PCT

OF

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-011427- -00000-0000

Fecha: 2011-02-01 18:19:42 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 247

Industria y Comercio

SUPERINTENDENCIA

11-11427

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE

INVENCIÓN

TITULO: COMPUESTOS QUIMICOS 251

SOLICITANTE: ASTRAZENECA AB

DIRECCIÓN: S-SE-151 85 Södertälje, Suecia

APODERADO: CARLOS R. OLARTE

BOGOTÁ 01 de Febrero de 2011

P2011/000016

02-02-2011

OLARTEM

OLARTE MOURE & ASC

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-011427- -00000-0000
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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000016**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: **ASTRAZENECA AB**
Dirección: S-SE-151 85 Södertälje
Nacionalidad o Domicilio: Suecia
Lugar de Constitución: Suecia

Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Diagonal 34 No. 5-28 Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [x] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5) **PCT (86)**

Solicitud Internacional No. PCT/GB2009/050773 Fecha Julio 2, 2009

Publicación Internacional No. WO 2010/001169 Fecha Enero 7, 2010

(6) **Título (54)** **COMPUESTOS QUÍMICOS 251**

Clasificación Internacional (51) A61K 31/426, A61K 31/427, A61P 35/00, C07D 277/34

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Julio 2, 2008	61/077.639
US	Junio 2, 2009	61/183,278

(9) **Comprobante de pago No.** 11- **Fecha** Febrero de 2011

(10) **ANEXOS**

2

[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 Exp. Nº 08-139.814

[ ] Documento de cesión del inventor al solicitante o a su causante.

[ ] Declaraciones.

[x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

[x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

[x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

[ ] Traducción del examen preliminar internacional efectuado por la IPEA.

[ ] De ser el caso, copia del contrato de acceso.

[ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

[ ] De ser el caso, certificado de depósito del material biológico.

[ ] Arte final 12 x 12.

[ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

[ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.

[x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

LISTA DE INVENTORES

PCT/GB2009/050773

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Nacioanalidad: Estadounidense

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Nacioanalidad: Estadounidense

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Estados Unidos
Nacioanalidad: China

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 009206

Bogotá D.C., Febrero 01 de 2011 - 16:51:59

RECIBIDO DE : OLARTERAISBECK NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	353914470	01/02/2011	4.568.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	571.000.00	571.000.00
				$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: _____
****

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-011427- -00000-0000

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5

Traducción oficial de un documento cuyo original está en inglés

No. 11426

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

En Estocolmo, este día 14 de Agosto de 2007.

(Firmado)

Hay un sello del Ministerio de Relaciones Exteriores de Suecia.

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

Firma de Agneta S...

Y sello de ...

Firma: Mohamed Hussein.

Fecha: 20 de Agosto de 2007.

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

Certificación Notarial

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

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

Ex oficio:

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

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

Apostilla adjunta:

APOSTILLE
(Convention du La Haye du 5 octobre 1961)

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

Certificación:

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

Fecha: 13 de Noviembre de 2007.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

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

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

X

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

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

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

Power of Attorney

Poder

The undersigned, El suscrito,

AstraZeneca AB

domiciled in domiciliado en

Vastra Malarenamnen 9 S-151 85 Sodertalje, 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 anto 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: SODERTALJE

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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:- Crowns

Stockholm 2007-10-26
Ex officio:

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

Anders Burén
Authorized Signatory

10

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	Certificación Notarial
On this date,	En esta fecha,
The undersigned Notary Public certifies:	el Notario Público suscrito certifica:
1. That	1. Que
of legal age and domiciled in	mayor de edad y domiciliado
signed the foregoing document.	suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as DULY AUTHORISED SIGNATORY of ASTRAZENECA AB	2. Que el otorgante ha suscrito el referido documento en su carácter de de
3. That ASTRAZENECA AB having its principal place of business located in SODERTALJE, SWEDEN	4. Que con sede principal ubicada en
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.	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. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):	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):
1. CERTIFICATE OF INCORPORATION OF ASTRAZENECA AB	
2. AUTHORISATION IN FAVOUR OF SIGNATORY	

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

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

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 REYES
Licencia 376 - 1993 Minjusticia

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

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

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

Certificación Notarial

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

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

Ex oficio:

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

Apostilla adjunta:

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

13

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 REYES
Licencia 376 - 1993 Minjusticia

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:**



Bolagsverket

851 81 Sundsvall
Besöksadress: 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
ANNIE-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

No. 11436

The Ministry for Foreign Affairs in Stockholm, hereby certifies that

Mrs. Anna-Karin Björa

Swedish Companies Registration Office, Sundsvall

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

For Stockholm this 14th day of August 2007

FEE PAID

Agneta Ödeen Lund

SIGNATURE OF Agneta Ödeen Lund

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
7 January 2010 (07.01.2010)

PCT

(10) International Publication Number
WO 2010/001169 A2

(51) International Patent Classification:
A61K 31/426 (2006.01)

(21) International Application Number:
PCT/GB2009/050773

(22) International Filing Date:
2 July 2009 (02.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/077,639	2 July 2008 (02.07.2008)	US
61/183,278	2 June 2009 (02.06.2009)	US

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

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DAKIN, Leslie** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **DOWLING, James, Edward** [US/US]; Astrazeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **LAMB, Michelle** [US/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **READ, Jon** [GB/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **SU, Qibin** [CN/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US). **ZHENG, Xiaolan** [CN/US]; AstraZeneca R & D Boston, 35 Gatehouse Drive, Waltham, Massachusetts 02451 (US).

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

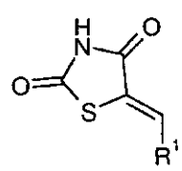
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG,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

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(54) Title: CHEMICAL COMPOUNDS 251



(I)

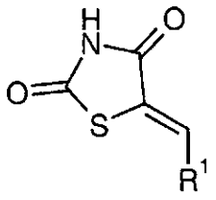
(57) Abstract: The invention relates to chemical compounds of formula (I), and salts thereof. In some embodiments, the invention relates to inhibitors or modulators of PIM-1 and/or PIM-2, and/or PIM-3 protein kinase activity or enzyme function. In still further embodiments, the invention relates to pharmaceutical compositions comprising compounds disclosed herein, and their use in the prevention and treatment of PIM kinase related conditions and diseases, preferably cancer.

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CHEMICAL COMPOUNDS 251

FIELD OF INVENTION

The invention relates to chemical compounds of formula I,



formula I

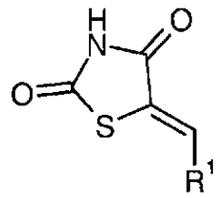
and salts thereof. In some embodiments, the invention relates to inhibitors or modulators of PIM-1 and/or PIM-2, and/or PIM-3 protein kinase activity or enzyme function. In still further embodiments, the invention relates to pharmaceutical compositions comprising compounds disclosed herein, and their use in the prevention and treatment of PIM kinase related conditions and diseases, preferably cancer.

BACKGROUND

PIM-1 gene was first identified as a proviral insertion site in Moloney murine leukemia virus-induced T-cell lymphoma. PIM-1 gene translates a Ser/Thr protein kinase. The known PIM kinase family also includes PIM-2 and PIM-3. Mice studies suggest that physiologically the PIM kinases are involved in growth factor and cytokine signaling. Deregulated PIM kinase expression occurs a in large number of hematopoietic tumors, such as myeloid and lymphoblastic leukemias and lyphomas. PIM kinases are also expressed in solid tumors, such as prostate cancer and pancreatic cancer, and transgenic mice which express PIM-1 develop T-cell lymphoma. Dhanasekaran et al., (2001). Nature 412: 822–826 and Li et al., (2006) Cancer Res 66: 6741–6747. Accordingly, it is believed that PIM Kinase inhibitors will be useful in the treatment and/or prevention of cancer. Thus, there is a need to identify inhibitors of PIM kinases.

SUMMARY OF INVENTION

The invention relates to chemical compounds of formula I,



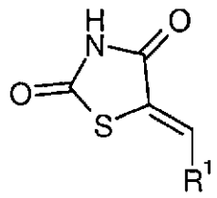
formula I

and salts thereof. In some embodiments, the invention relates to inhibitors or modulators of PIM-1 and/or PIM-2, and/or PIM-3 protein kinase activity or enzyme function. In still further embodiments, the invention relates to pharmaceutical compositions comprising compounds disclosed herein, and their use in the prevention and treatment of PIM kinase related conditions and diseases, preferably cancer.

DETAILED DESCRIPTION

The invention relates to a method of treating or preventing cancer comprising,

a) providing a pharmaceutical composition comprising a compound of formula I,



formula I,

or pharmaceutically acceptable salts thereof, functioning to inhibit a PIM kinase, wherein

R^1 is selected from a carbocyclyl, aryl, and heterocyclyl, wherein R^1 is optionally substituted with one or more, the same or different, R^2;

R^2 is selected from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^2 is optionally substituted with one or more, the same or different, R^3;

R^3 is selected from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^3 is optionally substituted with one or more, the same or different, R^4;

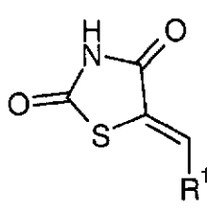
R^4 is selected from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^4 is optionally substituted with one or more, the same or different, R^5; and

R^5 is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl; and

b) administering said pharmaceutical composition to a subject diagnosed with, exhibiting symptoms of, or at risk for cancer with the proviso that said compound of formula I is not 5-[[2-[(2,6-dichloro-3-methylphenyl)amino]phenyl]methylene]-2,4-thiazolidinedione.

In some embodiments, the invention relates to a method of treating or preventing cancer comprising,

a) providing a pharmaceutical composition comprising a compound of formula I,



formula I,

or salts thereof, functioning to inhibit a PIM kinase, wherein

R^1 is selected from a carbocyclyl, aryl, and heterocyclyl, wherein R^1 is optionally substituted with one or more, the same or different, R^2;

R^2 is selected from halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, and heterocyclyl, wherein R^2 is optionally substituted with one or more, the same or different, R^3;

R^3 is selected from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^3 is optionally substituted with one or more, the same or different, R^4;

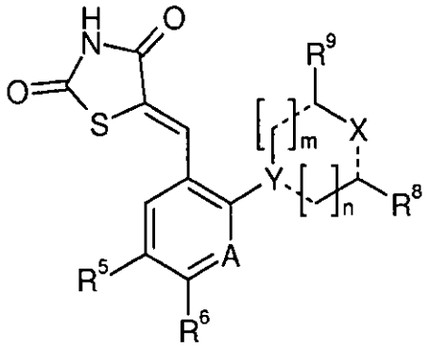
R^4 is selected from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^4 is optionally substituted with one or more, the same or different, R^5; and

R^5 is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl; and

b) administering said pharmaceutical composition to a subject diagnosed with, exhibiting symptoms of, or at risk for cancer under conditions such that cancer is reduced or prevented.

In further embodiments, the invention relates to a method of treating cancer comprising administering to a subject in need thereof a pharmaceutical composition comprising a compound of the formula disclosed herein, wherein said cancer is selected from a leukemia, lymphoma, prostate cancer, pancreatic cancer or other solid tumors.

In further embodiments, the invention relates to a compound of formula IA,



formula IA,

or salts thereof, wherein,

--- is individually at each occurrence selected from a single and double bond;

n is selected from 0, 1, or 2;

m is selected from 0, 1, or 2;

A is selected from N and CR^7;

X is selected from O, S, CHR^{10} and NR^{11};

Y is selected from N, CH, and C;

R^5, R^6, and R^7 are each individually and independently from hydrogen, C_{1-6}alkyl, halogen, cyano, nitro, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, carbocyclyl, aryl, and heterocyclyl, wherein R^5, R^6, and R^7 are each optionally substituted with one or more, the same or different, R^{12};

R^8 and R^9 are each individually and independently selected from hydrogen, amino, hydroxyl, mercapto, C_{1-6}alkyl, C_{1-6}alkylamino, carbocyclyl, aryl, and heterocyclyl wherein R^8 and R^9 are each optionally substituted with one or more, the same or different, R^{15};

R^{10} is selected from hydrogen, C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{12};

R^{11} is selected from hydrogen, formyl, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, C_{1-6}alkoxycarbonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{11} is optionally substituted with one or more, the same or different, R^{12};

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R^{12} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{12} is optionally substituted with one or more, the same or different, R^{16};

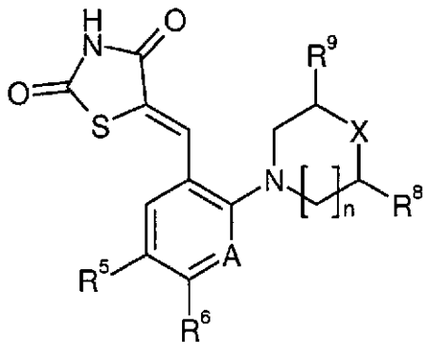
R^{15} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, and C_{1-6}alkoxycarbonyl wherein R^{15} is optionally substituted with one or more, the same or different, R^{12};

R^{16} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, and *N*-methyl-*N*-ethylsulfamoyl; and

provided that R^5, R^6, and R^7 are not all hydrogen and

provided the compound is not 5-((5-nitro-2-(1-piperidinyl)phenyl)methylene)-2,4-thiazolidinedione or 5-((2-(4-morpholinyl)-5-nitrophenyl)methylene)-2,4-thiazolidinedione.

In some embodiments, the invention relates to a compound of formula ID,



formula ID,

or salts thereof, wherein,

n is selected from 0, 1, or 2;

A is selected from N and CR^7;

X is selected from O, S, CHR^{10} and NR^{11};

R^5, R^6, and R^7 are each individually and independently from hydrogen, C_{1-6}alkyl, halogen, cyano, nitro, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, carbocyclyl, aryl, and heterocyclyl, wherein R^5, R^6, and R^7 are each optionally substituted with one or more, the same or different, R^{12};

R^8 and R^9 are each individually and independently selected from hydrogen, amino, hydroxyl, mercapto, C_{1-6}alkyl, C_{1-6}alkylamino, carbocyclyl, aryl, and heterocyclyl wherein R^8 and R^9 are each optionally substituted with one or more, the same or different, R^{15};

R^{10} is selected from hydrogen, C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{12};

R^{11} is selected from hydrogen, formyl, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, C_{1-6}alkoxycarbonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{11} is optionally substituted with one or more, the same or different, R^{12};

R^{12} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino,

diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{12} is optionally substituted with one or more, the same or different, R^{16};

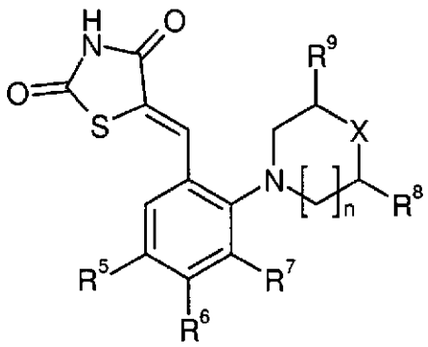
R^{15} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, and C_{1-6}alkoxycarbonyl wherein R^{15} is optionally substituted with one or more, the same or different, R^{12};

R^{16} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, aminomethyl, aminoethyl, aminopropyl, aminobutyl, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, and *N*-methyl-*N*-ethylsulfamoyl.

In some embodiments with regard to any of the compound formula provided herein, R^5, R^6, and R^7 are not all hydrogen.

In some embodiments with regard to any of the compound formula provided herein, R^5, R^6, and R^7 are not 5-((5-nitro-2-(1-piperidinyl)phenyl)methylene)-2,4-thiazolidinedione or 5-((2-(4-morpholinyl)-5-nitrophenyl)methylene)-2,4-thiazolidinedione.

In some embodiments, the invention relates to a compound of formula IB,



formula IB,

or salts thereof, wherein,

n is selected from 0, 1, or 2;

X is selected from O, CHR^{10} and NR^{11};

R^5, R^6, and R^7 are each individually and independently from hydrogen, halogen, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, and *N*-methyl-*N*-ethylsulfamoyl;

R^8 and R^9 are each individually and independently selected from hydrogen, amino, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkylamino, wherein R^8 and R^9 are each optionally substituted with one or more, the same or different, R^{15};

R^{10} is selected from hydrogen, $C_{1\text{-}6}$alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, $C_{1\text{-}6}$alkoxy, $C_{1\text{-}6}$alkylthio, $C_{1\text{-}6}$alkylamino, $(C_{1\text{-}6}\text{alkyl})_2$amino, $C_{1\text{-}6}$alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{12};

R^{11} is selected from hydrogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkanoyl, $C_{1\text{-}6}$alkylsulfinyl, $C_{1\text{-}6}$alkylsulfonyl, arylsulfonyl, $C_{1\text{-}6}$alkoxycarbonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{11} is optionally substituted with one or more, the same or different, R^{12};

R^{12} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl,

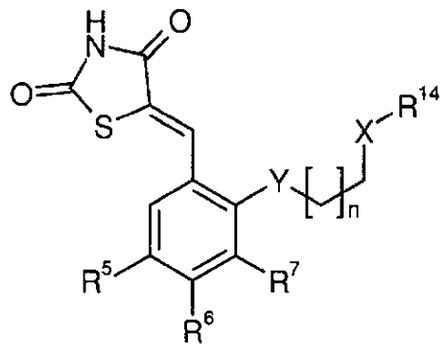
methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{12} is optionally substituted with one or more, the same or different, R^{16};

R^{15} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, and C_{1-6}alkoxycarbonyl wherein R^{15} is optionally substituted with one or more, the same or different, R^{12};

R^{16} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, and *N*-methyl-*N*-ethylsulfamoyl.

In some embodiments, with regard to any of the compound formula provided herein, said compound is not, 5-[[2-(4-methyl-1-piperazinyl)phenyl]methylene]-2,4-thiazolidinedione or 5-[[2-[(2,6-dichloro-3-methylphenyl)amino]phenyl]methylene]-2,4-thiazolidinedione.

In further embodiments, the invention relates to a compound of formula IC,



formula IC,

or salts thereof, wherein,

n is selected from 0, 1, 2, 3, 4, 5, 6, 7 or 8;

X is selected from O, S, CHR^{10} and NR^{11};

Y is selected from O, S, and NR^{13};

R^5, R^6, and R^7 are each individually and independently from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, C_{1-6}dialkylamino, carbocyclyl, aryl, and heterocyclyl, wherein R^5, R^6, and R^7 are each optionally substituted with one or more, the same or different, R^{12};

R^{10} is selected from hydrogen, C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{12};

R^{11}, R^{13}, and R^{14} are each individually and independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, and C_{1-6}alkoxycarbonyl wherein R^{11} is optionally substituted with one or more, the same or different, R^{12};

or R^{11} and R^{14}, taken together with the atoms to which they are attached form a five, six, or seven membered heterocyclic ring optionally substituted with one or more, the same or different, R^{12};

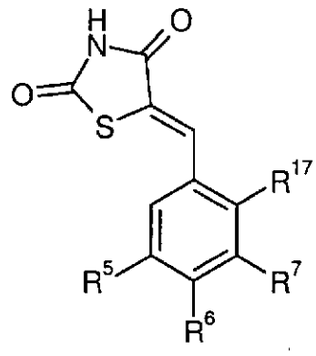
R^{12} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl.

In some embodiments with regard to any of the compound formula provided herein, Y is NR^{13}, wherein R^{13} is a C_{1-6}alkyl.

In some embodiments with regard to any of the compound formula provided herein, R^5 is a halogenated C_{1-6}alkyl.

In some embodiments with regard to any of the compound formula provided herein, R^7 is a halogen.

In some embodiments, the invention relates to a compound of formula IX,



formula IX,

or salts thereof, wherein

R^5 is selected from hydrogen, C_{1-6}alkoxy, carbamoyl, and halogenated C_{1-6}alkyl;

R^6 is selected from hydrogen, halogen, C_{1-6}alkoxy, and 2-(1-piperidyl)ethoxy;

R^7 is selected from hydrogen, halogen, and C_{1-6}alkoxy;

R^{17} is a heterocarbocylcyl, wherein R^{17} is optionally substituted with one or more, the same or different, R^{18};

R^{18} is selected from halogen, formyl, amino, C_{1-6}alkyl, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, carbocyclyl, aryl, heterocyclyl, wherein R^{18} is optionally substituted with one or more, the same or different, R^{19};

R^{19} is selected from amino, C_{1-6}alkyl, hydroxy, carbocyclyl, and heterocyclyl wherein R^{19} is optionally substituted with one or more, the same or different, R^{20}; and

R^{20} is selected from amino, C_{1-6}alkyl, and halogen.

In further embodiments, R^{17} is selected from (3R)-3-aminopyrrolidin-1-yl, (3R)-3-dimethylaminopyrrolidin-1-yl, (3S)-3-(3-aminopropylamino)pyrrolidin-1-yl, (3S)-3-(5-aminopentanoylamino)pyrrolidin-1-yl, (3S)-3-amino-1-piperidyl, (3S)-3-aminopyrrolidin-1-yl, (3S)-3-dimethylaminopyrrolidin-1-yl, (3S,5R)-3,5-

dimethylpiperazin-1-yl, 1,4-diazepan-1-yl, 2-(1-piperidyl)ethoxy, 2-diethylaminoethoxy, 2-dimethylaminoethyl-methyl-amino, 2-hydroxyethoxy, 2-morpholinoethoxy, 3-(2-aminoethylamino)pyrrolidin-1-yl, 3-(2-hydroxyethylamino)pyrrolidin-1-yl, 3-(2-methylaminoethylamino)pyrrolidin-1-yl, 3-(3-aminopropanoylamino)pyrrolidin-1-yl, 3-(3-aminopropylamino)pyrrolidin-1-yl, 3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-piperidyl, 3-(aminomethyl)-1-piperidyl, 3-(aminomethyl)pyrrolidin-1-yl, 3-acetamidopyrrolidin-1-yl, 3-aminopyrrolidin-1-yl, 3-dimethylaminopropoxy, 3-dimethylaminopropyl-methyl-amino, 3-dimethylaminopyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl, 3-pyridyl, 4-(1-methyl-4-piperidyl)piperazin-1-yl, 4-(1-piperidyl)-1-piperidyl, 4-(2-aminoethyl)piperazin-1-yl, 4-(2-hydroxyethyl)-1,4-diazepan-1-yl, 4-(2-hydroxyethyl)-1-piperidyl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(2-methylaminoethyl)piperazin-1-yl, 4-(2-morpholinoethyl)piperazin-1-yl, 4-(3-aminopropanoyl)-1,4-diazepan-1-yl, 4-(3-aminopropanoyl)piperazin-1-yl, 4-(3-aminopropyl)piperazin-1-yl, 4-(3-hydroxypropyl)piperazin-1-yl, 4-(3-methyl-1,2,4-oxadiazol-5-yl)-1-piperidyl, 4-(4-aminobutanoyl)-1,4-diazepan-1-yl, 4-(4-aminobutanoyl)piperazin-1-yl, 4-(4-chloro-2-fluoro-phenyl)piperazin-1-yl, 4-(4-fluorophenyl)piperazin-1-yl, 4-(4-pyridylmethyl)piperazin-1-yl, 4-(5-aminopentanoyl)-1,4-diazepan-1-yl, 4-(5-aminopentanoyl)piperazin-1-yl, 4-(azetidine-3-carbonyl)piperazin-1-yl, 4-(benzo[1,3]dioxol-5-ylmethyl)piperazin-1-yl, 4-(cyclopropylmethyl)piperazin-1-yl, 4-(hydroxymethyl)-1-piperidyl, 4-(piperidine-3-carbonyl)-1,4-diazepan-1-yl, 4-(piperidine-3-carbonyl)piperazin-1-yl, 4-(piperidine-4-carbonyl)piperazin-1-yl, 4-[(2-chlorophenyl)methyl]piperazin-1-yl, 4-[3-(aminomethyl)benzoyl]piperazin-1-yl, 4-[4-(piperazin-1-ylmethyl)benzoyl]piperazin-1-yl, 4-acetylpiperazin-1-yl, 4-amino-1-piperidyl, 4-butyl-1,4-diazepan-1-yl, 4-cyclopentylpiperazin-1-yl, 4-dimethylamino-1-piperidyl, 4-hydroxy-1-piperidyl, 4-isobutylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-morpholino-1-piperidyl, 4-pyridyl, 4-pyrrolidin-1-yl-1-piperidyl, 4-tert-butoxycarbonylpiperazin-1-yl, 4-tert-butylpiperazin-1-yl, morpholino, piperazin-1-yl, and pyrrolidin-1-yl.

