 387:	Ciclopentil	Me	OMe	H	H	

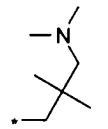
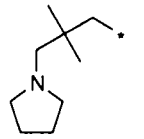
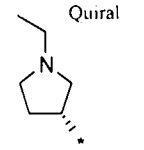
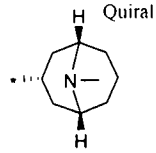
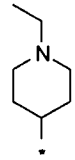
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 388:	Ciclopentil	Me	F	H	H	 Quiral
Ejemplo 389:	Ciclopentil	Me	Cl	H	F	
Ejemplo 390:	Ciclopentil	Me	Cl	H	H	
Ejemplo 391:	Ciclopentil	Me	Cl	H	H	
Ejemplo 392:	Ciclopentil	Me	Cl	H	H	
Ejemplo 393:	Ciclopentil	Me	Cl	H	F	

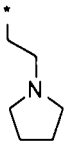
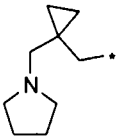
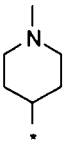
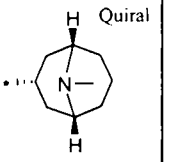
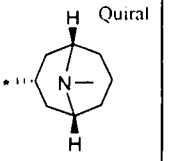
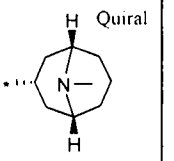
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 394:	Ciclopentil	Me	Cl	H	F	
Ejemplo 395:	Ciclopentil	Me	F	H	F	
Ejemplo 396:	Ciclopentil	Me	F	H	F	
Ejemplo 397:	Ciclopentil	Me	F	H	F	
Ejemplo 398:	Ciclopentil	Me	OMe	H	F	
Ejemplo 399:	Ciclopentil	Me	OMe	H	F	 Quiral

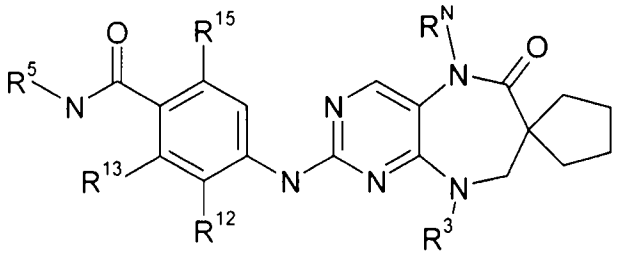
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 400:	Ciclopentil	Me	F	H	F	
Ejemplo 401:	Ciclopentil	Me	OMe	H	H	
Ejemplo 402:	Ciclopentil	Me	Cl	H	H	
Ejemplo 403:	Ciclopentil	Me	OMe	H	H	
Ejemplo 404:	Ciclopentil	Me	OMe	H	F	
Ejemplo 405:	Ciclopentil	Me	OMe	H	F	

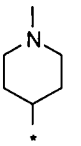
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 406:	Ciclopentil	Me	F	H	H	
Ejemplo 407:	Ciclopentil	Me	OMe	H	F	
Ejemplo 408:	Ciclopentil	Me	OCH_2O		H	
Ejemplo 430:	Ciclohexil	Me	OMe	H	H	
Ejemplo 431:	Ciclohexil	Me	OMe	H	H	
Ejemplo 432:	Ciclohexil	Me	OMe	H	H	 Quiral

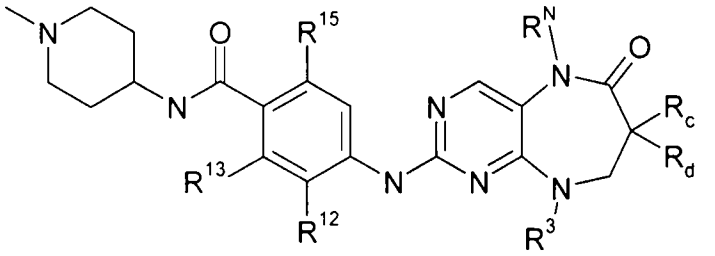
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 433:	Ciclohexil	Me	OMe	H	H	
Ejemplo 434:	Ciclohexil	Me	F	H	F	
Ejemplo 435:	Ciclohexil	Me	F	H	H	 Quiral
Ejemplo 436:	Ciclohexil	Me	F	H	F	
Ejemplo 437:	Ciclohexil	Me	Cl	H	F	
Ejemplo 438:	Ciclohexil	Me	OMe	H	F	 Quiral

Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 439:	Ciclohexil	Me	OMe	H	H	
Ejemplo 440:	Ciclohexil	Me	OMe	H	H	
Ejemplo 441:	Ciclohexil	Me	OMe	H	H	
Ejemplo 442:	Ciclohexil	Me	OMe	H	F	
Ejemplo 443:	Ciclohexil	Me	OMe	H	F	

Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 444:	Ciclohexil	Me	OMe	H	F	
Ejemplo 445:	Ciclohexil	Me	OMe	H	F	
Ejemplo 446:	Ciclohexil	Me	F	H	H	
Ejemplo 448:	Ciclopentil	Me	F	H	F	 Quiral
Ejemplo 449:	Ciclohexil	Me	F	H	F	 Quiral
Ejemplo 450:	Ciclohexil	H	F	H	H	 Quiral



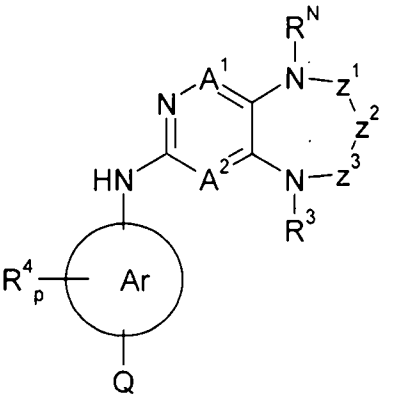
Ejemplo	R^3	R^N	R^{12}	R^{13}	R^{15}	R^5
Ejemplo 409:	Ciclopentil	Me	OMe	H	H	



Ejemplo	R^3	R_c	R_d	R^N	R^{12}	R^{13}	R^{15}
Ejemplo 3:	Ciclopentil	Me Racemato		Me	OMe	H	H
Ejemplo 236:	Ciclopentil	Et	H	Me	OMe	H	H
Ejemplo 237:	Ciclopentil	H	Et	Me	OMe	H	H
Ejemplo 238:	Ciclopentil	^{n}Pr	H	Me	OMe	H	H
Ejemplo 239:	Ciclopentil	H	^{n}Pr	Me	OMe	H	H
Ejemplo 240:	Ciclopentil	Me	H	Me	OMe	H	H
Ejemplo 241:	Ciclopentil	H	Me	Me	OMe	H	H

REIVINDICACIONES

1. Un compuesto de fórmula (I):



(I)

donde

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un anillo heteroaril opcionalmente sustituido que comprende 1, 2 ó 3 heteroátomos cada uno independientemente seleccionado de nitrógeno, oxígeno o azufre;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo

opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

R^N representa hidrógeno, $-NH_2$, $-OH$, $-CN$, $-C{\equiv}CH$, $-C(=O)NH_2$, C_{1-3}alquil, C_{1-3}alquilamino, C_{1-3}alquiltio, C_{1-3}alquiloxi, C_{1-3}alquilcarbonil, $-CHO$ o $-SO_2Me$

p es 0, 1 ó 2;

Q es $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, $-(C_{1-3}$alquil opcionalmente sustituido$)_g-NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ o –(anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno o azufre)$-L_n-R^5{}_m$;

g es 0 ó 1;

k es 0, 1 ó 2;

R^a representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^b representa $-L_n-R^5{}_m$, o R^a y R^b junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a2} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b2} representa $-L_n-R^5{}_m$, o R^{a2} y R^{b2} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a3} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b3} representa $-L_n-R^5{}_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, o R^{a3} y R^{b3} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a4} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b4} representa $-L_n-R^5{}_m$, o R^{a4} y R^{b4} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a5} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b5} representa $-L_n-R^5{}_m$, o R^{a5} y R^{b5} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a6} representa $-L_n-R^5{}_m$;

R^{a7} representa $-L_n-R^5{}_m$;

R^{a8} representa $-L_n-R^5{}_m$;

R^{a9} representa $-L_n-R^5{}_m$;

R^{a10} representa $-L_n-R^5{}_m$;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido, grupo C_{7-12}policicloalquil opcionalmente sustituido, grupo C_{7-12}policicloalquenil opcionalmente sustituido, grupo C_{5-12}espirocicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1

m es 1 ó 2

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azaciclohéptil opcionalmente sustituido, granatano opcionalmente sustituido, oxogranatano opcionalmente sustituido y $-NR^8R^9$;

R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido;

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil–C_{3-10}cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil–

C_{6-14}aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril–C_{1-4}alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

X^1 es O o S;

X^2 es O, S o H_2;

Ar representa un anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno o azufre; y

A^1, A^2 cada uno independientemente representa un N o CH;

y donde

cuando Z^1 es C=O, Z^2 es CR^cR^d o NR^c, y Z^3 es CR^1R^2;

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c representa hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido; u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d, o R^1 y R^c juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

o cuando Z^2 es C=O, Z^1 es $CR^{12}R^{g2}$ y Z^3 es CR^1R^2;

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^{f2}, R^{g2} cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^{f2} y R^{g2} junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos, u opcionalmente uno de R^1 y R^3, o R^2 y R^3 juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

o cuando Z^3 es C=O, Z^2 es $CR^{c3}R^{d3}$ o NR^{e3} y Z^1 es $CR^{f3}R^{g3}$;

R^{c3}, R^{d3} cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^{c3} y R^{d3} junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^{e3} representa hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido;