In further embodiments, the invention relates to a compound selected from:

5-({2-[(3S)-3-aminopiperidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3R)-3-aminopiperidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[2-(4-aminopiperidin-1-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({2-[3-(aminomethyl)piperidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(1,4-diazepan-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-cyclopentylpiperazin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(4-fluorophenyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-pyrrolidin-1-ylpiperidin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(1-methylethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-methylpropyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-hydroxyethyl)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(4-chloro-2-fluorophenyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[3-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-chlorobenzyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-morpholin-4-ylethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(cyclopropylmethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-morpholin-4-ylpiperidin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(3-hydroxypropyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(dimethylamino)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-{[3-(dimethylamino)propyl](methyl)amino}-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-hydroxyethyl)-1,4-diazepan-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[2-(4-butyl-1,4-diazepan-1-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-hydroxyethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-morpholin-4-yl-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[2-(4-tert-butylpiperazin-1-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[2-(1,4'-bipiperidin-1'-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-bromo-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione; and

5-({2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione,

(5Z)-5-({3-[3-(4-methylpiperazin-1-yl)propoxy]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

2-{3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenoxy}acetamide;

(5Z)-5-{[3-(3-piperidin-1-ylpropoxy)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

(5Z)-5-({3-[(4-methylpiperazin-1-yl)methyl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

N-[2-(dimethylamino)ethyl]-2'-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-N-methylbiphenyl-4-sulfonamide;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-methoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({5-chloro-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-4-methylphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-fluorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-methylphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({5-bromo-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-3-fluorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-chloro-6-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-(aminomethyl)pyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-(aminomethyl)pyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-methoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-bromophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-bromophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-ethoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(2-methylpropoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclohexylmethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclohexyloxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R,4R)-3-amino-4-hydroxypiperidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-{[3-chloro-2-(1,4-diazepan-1-yl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(1-methylethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-(1-methylethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-ethoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-{[4-(aminomethyl)benzyl]amino}piperidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({3-chloro-2-[(3R)-3-{[2-(methylamino)ethyl]amino}piperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S,4S)-3-amino-4-hydroxypyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({3-chloro-2-[4-methyl-3-(methylamino)piperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-{[2-(3-amino-4-methylpiperidin-1-yl)-3-chlorophenyl]methylidene}-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(2,2,2-trifluoroethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-(2,2,2-trifluoroethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(2-methoxyethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-(2-methoxyethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclopentyloxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclobutyloxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

4-[(3R)-3-aminopiperidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide;

4-[(3S)-3-aminopiperidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide;

4-[(3R)-3-aminopiperidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzoic acid;

4-[(3S)-3-aminopyrrolidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzoic acid;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]biphenyl-3-yl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[2-(3-aminopropoxy)-5-methoxyphenyl]methylidene}-1,3-thiazolidine-2,4-dione;

N-{4-[3-(dimethylamino)pyrrolidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}acetamide;

(5Z)-5-[(3-chloro-2-{(3R)-3-[(2-hydroxyethyl)amino]piperidin-1-yl}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

(5Z)-5-[(3-chloro-2-{(3R)-3-[(3-hydroxypropyl)amino]piperidin-1-yl}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-1-methyl-1H-imidazole-2-carboxamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-methoxyacetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-1-methyl-1H-pyrazole-3-carboxamide;

N^2-carbamoyl-N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]glycinamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-pyridin-3-ylacetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-pyridin-4-ylacetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-1-methyl-1H-pyrazole-4-carboxamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-(1-oxidothiomorpholin-4-yl)acetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-4-sulfamoylbutanamide;

N'-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-N,N-dimethylbutanediamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-N~2~,N~2~-dimethylglycinamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-cyanoacetamide;

N^2-acetyl-N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]glycinamide;

(5Z)-5-({3-chloro-2-[(3R)-3-(dipropylamino)piperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-[(3-chloro-2-{(3R)-3-[(3,3,3-trifluoropropyl)amino]piperidin-1-yl}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

5-[(5-methoxy-2-{3-[(1-methylethyl)amino]propoxy}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

(5Z)-5-({5-amino-2-[3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione; and

5-[(2-amino-4,5-dimethoxyphenyl)methylidene]-1,3-thiazolidine-2,4-dione,

or salts thereof.

In some embodiments, the invention relates to any of the compounds disclosed herein that are in the (Z) isomer.

In some embodiments, the invention relates to any of the compounds disclosed herein that are in the (E) isomer.

In some embodiments, the invention relates to compositions comprising a mixture of the (Z) and (E) isomers.

In some embodiments, the invention relates to a pharmaceutical composition comprising a substituted 5-(3-halo-2-[piperidin-1-yl]phenylmethylidene)-1,3-thiazolidine-2,4-dione functioning to inhibit a PIM kinase.

In further embodiments, the invention relates to a pharmaceutical composition comprising a compound of formula I, IA, IB, IC, ID, or IX or a pharmaceutically acceptable salt thereof.

In further embodiments, the invention relates to a method of inhibiting a PIM kinase comprising, providing a compound of formula I, IA, IB, IC, ID, or IX, as defined herein, and mixing a PIM kinase and said compound under conditions such that PIM kinase phosphorylation is inhibited.

In further embodiments, said method is an in vitro method.

In further embodiments, said method is an in vivo method.

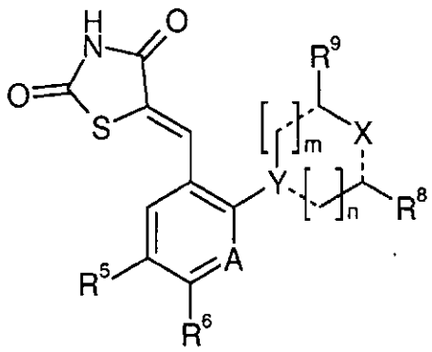
In further embodiments, the invention relates to a method of inhibiting a PIM kinase in a subject comprising administering to the subject a therapeutically effective amount of a compound of any of the formula disclosed herein or a pharmaceutically acceptable salt thereof.

In further embodiments, said PIM kinase is selected from PIM-1, PIM-2, and PIM-3.

In further embodiments, the invention relates to the use of a compound of the formula I, IA, IB, IC, ID, or IX, or a pharmaceutically acceptable salt thereof, as defined herein, for the manufacture of a medicament for the production of a PIM kinase inhibitory effect in a subject.

In further embodiments, the invention relates to the use of a compound of the formula I, IA, IB, IC, ID, or IX, or a pharmaceutically acceptable salt thereof, as disclosed herein, for the manufacture of a medicament for the production of an anti-cancer effect in a subject.

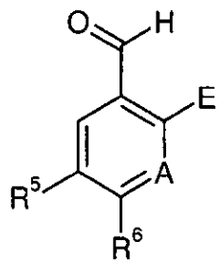
In some embodiments, the invention relates to a method of making a compound of formula IA as defined herein,



formula IA,

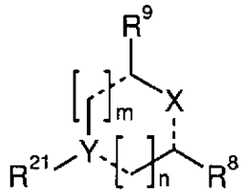
or salt thereof, comprising

a) mixing a compound of formula XI,



formula XI,

or salt thereof, wherein E is a halogen, and R^5, R^6, and A are defined herein, with a compound of formula XII,



formula XII,

or salt thereof, wherein

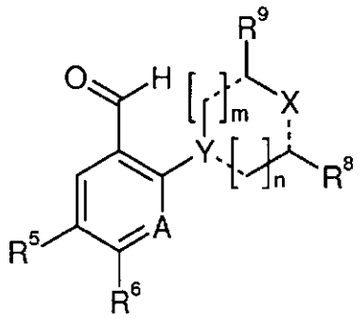
---, R^8, R^9, n, m, Y and X are defined herein,

if Y is N, then R^{21} is hydrogen,

if Y is C, then R^{21} is selected from boronic acid and a boronic ester, and

if Y is CH, then R^{21} is selected from a metal halide,

under conditions such that composition comprising a compound of formula XIII,



formula XIII,

or salt thereof, is formed; and

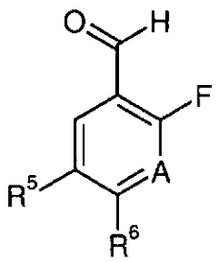
b) mixing the compound of formula XIII and thiazolidine-2,4-dione under conditions such that a compound of formula IA is formed.

In further embodiments, said metal halide is selected from lithium chloride and magnesium bromide.

In further embodiments, said boronic ester is a dialkyl boronic ester, such as diethyl boronic ester, or a cyclic boronic ester, such as the boronic ester of 1,2-alkyldiols, such as 1,3,2-dioxaborolane, or cycloalkyldiols which may be optionally substituted.

In further embodiments, the invention relates to a method of making a compound of formula ID, or salt thereof comprising

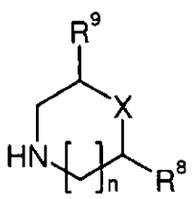
a) mixing a compound of formula II,



formula II,

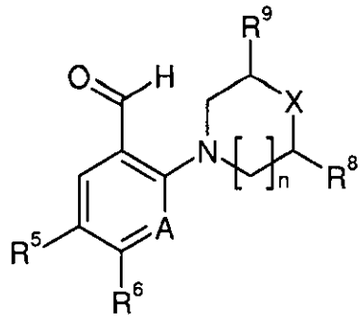
or salt thereof, wherein R^5, R^6, and A are defined herein,

with a compound of formula III,



formula III,

or salt thereof, wherein R^8, R^9, n, and X are defined herein, under conditions such that composition comprising a compound of formula IV,

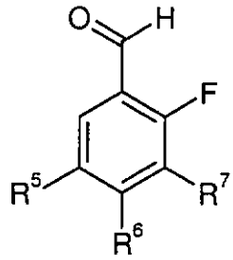


formula IV

or salt thereof, is formed; and

b) mixing the compound of formula IV and thiazolidine-2,4-dione under conditions such that a compound of formula ID is formed.

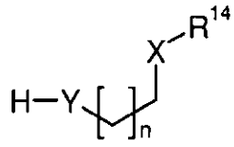
In further embodiments, the invention relates to a method of making a compound of formula IC, or salt thereof comprising a) mixing a compound of formula V,



formula V,

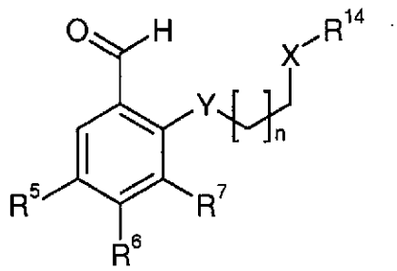
or salt thereof, wherein R^5, R^6, and R^7 are defined herein,

with a compound of formula VI,



formula VII,

or salt thereof, wherein R^{14}, n, X and Y are defined herein, under conditions such that a composition comprising a compound of formula VIII,



formula VIII

or salt thereof, is formed; and

b) mixing the compound of formula VIII and thiazolidine-2,4-dione under conditions such that a compound of formula IC is formed.

In some embodiments, the invention relates to compounds of formula I, IA, IB, IC, ID, or IX provided that they are not selected from 5-((2-dipropylamino-5-nitrophenyl)methylene)-2,4-thiazolidinedione;

5-((5-nitro-2-(1-piperidinyl)phenyl)methylene)-2,4-thiazolidinedione;

5-((2-(4-morpholinyl)-5-nitrophenyl)methylene)-2,4-thiazolidinedione;

5-[[2-(4-methyl-1-piperazinyl)phenyl]methylene]-2,4-thiazolidinedione;

5-[[2-[(2,6-dichloro-3-methylphenyl)amino]phenyl]methylene]-2,4-thiazolidinedione;

[2S-[2α(Z),4α]]-1-([1,1'-biphenyl]-4-ylsulfonyl)-N-[2-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenyl]-4-(methylthio)-2-pyrrolidinemethanamine;

1,1-dimethylethyl ester [[2S-[2α(Z),4α]]-3-[[[1-([1,1'-biphenyl]-4-ylsulfonyl)-4-(methylthio)-2-pyrrolidinyl]methyl]amino]-4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenyl] carbamic acid; and

[2S-[2α(Z),4α]]-N-[5-amino-2-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenyl]-1-([1,1'-biphenyl]-4-ylsulfonyl)-4-(methylthio)-2-pyrrolidinemethanamine.

It is the Applicants understanding that WO 2001002377 discloses 5-((2-dipropylamino-5-nitrophenyl)methylene)-2,4-thiazolidinedione,

5-((5-nitro-2-(1-piperidinyl)phenyl)methylene)-2,4-thiazolidinedione, and 5-((2-(4-morpholinyl)-5-nitrophenyl)methylene)-2,4-thiazolidinedione.

It is the Applicants understanding that WO 9814433 discloses

5-[[2-(4-methyl-1-piperazinyl)phenyl]methylene]-2,4-thiazolidinedione.

It is the Applicants understanding that US Patent No. 6,211,209 discloses, 5-[[2-[(2,6-dichloro-3-methylphenyl)amino]phenyl]methylene]-2,4-thiazolidinedione.

It is the Applicants understanding that WO 9705135 discloses, [2S-[2α(Z),4α]]-1-([1,1'-biphenyl]-4-ylsulfonyl)-N-[2-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenyl]-4-(methylthio)-2-pyrrolidinemethanamine, 1,1-dimethylethyl ester [[2S-[2α(Z),4α]]-3-[[[1-([1,1'-biphenyl]-4-ylsulfonyl)-4-(methylthio)-2-pyrrolidinyl]methyl]amino]-4-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenyl]-carbamic acid, and [2S-[2α(Z),4α]]-N-[5-amino-2-[(2,4-dioxo-5-thiazolidinylidene)methyl]phenyl]-1-([1,1'-biphenyl]-4-ylsulfonyl)-4-(methylthio)-2-pyrrolidinemethanamine.

The preceding understandings are not intended to be admissions.

In some embodiments, compounds disclosed herein could be used in the clinic either as a single agent by itself or in combination with other clinically relevant agents. This compound could also prevent the potential cancer resistance mechanisms that may arise due to mutations in a set of genes.

The anti-cancer treatment defined herein 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) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulfan and nitrosoureas); antimetabolites (for example 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); and proteosome inhibitors (for example bortezomib [Velcade®]); and the agent anegrilide [Agrylin®]; and the agent alpha-interferon

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

(iii) agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine 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, AZD1839),

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),

for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family, for example inhibitors or phosphotidylinositol 3-kinase (PI3K) and for example inhibitors of mitogen activated protein kinase kinase (MEK1/2) and for example inhibitors of protein kinase B (PKB/Akt), for example inhibitors of Src tyrosine kinase family and/or Abelson (Abl) tyrosine kinase family such as AZD0530 and dasatinib (BMS-354825) and imatinib mesylate (Gleevec™); and any agents that modify STAT signaling.

(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™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

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

(vii) 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; and

(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 approaches using the immunomodulatory drugs thalidomide and lenalidomide [Revlimid®].

Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. Such combination products employ the compounds of this invention, or pharmaceutically acceptable salts thereof, within the dosage range described hereinbefore and the other pharmaceutically-active agent within its approved dosage range.

The invention relates to phosphorylation inhibitors of PIM kinases. In still further embodiments, the invention relates to pharmaceutical composition comprising compounds disclosed herein and their use in the prevention and treatment of cancer.

It is understood the compositions disclosed herein may exist in solid and solution form tautomers. For example, imidazole and imidazole containing heterocycles may be drawn in a formula such that one or the other of the nitrogens contain a hydrogen atom. However, as provided herein, embodiments of such a formula are considered to encompass alternative tautomeric forms.

As used herein, "alkyl" means a noncyclic straight chain or branched, unsaturated or saturated hydrocarbon such as those containing from 1 to 10 carbon atoms, while the term "lower alkyl" or "C_{1-6}alkyl" has the same meaning as alkyl but contains from 1 to 6 carbon atoms. The term "higher alkyl" has the same meaning as alkyl but contains from 7 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-septyl, n-octyl, n-nonyl, and the like; while saturated branched alkyls include isopropyl, sec-butyl, isobutyl, tert-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, and the like.

A "halogenated alkyl" refers to an alkyl group where one or more or all of the hydrogen(s) are substituted with halogen(s). A representative halogenated alkyl includes trifluoromethyl (i.e., $-CF_3$).

Non-aromatic mono or polycyclic alkyls are referred to herein as "carbocycles" or "carbocyclyl" groups. Representative saturated carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated carbocycles include cyclopentenyl and cyclohexenyl, aryls and the like.

"Heterocarbocycles" or heterocarbocyclyl" groups are carbocycles which contain from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur which may be saturated or unsaturated (but not aromatic), monocyclic or polycyclic, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. Heterocarbocycles include morpholinyl,

pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydroprimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Aryl" means an aromatic carbocyclic monocyclic or polycyclic ring such as phenyl or naphthyl.

As used herein, "heteroaryl" refers an aromatic heterocarbocycle having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and polycyclic ring systems. Polycyclic ring systems may, but are not required to, contain one or more non-aromatic rings, as long as one of the rings is aromatic. Representative heteroaryls are furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolinyl, isoquinolinyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, and quinazolinyl. It is contemplated that the use of the term "heteroaryl" includes N-alkylated derivatives such as a 1-methylimidazol-5-yl substituent.

As used herein, "heterocycle" or "heterocyclyl" refers to mono- and polycyclic ring systems having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom. The mono- and polycyclic ring systems may be aromatic, non-aromatic or mixtures of aromatic and non-aromatic rings. Heterocycle includes heterocarbocycles, heteroaryls, and the like.

"Alkylthio" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through a sulfur bridge. An example of an alkylthio is methylthio, (i.e., -S-CH_3).

"Alkoxy" refers to an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. Preferred alkoxy groups are methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy.

"Alkylamino" refers an alkyl group as defined above with the indicated number of carbon atoms attached through an amino bridge. An example of an alkylamino is methylamino, (i.e., -NH-CH_3).

"Alkanoyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a carbonyl bride (i.e., -(C=O)alkyl).

"Alkylsulfonyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a sulfonyl bridge (i.e., -$S(=O)_2$alkyl) such as mesyl and the like, and "Arylsulfonyl" refers to an aryl attached through a sulfonyl bridge (i.e., -$S(=O)_2$aryl).

"Alkylsulfamoyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a sulfamoyl bridge (i.e., -$NHS(=O)_2$alkyl), and an "Arylsulfamoyl" refers to an alkyl attached through a sulfamoyl bridge (i.e., (i.e., -$NHS(=O)_2$aryl).

"Alkylsulfinyl" refers to an alkyl as defined above with the indicated number of carbon atoms attached through a sulfinyl bridge (i.e. -S(=O)alkyl).

The term "substituted" refers to a molecule wherein at least one hydrogen atom is replaced with a substituent. When substituted, one or more of the groups are "substituents." The molecule may be multiply substituted. In the case of an oxo substituent ("=O"), two hydrogen atoms are replaced. Example substituents within this context may include halogen, hydroxy, alkyl, alkoxy, nitro, cyano, oxo, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, -NR_aR_b, -$NR_aC(=O)R_b$, -$NR_aC(=O)NR_aNR_b$, -$NR_aC(=O)OR_b$, -$NR_aSO_2R_b$, -$C(=O)R_a$, -$C(=O)OR_a$, -$C(=O)NR_aR_b$, -$OC(=O)NR_aR_b$, -OR_a, -SR_a, -SOR_a, -$S(=O)_2R_a$, -$OS(=O)_2R_a$ and -$S(=O)_2OR_a$. R_a and R_b in this context may be the same or different and independently hydrogen, halogen hydroxyl, alkyl, alkoxy, alkyl, amino, alkylamino, dialkylamino, carbocyclyl, carbocycloalkyl, heterocarbocyclyl, heterocarbocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl.

The term "optionally substituted," as used herein, means that substitution is optional and therefore it is possible for the designated atom to be unsubstituted.

As used herein, the terms "prevent" and "preventing" include the prevention of the recurrence, spread or onset. It is not intended that the present invention be limited to

complete prevention. In some embodiments, the onset is delayed, or the severity of the disease is reduced.

As used herein, the terms "treat" and "treating" are not limited to the case where the subject (e.g. patient) is cured and the disease is eradicated. Rather, embodiments, of the present invention also contemplate treatment that merely reduces symptoms, and/or delays disease progression.

As used herein, "salts" refer to derivatives of the disclosed compounds where the parent compound is modified making acid or base salts thereof. Examples of salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkylamines, or dialkylamines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. In preferred embodiment the salts are conventional non-toxic pharmaceutically acceptable salts including the quaternary ammonium salts of the parent compound formed, and non-toxic inorganic or organic acids. Preferred salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Subject" means any animal, preferably a human patient, livestock, or domestic pet.

"Cancer" refers any of various cellular diseases with malignant neoplasms characterized by the proliferation of cells. It is not intended that the diseased cells must actually invade surrounding tissue and metastasize to new body sites. Cancer can involve any tissue of the body and have many different forms in each body area. Within the context of certain embodiments, whether "cancer is reduced" may be identified by a variety of diagnostic manners known to one skill in the art including, but not limited to, observation the reduction in size or number of tumor masses or if an increase of apoptosis of cancer cells observed, e.g., if more than a 5 % increase in apoptosis of cancer cells is observed for a sample compound compared to a control without the compound. It may also be identified by a change in relevant biomarker or gene expression profile, such as PSA for prostate cancer, her2 for breast cancer, or others.

The present pharmaceutical compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use.

Administration may be topical, i.e., substance is applied directly where its action is desired, enteral or oral, i.e., substance is given via the digestive tract, parenteral, i.e., substance is given by other routes than the digestive tract such as by injection.

In a preferred embodiment, the active compound and optionally another therapeutic or prophylactic agent are formulated in accordance with routine procedures as pharmaceutical compositions adapted for intravenous administration to human beings. Typically, the active compound for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the compositions can also include a solubilizing agent. Compositions for intravenous administration can optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule. Where the active compound is to be administered by infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the active compound is administered by

injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

Compositions for oral delivery can be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions can contain one or more optional agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. A time delay material such as glycerol monostearate or glycerol stearate can also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. Such vehicles are preferably of pharmaceutical grade.

Compositions for use in accordance with the present invention can be formulated in conventional manner using one or more physiologically acceptable carriers or excipients. Thus, the compound and optionally another therapeutic or prophylactic agent and their physiologically acceptable salts and solvates can be formulated into pharmaceutical compositions for administration by inhalation or insufflation (either through the mouth or the nose) or oral, parenteral or mucosol (such as buccal, vaginal, rectal, sublingual) administration. In one embodiment, local or systemic parenteral administration is used.

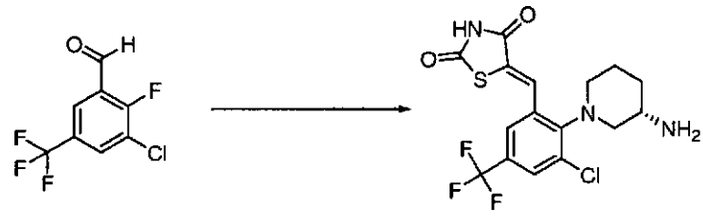
For oral administration, the compositions can take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulfate). The tablets can be coated by methods well known in the art. Liquid preparations for oral administration can take the form of, for example, solutions, syrups or suspensions, or they can be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending

agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations can also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

EXPERIMENTAL

The following is intended to provide examples on methods of making and using embodiments of the invention. It is not intended to limit the scope.

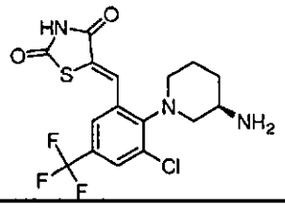
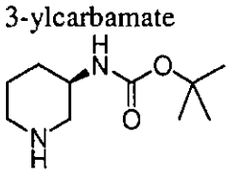
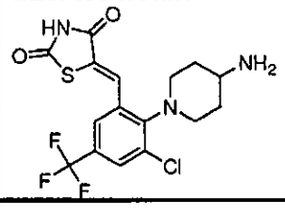
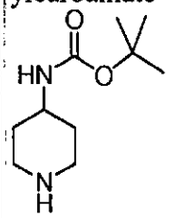
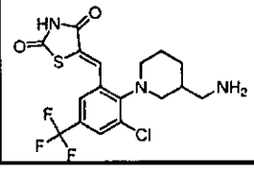
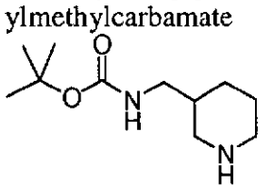
Example 1:

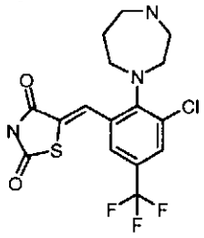
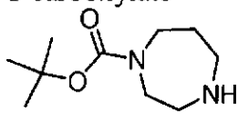
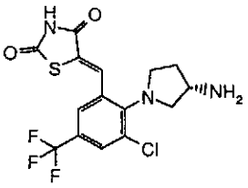
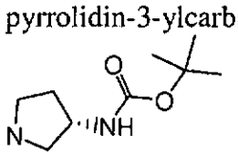


(*S,Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione trifluoroacetate:

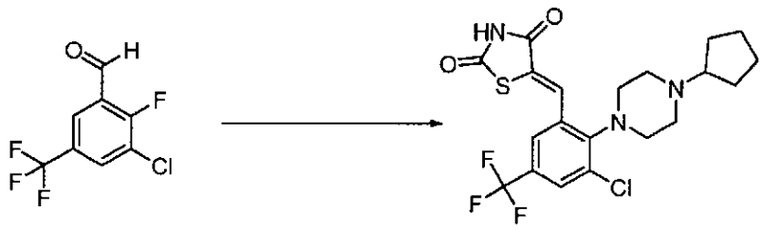
A 40 mL vial was charged with a magentic stir bar, 3-chloro-2-fluoro-5-(trifluoromethyl)benzaldehyde (0.134 ml, 1.10 mmol), acetonitrile (2.76 ml), (*S*)-*tert*-butyl piperidin-3-ylcarbamate (0.221 g, 1.10 mmol), and K_2CO_3 (0.229 g, 1.66 mmol). The vial was heated to 70 °C with stirring for 2 h. The vessel was cooled to rt and the mixture was diluted with DCM and filtered. The filtrate was conc. *in vacuo* to afford the substituted aldehyde which was dissolved in EtOH (2.76 ml). Thiazolidine-2,4-dione (0.155 g, 1.32 mmol) and piperidine (9.40 mg, 0.11 mmol) were then added. The mixture was heated to reflux for 4 h before being allowed to cool to rt and the mixture was conc. *in vacuo*. The product was dissolved DCM (2 mL) and TFA (1 mL) and stirred at rt for 1 h before being conc. *in vacuo*. The residue was dissolved in DMSO (~ 2 mL) and purified via reverse phase HPLC to afford (*S,Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione trifluoroacetate (0.214 g, 37.3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12.78 (s, 1 H) 7.95 (m, 3 H) 7.79 (s, 1 H) 7.62 (s, 1 H) 3.40-3.20 (s, 5 H) 2.12-2.06 (m, 1H) 1.79-1.70 (m 1H) 1.65-1.60 (m, 1 H) 1.52-1.41 (m, 1 H); *m/z* 406.

The following examples were prepared by the procedure of Example 1, using the appropriate starting materials. The following parent compounds obtained after chromatography may be converted to their corresponding hydrochloride salts using the procedure in Example 6, or a similar procedure.