R^{f3}, R^{g3} cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^{f3} y R^{g3} junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos; u opcionalmente uno de R^{c3} y R^{f3}, o R^{d3} y R^{g3}, o R^{e3} y R^{f3} juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo

o cuando Z^1 es CR^fR^g, Z^2 es CR^cR^d o NR^e, y Z^3 es CR^1R^2;

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y

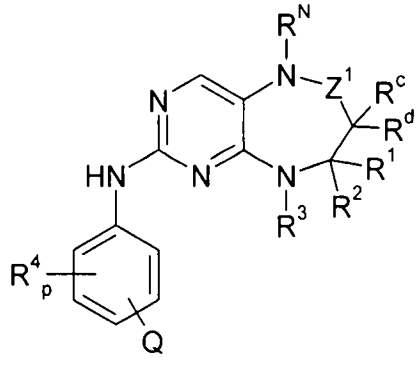
R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c representa hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido;

R^f, R^g cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^f y R^g junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos; u opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d, o R^1 y R^{c3} juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo,

o sales farmacológicamente aceptables del mismo.

2. Un compuesto de fórmula (II):



(II)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y

R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil opcionalmente sustituido de 4 a 12 miembros que comprende 1 ó 2 heteroátomos; u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

R^N representa hidrógeno, $-NH_2$, –OH, –CN, –C=CH, $-C(=O)NH_2$, C_{1-3}alquil, C_{1-3}alquilamino, C_{1-3}alquiltio, C_{1-3}alquiloxi, C_{1-3}alquilcarbonil, –CHO o $-SO_2Me$;

p es 0, 1 ó 2;

Q es $-C(=X^1)-NR^aR^b$, $-S(O)_2-NR^{a2}R^{b2}$, $-(C_{1-3}$alquil opcionalmente sustituido$)_g-NR^{a3}R^{b3}$, $-S(O)_k-R^{a8}$, $-C(=X^2)-OR^{a9}$, $-OR^{a10}$ o –(anillo aromático o heteroaromático de 5 ó 6 miembros que comprende opcionalmente al menos un heteroátomo del anillo seleccionado de nitrógeno, oxígeno o azufre)$-L_n-R^5{}_m$;

g es 0 ó 1;

k es 0, 1 ó 2;

R^a representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^b representa $-L_n-R^5{}_m$, o R^a y R^b junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a2} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b2} representa $-L_n-R^5{}_m$, o R^{a2} y R^{b2} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a3} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b3} representa $-L_n-R^5{}_m$, $-SO_2NR^{a4}R^{b4}$, $-C(=O)NR^{a5}R^{b5}$, $-SO_2R^{a6}$, $-C(=O)OR^{a7}$, o R^{a3} y R^{b3} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a4} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b4} representa $-L_n-R^5{}_m$, o R^{a4} y R^{b4} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a5} representa H o un grupo C_{1-6}alquil opcionalmente sustituido, y R^{b5} representa $-L_n-R^5{}_m$, o R^{a5} y R^{b5} junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales;

R^{a6} representa $-L_n-R^5{}_m$;

R^{a7} representa $-L_n-R^5{}_m$;

R^{a8} representa $-L_n-R^5{}_m$;

R^{a9} representa $-L_n-R^5{}_m$;

R^{a10} representa $-L_n-R^5{}_m$;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil-C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril-C_{1-4}alquil opcionalmente sustituido, C_{3-}

$_{12}$cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1

m es 1 ó 2

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azaciclohéptil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido;

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril$-C_{1-4}$alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales; y Z^1 es C=O o CR^fR^g donde R^f, R^g cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^f y R^g junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos,

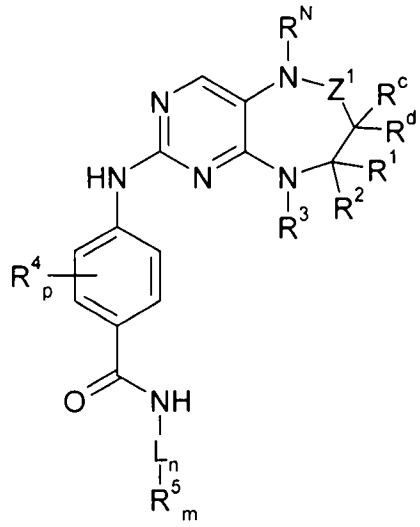
o sales farmacológicamente aceptables del mismo.

3. Un compuesto de acuerdo a la Reivindicación 1 ó 2 donde R^N representa C_{1-3}alquil.

4. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 3 donde R^N representa metil o etil.

5. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 4 donde Q representa $-C(=X^1)-NR^aR^b$, donde X^1 es O, o $-CH_2-NR^{a3}R^{b3}$.

6. Un compuesto de fórmula (IIa):



(IIa)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y

R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos; u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

R^N representa hidrógeno, $-NH_2$, –OH, –CN, –C=CH, $-C(=O)NH_2$, C_{1-3}alquil, C_{-1-3}alquilamino, C_{1-3}alquiltio, C_{1-3}alquiloxi, C_{1-3}alquilcarbonil, –CHO o $-SO_2Me$;

p es 0, 1 ó 2;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-}

$_{12}$cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1

m es 1 ó 2

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azaciclohéptil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

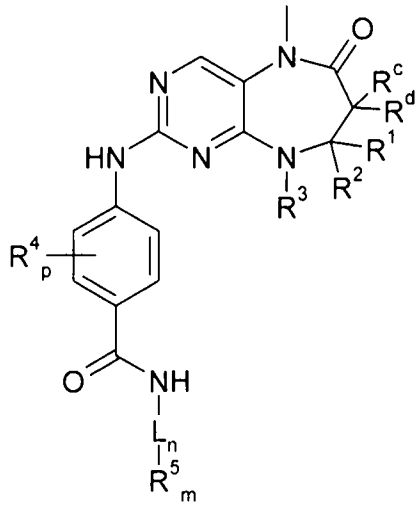
R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido;

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril$-C_{1-4}$alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales; y Z^1 es C=O o CR^fR^g donde R^f, R^g cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^f y R^g junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos,

o sales farmacológicamente aceptables del mismo.

7. Un compuesto de acuerdo a la Reivindicación 6 donde Z^1 es C=O o CH_2.

8. Un compuesto de fórmula (III):



(III)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno o un grupo C_{1-6}alquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que

comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos; u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^4 cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

p es 0, 1 ó 2;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1;

m es 1 ó 2;

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azaciclohéptil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido; y

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril$-C_{1-4}$alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales,

o una sal farmacológicamente aceptable del mismo.

9. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 6 a 8 donde R^1 y R^2 son hidrógeno.

10. Un compuesto de acuerdo a la Reivindicación 9 donde uno de R^c o R^d es hidrógeno.

11. Un compuesto de acuerdo a la Reivindicación 10 donde uno de R^c o R^d es hidrógeno y el otro es metil.

12. Un compuesto de acuerdo a la Reivindicación 9 donde R^c y R^d son metil.

13. Un compuesto de acuerdo a la Reivindicación 9 donde R^c y R^d juntos representan un puente etileno.

14. Un compuesto de acuerdo a la Reivindicación 9 donde R^c y R^d pueden ser idénticos o diferentes y representan hidrógeno o un grupo C_1-C_6alquil opcionalmente sustituido por uno o

más sustituyentes seleccionados de C_{1-3}alquiloxi, C_{1-3}alquiltio, C_{1-3}alquil–$S(O)_2$, C_{1-3}alquilamino y di–(C_{1-3}alquil)amino.

15. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 14 donde R^3 representa ciclopentil o ciclohexil.

16. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 15 donde cuando p es 1, R^4 representa metoxi, metil, etoxi, cloro o flúor.

17. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 15 donde cuando p es 2, cada R^4 puede ser igual o diferente y seleccionado de metoxi, metil, etoxi, etil, propargiloxi, cloro o flúor.

18. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 15 donde cuando p es 2 y cuando cada R^4 es adyacente, ambos R^4 junto con los átomos del anillo aromático al cual están unidos forman un anillo insaturado de 4 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos.

19. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 18 donde cuando n es 1, L representa un C_{2-10}alquil opcionalmente sustituido o un enlazador C_{3-12}cicloalquil opcionalmente sustituido.

20. Un compuesto de acuerdo a la Reivindicación 19 donde cuando n es 1, L representa ciclohexil, $-C(CH_3)_2-CH_2-$ o $-CH_2-C(CH_3)_2-CH_2-$.

21. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 20 donde n es 0.

22. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 1 a 21 donde m es 1 y R^5 representa hidrógeno, $-NR^8R^9$ o un piperidinil, morfolinil, pirrolidinil, sulfoxomorfolinil, piperazinil, tiomorfolinil, tropenil, granatanil, oxogranatanil o

azaciclohéptil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8.

23. Un compuesto de acuerdo a la Reivindicación 22 donde R^5 representa un piperidinil, pirrolidinil, o granatanil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8.

24. Un compuesto de acuerdo a la Reivindicacións 22 ó 23 donde R^8 representa metil, etil o propil, y/o R^9 representa metil, etil o propil.

25. Un compuesto de acuerdo a la Reivindicación 8 donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido o C_{6-14}aril opcionalmente sustituido; p es 0 ó 1; R^4 representa OMe, OH, Me, Et, Pr, OEt, NHMe, NH_2, F, Cl, Br, O–propargil, O–butinil, CN, SMe, NMe_2, $CONH_2$, etinil, propinil, butinil o alil; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno en el anillo; n denota 0 ó 1; m denota 1 ó 2; R^5 denota hidrógeno o un grupo, que es enlazado a L a través de un átomo de carbono, seleccionado de entre $-NR^8R^9$, piperidinil, piperazinil, pirrolidinil, piperazinilcarbonil, tropenil, morfolinil, granatanil, oxogranatanil y azaciclohéptil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa hidrógeno, C_{1-6}alquil, $-C_{1-4}$alquil–C_{3-10}cicloalquil, C_{3-10}cicloalquil, C_{6-14}aril, $-C_{1-4}$alquil–C_{6-14}aril, piranil, piridinil, pirimidinil, C_{1-4}alquiloxicarbonil, C_{6-14}arilcarbonil, C_{1-4}alquilcarbonil, C_{6-14}arilmetiloxicarbonil, C_{6-14}arilsulfonil, C_{1-4}alquilsulfonil o C_{6-14}aril–C_{1-4}alquilsulfonil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me o Et, o R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables del mismo.