Ex.	Compound	^{1}H NMR (300 MHz)	m/z	SM
2	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione trifluoroacetate 	12.79 (s, 1 H) 7.98 (s, 2 H) 7.95 (s, 1 H) 7.79 (s, 1 H) 7.62 (s, 1 H) 3.31-3.20 (m, 5 H) 2.12-2.09 (m, 1 H) 1.85 - 1.77 (m, 1 H) 1.66-1.63 (m, 1 H) 1.45-1.40 (m, 1 H)	406	(*R*)-*tert*-butyl piperidin-3-ylcarbamate 
3	(*Z*)-5-(2-(4-aminopiperidin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione trifluoroacetate 	12.76 (s, 1 H) 7.99 (s, 1 H) 7.91 (s, 2 H) 7.78 (s, 1 H) 7.60 (s, 1 H) 3.33-3.18 (m, 5 H) 1.94 (d, 2 H) 1.71-1.60 (m, 2 H)	406	*tert*-butyl piperidin-4-ylcarbamate 
4	(*Z*)-5-(2-(3-(aminomethyl)piperidin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione trifluoroacetate 	12.78 (s, 1 H) 7.93 (s, 1 H) 7.84 (s, 1 H) 7.75 (s, 1 H) 7.61 (s, 1 H) 3.31-3.05 (m, 6 H) 2.79-2.71 (m, 1 H) 1.95-1.89 (m, 2 H) 1.72-1.55 (m, 2 H) 1.29-1.10 (m, 1 H)	421	*tert*-butyl piperidin-3-ylmethylcarbamate 

5A	(Z)-5-(3-chloro-2-(1,4-diazepan-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.83 (brs, 1 H) 9.20 (brs, 2 H) 8.05 (d, 1 H) 7.90 (s, 1 H) 7.66 (d,1 H) 3.51 (brs, 2 H) 3.35 (d, 2 H) 3.26 - 3.03 (m, 4 H) 2.27 – 1.99 (m, 2 H)	405	*tert*-butyl 1,4-diazepane-1-carboxylate 
5B	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione 	12.73 (brs, 1 H) 8.29 (brs, 3 H) 7.93 (s, 1 H) 7.83 (s, 1 H) 7.66 (s, 1 H) 3.88 (brs, 1 H) 3.66 (dd, 1 H), 3.52 - 3.27 (m, 3 H) 2.42-2.19 (m, 1 H) 2.12-1.88 (m, 1 H)	392	*tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate 

Example 6:

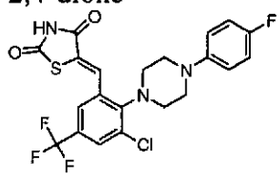
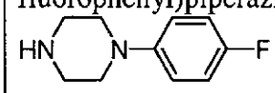
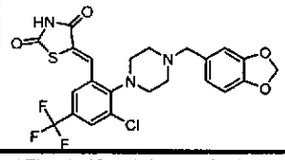
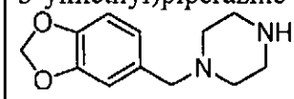
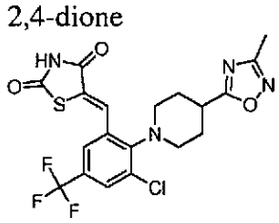
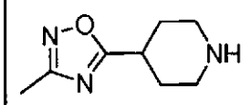


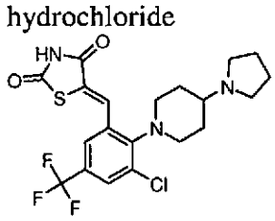
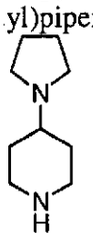
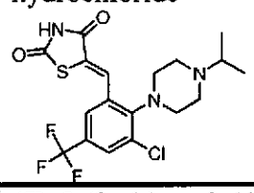
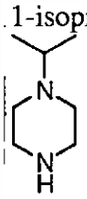
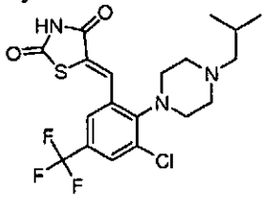
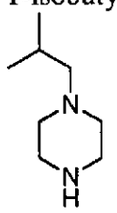
(Z)-5-(3-chloro-2-(4-cyclopentylpiperazin-1-yl)-5 (trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride:

A 40 mL vial was charged with a magnetic stir bar, 3-chloro-2-fluoro-5-(trifluoromethyl)benzaldehyde (0.134 ml, 1.10 mmol), acetonitrile (2.76 ml), 1-cyclopentylpiperazine (0.213 g, 1.38 mmol), and K_2CO_3 (0.229 g, 1.66 mmol). The vial was heated to 70 °C with stirring for 2 h. The vessel was then cooled to rt and the

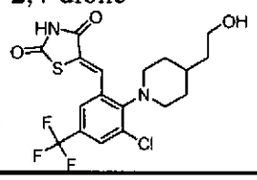
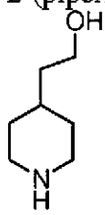
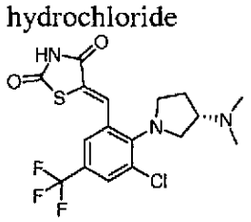
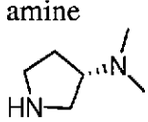
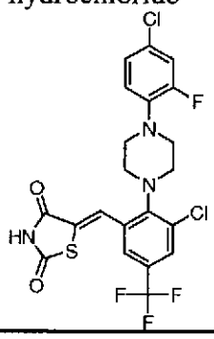
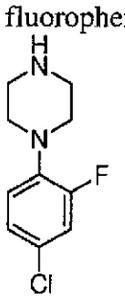
mixture was diluted with DCM and filtered. The filtrate was conc. *in vacuo* to afford the substituted aldehyde which was dissolved in EtOH (2.76 ml). Thiazolidine-2,4-dione (0.155 g, 1.32 mmol) and piperidine (9.40 mg, 0.11 mmol) were then added and the mixture was heated to reflux for 4 h before being allowed to cool to rt. The mixture was then conc. *in vacuo* to afford the product which was dissolved in DMSO (~ 2 mL) and purified via reverse phase HPLC to afford fractions that were conc. *in vacuo*, suspended in methanol (~5 mL) and 1N HCl in diethyl ether (~2 mL). This mixture was conc. *in vacuo* to afford (Z)-5-(3-chloro-2-(4-cyclopentylpiperazin-1-yl)-5-(trifluoromethyl) benzylidene)thiazolidine-2,4-dione hydrochloride (0.215 g, 39.3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12.78 (s, 1 H) 7.96 (s, 1 H) 7.83 (s, 1 H) 7.63 (s, 1 H) 3.77-3.50 (m, 5 H) 3.30-3.22 (m, 2 H) 3.08-2.99 (m, 2 H) 2.03-1.99 (m, 2 H) 1.84-1.61 (m, 4 H) 1.60-1.50 (m, 2 H); *m/z* 461.

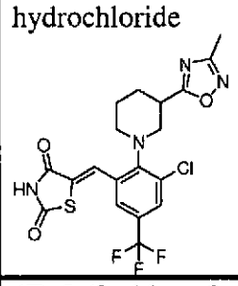
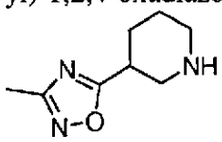
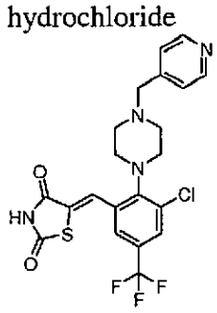
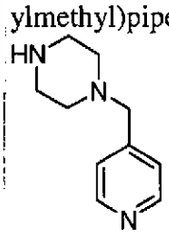
The following examples were prepared by the procedure of Example 6, using the appropriate starting materials. The following parent compounds obtained after chromatography may be converted to their corresponding hydrochloride salt in a manner similar as described in example 6.

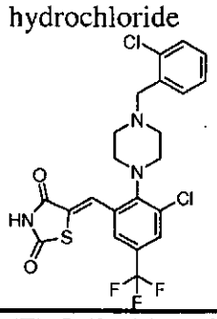
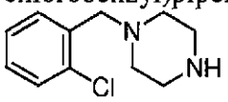
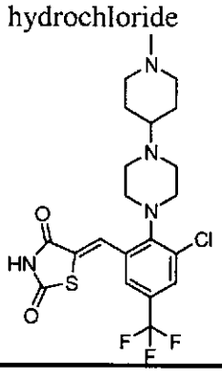
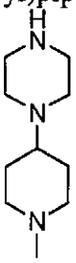
Ex.	Compound	^{1}H NMR	m/z	SM
7	(Z)-5-(3-chloro-2-(4-(4-fluorophenyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione 	12.74 (s, 1 H) 7.89 - 8.01 (m, 2 H) 7.62 (s, 1 H) 6.99 - 7.13 (m, 4 H) 3.34-3.23 (m, 8 H)	486	1-(4-fluorophenyl)piperazine 
8	(Z)-5-(2-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione trifluoroacetate 	12.77 (s, 1 H) 7.97 (d, 1 H) 7.97 (s, 1 H) 7.77 (s, 1 H) 7.63 (s, 1 H) 7.10 (s, 1 H) 7.02 (s, 2 H) 6.08 (s, 2 H) 4.34 (s, 2 H) 3.58-3.11 (m, 8 H)	526	1-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine 
9	(Z)-5-(3-chloro-2-(4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione 	12.72 (s, 1 H) 7.91 (s, 1 H) 7.84 (s, 1 H) 7.61 (s, 1 H) 3.33-3.18 (m, 4 H) 2.79-2.71 (m, 1 H) 2.33 (s, 3 H) 2.06 (d, 2 H) 1.98-1.80 (m, 2 H)	473	3-methyl-5-(piperidin-4-yl)-1,2,4-oxadiazole 

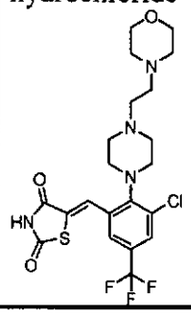
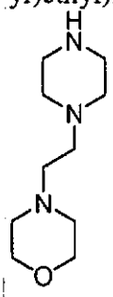
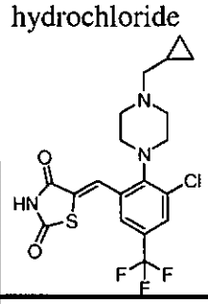
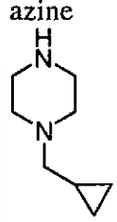
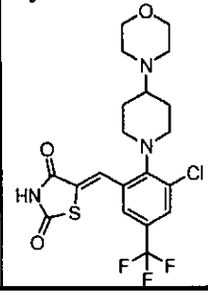
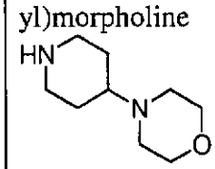
10	(Z)-5-(3-chloro-2-(4-(pyrrolidin-1-yl)piperidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.78 (s, 1 H) 7.92 (s, 1 H) 7.79 (s, 1 H) 7.60 (s, 1 H) 3.33 - 3.20 (m, 5 H) 3.12 - 3.03 (m, 4 H) 2.09 (d, 2 H) 1.97 - 1.78 (m, 6 H)	461	4-(pyrrolidin-1-yl)piperidine 
11	(Z)-5-(3-chloro-2-(4-isopropylpiperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.80 (s, 1 H) 7.96 (s, 1 H) 7.82 (s, 1 H) 7.62 (s, 1 H) 3.85 (t, 2 H) 3.55-3.52 (m, 1 H) 3.41 (d, 2 H) 3.26 (d, 2 H) 3.10 - 3.06 (m, 2 H) 1.32 (d, 6 H)	434	1-isopropylpiperazine 
12	(Z)-5-(3-chloro-2-(4-isobutylpiperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.80 (s, 1 H) 7.96 (d, 1 H) 7.80 (s, 1 H) 7.63 (s, 1 H) 3.87 (brs, 2 H) 3.52 (d, 2 H) 3.27 (brs, 2 H) 3.11 - 3.00 (m, 4 H) 2.10 (qq, 1 H) 1.00 (d, 6 H)	450	1-isobutylpiperazine 

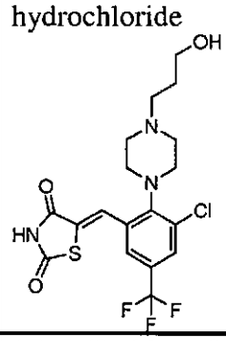
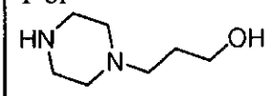
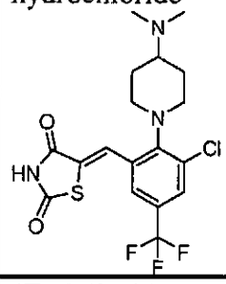
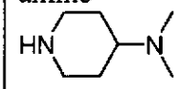
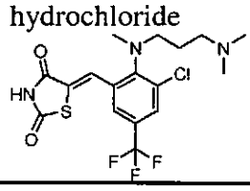
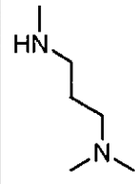
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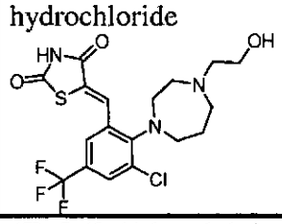
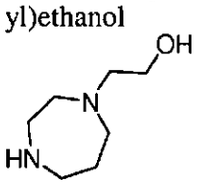
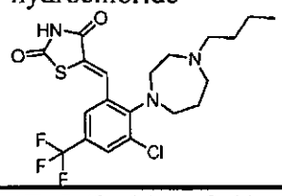
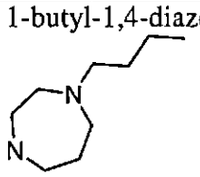
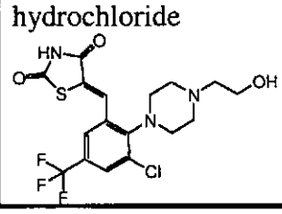
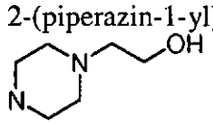
13	(Z)-5-(3-chloro-2-(4-(2-hydroxyethyl)piperidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione 	12.73 (s, 1 H) 7.87 (s, 1 H) 7.83 (s, 1 H) 7.59 (s, 1 H) 3.46 (t, 2 H) 3.23 (t, 2 H) 3.07 (brs, 2 H) 1.70 (d, 2 H) 1.61 - 1.52 (m, 1 H) 1.42 (q, 2 H) 1.33 - 1.20 (m, 2 H)	437	2-(piperidin-4-yl)ethanol 
14	(*S*,*Z*)-5-(3-chloro-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.65 (s, 1 H) 7.82 (s, 1 H) 7.72 (s, 1 H) 7.53 (s, 1 H) 3.59 - 3.50 (m, 1 H) 3.38 - 3.30 (m, 4 H) 2.56 (s, 6 H) 2.31 - 2.28 (m, 1 H) 2.09 - 2.01 (m, 1 H)	421	(*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
15	(Z)-5-(3-chloro-2-(4-(4-chloro-2-fluorophenyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.75 (brs, 1 H) 8.06 – 7.90 (m, 2 H) 7.64 (d, 1 H) 7.38 (dd, 1 H) 7.23 (dd, 1 H) 7.11 (t, 1 H) 3.42 (m, 4 H) 3.15 (d, 4 H)	520	1-(4-chloro-2-fluorophenyl)piperazine 

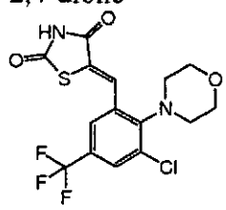
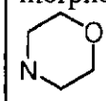
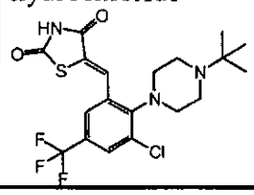
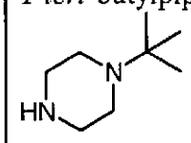
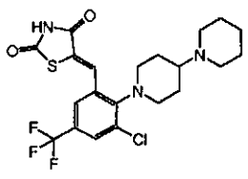
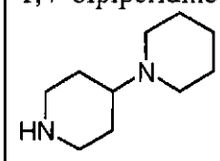
16	(Z)-5-(3-chloro-2-(3-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 		471	3-methyl-5-(piperidin-3-yl)-1,2,4-oxadiazole 
17	(Z)-5-(3-chloro-2-(4-(pyridin-4-ylmethyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.75 (brs, 1H) 8.78 (d, 2 H) 7.98 (s, 1 H) 7.74 (brs, 1 H) 7.71 (s, 1 H) 7.64 (s, 1 H) 4.44 (brs, 2 H) 3.44 (brs, 4 H) 3.17 (s, 4 H)	483	1-(pyridin-4-ylmethyl)piperazine 

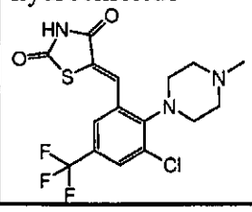
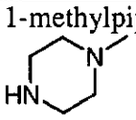
18	(Z)-5-(3-chloro-2-(4-(2-chlorobenzyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	7.98 (d, 1 H) 7.73 (dd, 1 H) 7.68 - 7.59 (m, 2 H) 7.58 - 7.42 (m, 3 H) 4.53 (brs, 2 H) 3.75-3.30 (m, 8 H)	517	1-(2-chlorobenzyl)piperazine 
19	(Z)-5-(3-chloro-2-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	10.68 (brs, 1 H) 7.92 (d, 1 H) 7.78 (brs, 1 H) 7.58 (s, 1 H) 3.73 - 3.63 (m, 1 H) 3.61-3.41 (m, 6 H) 3.10 (brs, 3 H) 2.93 (brs, 3 H) 2.67 (s, 3 H) 2.39 - 2.18 (m, 2 H) 2.07 (brs, 2 H)	489	1-(1-methylpiperidin-4-yl)piperazine 

20	(Z)-5-(3-chloro-2-(4-(2-morpholinoethyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	11.12 (brs, 1 H) 7.91 (d, 1 H) 7.79 (brs, 1 H) 7.59 (s, 1 H) 3.80-2.81 (m, 20 H)	505	4-(2-(piperazin-1-yl)ethyl)morpholine 
21	(Z)-5-(3-chloro-2-(4-(cyclopropylmethyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.59 (brs, 1 H) 7.76 (d, 1 H) 7.61 (brs, 1 H) 7.43 (s, 1 H) 3.62 (brs, 2 H) 3.44 - 3.24 (m, 2 H) 3.10 (brs, 2 H) 2.87 (d, 4 H) 0.94 (brs, 1 H) 0.54 - 0.31 (m, 2 H) 0.32 - 0.08 (m, 2 H)	447	1-(cyclopropylmethyl)piperazine 
22	(Z)-5-(3-chloro-2-(4-morpholinopiperidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.92 (brs, 1 H) 8.08 (d, 1 H) 7.95 (brs, 1 H) 7.76 (s, 1 H) 4.14 (brs, 3 H) 3.98 (brs, 2 H) 3.58 (brs, 3 H) 3.53 - 3.34 (m, 3 H) 3.28 (brs, 2 H) 2.32 (brs, 2 H) 1.92 (d, 2 H)	476	4-(piperidin-4-yl)morpholine 

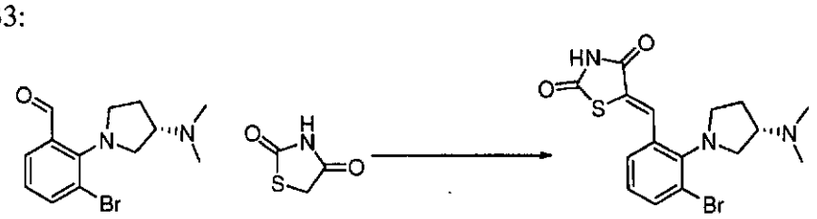
23	(Z)-5-(3-chloro-2-(4-(3-hydroxypropyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.90 (brs, 1 H) 10.52 (brs, 1 H) 7.98 (d, 1 H) 7.84 (brs, 1 H) 7.65 (s, 1 H) 3.90 - 3.65 (m, 2 H) 3.57 - 3.41 (m, 5 H) 3.30 - 3.06 (m, 5 H) 1.96 - 1.73 (m, 2 H)	450	3-(piperazin-1-yl)propan-1-ol 
24	(Z)-5-(3-chloro-2-(4-(dimethylamino)piperidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.79 (brs, 1 H) 7.94 (d, 1 H) 7.82 (s, 1 H) 7.61 (s, 1 H) 3.84 (brs, 1 H) 3.46 - 3.18 (m, 4 H) 2.75 (d, 6 H) 2.10 (d, 2 H) 1.74 (dd, 2 H)	434	*N,N*-dimethylpiperidin-4-amine 
25	(Z)-5-(3-chloro-2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.81 (brs, 1 H) 7.98 (d, 1 H) 7.81 (s, 1 H) 7.65 (d, 1 H) 3.15 (t, 2 H) 3.02 (brs, 2 H) 2.89 (s, 3 H) 2.72 (d, 6 H) 1.99 - 1.74 (m, 2 H)	422	*N1,N1,N3*-trimethylpropane-1,3-diamine 

26	(Z)-5-(3-chloro-2-(4-(2-hydroxyethyl)-1,4-diazepan-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	8.04 (brs, 1 H) 7.79 (d, 1 H) 7.63 (s, 1 H) 3.83 (t, 3 H) 3.71 (m, 2 H) 3.56 (m, 3 H) 3.33 (m, 6 H) 2.21 (m, 2 H)	451	2-(1,4-diazepan-1-yl)ethanol 
27	(Z)-5-(2-(4-butyl-1,4-diazepan-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	10.76 (brs, 1 H) 8.06 (d, 1 H) 7.91 (brs, 1 H) 7.66 (d,1 H) 3.69 (m, 3 H) 3.57 (brs, 1 H) 3.46 (m, 3 H) 3.14 (m, 3 H) 2.34 (brs, 1 H) 2.16 (brs, 1 H) 1.73 (d, 2 H) 1.32 (m, 2 H) 0.93 (t, 3 H)	463	1-butyl-1,4-diazepane 
28	(Z)-5-(3-chloro-2-(4-(2-hydroxyethyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	7.98 (d, 1 H) 7.82 (brs, 1 H) 7.64 (d,1 H) 5.40 (brs, 1 H) 3.74 (m, 4 H) 3.56 (m, 3 H) 3.27 (m, 3 H) 3.18 (brs, 1 H) 3.11 (brs, 1 H)	436	2-(piperazin-1-yl)ethanol 

29	(Z)-5-(3-chloro-2-morpholino-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione 	12.76 (brs, 1 H) 7.94 (m, 2 H) 7.63 (d, 1 H) 3.71 (t, 4 H) 3.20 (brs, 4 H)	394	morpholine 
30	(Z)-5-(2-(4-*tert*-butylpiperazin-1-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.80 (brs, 1 H) 8.00 (d, 1 H) 7.85 (brs, 1 H) 7.65 (d, 1 H) 3.82 (m, 2 H) 3.56 (d, 2 H) 3.29 (dd, 2 H) 3.04 (m, 2 H) 1.39 (s, 9 H)	449	1-*tert*-butylpiperazine 
31	(Z)-5-(2-(1,4'-bipiperidin-1'-yl)-3-chloro-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	9.75 (brs, 1 H) 7.94 (d, 1 H) 7.81 (brs, 1 H) 7.62 (s, 1 H) 3.29 (m, 7 H) 2.96 (m, 2 H) 2.14 (d, 2 H) 1.78 (m, 7 H) 1.44 (brs, 1 H)	474	1,4'-bipiperidine 

32	(Z)-5-(3-chloro-2-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	7.94 (brs, 1 H) 7.75 (d, 1 H) 7.63 (s, 1 H) 3.56 - 3.38 (m, 3 H) 3.31 - 3.21 (m, 5 H) 2.92 (s, 3 H)	406	1-methylpiperazine 

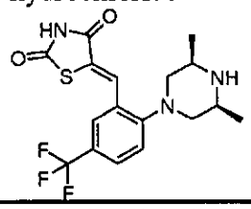
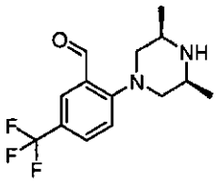
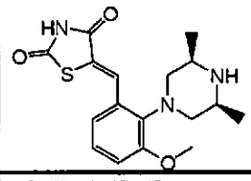
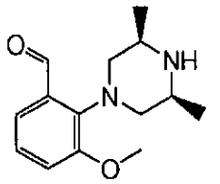
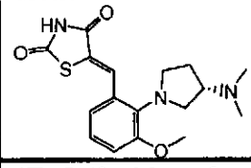
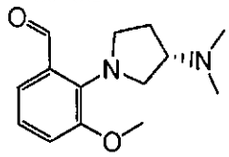
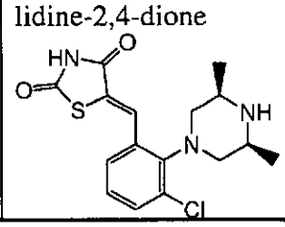
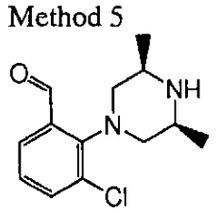
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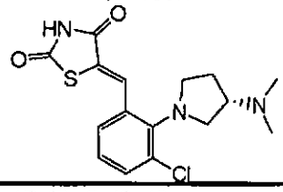
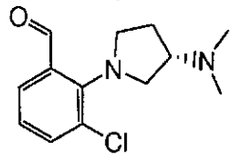
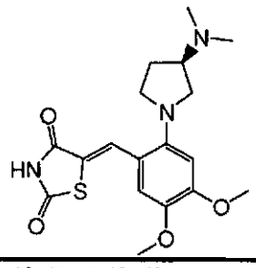
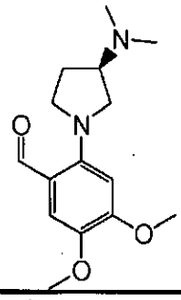
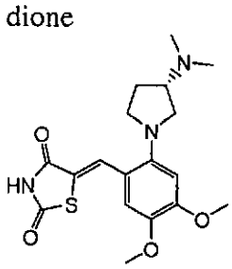
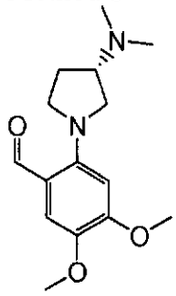


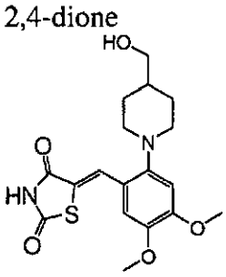
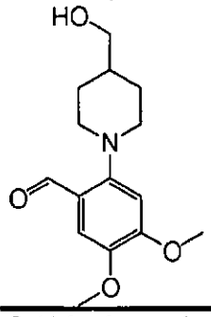
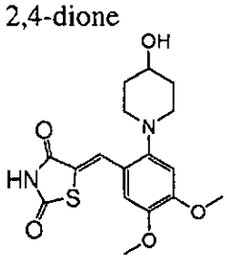
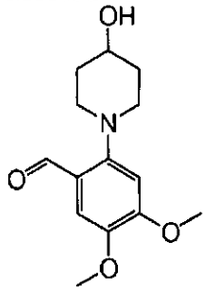
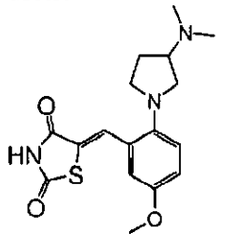
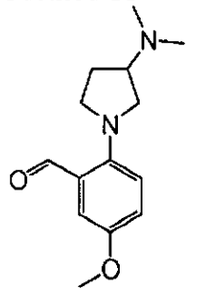
(*S,Z*)-5-(3-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride:

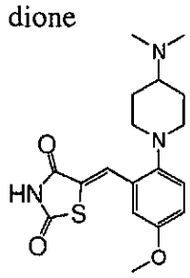
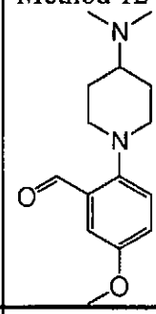
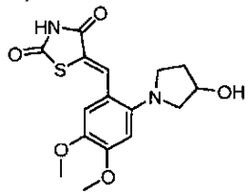
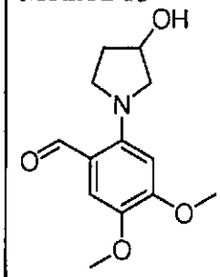
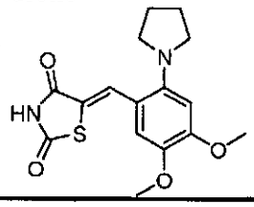
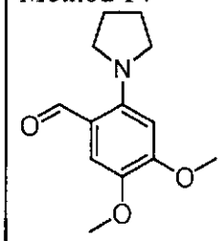
A 100 mL round bottom flask was charged with a magnetic stir bar, (*S*)-3-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde (Method 1) (0.370 g, 1.24 mmol), thiazolidine-2,4-dione (0.146 g, 1.24 mmol), and ethanol (4.15 ml). Piperidine (0.012 ml, 0.12 mmol) was then added and the reaction was heated to reflux for 2 h. Once the reaction was judged to be complete by LCMS, it was allowed to cool to rt and was conc. *in vacuo* to afford the product which was purified on 40 g of silica gel using ethyl acetate / methanol (3:1) as eluent to afford the free base which was suspended in methanol (~ 5 mL) and 1N HCl in diethyl ether (2 mL) and conc. *in vacuo* to afford (*S,Z*)-5-(3-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride (0.141 g, 26.2 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12.68 (s, 1 H) 7.91 (s, 1 H) 7.77 (d, 1 H) 7.48 (d, 1 H) 7.33 (t, 1 H) 4.10 - 4.02 (m, 1 H) 3.62 (t, 2 H) 3.50 - 3.45 (m, 2 H) 2.81 (s, 6 H) 2.42 - 2.38 (m, 1 H) 2.31 - 2.21 (m, 1 H); *m/z* 398.

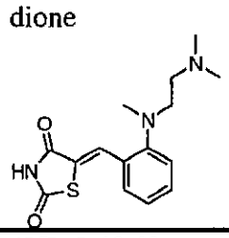
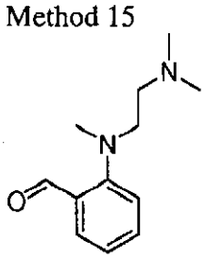
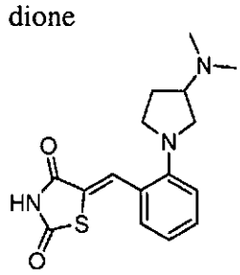
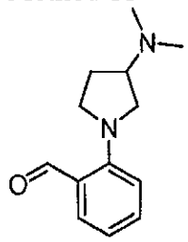
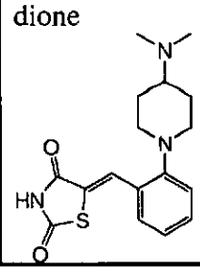
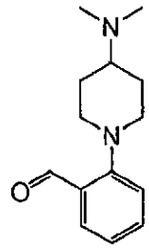
The following examples were prepared by the procedure of Example 33, using the appropriate starting materials. The following parent compounds obtained after chromatography (normal or reverse phase) may be converted to its corresponding hydrochloride salt as described in example 33, or similar procedure.

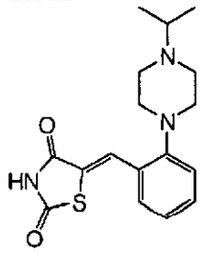
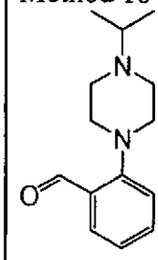
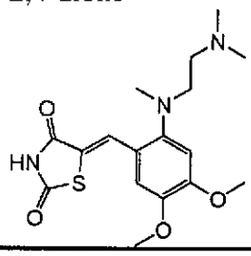
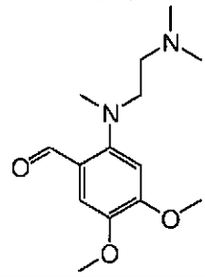
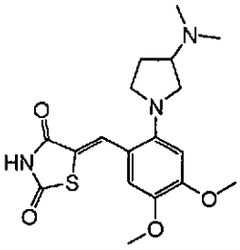
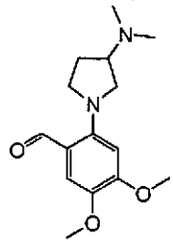
Ex.	Compound	^{1}H NMR	m/z	SM
34	(Z)-5-(2-((*3S,5R*)-3,5-dimethylpiperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.63 (s, 1 H) 8.99 - 8.94 (m, 1 H) 7.77 (d, 1 H) 7.72 (s, 2 H) 7.40 (d, 1 H) 3.49 - 3.43 (m, 2 H) 3.32 (d, 2 H) 2.92 (t, 2 H) 1.25 (d, 6 H)	387	2-((*3S,5R*)-3,5-dimethylpiperazin-1-yl)-5-(trifluoromethyl)benzaldehyde Method 2 
35	(Z)-5-(2-((*3S,5R*)-3,5-dimethylpiperazin-1-yl)-3-methoxybenzylidene) thiazolidine-2,4-dione 	7.87 (brs, 1 H) 7.24 (t, 1 H) 7.20 - 7.10 (m, 1 H) 7.02 (d, 1 H) 3.81 (s, 3 H) 3.48 - 3.23 (m, 2 H) 3.17 (t, 2 H) 2.89 (d, 2 H) 1.30 - 1.09 (m, 6 H)	348	2-((*3S,5R*)-3,5-dimethylpiperazin-1-yl)-3-methoxybenzaldehyde Method 3 
36	(*S,Z*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-3-methoxybenzylidene) thiazolidine-2,4-dione 	7.89 (s, 1 H) 7.26 (m, 1 H) 7.10 (m, 2 H) 3.84 (s, 3 H) 3.41 - 3.29 (m, 7 H) 3.24 - 3.13 (m, 4 H) 2.18 (m, 1 H) 1.99 (m, 1 H)	348	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-3-methoxybenzaldehyde Method 4 
37	(Z)-5-(3-chloro-2-((*3S,5R*)-3,5-dimethylpiperazin-1-yl)benzylidene)thiazolidine-2,4-dione 	7.80 (s, 1 H) 7.50 (brs, 1 H) 7.38 (d, 1 H) 7.30 (brs, 1 H) 3.34-3.02 (m, 6 H) 1.26 - 1.09 (m, 6 H)	352	3-chloro-2-((3S,5R)-3,5-dimethylpiperazin-1-yl)benzaldehyde Method 5 

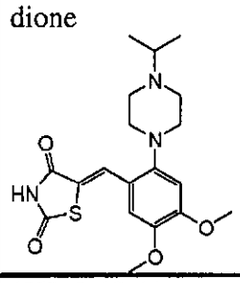
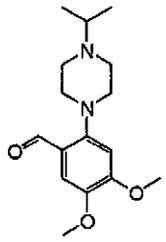
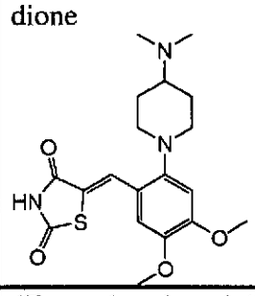
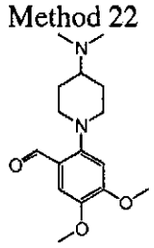
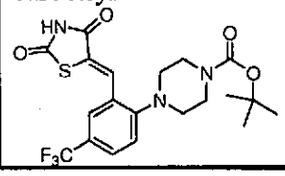
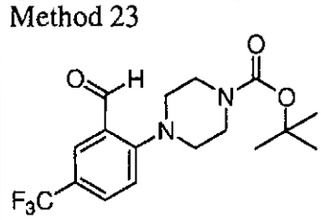
38	(*S,Z*)-5-(3-chloro-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione 	7.73 (s, 1 H) 7.52 - 7.47 (m, 2 H) 7.47 (s, 1 H) 7.33 - 7.31 (m, 1 H) 3.58 - 3.52 (m, 1 H) 3.48 (m, 1 H) 3.37 - 3.27 (m, 3 H) 2.56 (s, 6 H) 2.26 - 2.35 (m, 1 H) 2.08 (m, 1 H)	352	(*S*)-3-chloro-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde Method 6 
39	(*R,Z*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione 	7.75 (s, 1 H) 6.98 (s, 1 H) 6.68 (s, 1 H) 3.83 (s, 3 H) 3.72 (s, 3 H) 3.24 - 3.06 (m, 4 H) 2.50 (m, 1 H) 2.32 (s, 6 H) 2.12 (m, 1 H) 1.84 (m, 1 H)	378	(*R*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde Method 7 
40	(*S,Z*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione 	7.76 (s, 1 H) 6.98 (s, 1 H) 6.68 (s, 1 H) 3.83 (s, 3 H) 3.72 (s, 3 H) 3.26 – 3.01 (m, 5 H) 2.32 (s, 6 H) 2.15 – 2.09 (m, 1 H) 1.90 – 1.81 (m, 1 H)	378	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde Method 8 

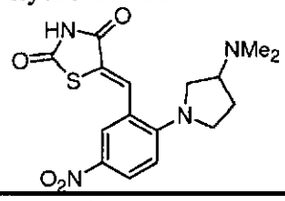
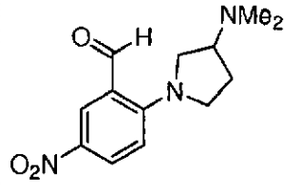
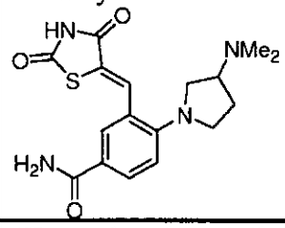
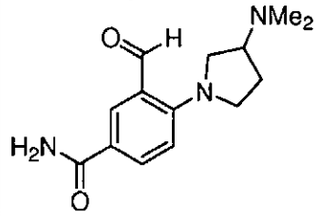
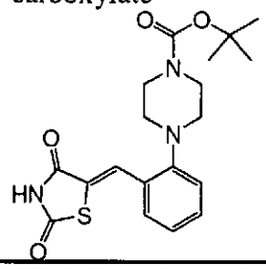
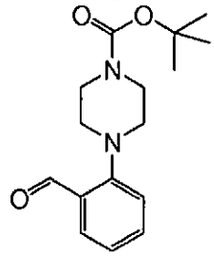
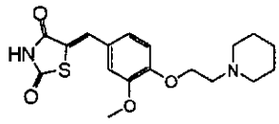
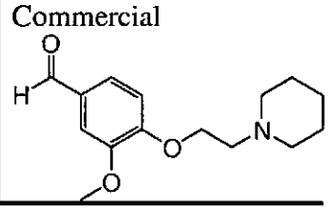
41	(5Z)-5-{2-[4-(hydroxymethyl)piperidin-1-yl]-4,5-dimethoxybenzylidene}-1-,3-thiazolidine-2,4-dione 	12.44 (brs, 1 H) 7.94 (s, 1 H) 7.05 - 6.87 (m, 1 H) 6.80 (s, 1 H) 4.54 (t, 1 H) 3.85 (s, 3 H) 3.76 (s, 3 H) 3.17 (d, 1 H) 3.03 (d, 2 H) 2.71 (t, 2 H) 1.75 (brs, 2 H) 1.56 - 1.26 (m, 3 H)	379	2-(4-(hydroxymethyl)piperidin-1-yl)-4,5-dimethoxybenzaldehyde Method 9 
42	(5Z)-5-[2-(4-hydroxypiperidin-1-yl)-4,5-dimethoxybenzylidene]-1,3-thiazolidine-2,4-dione 	12.50 (brs, 1 H) 8.02 (s, 1 H) 6.99 (s, 1 H) 6.92 - 6.82 (m, 1 H) 4.79 (d, 1 H) 3.90 (s, 3 H) 3.82 (s, 3 H) 3.74 - 3.58 (m, 1 H) 3.13 - 2.96 (m, 2 H) 2.88 - 2.71 (m, 2 H) 2.01 - 1.81 (m, 2 H) 1.78 - 1.58 (m, 2 H)	365	2-(4-hydroxypiperidin-1-yl)-4,5-dimethoxybenzaldehyde Method 10 
43	(5Z)-5-{2-[3-(dimethylamino)pyrrolidin-1-yl]-5-methoxybenzylidene}-1,3-thiazolidine-2,4-dione 	7.51 (s, 1 H) 7.03 (d, 1 H) 6.99 (d, 1 H) 6.84 (dd, 1 H) 3.72 (s, 3 H) 3.09 - 3.21 (m, 1 H) 2.82 - 3.09 (m, 4 H) 2.23 (s, 6 H) 2.06 (d, 1 H) 1.73 - 1.85 (m, 1 H)	348	2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methoxybenzaldehyde Method 11 

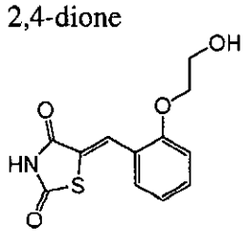
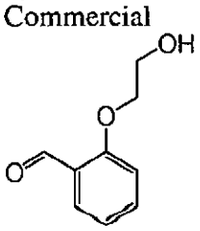
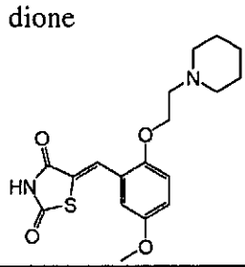
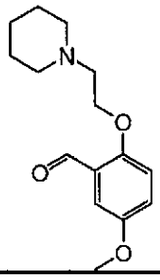
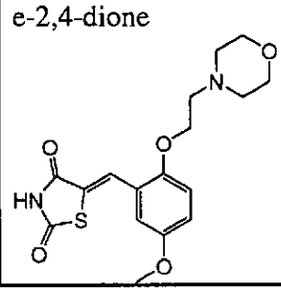
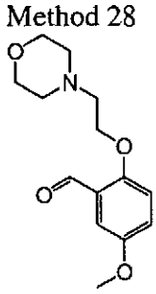
44	(5Z)-5-{2-[4-(dimethylamino)piperidin-1-yl]-5-methoxybenzylidene}-1,3-thiazolidine-2,4-dione 	7.59 (s, 1 H) 7.11 – 6.99 (m, 2 H) 6.85 (dd, 1 H) 3.75 (s, 3 H) 3.03 (m, 2 H) 2.64 - 2.54 (m, 2 H) 2.44 - 2.33 (m, 7 H) 1.91 (s, 2 H) 1.62 (dd, 2 H)	362	2-(4-(dimethylamino)piperidin-1-yl)-5-methoxybenzaldehyde Method 12 
45	(5Z)-5-[2-(3-hydroxypyrrolidin-1-yl)-4,5-dimethoxybenzylidene]-1,3-thiazolidine-2,4-dione 	12.32 (brs, 1 H) 7.88 (s, 1 H) 6.93 (s, 1 H) 6.66 (s, 1 H) 4.34 (brs, 1 H) 3.83 (s, 3 H) 3.72 (s, 3 H) 3.55 - 3.29 (m, 3 H) 3.22 (brs, 1 H) 2.90 (d, 1 H) 2.16 - 1.94 (m, 1 H) 1.84 (d, 1 H)	351	2-(3-hydroxypyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde Method 13 
46	(5Z)-5-(4,5-dimethoxy-2-pyrrolidin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione 	12.21 (brs, 1 H) 7.86 (s, 1 H) 6.94 (s, 1 H) 6.65 (s, 1 H) 3.83 (s, 3 H) 3.72 (s, 3 H) 3.12 (brs, 4 H) 1.90 (brs, 4 H)	335	4,5-dimethoxy-2-(pyrrolidin-1-yl)benzaldehyde Method 14 

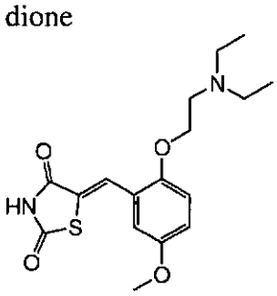
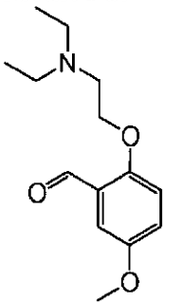
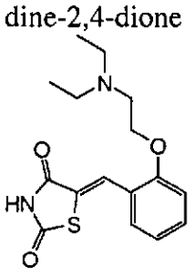
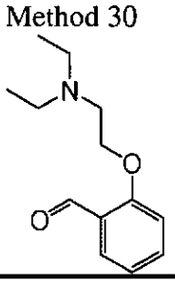
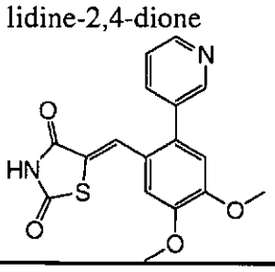
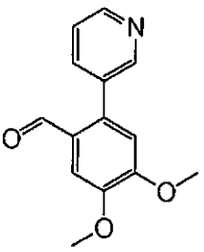
47	(5Z)-5-{2-[[2-(dimethylamino)ethyl](methyl)amino]benzylidene}-1,3-thiazolidine-2,4-dione 	7.62 (s, 1 H) 7.48 (d, 1 H) 7.32 (t, 1 H) 7.17 (d, 1 H) 7.10 (t, 1 H) 3.06 (t, 2 H) 2.86 - 2.62 (m, 5 H) 2.36 (s, 6 H)	306	2-((2-(dimethylamino)ethyl)(methyl)amino)benzaldehyde Method 15 
48	(5Z)-5-{2-[3-(dimethylamino)pyrrolidin-1-yl]benzylidene}-1,3-thiazolidine-2,4-dione 	7.52 (s, 1 H) 7.27 - 7.21 (m, 1 H) 7.14 - 7.05 (m, 1 H) 6.84 (d, 1 H) 6.77 (t, 1 H) 3.17 (s, 1 H) 3.16 - 3.09 (m, 1 H) 3.06 - 2.94 (m, 2 H) 2.86 - 2.77 (m, 1 H) 2.16 - 2.11 (m, 6 H) 2.03 - 1.92 (m, 1 H) 1.66 (dd, 1 H)	318	2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde Method 16 
49	(5Z)-5-{2-[4-(dimethylamino)piperidin-1-yl]benzylidene}-1,3-thiazolidine-2,4-dione 	7.64 (s, 1 H) 7.50 (d, 1 H) 7.35 - 7.27 (m, 1 H) 7.12 (t, 2 H) 3.22 (m, 2 H) 2.88 (m, 1 H) 2.68 (t, 2 H) 2.63 (s, 6 H) 2.04 (s, 2 H) 1.73 (td, 2 H)	332	2-(4-(dimethylamino)piperidin-1-yl)benzaldehyde Method 17 

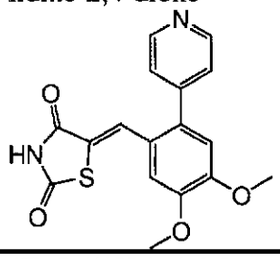
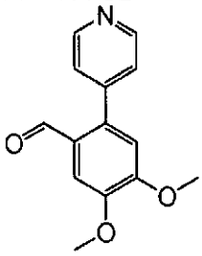
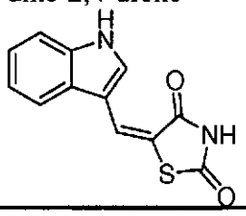
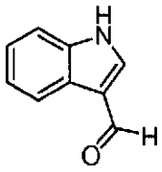
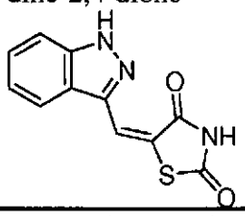
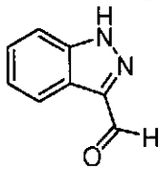
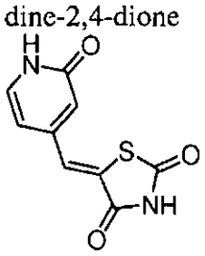
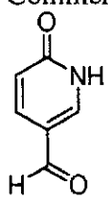
50	(5Z)-5-[2-(4-isopropylpiperazin-1-yl)benzylidene]-1,3-thiazolidine-2,4-dione 	7.80 (s, 1 H) 7.49 - 7.43 (m, 1 H) 7.43 - 7.39 (m, 1 H) 7.22 - 7.13 (m, 2 H) 2.99 - 2.88 (m, 5 H) 2.80 (s, 4 H) 1.13 - 1.04 (m, 6 H)	332	2-(4-isopropylpiperazin-1-yl)benzaldehyde Method 18 
51	(5Z)-5-{2-[[2-(dimethylamino)ethyl](methyl)amino]-4,5-dimethoxybenzylidene}-1,3-thiazolidine-2,4-dione 	7.78 (s, 1 H) 7.02 (s, 1 H) 6.85 (s, 1 H) 3.83 (s, 3 H) 3.76 (s, 3 H) 3.11 - 2.98 (m, 2 H) 2.76 - 2.65 (m, 5 H) 2.37 (s, 6 H)	364	2-((2-(dimethylamino)ethyl)(methyl)amino)-4,5-dimethoxybenzaldehyde Method 19 
52	(5Z)-5-{2-[3-(dimethylamino)pyrrolidin-1-yl]-4,5-dimethoxybenzylidene}-1,3-thiazolidine-2,4-dione 	7.76 (s, 1 H), 6.98 (s, 1 H), 6.68 (s, 1 H), 3.83 (s, 3 H), 3.72 (s, 3 H), 3.25 (m, 1 H), 3.13 (m, 2 H), 3.06 (m, 2 H), 2.32 (s, 6 H), 2.15 – 2.09 (m, 1 H) 1.90 – 1.81 (m, 1 H)	378	2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde Method 20 

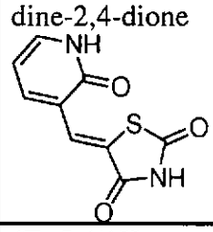
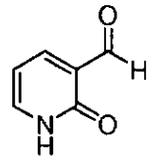
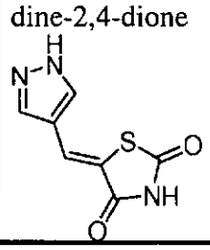
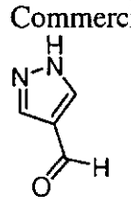
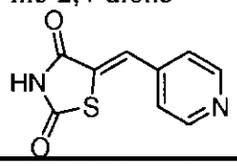
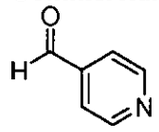
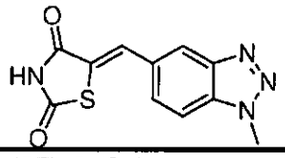
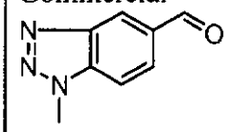
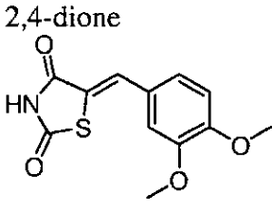
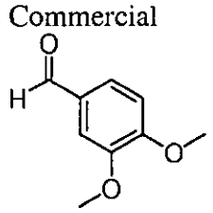
53	(5Z)-5-{2-(4-isopropylpiperazin-1-yl)-4,5-dimethoxybenzylidene}-thiazolidine-2,4-dione 	7.86 (s, 1 H) 6.95 (s, 1 H) 6.77 (s, 1 H) 3.81 (s, 3 H) 3.76 - 3.67 (m, 3 H) 2.91 - 2.79 (m, 5 H) 2.71 (s, 4 H) 1.08 - 1.00 (m, 6 H)	392	2-(4-isopropylpiperazin-1-yl)-4,5-dimethoxybenzaldehyde Method 21 
54	(5Z)-5-{2-(4-(dimethylamino)piperidin-1-yl)-4,5-dimethoxybenzylidene}-thiazolidine-2,4-dione 	7.48 (s, 1 H) 6.82 (s, 1 H) 6.51 (s, 1 H) 3.58 (s, 3 H) 3.51 (s, 3 H) 2.87 (d, 2 H) 2.47 (m, 3 H) 2.35 (s, 6 H) 1.79 (d, 2 H) 1.49 (d, 2 H)	392	2-(4-(dimethylamino)piperidin-1-yl)-4,5-dimethoxybenzaldehyde Method 22 
55	(Z)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)piperazine-1-carboxylate 	12.65 (s, 1 H) 7.82 (s, 1 H) 7.72 (s, 1 H) 7.53 (s, 1 H) 3.59 - 3.50 (m, 1 H) 3.38 - 3.30 (m, 4 H) 2.56 (s, 6 H) 2.31 - 2.28 (m, 1 H) 2.09 - 2.01 (m, 1 H)	458	*tert*-butyl 4-(2-formyl-4-(trifluoromethyl)phenyl)piperazine-1-carboxylate Method 23 