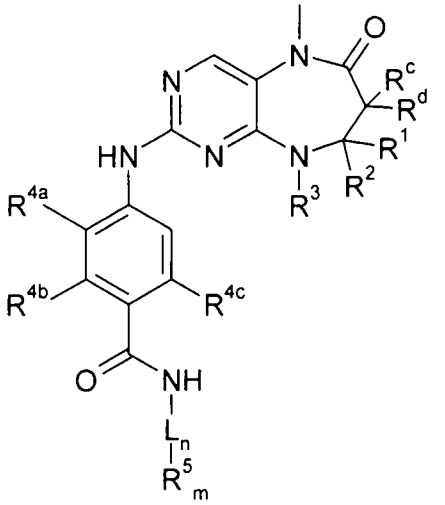
26. Un compuesto de acuerdo a la Reivindicación 25 donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; p es 0, 1 ó 2; R^4 cada uno independientemente representa un fluoro o OMe; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y piperidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me o Et, o R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables del mismo.

27. Un compuesto de acuerdo a la Reivindicación 25 donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; p es 0, 1 ó 2; R^4 cada uno independientemente representa un fluoro o OMe; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y pirrolidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me o Et, o R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables del mismo.

28. Un compuesto de acuerdo a la Reivindicación 25 donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; p es 0, 1 ó 2; R^4 cada uno independientemente representa un fluoro o OMe; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y granatanil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me o Et, o

R^c y R^d juntos representan un puente etileno, o sales farmacológicamente aceptables del mismo.

29. Un compuesto de fórmula (IIIa):



(IIIa)

donde

R^1, R^2 cada uno independientemente representa un hidrógeno o un grupo C_{1-6}alquil opcionalmente sustituido, o R^1 y R^2 junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^c, R^d cada uno independientemente representa un hidrógeno, un grupo C_{1-6}alquil opcionalmente sustituido o un grupo C_{3-6}cicloalquil opcionalmente sustituido, o R^c y R^d junto con el átomo de carbono al cual están unidos forman un anillo saturado o insaturado de 3 a 6 miembros que comprende opcionalmente de 1 a 2 heteroátomos;

R^3 representa hidrógeno, un grupo C_{1-12}alquil opcionalmente sustituido, un grupo C_{2-12}alquenil opcionalmente sustituido, un grupo C_{2-12}alquinil opcionalmente sustituido, un grupo C_{6-14}aril opcionalmente sustituido, un grupo C_{3-12}cicloalquil opcionalmente sustituido, un grupo C_{3-12}cicloalquenil opcionalmente sustituido, un grupo C_{7-12}policicloalquil opcionalmente sustituido, un grupo C_{7-12}policicloalquenil opcionalmente sustituido, un grupo C_{5-12}espirocicloalquil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que

comprende 1 ó 2 heteroátomos, o un grupo heterocicloalquenil de 4 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos; u

opcionalmente uno de R^1 y R^3, o R^2 y R^3, o R^1 y R^c, o R^2 y R^d juntos representan un puente C_{1-4}alquil saturado o insaturado que comprende opcionalmente 1 heteroátomo;

R^{4a}, R^{4b}, R^{4c} cada uno independientemente representa –CN, hidroxi, $-NR^6R^7$, $-NR^6SO_2R^7$, halógeno, un grupo C_{1-6}alquil opcionalmente sustituido, un grupo C_{3-7}cicloalquil opcionalmente sustituido, un grupo C_{2-6}alquenil opcionalmente sustituido, un grupo C_{2-6}alquinil opcionalmente sustituido, un grupo C_{1-5}alquiloxi opcionalmente sustituido, un grupo C_{3-6}cicloalquiloxi opcionalmente sustituido, un grupo C_{2-5}alqueniloxi opcionalmente sustituido, un grupo C_{2-5}alquiniloxi opcionalmente sustituido, un grupo C_{1-6}alquitio opcionalmente sustituido, un grupo C_{1-6}alquilsulfoxo opcionalmente sustituido o un grupo C_{1-6}alquilsulfonil opcionalmente sustituido, un grupo heterocicloalquil de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos, o un grupo heterocicloalcoxi de 3 a 12 miembros opcionalmente sustituido que comprende 1 ó 2 heteroátomos;

p es el número de grupos $R^{4a, 4b, 4c}$ que no son hidrógeno y es seleccionado de 0, 1 ó 2;

L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido, C_{2-10}alquenil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{2-4}$alquil–C_{6-14}aril opcionalmente sustituido, $-C_{6-14}$aril–C_{1-4}alquil opcionalmente sustituido, C_{3-12}cicloalquil opcionalmente sustituido y heteroaril opcionalmente sustituido que comprende 1 ó 2 átomos de nitrógeno;

n es 0 ó 1;

m es 1 ó 2;

R^5 representa un grupo seleccionado de entre hidrógeno, morfolinil opcionalmente sustituido, piperidinil opcionalmente sustituido, piperazinil opcionalmente sustituido, piperazinilcarbonil opcionalmente sustituido, pirrolidinil opcionalmente sustituido, tropenil opcionalmente sustituido, dicetometilpiperazinil opcionalmente sustituido, sulfoxomorfolinil opcionalmente sustituido, sulfonilmorfolinil opcionalmente sustituido, tiomorfolinil opcionalmente sustituido, azaciclohéptil opcionalmente sustituido, granatanil opcionalmente sustituido, oxogranatanil opcionalmente sustituido y $-NR^8R^9$;

R^6, R^7 cada uno independientemente representa un hidrógeno o un grupo C_{1-4}alquil opcionalmente sustituido; y

R^8, R^9 cada uno independientemente representa un hidrógeno, C_{1-6}alquil opcionalmente sustituido, $-C_{1-4}$alquil$-C_{3-10}$cicloalquil opcionalmente sustituido, C_{3-10}cicloalquil opcionalmente sustituido, C_{6-14}aril opcionalmente sustituido, $-C_{1-4}$alquil$-C_{6-14}$aril opcionalmente sustituido, piranil opcionalmente sustituido, piridinil opcionalmente sustituido, pirimidinil opcionalmente sustituido, C_{1-4}alquiloxicarbonil opcionalmente sustituido, C_{6-14}arilcarbonil opcionalmente sustituido, C_{1-4}alquilcarbonil opcionalmente sustituido, C_{6-14}arilmetiloxicarbonil opcionalmente sustituido, C_{6-14}arilsulfonil opcionalmente sustituido, C_{1-4}alquilsulfonil opcionalmente sustituido, C_{6-14}aril$-C_{1-4}$alquilsulfonil opcionalmente sustituido, o R^8 y R^9 junto con el átomo de nitrógeno al cual están unidos forman un anillo heterocíclico saturado o insaturado, puenteado o no puenteado, de 3 a 7 miembros que comprende opcionalmente de 1 a 2 heteroátomos adicionales,

o una sal farmacológicamente aceptable del mismo.

30. Un compuesto de acuerdo a la Reivindicación 29 donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y piperidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me o Et, o R^c y R^d juntos representan un puente etileno; p es 0, 1 ó 2; y cuando p es 1, R^{4b} y R^{4c} son hidrógeno y R^{4a} representa metoxi, metil, etoxi, cloro o flúor; y cuando p es 2, o bien R^{4b} es hidrógeno y R^{4a} y R^{4c} pueden ser iguales o diferentes y seleccionados de metoxi, metil, etoxi, cloro o flúor, o R^{4c} es hidrógeno y R^{4a} y R^{4b} juntos forman un puente OCH_2O, o sales farmacológicamente aceptables del mismo.

31. Un compuesto de acuerdo a la Reivindicación 29 donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-}

$_6$heterocicloalquil opcionalmente sustituido; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y pirrolidinil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me o Et, o R^c y R^d juntos representan un puente etileno; p es 0, 1 ó 2; y cuando p es 1, R^{4b} y R^{4c} son hidrógeno y R^{4a} representa metoxi, metil, etoxi, cloro o flúor; y cuando p es 2, o bien R^{4b} es hidrógeno y R^{4a} y R^{4c} pueden ser iguales o diferentes y seleccionados de metoxi, metil, etoxi, cloro o flúor, o R^{4c} es hidrógeno y R^{4a} y R^{4b} juntos forman un puente OCH_2O, o sales farmacológicamente aceptables del mismo.

32. Un compuesto de acuerdo a la Reivindicación 29 donde R^3 representa un grupo C_{1-10}alquil opcionalmente sustituido, C_{3-7}cicloalquil opcionalmente sustituido, C_{3-6}heterocicloalquil opcionalmente sustituido; L representa un enlazador seleccionado de C_{2-10}alquil opcionalmente sustituido; n denota 0 ó 1; m denota 1 ó 2; R^5 denota un grupo seleccionado de entre $-NR^8R^9$ y granatanil cada uno opcionalmente sustituido por uno o más grupos como es definido para R^8; R^8, R^9 cada uno independientemente representa C_{1-6}alquil; R^1, R^2 son hidrógeno; R^c, R^d son cada uno independientemente seleccionados de hidrógeno, Me o Et, o R^c y R^d juntos representan un puente etileno; p es 0, 1 ó 2; y cuando p es 1, R^{4b} y R^{4c} son hidrógeno y R^{4a} representa metoxi, metil, etoxi, cloro o flúor; y cuando p es 2, o bien R^{4b} es hidrógeno y R^{4a} y R^{4c} pueden ser iguales o diferentes y seleccionados de metoxi, metil, etoxi, cloro o flúor, o R^{4c} es hidrógeno y R^{4a} y R^{4b} juntos forman un puente OCH_2O, o sales farmacológicamente aceptables de los mismos.