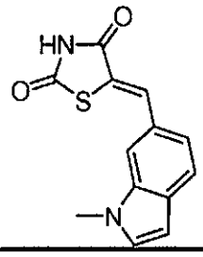
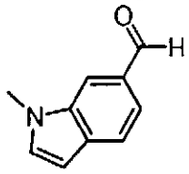
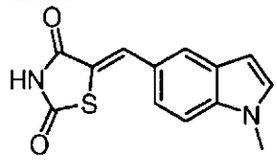
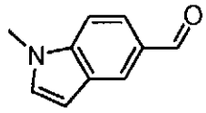
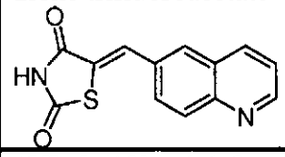
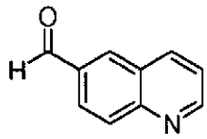
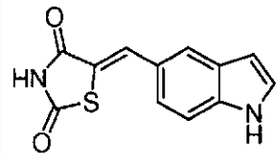
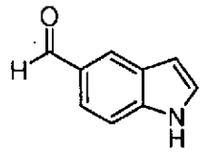
56	(Z)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-5-nitrobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.64 (s, 1 H) 8.22 (d, 1 H) 8.12 (d, 1 H) 7.95 (d, 1 H) 7.04 (d, 1 H) 3.95 - 3.90 (m, 1 H) 3.70 - 3.65 (m, 2 H) 3.56 - 3.51 (m, 2 H) 2.79 (s, 6 H) 2.41 - 2.35 (m, 1 H) 2.34 - 2.22 (m, 1 H)	363	2-(3-(dimethylamino)pyrrolidin-1-yl)-5-nitrobenzaldehyde Method 24 
57	(Z)-4-(3-(dimethylamino)pyrrolidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzamide hydrochloride 	12.47 (s, 1 H) 7.92 - 7.84 (m, 4 H) 7.23 (s, 1 H) 7.03 (d, 1 H) 3.98 - 3.91 (m, 1 H) 3.53 - 3.49 (m, 2 H) 3.46 - 3.39 (m, 2 H) 2.79 (s, 6 H) 2.34 - 2.19 (m, 2 H)	361	4-(3-(dimethylamino)pyrrolidin-1-yl)-3-formylbenzamide Method 25 
58	(Z)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carboxylate 	12.55 (s, 1 H) 7.92 (s, 1 H) 7.46 – 7.44 (m, 2 H) 7.21 –7.18 (m, 2 H) 3.48 (brs, 4 H) 2.86 (brs, 4 H) 1.43 (s, 9 H)	389	*tert*-butyl 4-(2-formylphenyl)piperazine-1-carboxylate Method 26 
59	(Z)-5-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzylidene)thiazolidine-2,4-dione 	7.78 (s, 1 H) 7.27 (s, 1 H) 7.21 (s, 2 H) 4.47 (t, 2 H) 3.84 (s, 3 H) 3.49 (t, 4 H) 3.04 (brs, 2 H) 1.80 (d, 4 H) 1.64 (brs, 1 H) 1.43 (brs, 1 H)	363	3-methoxy-4-(2-(piperidin-1-yl)ethoxy)benzaldehyde Commercial 

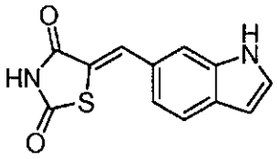
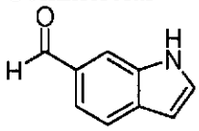
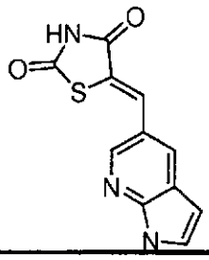
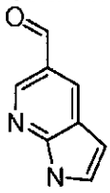
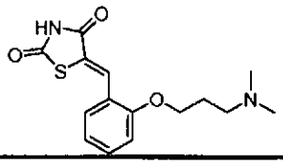
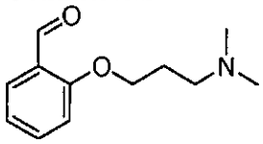
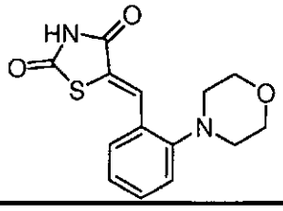
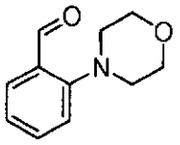
60	(Z)-5-(2-(2-hydroxyethoxy)benzylidene)thiazolidine-2,4-dione 	12.58 (brs, 1 H) 8.06 (s, 1 H) 7.57 - 7.32 (m, 2 H) 7.26 - 7.03 (m, 2 H) 4.95 (brs, 1 H) 4.13 (t, 2 H) 3.77 (brs, 2 H)	266	2-(2-hydroxyethoxy)benzaldehyde Commercial 
61	(Z)-5-(5-methoxy-2-(2-(piperidin-1-yl)ethoxy)benzylidene)thiazolidine-2,4-dione 	7.80 (s, 1 H) 7.10 (d, 1 H) 7.04 – 6.95 (m, 2 H) 4.22 (t, 2 H) 3.75 (s, 3 H) 3.07 (t, 2 H) 2.84 (s, 4 H) 1.62 (dq, 4 H) 1.46 (d, 2 H)	363	5-methoxy-2-(2-(piperidin-1-yl)ethoxy)benzaldehyde Method 27 
62	(Z)-5-(5-methoxy-2-(2-morpholinoethoxy)benzylidene)thiazolidine-2,4-dione 	7.99 (s, 1 H) 7.22 - 7.10 (m, 1 H) 7.09 – 6.97 (m, 1 H) 6.91 (d, 1 H) 4.17 (t, 2 H) 3.76 (s, 3 H) 3.64 - 3.51 (m, 4 H) 2.75 (t, 2 H) 2.51 - 2.62 (m, 4 H)	365	5-methoxy-2-(2-morpholinoethoxy)benzaldehyde Method 28 

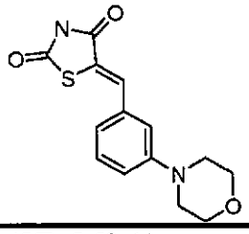
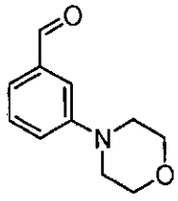
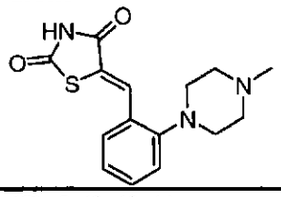
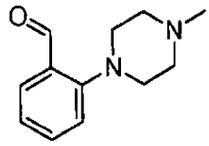
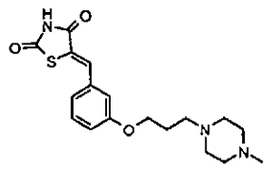
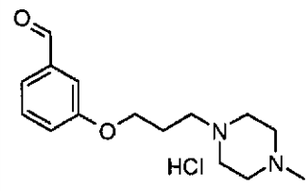
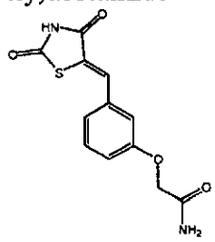
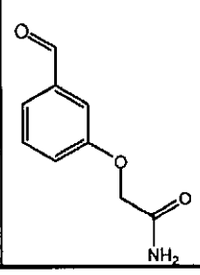
63	(Z)-5-(2-(2-(diethylamino)ethoxy)-5-methoxybenzylidene)thiazolidine-2,4-dione 	7.77 (s, 1 H) 7.08 - 7.05 (m, 1 H) 7.03 – 6.95 (m, 2 H) 4.19 (t, 2 H) 3.75 (s, 3 H) 3.25 - 3.14 (m, 2 H) 2.95 (q, 4 H) 1.17 - 1.08 (m, 6 H)	352	2-(2-(diethylamino)ethoxy)-5-methoxybenzaldehyde Method 29 
64	(Z)-5-(2-(2-(diethylamino)ethoxy)benzylidene)thiazolidine-2,4-dione 	7.84 (s, 1 H) 7.47 (d, 1 H) 7.43 - 7.35 (m, 1 H) 7.14 - 7.04 (m, 2 H) 4.24 (t, 2 H) 3.20 (m, 2 H) 2.90 (q, 4 H) 1.13 (t, 6 H)	321	2-(2-(diethylamino)ethoxy)benzaldehyde Method 30 
65	(Z)-5-(4,5-dimethoxy-2-(pyridin-3-yl)benzylidene)thiazolidine-2,4-dione 	12.55 (brs, 1 H) 8.73 - 8.61 (m, 1 H) 8.58 (brs, 1 H) 7.81 (dd, 1 H) 7.53 (dd, 1 H) 7.46 (s, 1 H) 7.13 (d, 2 H) 3.89 (d, 6 H)	343	4,5-dimethoxy-2-(pyridin-3-yl)benzaldehyde Method 31 

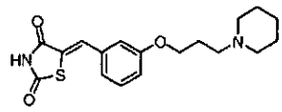
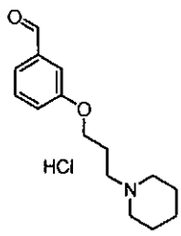
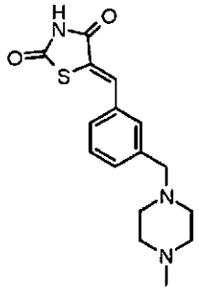
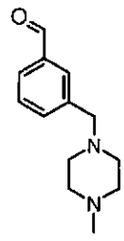
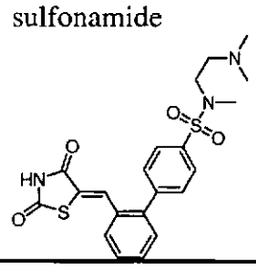
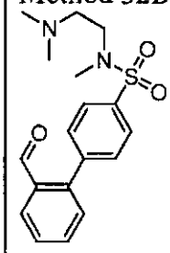
66	(Z)-5-(4,5-dimethoxy-2-(pyridin-4-yl)benzylidene)thiazolidine-2,4-dione 	12.58 (brs, 1 H) 8.67 (d, 2 H) 7.48 (d, 1 H) 7.41 (d, 2 H) 7.12 (d, 2 H) 3.89 (s, 6 H)	343	4,5-dimethoxy-2-(pyridin-4-yl)benzaldehyde Method 32 
67	(Z)-5-((1H-indol-3-yl)methylene)thiazolidine-2,4-dione 	7.21 (dddd, 2 H) 7.50 (d, 1 H) 7.71 (d, 1 H) 7.87 (d, 1 H) 7.99 (s, 1 H) 12.07 (brs, 2 H)	245	1H-indole-3-carbaldehyde Commercial 
68	(Z)-5-((1H-indazol-3-yl)methylene)thiazolidine-2,4-dione 	7.28 (t, 1 H) 7.52 - 7.39 (m, 1 H) 7.64 (d, 1 H) 8.22 - 8.03 (m, 2 H) 12.41 (d, 1 H) 13.96 (s, 1 H)	246	1H-indazole-3-carbaldehyde Commercial 
69	(Z)-5-((6-oxo-1,6-dihydropyridin-3-yl)methylene)thiazolidine-2,4-dione 	11.99 (brs, 1 H) 7.74 (brs, 1 H) 7.69 - 7.58 (m, 1 H) 7.27 (s, 1 H) 6.43 (d, 1 H)	223	6-oxo-1,6-dihydropyridine-3-carbaldehyde Commercial 

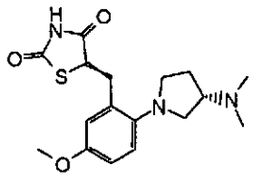
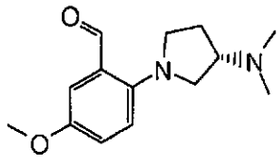
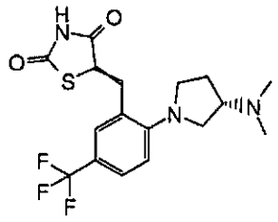
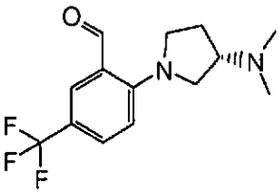
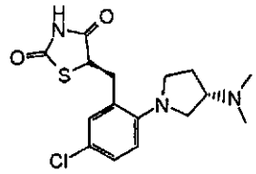
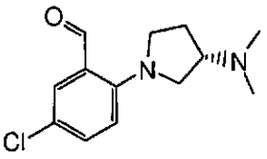
70	(Z)-5-((2-oxo-1,2-dihydropyridin-3-yl)methylene)thiazolidine-2,4-dione 	12.43 (brs, 1 H) 12.16 (brs, 1 H) 7.73 (s, 1 H) 7.69 (dd, 1 H) 7.57 (d, 1 H) 6.38 (t, 1 H)	223	2-oxo-1,2-dihydropyridine-3-carbaldehyde Commercial 
71	(Z)-5-((1H-pyrazol-4-yl)methylene)thiazolidine-2,4-dione 	13.51 (brs, 1 H) 12.37 (brs, 1 H) 8.20 (s, 1 H) 7.82 (s, 1 H) 7.74 (s, 1 H)	196	1*H*-pyrazole-4-carbaldehyde Commercial 
72	(Z)-5-(pyridin-4-ylmethylene)thiazolidine-2,4-dione 	12.61 (brs, 1 H) 8.71 (d, 2 H) 7.74 (s, 1 H) 7.53 (d, 2 H)	207	4-pyridinecarboxaldehyde Commercial 
73	(5Z)-5-[(1-methyl-1H-1,2,3-benzotriazol-5-yl)methylene]-1,3-thiazolidine-2,4-dione 	12.65 (brs, 1 H) 8.28 (s, 1 H) 8.00-7.98 (m, 2 H) 7.76 (d, 1 H) 4.33 (s, 3 H)	259	1-methyl-1H-benzo[d][1,2,3]triazole-5-carbaldehyde Commercial 
74	(5Z)-5-(3,4-dimethoxybenzylidene)-1,3-thiazolidine-2,4-dione 	12.51 (brs, 1 H) 7.74 (s, 1 H) 7.19 – 7.09 (m, 3 H) 3.82 (s, 3 H) 3.80 (s, 3 H)	266	3,4-dimethoxybenzaldehyde Commercial 

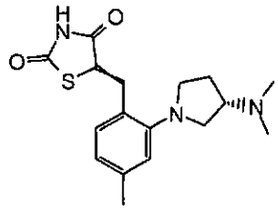
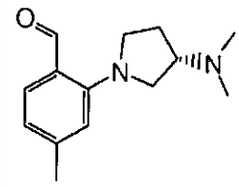
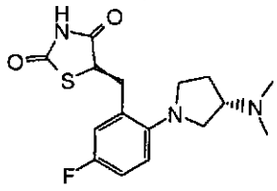
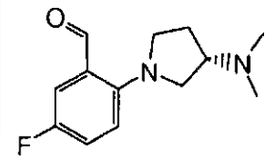
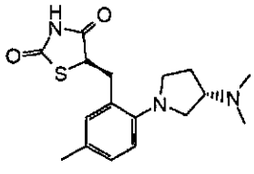
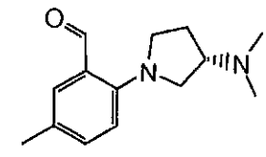
75	(5Z)-5-[(1-methyl-1H-indol-6-yl)methylene]-1,3-thiazolidine-2,4-dione 	12.49 (brs, 1 H) 7.92 (s, 1 H) 7.68 (d, 1 H) 7.54 (s 1 H) 7.25 (d, 1 H) 6.50 (s, 1 H) 3.84 (s, 3 H)		1-methyl-1H-indole-6-carbaldehyde Commercial 
76	(5Z)-5-[(1-methyl-1H-indol-5-yl)methylene]-1,3-thiazolidine-2,4-dione 	12.45 (brs, 1 H) 7.90 (s, 1 H) 7.84 (d, 1 H) 7.59 (d, 1 H) 7.44 (d, 1 H) 7.38 (d 1 H) 6.57 (d, 1 H) 3.82 (s, 3 H)	259	1-methyl-1H-indole-5-carbaldehyde Commercial 
77	(5Z)-5-(quinolin-6-ylmethylene)-1,3-thiazolidine-2,4-dione trifluoroacetate 	12.70 (brs, 1 H) 8.97 (d, 1 H) 8.51 (d, 1 H) 8.24 (s, 1 H) 8.12 (d, 1 H) 7.96 – 7.93 (m, 2 H) 7.64 – 7.61 (m, 1 H)	257	quinoline-6-carbaldehyde Commercial 
78	(5Z)-5-(1*H*-indol-5-ylmethylene)-1,3-thiazolidine-2,4-dione 	12.43 (brs, 1 H) 11.44 (brs, 1 H) 7.85 (d, 1 H) 7.53 – 7.51 (m, 2 H) 7.45 – 7.44 (m, 1 H) 7.33 (d, 1 H) 6.56 (s, 1 H)	245	1*H*-indole-5-carbaldehyde Commercial 

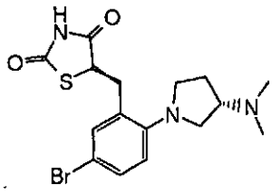
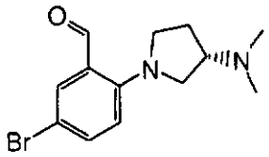
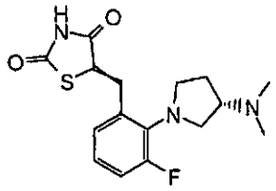
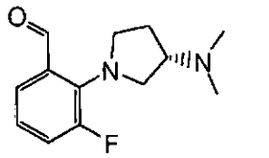
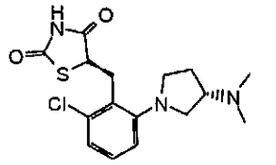
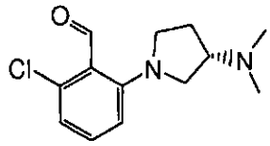
79	(5Z)-5-(1*H*-indol-6-ylmethylene)-1,3-thiazolidine-2,4-dione trifluoroacetate 	12.47 (brs, 1 H) 11.48 (brs, 1 H) 7.90 (s, 1 H) 7.69 – 7.66 (m, 2 H) 7.55 – 7.52 (m, 1 H) 7.23 (d, 1 H) 6.51 (s, 1 H)	245	1*H*-indole-6-carbaldehyde Commercial 
80	(5Z)-5-(1H-pyrrolo[2,3-b]pyridin-5-ylmethylene)-1,3-thiazolidine-2,4-dione 	12.02 (brs, 1 H) 8.49 (d, 1 H) 8.15 (d, 1 H) 7.92 (s, 1 H) 7.58 (t, 1 H) 6.59 (brs, 1 H)	246	1*H*-pyrrolo[2,3-b]pyridine-5-carbaldehyde Commercial 
81	(5Z)-5-{2-[3-(dimethylamino)propoxy]benzylidene}-1,3-thiazolidine-2,4-dione 	8.16 (s, 1 H) 7.76 (s, 1 H) 7.48 (d, 1 H) 7.34 (s, 1 H) 7.08 (d, 1 H) 4.11 (t, 2 H) 2.86 (t, 2 H) 2.53 (s, 6 H) 2.10 – 1.98 (m, 2 H)	307	2-[3-(dimethylamino)propoxy]benzaldehyde Commercial 
82	(5Z)-5-(2-morpholin-4-ylbenzylidene)-1,3-thiazolidine-2,4-dione 	7.89 (s, 1 H) 7.46 (d, 1 H) 7.45 - 7.41 (m, 1 H) 7.22 - 7.14 (m, 2 H) 3.80 - 3.69 (m, 4 H) 2.93 - 2.82 (m, 4 H)	291	2-morpholin-4-ylbenzaldehyde Commercial 

83	(5Z)-5-(3-morpholin-4-ylbenzylidene)-1,3-thiazolidine-2,4-dione trifluoroacetate 	12.58 (brs, 1 H) 7.74 (s, 1 H) 7.37 (t, 1 H) 7.12 (s, 1 H) 7.07 (dd, 1 H) 7.00 (d, 1 H) 3.79 - 3.69 (m, 4 H) 3.20 - 3.09 (m, 4 H)	290	3-morpholin-4-ylbenzaldehyde Commercial 
84A	(5Z)-5-[2-(4-methylpiperazin-1-yl)benzylidene]-1,3-thiazolidine-2,4-dione 	7.78 (s, 1 H) 7.46 (d, 1 H) 7.42 - 7.35 (m, 1 H) 7.19 - 7.11 (m, 2 H) 2.94 (t, 4 H) 2.70 (brs, 4 H) 2.40 (s, 3 H)	304	2-(4-methylpiperazin-1-yl)benzaldehyde Commercial 
84B	(Z)-5-(3-(3-(4-methylpiperazin-1-yl)propoxy)benzylidene)thiazolidine-2,4-dione 	11.37 (brs, 1 H) 7.54 (s, 1 H) 7.38 (t, 1H) 7.12 (m, 2 H), 6.96 (m, 1 H) 4.58 (s, 3 H) 4.05 (t, 2 H) 3.00 - 2.55 (m, 10 H) 1.93 (m, 2 H)	362	3-(3-(4-methylpiperazin-1-yl)propoxy)benzaldehyde hydrochloride 
84C	(Z)-2-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetamide 	12.62 (s, 1 H) 7.73 (s, 1 H) 7.60 (s, 1 H) 7.44 (t, 1 H) 7.41 (s, 1 H) 7.19 (d, 1 H) 7.14 (m, 1 H) 7.05 (dd, 1 H) 4.48 (s, 2 H)	279	2-(3-formylphenoxy)acetamide 

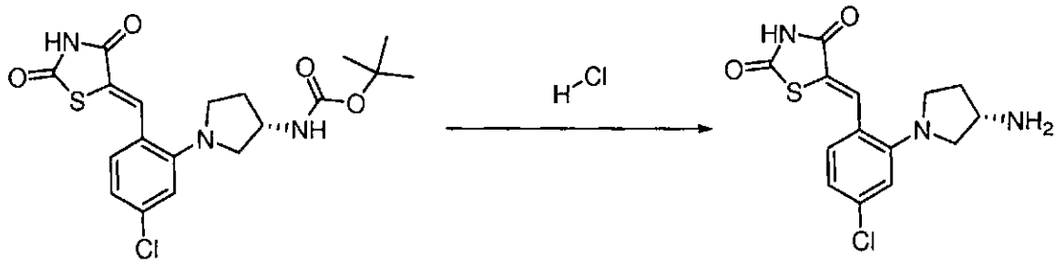
84D	(Z)-5-(3-(3-(piperidin-1-yl)propoxy)benzylidene)thiazolidine-2,4-dione 	7.30 (t, 1 H) 7.24 (s, 1 H) 7.08 (m, 2 H) 6.85 (dd, 1 H) 4.01 (t, 2 H) 2.45 (t, 2 H) 2.40 (m, 4 H) 1.88 (m, 2 H) 1.50 (m, 4 H) 1.38 (m, 2 H)	347	3-(3-(piperidin-1-yl)propoxy)benzaldehyde hydrochloride 
84E	(Z)-5-(3-((4-methylpiperazin-1-yl)methyl)benzylidene)thiazolidine-2,4-dione 	7.59 (s, 1 H) 7.51 (s, 1 H) 7.46 (m, 2 H) 7.34 (m, 1 H) 3.59 (s, 2 H) 2.96 (m, 4 H) 2.59 (m, 4 H) 2.58 (s, 3 H)	318	3-((4-methylpiperazin-1-yl)methyl)benzaldehyde 
84F	(Z)-*N*-(2-(dimethylamino)ethyl)-2'-((2,4-dioxothiazolidin-5-ylidene)methyl)-*N*-methylbiphenyl-4-sulfonamide 	7.90 (d, 2 H) 7.69 (d, 1 H) 7.65-7.49 (m, 4 H) 7.49 - 7.40 (m, 1 H) 7.31 (s, 1 H) 3.24 (t, 2 H) 2.83 (t, 2 H) 2.78 (s, 3 H) 2.48 (s, 6 H)	445	*N*-(2-(dimethylamino)ethyl)-2'-formyl-*N*-methylbiphenyl-4-sulfonamide Method 32B 

84G	(*S*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methoxybenzylidene)thiazolidine-2,4-dione 		348	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methoxybenzaldehyde Method 104 
84H	(*S*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione 	12.55 (s, 1 H) 11.25 (brs, 1 H) 7.95 (s, 1 H) 7.78 (s, 1 H) 7.60 (m, 1 H), 7.15 (m, 1 H) 4.00 (m, 1 H) 3.65 (m, 2 H) 3.40 (m, 1 H) 3.32 (m, 1 H) 2.80 (s, 6 H) 2.35 (m, 1 H) 2.20 (m, 1 H)	386	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-(trifluoromethyl)benzaldehyde Method 105 
84I	(*S*)-5-(5-chloro-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione 	12.55 (s, 1 H) 7.81 (s, 1H), 7.93 (m, 2H), 7.12 (m, 1H), 3.90(m, 1H), 3.45-3.30 (m, 2H), 3.29 (m, 1H), 3.15 (m, 1H), 2.80 (s, 6H), 2.35 (m, 1H), 2.20 (m, 1H)	352	(*S*)-5-chloro-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde Method 106 

84J	(*S*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-4-methylbenzylidene)thiazolidine-2,4-dione 		332	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-4-methylbenzaldehyde Method 107 
84K	(*S*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-5-fluorobenzylidene)thiazolidine-2,4-dione 	12.55 (s, 1 H) 11.40 (s, 1 H) 7.80 (s, 1 H) 7.30-7.15 (m, 3 H) 3.92 (m, 1 H) 3.45 (m, 1 H) 3.35 (m, 1 H) 3.18 (m, 1 H) 3.15 (m, 1 H) 3.80 (d, 6 H) 2.30 (m, 1 H), 2.20 (m, 1H)	336	(S)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-fluorobenzaldehyde Method 108 
84L	(*S*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methylbenzylidene)thiazolidine-2,4-dione 		332	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methylbenzaldehyde Method 109 

84M	(*S*)-5-(5-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione 		397	(*S*)-5-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde Method 110 
84N	(*S*)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-3-fluorobenzylidene)thiazolidine-2,4-dione 	12.55 (s, 1 H) 10.34 (s, 1 H) 7.87 (d, 1H) 7.33-7.21 (m, 3 H) 3.93 (m, 1 H) 3.40 (m, 2 H) 3.25 (m, 1 H) 3.18 (m, 1 H) 2.79 (s, 6 H) 2.26 (m, 1H) 2.12 (m, 1H)	336	(S)-2-(3-(dimethylamino)pyrrolidin-1-yl)-3-fluorobenzaldehyde Method 111 
84O	(*S*)-5-(2-chloro-6-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione 		352	(*S*)-2-chloro-6-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde Method 112 

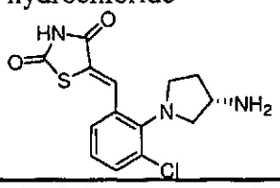
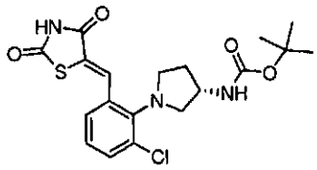
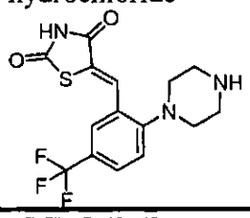
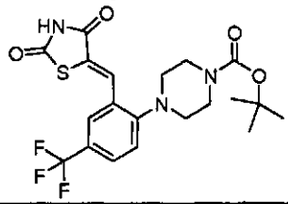
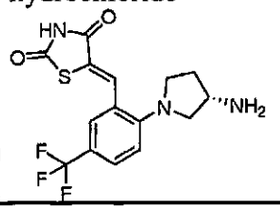
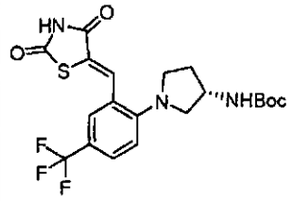
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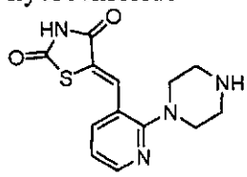
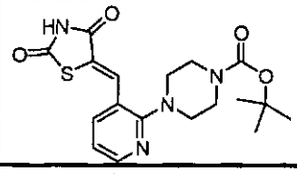
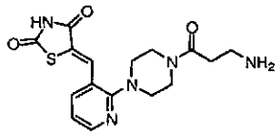
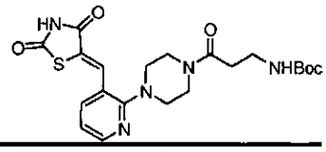
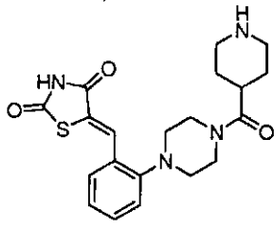
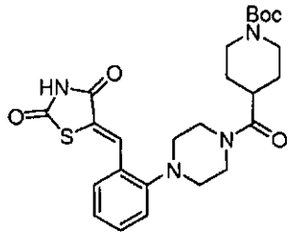


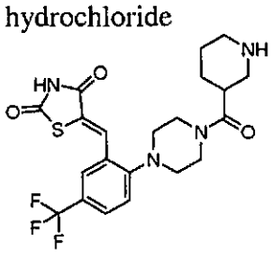
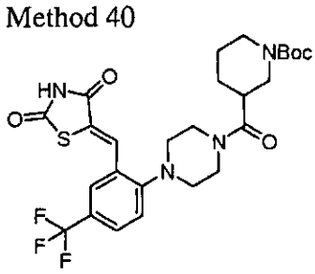
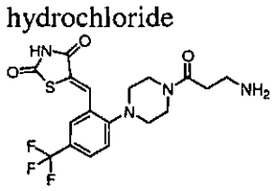
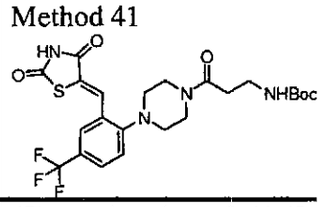
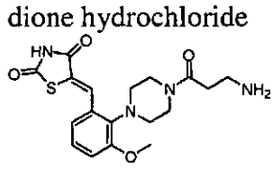
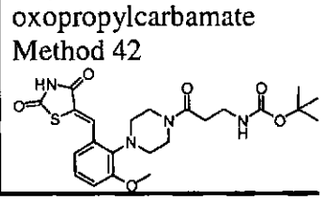
(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-4-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride:

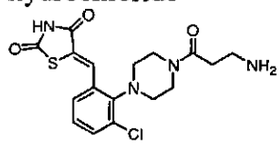
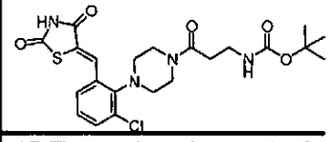
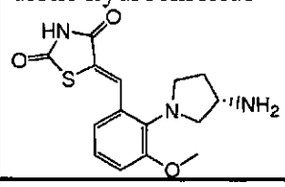
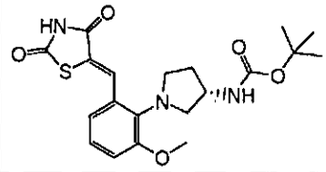
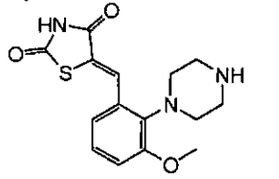
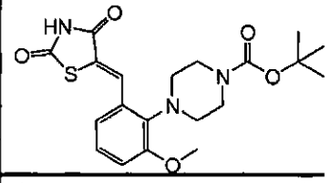
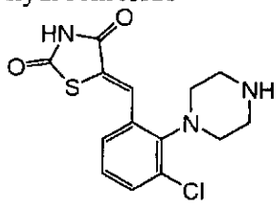
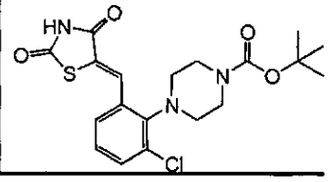
A 100 mL round bottom flask was charged with a magnetic stir bar, (*S,Z*)-*tert*-butyl1-(5-chloro-2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate (Method 33) (1.300 g, 3.07 mmol), MeOH (10.22 ml), and a 1N sol'n of HCl in diethyl ether (2.294 ml, 46.00 mmol). The reaction mixture was allowed to stir overnight at rt before being conc. *in vacuo* to afford the product as its hydrochloride salt. This material was dissolved in DMSO and purified via reverse phase HPLC to afford fractions that were conc. *in vacuo*, suspended in methanol (~ 5 mL) and 1N HCl in diethyl ether (~2 mL). This mixture was conc. *in vacuo* to afford (*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-4-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride (0.710 g, 64.3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12.51 (s, 1 H) 8.36 (s, 2 H) 7.85 (s, 1 H) 7.35 (d, 1 H) 6.96 (dd, 2 H) 3.90 - 3.75 (m, 1 H) 3.55- 3.47 (m, 1 H) 3.40 (dd, 1 H) 3.31 - 3.21 (m, 1 H) 3.18 - 3.10 (m, 1 H) 2.29 - 2.18 (m, 1 H) 2.10 - 1.96 (m, 1 H); *m/z* 325.

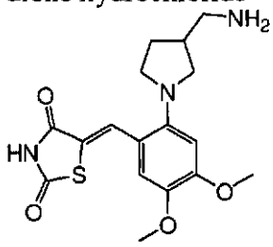
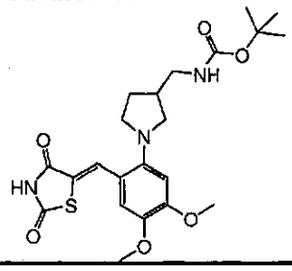
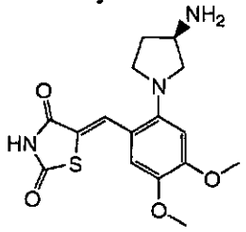
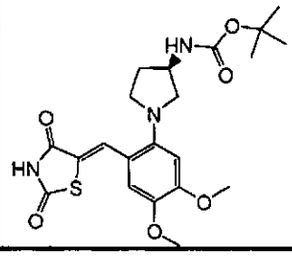
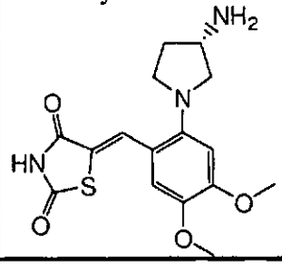
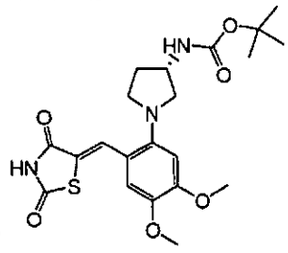
The following examples were prepared by the procedure of Example 85, using the appropriate starting materials. The following parent compounds obtained after chromatography may be converted to their corresponding hydrochloride salt in a manner similar as described in example 85, or similar procedure.

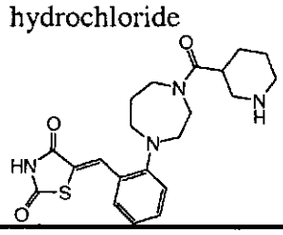
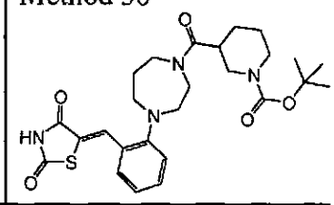
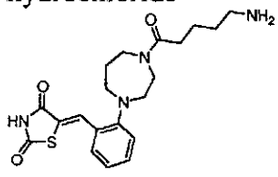
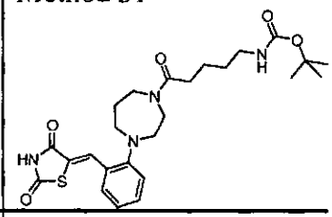
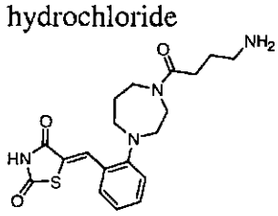
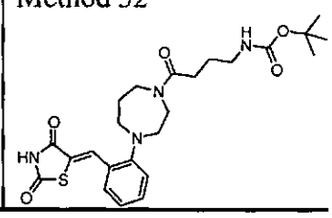
Ex.	Compound	^{1}H NMR	m/z	SM
86	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.69 (s, 1 H) 8.35 (brs, 2 H) 7.94 (s 1 H) 7.57 (d, 1 H) 7.41 - 7.35 (m, 2 H) 3.95 - 3.88 (m, 1 H) 3.53 - 3.26 (m, 4 H) 2.37 - 2.31 (m, 1 H) 2.08 - 2.01 (m, 1 H)	324	(*S,Z*)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate Method 34 
87	(*Z*)-5-(2-(piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.69 (s, 1 H) 9.32 (brs, 2 H) 7.79 (d, 1 H) 7.71 (d, 2 H) 7.37 (d, 1 H) 3.23 (s, 8 H)	358	(*Z*)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)piperazine-1-carboxylate Method 35 
88	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.53 (s, 1 H) 8.17 (brs, 2 H) 7.95 (s, 1 H) 7.65 (s, 1 H) 7.59 (d 1 H) 7.05 (d, 1 H) 3.90 - 3.81 (m, 1 H) 3.56 (q, 1 H) 3.47 - 3.35 (m, 2 H) 3.18 (dd, 1 H) 2.33 - 2.18 (m, 1 H) 2.09 - 1.99 (m, 1 H)	358	(*S,Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)pyrrolidin-3-ylcarbamate Method 36 

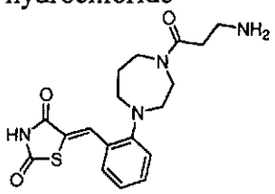
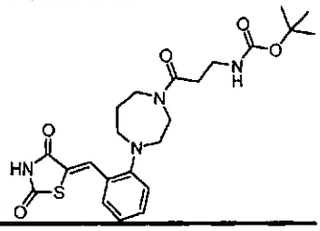
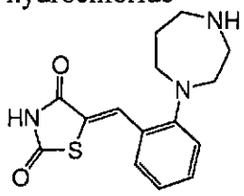
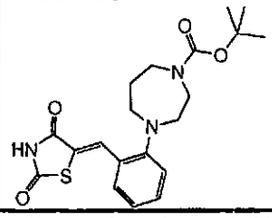
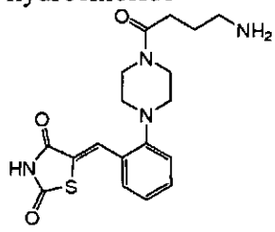
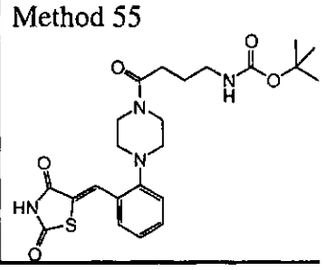
89	(Z)-5-((2-(piperazin-1-yl)pyridin-3-yl)methylene)thiazolidine-2,4-dione hydrochloride 	12.65 (s, 1 H) 8.39 (s, 1 H) 8.33 (d, 1 H) 7.83 (d, 1 H) 7.63 (s, 1 H) 7.15 (dd, 1 H) 3.41 (brs, 4 H) 3.17 (brs, 4 H)	291	(Z)-*tert*-butyl 4-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)pyridin-2-yl)piperazine-1-carboxylate Method 37 
90	(Z)-5-((2-(4-(3-aminopropanoyl)piperazin-1-yl)pyridin-3-yl)methylene)thiazolidine-2,4-dione trifluoroacetate 	12.60 (s, 1 H) 8.32 (d, 1 H) 7.82 (s, 1 H) 7.68 (s, 1 H) 7.63 (brs, 2 H) 7.12 (dd, 1 H) 3.57 (d, 4 H) 3.17 (d, 4 H) 3.00 (q, 2 H) 2.70 (t, 2 H)	362	(Z)-*tert*-butyl 3-(4-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)pyridin-2-yl)piperazin-1-yl)-3-oxopropylcarbamate Method 38 
91	(Z)-5-(2-(4-(piperidine-4-carbonyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione 	9.00 (brs, 1 H) 8.67 (brs, 1 H) 8.18 (s, 1 H) 7.57 - 7.52 (m, 1 H) 7.30 -7.16 (m, 1 H) 3.71 (s, 1 H) 3.63 (s, 1 H) 3.34 (s, 3 H) 3.31 - 3.22 (m, 2 H) 3.13 (s, 3 H) 3.01 -2.87 (m, 5 H) 1.85 - 1.77 (m, 4 H)	401	(Z)-*tert*-butyl 4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)piperidine-1-carboxylate Method 39 

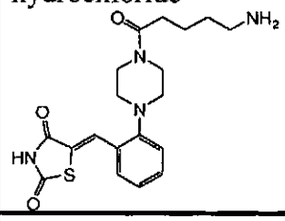
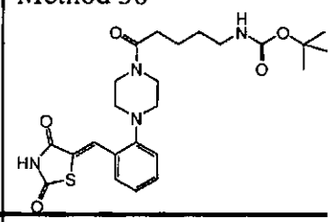
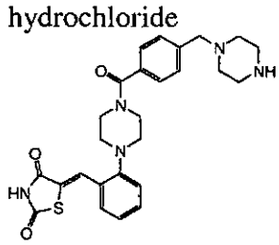
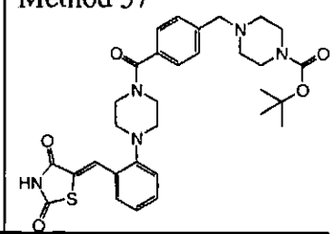
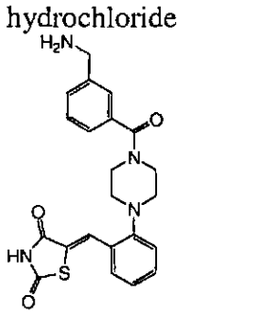
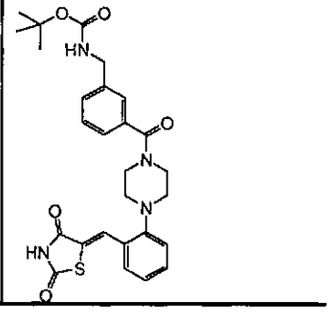
92	(Z)-5-(2-(4-(piperidine-3-carbonyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.68 (s, 1 H) 8.87 (s, 1 H) 7.78 - 7.69 (m, 3 H) 7.32 (d, 1 H) 3.68 - 3.64 (m, 8 H) 3.38 (tt, 1 H) 3.13 - 2.98 (m, 4 H) 1.75 - 1.56 (m, 4 H)	469	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)piperazine-1-carbonyl)piperidine-1-carboxylate Method 40 
93	(Z)-5-(2-(4-(3-aminopropanoyl)piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.67 (s 1 H) 7.93 (brs, 2 H) 7.78 - 7.68 (m, 3 H) 7.32 (d, 1 H) 3.69 - 3.59 (m, 8 H) 3.00 - 2.74 (m, 4 H)	429	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)piperazin-1-yl)-3-oxopropylcarbamate Method 41 
94	(Z)-5-(2-(4-(3-aminopropanoyl)piperazin-1-yl)-3-methoxybenzylidene) thiazolidine-2,4-dione hydrochloride 	12.53 (brs, 1 H) 8.21 (s, 1 H), 7.58 (brs, 3 H), 7.24 (t, 1 H) 7.11 (d, 1 H) 7.00 (d, 1 H) 3.75 (s, 3 H) 3.35 (brs, 4 H) 3.09 - 2.85 (m, 4 H) 2.65 (brs, 2 H)	391	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)piperazin-1-yl)-3-oxopropylcarbamate Method 42 

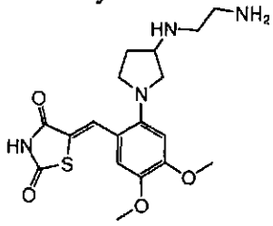
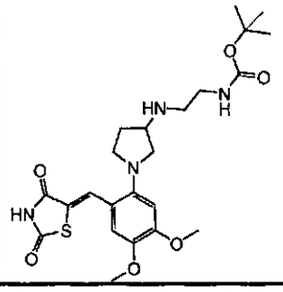
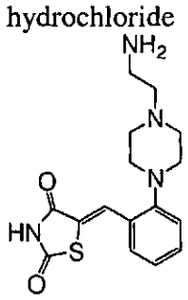
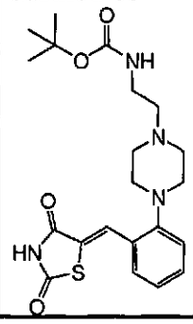
95	(Z)-5-(2-(4-(3-aminopropanoyl)piperazin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.69 (brs, 1 H) 8.12 (s, 1 H) 7.67 (brs, 2 H) 7.55 (dd, 1 H) 7.49 - 7.40 (m, 1 H) 7.35 (t, 1 H) 4.17 (brs, 1 H) 3.75 (brs, 1 H) 3.35 (brs, 3 H) 3.13 - 2.84 (m, 5 H) 2.74 (brs, 2 H)	395	(Z)-*tert*-butyl 3-(4-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)-3-oxopropylcarbamate Method 43 
96	(*S*,Z)-5-(2-(3-aminopyrrolidin-1-yl)-3-methoxybenzylidene) thiazolidine-2,4-dione hydrochloride 	12.43 (s, 1 H) 7.94 (s, 1 H) 7.86 (brs, 1 H) 7.16 (t, 1 H) 7.05 (d, 1 H) 6.91 (d, 1 H) 3.71 (s, 3 H) 3.30 (dd, 1 H) 3.17 - 3.08 (m, 1 H) 3.08 - 2.91 (m, 2 H) 2.23 - 2.06 (m, 2 H), 1.80 - 1.75 (m, 1 H)	320	(*S*,Z)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)pyrrolidin-3-ylcarbamate Method 44 
97	(Z)-5-(3-methoxy-2-(piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.45 (brs, 1 H) 8.59 (brs, 1 H) 7.99 (s, 1 H) 7.15 (t, 1 H) 7.02 (d, 1 H) 6.89 (d, 1 H) 3.67 (s, 3 H) 3.17 - 2.99 (m, 8 H)	320	(Z)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)piperazine-1-carboxylate Method 45 
98	(Z)-5-(3-chloro-2-(piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.72 (brs, 1 H) 9.19 (brs, 1 H) 8.01 (s, 1 H) 7.57 (dd, 1 H) 7.50 - 7.40 (m, 1 H) 7.36 (t, 1 H) 3.60 (brs, 2 H), 3.51 - 3.29 (m, 1 H) 3.29 - 3.12 (m, 2 H) 3.06 (brs, 3 H)	324	(Z)-*tert*-butyl 4-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carboxylate Method 46 

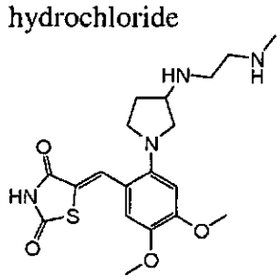
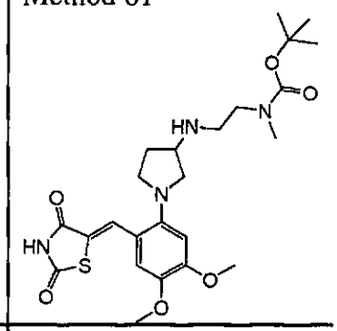
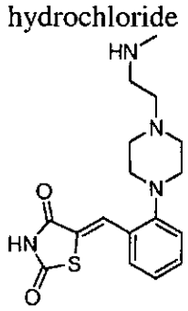
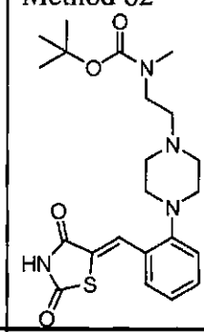
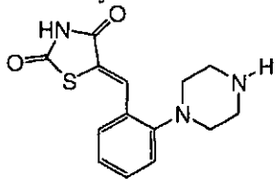
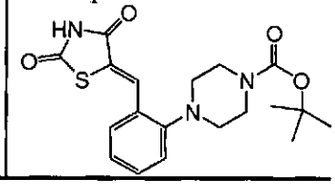
99	(Z)-5-(2-(3-(aminomethyl)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.40 (s, 1 H) 9.25 (s, 1 H) 7.88 (s, 1 H) 6.97 (s, 1 H) 6.73 (s, 1 H) 3.85 (s, 3 H) 3.81 (m, 1 H) 3.74 (s, 3 H) 3.40 - 3.31 (m, 2 H) 3.25 - 3.13 (m, 2 H) 2.59 (t, 3 H) 2.31 (dd, 1 H) 2.08 (d, 1 H)	364	(Z)-*tert*-butyl (1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-yl)methylcarbamate Method 47 
100	(*R*,Z)-5-(2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.39 (s, 1 H) 8.06 (s, 2 H) 7.89 (s, 1 H) 6.96 (s, 1 H) 6.65 (s, 1 H) 3.84 (s, 4 H) 3.73 (s, 3 H) 3.35 (d, 2 H) 3.20 (s, 1 H) 3.07 (d, 1 H) 2.28 (s, 1 H) 1.97 (s, 1 H)	350	(*R*,Z)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate Method 48 
101	(*S*,Z)-5-(2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.39 (s, 1 H) 8.08 (s, 2 H) 7.89 (s, 1 H) 6.96 (s, 1 H) 6.65 (s, 1 H) 3.84 (s, 4 H) 3.73 (s, 3 H) 3.45 - 3.30 (m, 2 H) 3.24 - 3.14 (m, 1 H) 3.12 - 3.00 (m, 1 H) 2.28 (s, 1 H) 1.98 (s, 1 H)	350	(*S*,Z)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate Method 49 

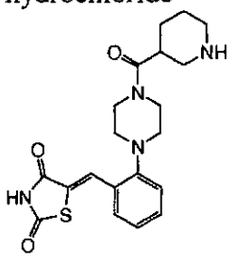
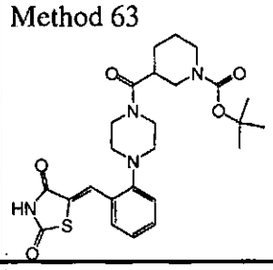
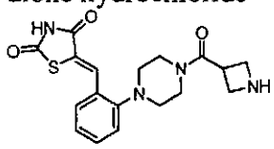
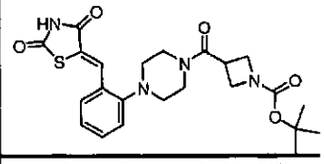
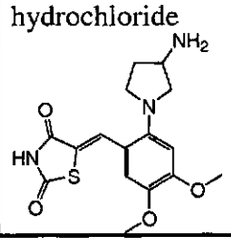
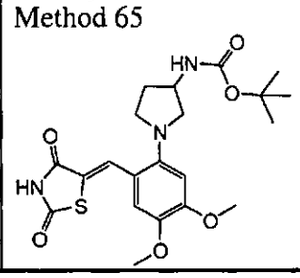
102	(Z)-5-(2-(4-(piperidine-3-carbonyl)-1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.49 (s, 1 H) 8.47 (s, 1 H) 7.82 (d, 1 H) 7.39 - 7.30 (m, 2 H) 7.16 (dd, 1 H) 7.06 (td, 1 H) 3.63 - 3.54 (m, 4 H) 3.29 - 3.06 (m, 9 H) 1.88 - 1.48 (m, 6 H)	415	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepane-1-carbonyl)piperidine-1-carboxylate Method 50 
103	(Z)-5-(2-(4-(5-aminopentanoyl)-1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.57 (s, 1 H) 7.90 (d, 1 H) 7.76 (s, 2 H) 7.47 - 7.36 (m, 2 H) 7.22 (t, 1 H) 7.12 (d, 1 H) 3.63 (d, 4 H) 3.22 (s, 1 H) 3.17 (s, 1 H) 3.05 (s, 2 H) 2.80 (s, 2 H) 2.41 (s, 1 H) 2.34 (s, 1 H) 1.91 (s, 1 H) 1.85 (s, 1 H) 1.57 (d, 4 H)	403	(Z)-*tert*-butyl 5-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepan-1-yl)-5-oxopentylcarbamate Method 51 
104	(Z)-5-(2-(4-(4-aminobutanoyl)-1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.49 (s, 1 H) 7.83 (d, 1 H) 7.65 (s, 2 H) 7.39 - 7.30 (m, 2 H) 7.20 - 7.12 (m, 1 H) 7.09 - 7.01 (m, 1 H) 3.61 - 3.50 (m, 4 H) 3.18 - 3.07 (m, 2 H) 2.98 (d, 2 H) 2.77 (ddd, 2 H) 2.37 (t, 2 H) 1.85 - 1.66 (m, 4 H).	389	(Z)-*tert*-butyl 4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepan-1-yl)-4-oxobutylcarbamate Method 52 

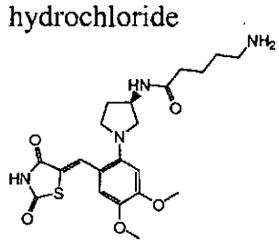
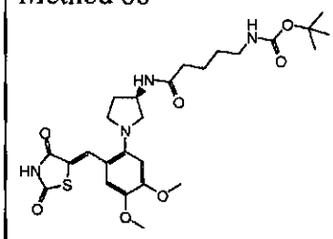
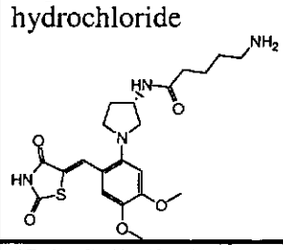
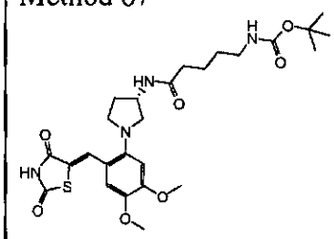
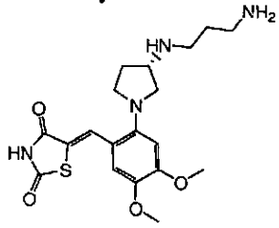
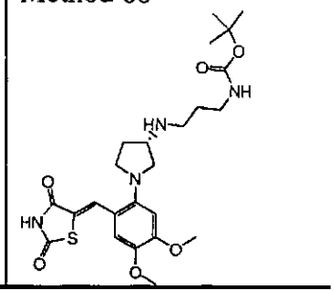
105	(Z)-5-(2-(4-(3-aminopropanoyl)-1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.50 (s, 1 H) 7.83 (s, 1 H) 7.63 (s, 2 H) 7.39 - 7.31 (m, 2 H) 7.16 (dd, 1 H) 7.10 - 7.01 (m, 1 H) 3.64 - 3.52 (m, 4 H) 3.20 - 3.09 (m, 2 H) 2.97 (dt, 4 H) 2.65 (dt, 2 H) 1.87-1.81 (m, 2 H)	375	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepan-1-yl)-3-oxopropylcarbamate Method 53 
106	(Z)-5-(2-(1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.57 (s, 1 H) 9.31 (s, 1 H) 7.91 (s, 1 H) 7.46 - 7.40 (m, 2 H) 7.26 (d, 1 H) 7.18 - 7.09 (m, 1 H) 3.36 (d, 2 H) 3.27 (d, 4 H) 3.19 (dd, 2 H) 2.10 - 2.01 (m, 2 H)	304	(Z)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepane-1-carboxylate Method 54 
107	(Z)-5-(2-(4-(4-aminobutanoyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.60 (s, 1 H) 7.95 (s, 4 H) 7.53 - 7.44 (m, 2 H) 7.26 - 7.17 (m, 2 H) 3.66 - 3.57 (m, 5 H) 2.89 (m, 4 H) 2.85 - 2.76 (m, 3 H) 1.85 - 1.76 (m, 2 H)	375	(Z)-*tert*-butyl 4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)-4-oxobutylcarbamate Method 55 

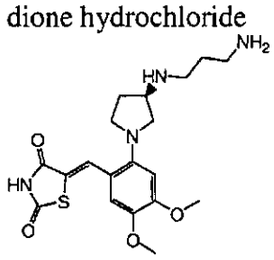
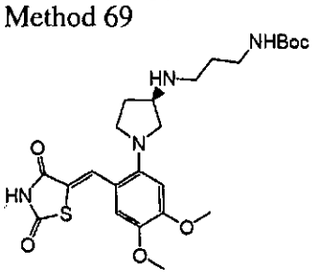
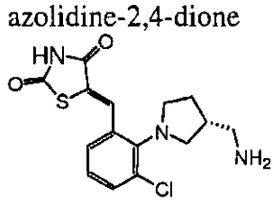
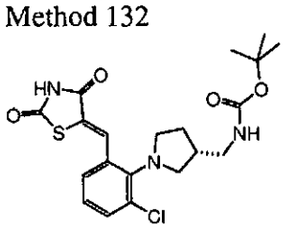
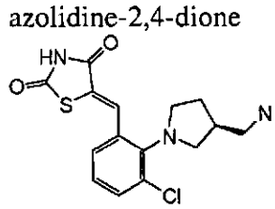
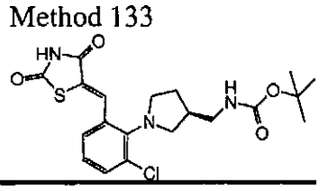
108	(Z)-5-(2-(4-(5-aminopentanoyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.66 (s, 1 H) 8.10 (s, 2 H) 7.99 (s, 1 H) 7.52 (s, 1 H) 7.51 - 7.47 (m, 1 H) 7.25 (t, 2 H) 3.67 (s, 4 H) 2.92 - 2.81 (m, 6 H) 2.44 (t, 2 H) 1.62 (s, 4 H)	389	(Z)-*tert*-butyl 5-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)-5-oxopentylcarbamate Method 56 
109	(Z)-5-(2-(4-(4-(piperazin-1-ylmethyl)benzoyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.57 (brs, 1 H) 9.70 (brs, 1 H) 7.94 (s, 1 H) 7.75 (d, 2 H) 7.52 (m, 2 H) 7.49 - 7.41 (m, 2 H) 7.21 (t, 2 H) 4.45 (brs, 2 H) 3.81 (brs, 2 H) 3.54 - 3.35 (m, 8 H) 3.27 (brs, 2 H) 2.89 (brs, 4 H)	492	(Z)-*tert*-butyl 4-(4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)benzyl)piperazine-1-carboxylate Method 57 
110	(Z)-5-(2-(4-(3-(aminomethyl)benzoyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.56 (s, 1 H) 8.18 (brs, 2 H) 7.95 (s, 1 H) 7.64 - 7.38 (m, 6 H) 7.36 - 7.11 (m, 2 H) 4.19 - 4.02 (m, 2 H) 3.82 (brs, 2 H) 3.52 (brs, 2 H) 2.92 (brs, 4 H)	423	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)benzylcarbamate Method 58 

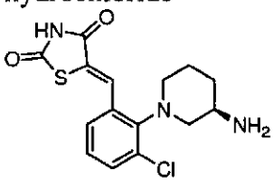
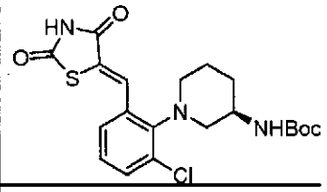
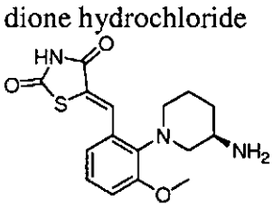
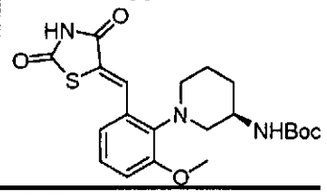
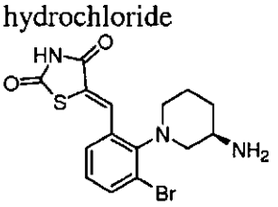
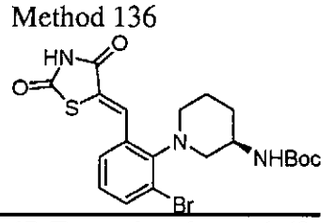
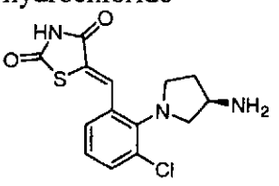
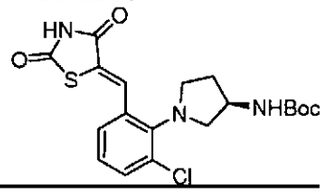
111	(Z)-5-(2-(3-(2-aminoethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.38 (s, 1 H) 9.99 (s, 1 H) 8.44 (s, 2 H) 7.86 (s, 1 H) 6.96 (s, 1 H) 6.76 (s, 1 H) 3.93 (s, 1 H) 3.84 (s, 3 H) 3.73 (s, 3 H) 3.45 - 3.33 (m, 2 H) 3.28 - 3.16 (m, 6 H) 2.32 (s, 1 H) 2.15 (s, 1 H)	393	(Z)-*tert*-butyl 2-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)ethylcarbamate Method 59 
112	(Z)-5-(2-(4-(2-aminoethyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.70 (s, 1 H) 11.43 (s, 1 H) 8.38 (s, 3 H) 7.86 (s, 1 H) 7.49 (m, 2 H) 7.25 (m, 2 H) 3.67 (m, 2 H) 3.42 - 3.30 (m, 8 H)	333	(Z)-*tert*-butyl 2-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)ethylcarbamate Method 60 

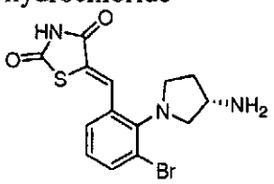
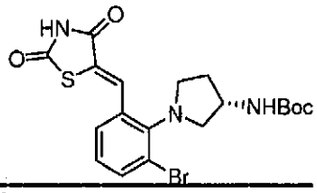
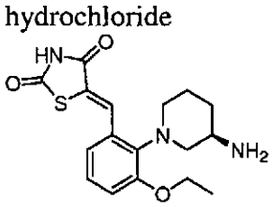
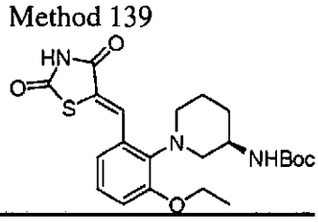
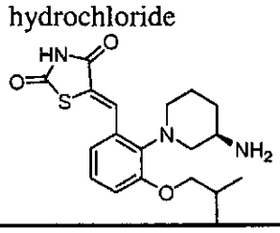
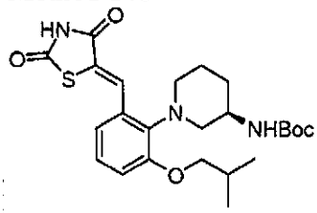
113	(Z)-5-(4,5-dimethoxy-2-(3-(2-(methylamino)ethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.39 (s, 1 H) 9.93 (brs, 1 H) 9.42 (brs, 1 H) 7.87 (s, 1 H) 6.98 (s, 1 H) 6.77 (s, 1 H) 4.00 – 3.91 (m, 1 H) 3.85 (s, 3 H) 3.74 (s, 3 H) 3.44 – 3.16 (m, 8 H) 2.62 (s, 3 H) 2.40 – 2.31 (m, 1 H) 2.20 – 2.14 (m, 1 H)	407	(Z)-*tert*-butyl 2-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)ethyl(methyl)carbamate Method 61 
114	(Z)-5-(2-(4-(2-(methylamino)ethyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.62 (s, 1 H) 11.28 (s, 1 H) 9.28 (s, 1 H) 7.87 (s, 1 H) 7.50 (t, 1 H) 7.26 (t, 1 H) 3.71 (m, 4 H) 3.57 (m, 2 H) 3.45 (m, 2 H) 3.26 (m, 4 H) 2.62 (s, 3 H)	347	(Z)-*tert*-butyl 2-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)ethyl(methyl)carbamate Method 62 
115	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione hydrochloride 	12.61 (s, 1 H) 9.21 (s, 1 H) 7.86 (s, 1 H) 7.49 (t, 2 H) 7.24 (t, 2 H), 3.25 (s, 4 H) 3.12 (s, 4 H)	290	*tert*-butyl-4-{2-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}piperazine-1-carboxylate Example 58 

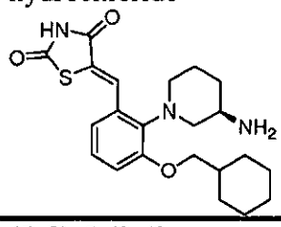
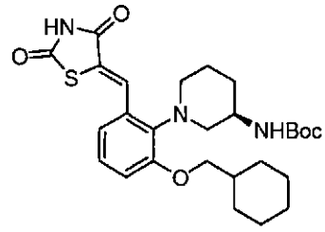
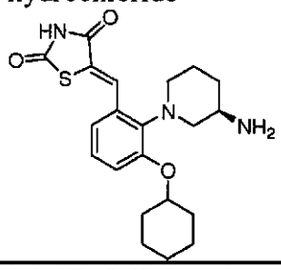
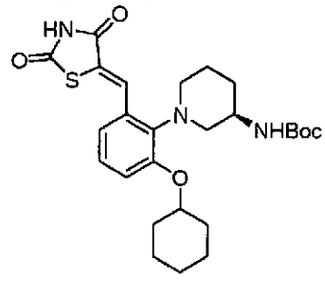
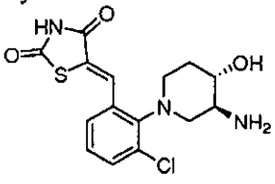
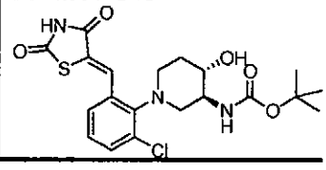
116	5-(2-(4-(piperidine-3-carbonyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.60 (s, 1 H) 9.10 (s, 1 H) 8.90 (s, 1 H) 7.94 (s, 1 H) 7.51 - 7.43 (m, 1 H) 7.21 (t, 2 H) 5.14 (m, 4 H) 3.67 (m, 3 H) 3.17 (m, 2 H) 2.91 - 2.88 (m, 4 H) 1.86 (s, 1 H) 1.81 - 1.71 (m, 2 H) 1.57 (d, 1 H)	401	*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)piperidine-1-carboxylate Method 63 
117	(5Z)-5-{2-[4-(azetidin-3-ylcarbonyl)piperazin-1-yl]benzylidene}-1,3-thiazolidine-2,4-dione hydrochloride 	12.59 (s, 1 H) 9.15 (s, 1 H) 8.86 (s, 1 H) 7.93 (s, 1 H) 7.47 (ddd, 2 H) 7.25 - 7.16 (m, 1 H) 4.15 - 4.05 (m, 4 H) 4.01 - 3.91 (m, 1 H) 3.71 (m, 2 H) 3.42 (s, 2 H) 2.89 (d, 4 H)	373	*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)azetidine-1-carboxylate Method 64 
118	(5Z)-5-[2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene]-1,3-thiazolidine-2,4-dione hydrochloride 	12.38 (s, 1 H) 8.34 (s, 2 H) 7.90 (s, 1 H) 6.96 (s, 1 H) 6.68 (s, 1 H) 3.89 - 3.80 (m, 4 H) 3.73 (s, 3 H) 3.46 - 3.34 (m, 2 H) 3.23 - 3.13 (m, 1 H) 3.10 (dd, 1 H) 2.28 (dd, 1 H) 2.01 (d, 1 H)	351	*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate Method 65 

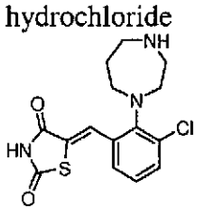
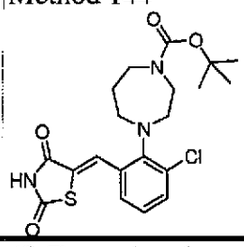
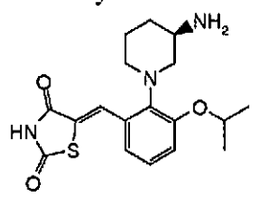
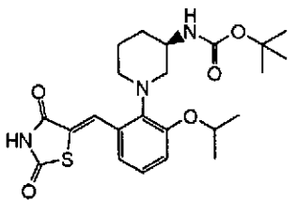
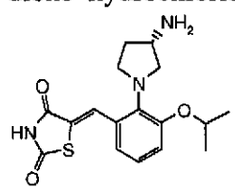
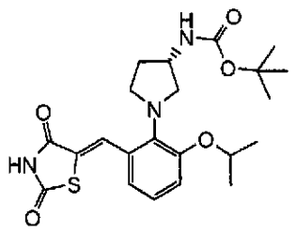
119	(*R*,*Z*)-5-amino-N-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-yl)pentanamide hydrochloride 	12.24 (s, 1 H) 8.07 (d, 1 H) 7.79 (s, 1 H) 7.60 (brs, 2 H) 6.88 (s, 1 H) 6.55 (s, 1 H) 4.22 (d, 1 H) 3.76 (s, 3 H) 3.65 (s, 3 H) 3.30 - 3.15 (m, 2 H) 3.15 - 2.98 (m, 1 H) 2.86 (dd, 1 H) 2.70 (d, 2 H) 2.17-1.92 (m, 3 H) 1.76 (brs, 1 H) 1.52 - 1.25 (m, 4 H)	449	(*R*,*Z*)-*tert*-butyl 5-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)-5-oxopentylcarbamate Method 66 
120	(*S*,*Z*)-5-amino-N-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-yl)pentanamide hydrochloride 	12.24 (s, 1 H) 8.07 (d, 1 H) 7.79 (s, 1 H) 7.60 (brs, 2 H) 6.88 (s, 1 H) 6.55 (s, 1 H) 4.22 (d, 1 H) 3.76 (s, 3 H) 3.65 (s, 3 H) 3.30 - 3.15 (m, 2 H) 3.15 - 2.98 (m, 1 H) 2.86 (dd, 1 H) 2.70 (d, 2 H) 2.17-1.92 (m, 3 H) 1.76 (brs, 1 H) 1.52 - 1.25 (m, 4 H)	449	(*S*,*Z*)-*tert*-butyl 5-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)-5-oxopentylcarbamate Method 67 
121	(*S*,*Z*)-5-(2-(3-(3-aminopropylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.50 (s, 1 H) 9.78 (s, 1 H) 7.92 (s, 1 H) 7.05 (s, 1 H) 6.85 (s, 1 H) 4.21 - 4.11 (m, 1 H) 3.93 (s, 3 H) 3.83 (s, 3 H) 3.42 - 3.25 (m, 8 H) 2.45 (m, 1 H) 2.20 (m, 1 H) 1.32 (m, 2 H)	407	(*S*,*Z*)-*tert*-butyl 3-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)propylcarbamate Method 68 

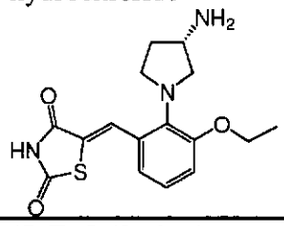
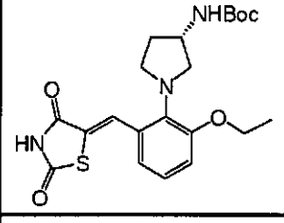
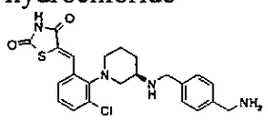
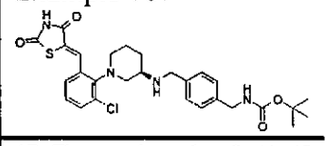
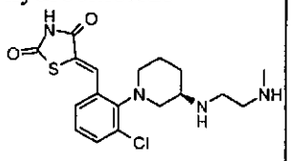
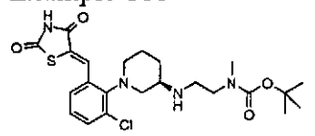
122A	(*R*,*Z*)-5-(2-(3-(3-aminopropylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.44 (s, 1 H) 9.78 (s, 1 H) 7.92 (s, 1 H) 7.05 (s, 1 H) 6.85 (s, 1 H) 4.21 - 4.11 (m, 1 H) 3.93 (s, 3 H) 3.83 (s, 3 H) 3.42 - 3.25 (m, 8 H) 2.45 (m, 1 H) 2.20 (m, 1 H) 1.32 (m, 2 H)	407	(*R*,*Z*)-*tert*-butyl 3-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)propylcarbamate Method 69 
122B	(*R*,*Z*)-5-(2-(3-(aminomethyl)pyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione 	(400 MHz, MeOD) ppm 8.08 (s, 1 H) 7.49 (dd, 2 H) 7.31 (t, 1 H) 3.56 (t, 1 H) 3.42 – 3.51 (m, 1 H) 3.38 (td, 1 H) 3.09 – 3.15 (m, 2 H) 2.71 – 2.78 (m, 1 H) 2.26 – 2.36 (m, 1 H) 1.86 – 1.96 (m, 1 H) 1.31 (dd, 1 H)	338	(*R*,*Z*)-*tert*-butyl (1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)methylcarbamate Method 132 
122C	(*S*,*Z*)-5-(2-(3-(aminomethyl)pyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione 	(400 MHz, MeOD) ppm 8.07 (s, 1 H) 7.49 (dd, 2 H) 7.31 (t, 1 H) 3.56 (t, 1 H) 3.42 – 3.51 (m, 2 H) 3.38 (td, 1 H) 3.07 – 3.16 (m, 2 H) 2.67 – 2.79 (m, 1 H) 2.24 – 2.36 (m, 1 H) 1.90 (dd, 1 H)	338	(*S*,*Z*)-*tert*-butyl (1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)methylcarbamate Method 133 

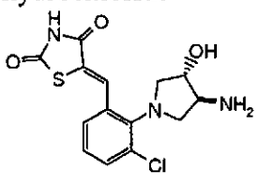
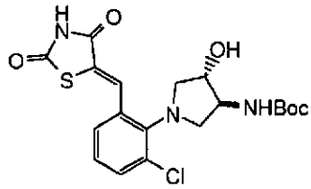
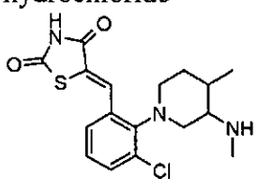
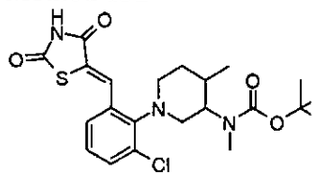
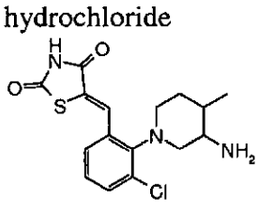
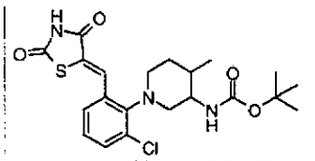
122D	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.70 (s, 1 H) 8.17 (brs, 3 H) 8.01 (s, 1 H) 7.52 (d, 1 H) 7.41-7.31 (m, 2 H) 3.40-3.10 (m, 4 H) 2.84-2.81 (m, 1 H) 2.12-2.10 (m, 1 H) 1.80-1.58 (m, 3 H)	338	(*R*,*Z*)-tert-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 134 
122E	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-methoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.60 (s, 1 H) 8.12 (brs, 4 H) 7.28-7.02 (m, 3 H) 3.82 (s, 3 H) 3.18-2.87 (m, 5 H) 2.10-2.07 (m, 1 H) 1.75-1.38 (m, 3 H)	334	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)piperidin-3-ylcarbamate Method 135 
122F	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-bromobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.70 (s, 1 H) 8.15 (brs, 3 H) 8.01 (s, 1 H) 7.74-7.69 (m, 1 H) 7.46 (d, 1 H) 7.26 (t, 1 H) 3.27-2.99 (m, 4 H) 2.82-2.80 (m, 1 H) 2.12-2.10 (m, 1 H) 1.76-1.40 (m, 3 H)	383	*(R,Z)-tert*-butyl 1-(2-bromo-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 136 
122G	(*R*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.67 (brs, 1 H) 8.30 (brs, 3 H) 7.93 (s, 1 H) 7.55 (d, 1 H) 7.41-7.31 (m, 2 H) 3.87 (brs, 1 H) 3.50-3.27 (m, 4 H) 2.40-2.28 (m, 1 H) 2.08-1.95 (m, 1 H)	324	(*R*,*Z*)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate Method 137 

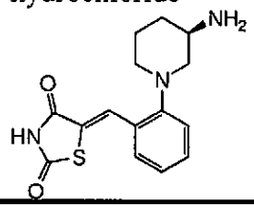
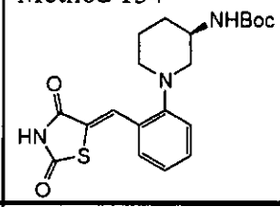
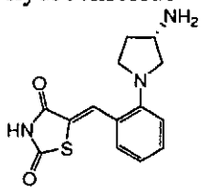
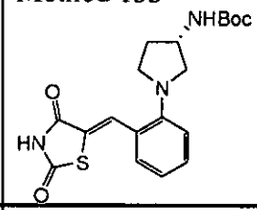
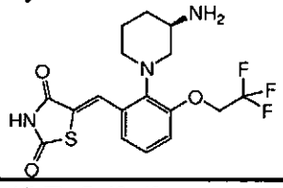
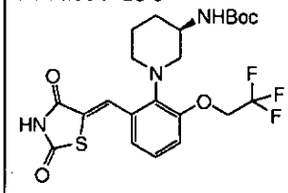
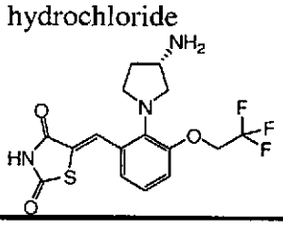
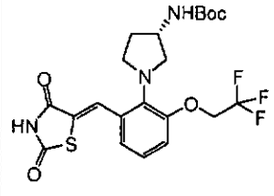
122H	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-bromobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.68 (brs, 1 H) 8.31 (brs, 3 H) 7.90 (s, 1 H) 7.75 (d, 1 H) 7.46 (d, 1 H) 7.29 (t, 1 H) 3.75 (brs, 1 H) 3.55 (t, 1 H) 3.38-3.25 (m, 3 H) 2.40-2.32 (m, 1 H) 2.12-2.02 (m, 1 H)	370	(*S*,*Z*)-*tert*-butyl 1-(2-bromo-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate Method 138 
122I	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-ethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.58 (s, 1 H) 8.13-8.09 (m, 4 H) 7.26-7.24 (m, 1 H) 7.16-7.14 (m, 1 H) 7.03-7.01 (m, 1 H) 4.07 (q, 2 H) 3.78-3.67 (m, 2 H) 3.22-3.07 (m, 3 H) 2.10-2.07 (m, 1 H) 1.76-1.55 (m, 3 H) 1.38 (t, 3 H)	348	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-ethoxyphenyl)piperidin-3-ylcarbamate Method 139 
122J	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-isobutoxyphenyl)piperidin-3-ylcarbamate hydrochloride 	12.60 (s, 1 H) 8.18 (brs, 3 H) 8.15 (s, 1 H) 7.26 (t, 1 H) 7.15 (d, 1 H) 7.02 (d, 1 H) 3.84-3.74 (m, 2 H) 3.20-3.02 (m, 4 H) 2.74 (d, 1 H) 2.14–2.07 (m, 2 H) 1.73-1.21 (m, 3 H) 1.03 (d, 6 H)	376	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-isobutoxyphenyl)piperidin-3-ylcarbamate Method 140 

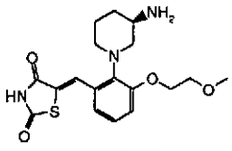
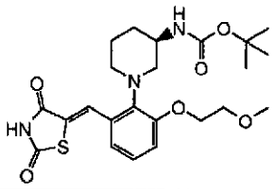
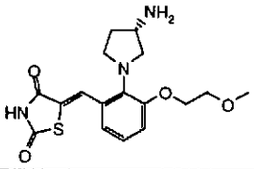
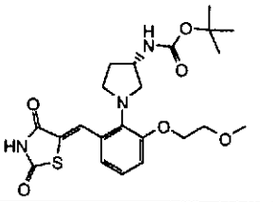
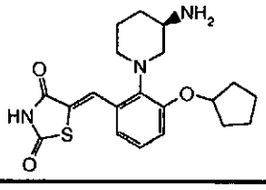
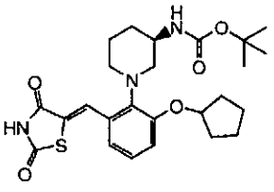
122K	(*R,Z*)-5-(2-(3-aminopiperidin-1-yl)-3-(cyclohexylmethoxy) benzylidene)thiazolidine-2,4-dione hydrochloride 	12.60 (s, 1 H) 8.14 (brs, 4 H) 7.25 (t, 1 H) 7.14 (d, 1 H) 7.00 (d, 1 H) 3.82 (brs, 2 H) 3.29-3.00 (m, 4 H) 2.75-2.72 (m, 1 H) 2.12-2.10 (m, 1 H) 1.86-1.50 (m, 8 H) 1.35-1.03 (m, 6 H)	416	(*R,Z*)-*tert*-butyl 1-(2-(cyclohexylmethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 141 
122L	(*R,Z*)-5-(2-(3-aminopiperidin-1-yl)-3-(cyclohexyloxy)benzylidene)thiazolidine-2,4-dione hydrochloride 		402	(*R,Z*)-*tert*-butyl 1-(2-(cyclohexyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 142 
122M	(±)-(Z)-5-(2-3-amino-4-hydroxypiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.68 (s, 1 H) 8.01 (brs, 4 H) 7.53 (d, 1 H) 7.44-7.42 (m, 1 H) 7.35 (t, 1 H) 5.72-5.70 (m, 1 H) 3.32-3.22 (m, 2 H) 3.20-3.11 (m, 3 H) 1.96-1.94 (m, 1 H) 1.40-1.37 (m, 1 H)	354	(±)-*tert*-butyl-1-(2-chloro-6-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-hydroxypiperidin-3-ylcarbamate Method 143 

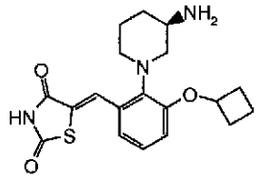
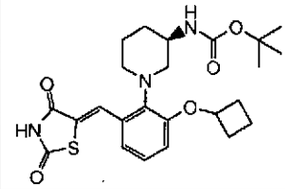
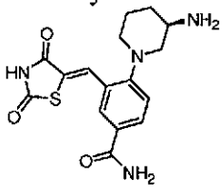
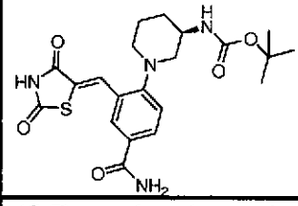
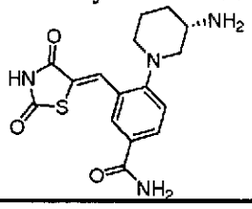
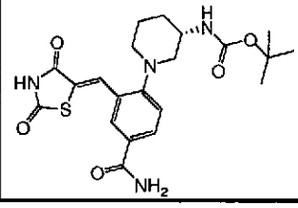
122N	(Z)-5-(3-chloro-2-(1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.73 (brs, 1 H), 9.18 (brs, 2 H), 8.04 (s, 1 H), 7.62 (d, 1 H), 7.41 (dt, 2 H), 3.65 (brs, 1 H), 3.34 - 3.30 (m, 5 H), 3.04 (brs, 2 H), 2.14 (brs, 2 H)	338	(*Z*)-*tert*-butyl 4-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepane-1-carboxylate Method 144 
122O	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-isopropoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.61 (brs, 1 H) 8.33 (brs, 3 H) 8.15 (brs, 1 H) 7.34-7.09 (m, 2 H) 6.99 (d, 1 H) 4.67 (ddd 1 H) 3.28 (brs, 1 H) 3.07 (brs, 3 H) 2.70 (brs, 1 H) 2.12 (brs, 1 H) 1.73 (brs, 1 H) 1.57 (brs, 1 H) 1.51 - 1.21 (m, 7 H)	362	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-isopropoxyphenyl)piperidin-3-ylcarbamate Method 145 
122P	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-isopropoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.58 (brs, 1 H) 8.52 (brs, 3 H) 8.08 (s, 1 H) 7.39-7.10 (m, 2 H) 6.99 (d, 1 H) 4.70 (d, 1 H) 3.78 (brs, 1 H) 3.52-3.33 (m, 1 H) 3.33 - 3.03 (m, 3 H) 2.28 (brs, 1 H) 2.00 (d, 1 H) 1.32 (d, 6 H)	348	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-isopropoxyphenyl)pyrrolidin-3-ylcarbamate Method 146 

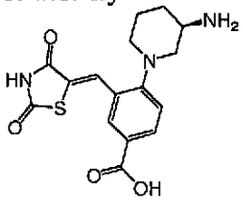
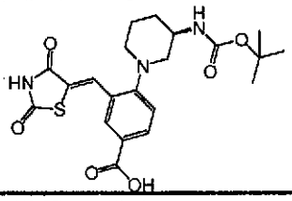
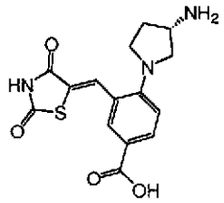
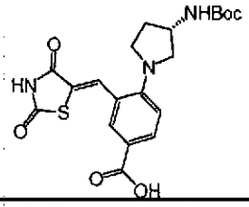
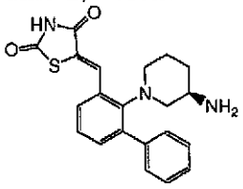
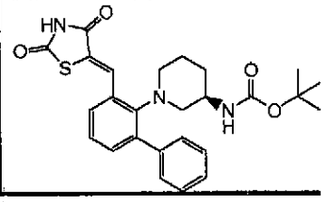
122Q	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-ethoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.58 (brs, 1 H) 8.48 (brs, 3 H) 8.09 (s, 1 H) 7.26 (t, 1 H) 7.16 (d, 1 H) 7.02 (d, 1 H) 4.09 (q, 2 H) 3.80 (d, 1 H) 3.47 (dd, 1 H) 3.28 (m, 1 H) 3.21 (dd, 1 H) 2.29 (d, 1 H) 2.01 (dd, 1 H) 1.40 (t, 3 H)	334	(*S,Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-ethoxyphenyl)pyrrolidin-3-ylcarbamate Method 147 
122R	(*R,Z*)-5-(2-(3-(4-(aminomethyl)benzylamino)piperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	9.62 (brs, 1 H) 8.46 (brs, 3 H) 7.66-7.49 (m, 5 H) 7.47-7.34 (m, 2 H) 4.26-4.12 (m, 2 H) 4.09-3.94 (m, 2 H) 3.42-3.25 (m, 4 H) 2.83 (brs, 1 H) 2.36 (s, 1 H) 1.85 (m, 1 H) 1.62 (d, 2 H)	457	(*R,Z*)-*tert*-butyl 4-((1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylamino)methyl)benzylcarbamate Example 167 
122S	(*R,Z*)-5-(3-chloro-2-(3-(2-(methylamino)ethylamino)piperidin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.68 (brs, 1 H) 9.68 (brs, 2 H) 9.21 (brs, 2 H) 8.05 (s, 1 H) 7.56 (d, 1 H) 7.50-7.42 (m, 1 H) 7.37 (t, 1 H) 3.75-3.65 (m, 5 H) 3.63-3.57 (m, 2 H) 3.16 (d, 1 H) 2.82 (brs, 1 H) 2.60 (brs, 3 H) 2.37-2.28 (m, 1 H) 1.80 (d, 1 H) 1.65 (m, 1H) 1.54 (brs, 1 H)	395	(*R,Z*)-*tert*-butyl 2-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylamino)ethyl(methyl)carbamate Example 168 

122T	(Z)-5-(2-((3S,4S)-3-amino-4-hydroxypyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.68 (brs, 1 H) 8.50 (brs, 3 H) 8.10-7.81 (m, 1 H) 7.58 (dd, 1 H) 7.51-7.27 (m, 2 H) 4.56-4.28 (m, 1 H) 3.84 (brs, 1 H) 3.66-3.40 (m, 4 H) 3.39-3.23 (m, 1 H)	339	*tert*-butyl (3*S*,4*S*)-1-(2-chloro-6-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-hydroxypyrrolidin-3-ylcarbamate Method 151 
122U	(Z)-5-(3-chloro-2-(4-methyl-3-(methylamino)piperidin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.69 (brs, 1 H) 8.63 (brs, 2 H) 8.02 (s, 1 H) 7.57 (d, 1 H) 7.47-7.31 (m, 2 H) 3.58 (m, 1 H) 3.07 (m, 1 H) 2.67 (brs, 1 H) 2.58 (brs, 3 H) 2.40 (m, 1 H) 1.87 (m, 1 H) 1.68 (m, 1 H) 1.29 (m, 1 H) 1.07 (d, 3 H) 0.87 (d, 1 H)	365	(Z)-tert-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-methylpiperidin-3-yl(methyl)carbamate Method 152 
122V	(Z)-5-(2-(3-amino-4-methylpiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 		351	(Z)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-methylpiperidin-3-ylcarbamate Method 153 

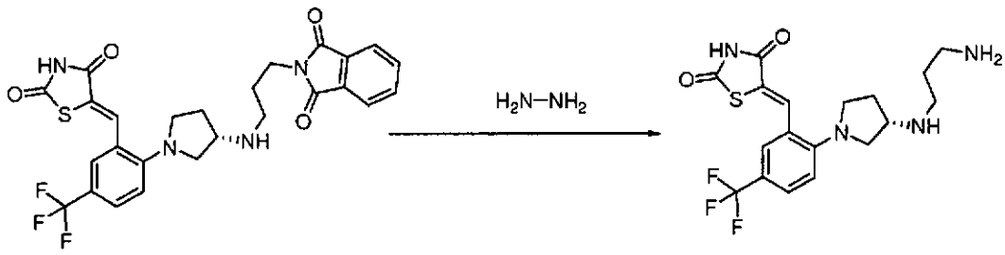
122W	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.58 (s, 1 H), 8.44 (brs, 3 H) 7.89 (s, 1 H) 7.54-7.34 (m, 2 H) 7.27-7.05 (m, 2 H) 3.26 (d, 2 H) 2.94 (d, 1 H), 2.87-2.61 (m, 2 H) 2.05 (brs, 1 H) 1.85 (brs, 1 H) 1.75-1.47 (m, 2 H)	304	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 154 
122X	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.49 (s, 1 H) 8.50 (brs, 3 H) 7.91 (s, 1 H) 7.44-7.22 (m, 2 H) 7.07-6.79 (m, 2 H) 3.83 (d, 1 H) 3.51-3.29 (m, 2 H) 3.28-3.17 (m, 2 H) 2.27 (dd, 1 H), 2.11-1.94 (m, 1 H)	290	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate Method 155 
122Y	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-(2,2,2-trifluoroethoxy)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.57 (brs, 1 H) 8.03 (brs, 1 H) 7.90 (brs, 3 H) 7.36-7.13 (m, 2 H) 7.07 (d, 1 H) 4.85-4.55 (m, 2 H) 2.98 (brs, 4 H) 2.74 (brs, 1 H) 2.02 (d, 1 H) 1.69 (d, 1 H) 1.54 (d, 1 H) 1.30 (brs, 1 H)	402	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2,2,2-trifluoroethoxy)phenyl)piperidin-3-ylcarbamate Method 156 
122Z	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-(2,2,2-trifluoroethoxy)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.52 (brs, 1 H) 8.21-7.91 (m, 4 H) 7.34-7.14 (m, 2 H) 7.07 (d, 1 H) 4.88-4.72 (m, 2 H) 3.74 (d, 1 H) 3.40 (dd, 1 H) 3.22 (td, 1 H) 3.18-3.10 (m, 1 H) 3.06 (dd, 1 H) 2.30-2.10 (m, 1 H) 1.90 (dd, 1 H)	388	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2,2,2-trifluoroethoxy)phenyl)pyrrolidin-3-ylcarbamate Method 157 

122AA	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-(2-methoxyethoxy)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.67 (brs, 1 H) 8.30 (brs, 3 H) 8.20 (brs, 1 H) 7.33 (brs, 1 H) 7.25 (brs, 1 H) 7.10 (d, 1 H) 4.68 (brs, 3 H) 4.22 (t, 2 H) 3.91-3.65 (m, 2 H) 3.42 (s, 3 H) 3.29 (brs, 1 H) 2.80 (brs, 1 H) 2.18 (brs, 1 H) 1.81 (brs, 1 H) 1.68 (brs, 1 H) 1.48 (brs, 1 H)	378	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)phenyl)piperidin-3-ylcarbamate Method 158 
122AB	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-(2-methoxyethoxy)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.58 (brs, 1 H) 8.42 (brs, 3 H) 8.10 (s, 1 H) 7.28 (t, 1 H) 7.23-7.11 (m, 1 H) 7.04 (d, 1 H) 4.27-3.97 (m, 2 H) 3.85 (d, 1 H) 3.78-3.63 (m, 2 H) 3.49 (dd, 1 H) 3.34 (s, 3 H) 3.27 (td, 1 H) 3.22-3.06 (m, 2 H) 2.30 (dd, 1 H) 2.02 (dd, 1 H)	364	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)phenyl)pyrrolidin-3-ylcarbamate Method 159 
122AC	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-(cyclopentyloxy)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.37 (brs, 1 H) 8.00 (brs, 3H) 7.93 (s, 1 H) 7.02 (d, 1 H) 6.91 (d, 1 H) 6.77 (d, 1 H) 3.02-2.91 (m, 1 H) 2.82 (d, 3 H) 2.48 (brs, 1 H) 1.89-1.40 (m, 12 H) 1.16 (brs, 1 H)	388	(*R*,*Z*)-*tert*-butyl 1-(2-(cyclopentyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 160 

122AD	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-cyclobutoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.60 (brs, 1 H) 8.14 (brs, 4 H) 7.23 (d, 1 H) 7.00 (dd, 2 H), 4.86-4.67 (m, 1 H) 3.25 (m, 1H) 3.05 (m, 2H) 2.74 (brs, 1 H) 2.49-2.35 (m, 2 H) 2.21-1.95 (m, 3 H) 1.93-1.76 (m, 2 H) 1.67 (td, 3 H) 1.42 (brs, 1 H)	374	(*R*,*Z*)-*tert*-butyl 1-(2-cyclobutoxy-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 161 
122AE	(*R*,*Z*)-4-(3-aminopiperidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzamide hydrochloride 		347	(*R*,*Z*)-*tert*-butyl 1-(4-carbamoyl-2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 162 
122AF	(*S*,*Z*)-4-(3-aminopiperidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzamide hydrochloride 		347	(*S*,*Z*)-*tert*-butyl 1-(4-carbamoyl-2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate Method 163 

122AG	(*R*,*Z*)-4-(3-aminopiperidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid hydrochloride 		348	(*R*,*Z*)-4-(3-(*tert*-butoxycarbonylamino)piperidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid Method 164 
122AH	(*S*,*Z*)-4-(3-aminopyrrolidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid 		333	(*S*,*Z*)-4-(3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid Method 165 
122AI	(*R*,*Z*)-5-((2-(3-aminopiperidin-1-yl)biphenyl-3-yl)methylene)thiazolidine-2,4-dione 	12.64 (brs, 1 H) 8.09 (brs, 3 H) 7.92 (s, 1 H) 7.56-7.36 (m, 4 H) 7.36 - 7.16 (m, 4 H) 3.06 (brs, 1 H) 3.00 (brs, 1 H) 2.72 (d, 1 H) 2.35 (brs, 2 H) 2.05 (brs, 1 H) 1.58 (brs, 2 H) 1.32-1.15 (m, 1 H)	380	(*R*,*Z*)-*tert*-butyl 1-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)biphenyl-2-yl)piperidin-3-ylcarbamate Method 166 

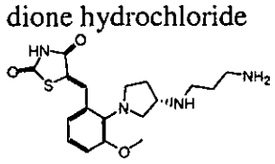
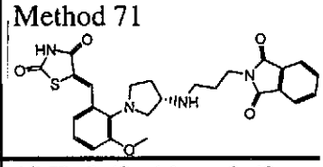
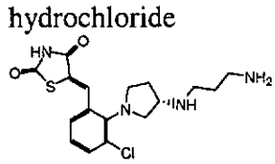
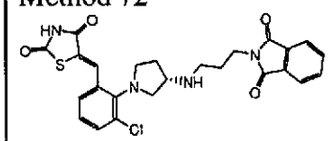
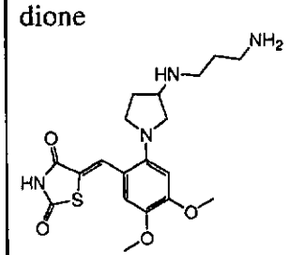
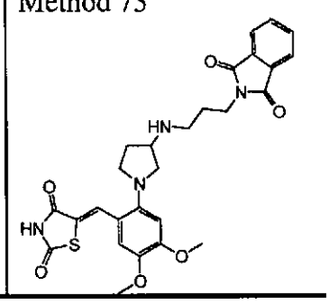
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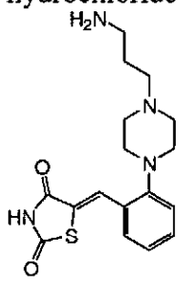
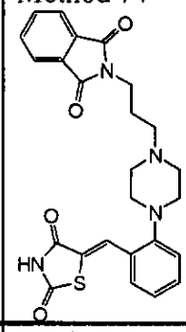
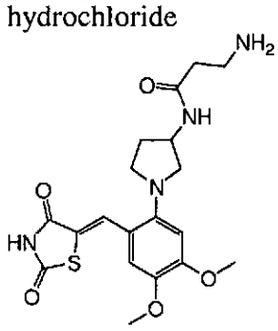
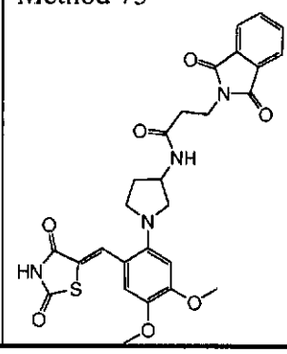


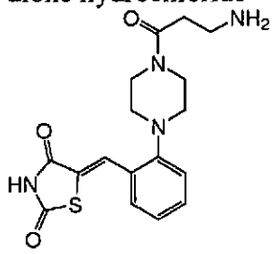
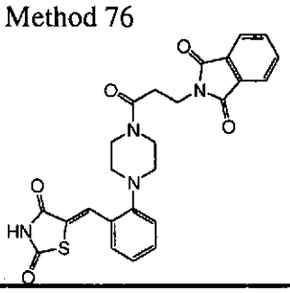
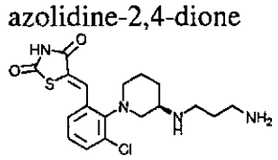
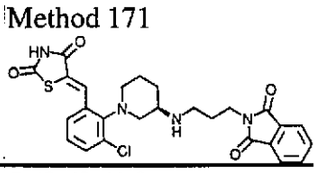
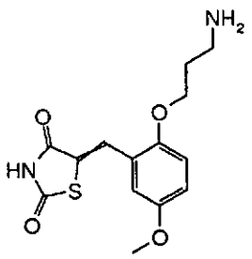
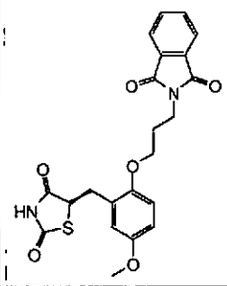
(*S*,*Z*)-5-(2-(3-(3-aminopropylamino)pyrrolidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione hydrochloride:

A 25 mL round bottom flask was charged with a magnetic stir bar, (*S*,*Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione (Method 70) (0.271 g, 0.50 mmol), EtOH (2.488 ml), and hydrazine (0.023 ml, 0.75 mmol). The reaction was stirred at rt for 30 min and then filtered through a bed of Celite. The filtrate was conc. *in vacuo* and purified via reverse phase HPLC (MeCN/water) to afford fractions that were conc. *in vacuo*, suspended in methanol (~ 5 mL) and 1N HCl in diethyl ether (~2 mL) and conc. *in vacuo* to afford (*S*,*Z*)-5-(2-(3-(3-aminopropylamino)pyrrolidin-1-yl)-5-(trifluoromethyl) benzylidene)thiazolidine-2,4-dione hydrochlride (0.071 g, 29.3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12.52 (s, 1 H) 9.49 (s, 1 H) 8.08 (brs, 2 H) 7.93 (s, 1 H) 7.67 (s, 1 H) 7.61 (d, 1 H) 7.08 (d, 1 H) 3.88 - 3.81 (m, 1 H) 3.53 - 3.33 (m, 4 H) 3.08 - 3.05 (m, 2 H) 2.92 - 2.89 (m, 2 H) 2.33 - 2.19 (m, 2 H) 2.04 - 1.96 (m, 2 H); *m/z* 415.

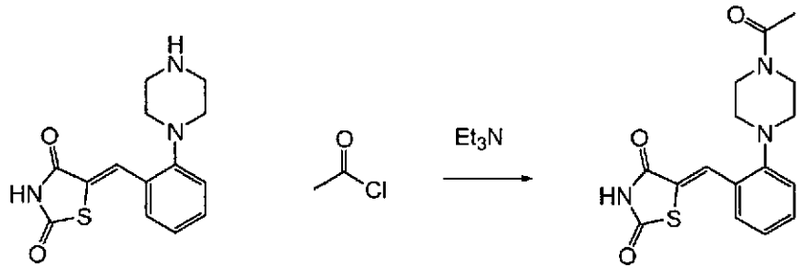
The following examples were prepared by the procedure of Example 123, using the appropriate starting materials. The following parent compounds obtained after chromatography may be converted to their corresponding hydrochloride salt in a manner similar as described in example 123.

Ex.	Compound	^{1}H NMR	m/z	SM
124	(*S*,*Z*)-5-(2-(3-(3-aminopropylamino)pyrrolidin-1-yl)-3-methoxybenzylidene)thiazolidine-2,4-dione hydrochloride 	12.59 (brs, 1 H) 9.30 (brs, 1 H) 8.09 (s, 1 H) 8.07 (brs, 1 H) 7.32 (t, 1 H) 7.21 (d, 1 H) 7.08 (d, 1 H) 3.87 (s, 3 H) 3.46 – 3.44 (m, 1 H) 3.39 – 3.25 (m, 2 H) 3.17 – 2.99 (m, 4 H) 2.96 – 2.91 (m 2 H) 2.19 – 2.10 (m, 2 H) 2.08-1.99 (m, 2 H)	377	(*S*,*Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)-3-methoxybenzylidene)thiazolidine-2,4-dione Method 71 
125	(*S*,*Z*)-5-(2-(3-(3-aminopropylamino)pyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride 	12.72 (brs, 1 H) 9.50 (brs, 1 H) 8.10 (brs, 2 H) 7.96 (s, 1 H) 7.60 (d, 1 H) 7.46 – 7.39 (m 2 H) 3.95 – 3.91 (m, 1 H) 3.51 – 3.20 (m, 4 H) 2.99 – 2.92 (m, 2 H) 2.44 – 2.38 (m, 2 H) 2.21 – 2.11 (m, 2 H) 2.08 – 1.99 (m, 2 H)	382	(*S*,*Z*)-5-(3-chloro-2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione Method 72 
126	(*Z*)-5-(2-(3-(3-aminopropylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione 	12.40 (s, 1 H) 9.78 (s, 1 H) 7.92 (s, 1 H) 7.05 (s, 1 H) 6.85 (s, 1 H) 4.21 - 4.11 (m, 1 H) 3.93 (s, 3 H) 3.83 (s, 3 H) 3.42 - 3.25 (m, 8 H) 2.45 (m, 1 H) 2.20 (m, 1 H) 1.32 (m, 2 H)	407	(*Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione Method 73 

127	(Z)-5