33. Un compuesto de acuerdo a una cualquiera de las Reivindicaciones 25, 26, 27, 28, 30, 31 ó 32 donde R^3 representa ciclopentil o ciclohexil.

34. Un compuesto de acuerdo a la Reivindicacións 33 donde R^8 representa metil, etil o propil, y/o R^9 representa metil, etil o propil.

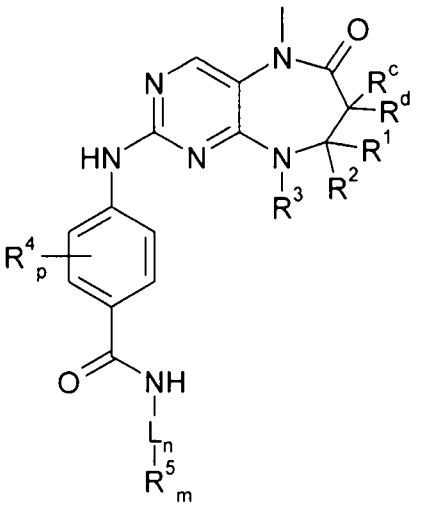
35. Un compuesto seleccionado de uno cualquiera de los Ejemplos o sales farmacológicamente aceptables del mismo.

36. Un compuesto seleccionado de uno cualquiera de los Ejemplos 4, 7, 26, 27, 47, 51, 53, 56, 77, 97, 99, 101, 104, 106, 108, 110, 113, 114, 135, 176, 182, 184, 191, 197, 202, 219, 234, 238, 239, 242, 269, 278, 279, 281, 282, 285, 289, 290, 293, 294, 295, 301, 302, 309, 310, 311, 330, 331, 390, 405, 411, 413, 416, 419, 429, 451, 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415, 417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 y 453, o sales farmacológicamente aceptables del mismo.

37. Un compuesto seleccionado de uno cualquiera de los Ejemplos 1, 2, 3, 6, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 25, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 52, 54, 55, 57, 58, 59, 60, 61, 62, 63, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 78, 79, 80, 81, 82, 83, 84, 85, 86, 88, 90, 91, 92, 93, 94, 95, 96, 98, 109, 181, 185, 188, 189, 193, 194, 199, 200, 201, 203, 205, 206, 207, 208, 209, 210, 212, 213, 217, 235, 236, 237, 240, 241, 243, 244, 245, 246, 280, 283, 288, 291, 292, 298, 299, 300, 303, 304, 305, 306, 307, 308, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 325, 326, 327, 328, 329, 333, 334, 335, 336, 337, 338, 340, 341, 342, 343, 344, 345, 346, 347, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 382, 383, 384, 385, 386, 387, 388, 389, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 406, 407, 408, 409, 412, 414, 415,

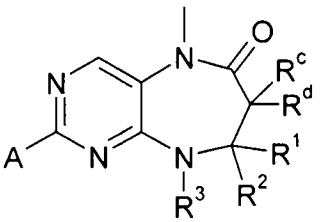
417, 418, 420, 421, 422, 423, 424, 425, 426, 427, 428, 430, 431, 432, 433, 434, 435, 436, 437, 438, 440, 441, 442, 443, 444, 445, 446 y 453, o sales farmacológicamente aceptables del mismo.

38. Un proceso para preparar un compuesto de fórmula general (III),



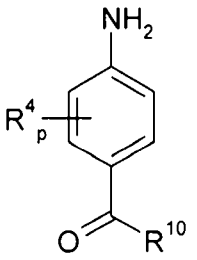
(III)

donde R^1–R^5, R^c, R^d m, n, p y L son como los definidos aquí anteriormente, que comprende reaccionar un compuesto de fórmula general (IV)



(IV)

donde R^1–R^3 son como los definidos aquí anteriormente y A es un grupo saliente, con un compuesto opcionalmente sustituido de fórmula general (V):



(V)

donde p y R^4 son como los definidos aquí anteriormente; y R^{10} denota OH, $NH–L_m–R^5{}_n$, OMe, OEt,

y cuando R^{10} denota OH, OMe o OEt opcionalmente después de la hidrólisis previa del grupo éster $–COR^{10}$, reaccionar con una amina de fórmula general (VI):

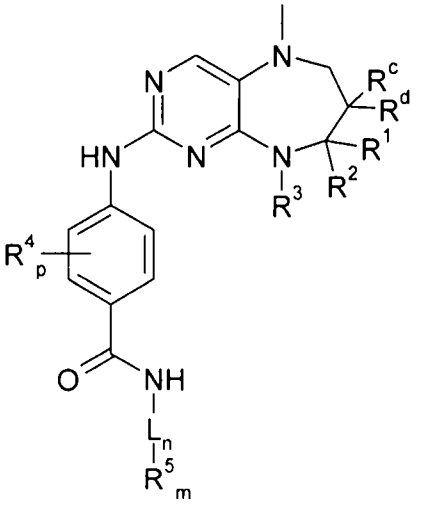
$$NH_2 –L_m–R^5{}_n$$

(VI)

donde R^5 es como el definido aquí anteriormente,

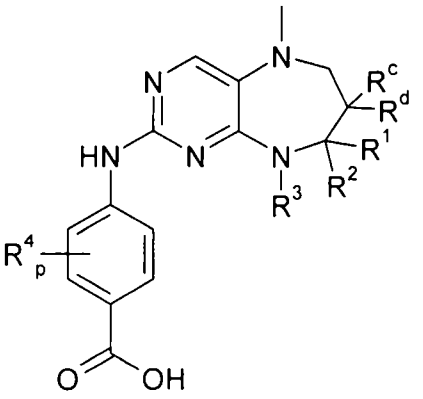
para dar un compuesto de fórmula (III).

39. Un proceso para preparar un compuesto de fórmula general (XI),



donde $R^1–R^5$, R^c, R^d m, n, p y L son como los definidos aquí anteriormente,

que comprende reaccionar un compuesto de fórmula general (XII)



(XII)

con una amina de fórmula general (VI):

$$NH_2 - L_m - R^5{}_n$$

(VI)

donde L y R^5 son como los definidos aquí anteriormente.

40. Una composición farmacéutica que comprende un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como es reivindicado en una cualquiera de las Reivindicaciones 1 a 37 en asociación con un portador, diluente o adyuvante farmacéuticamente aceptable.

41. Un proceso para la preparación de una composición farmacéutica como es reivindicado en la Reivindicación 40 el cual comprende mezclar un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como es definido en una cualquiera de la Reivindicaciones 1 a 37 con un portador, diluente o adyuvante farmacéuticamente aceptable.

42. Un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como es reivindicado en una cualquiera de las Reivindicaciones 1 a 37 para su uso en terapia.

43. Uso de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como es reivindicado en una cualquiera de las Reivindicaciones 1 a 37 en la fabricación de un medicamento para el tratamiento del cáncer.

44. Uso de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como es reivindicado en una cualquiera de las Reivindicaciones 1 a 37 en la fabricación de un medicamento para modular la actividad quinasa tipo polo (Plk).

45. Un método de tratar el cáncer el cual comprende administrar a un paciente una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como es reivindicado en una cualquiera de las Reivindicaciones 1 a 37.

46. Un método de modular la actividad quinasa tipo polo (Plk) el cual comprende administrar a un paciente en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de fórmula (I), (II), (IIa), (III) o (IIIa), o una sal farmacéuticamente aceptable del mismo, como es reivindicado en una cualquiera de las Reivindicaciones 1 a 37.

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(71) Applicant *(for all designated States except MG, US)*: **ASTRAZENECA AB** [SE/SE]; S-SE-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)*: **HALSALL, Christopher, Thomas** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **RUDGE, David, Alan** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **SIMPSON, Iain** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB). **WARD, Richard, Andrew** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield Cheshire SK10 4TG (GB).

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

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

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

Published:
— *with international search report*
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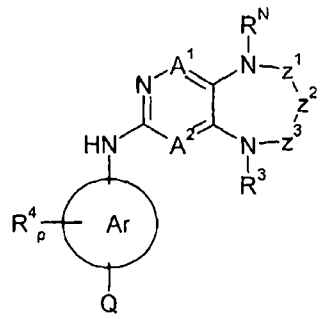
(88) Date of publication of the international search report:
6 March 2008

(54) Title: FUSED PYRIMIDO COMPOUNDS



(I)

(57) Abstract: There is provided a compound of formula (I):processes for the manufacure thereof, pharmaceutical compoitions thereof and uses in therapy.

WO 2008/003958 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2007/002490

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/522

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

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, 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.
E	WO 2007/095188 A (VERTEX PHARMA [US]; DAMIEN-CHARRIER JEAN [GB]; KAY DAVID [GB]; KNEGTEL) 23 August 2007 (2007-08-23) the whole document	1-46
A	US 2006/035902 A1 (LINZ GUENTER [DE] ET AL) 16 February 2006 (2006-02-16) the whole document	1-46
A	WO 03/020722 A (BOEHRINGER INGELHEIM PHARMA [DE]; HOFFMANN MATTHIAS [DE]; GRAUERT MATT) 13 March 2003 (2003-03-13) cited in the application the whole document	1-46

☐ Further documents are listed in the continuation of Box C.

☒ 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
8 January 2008	16/01/2008

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2007/002490

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

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

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

Although claims 45 and 46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2007/002490

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007095188 A	23-08-2007	NONE	
US 2006035902 A1	16-02-2006	AR 052404 A1	21-03-2007
		AU 2005274340 A1	23-02-2006
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-138249- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1001

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SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

1602

Edgar Navarro

Firma Responsable

Fecha 30-12-08

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia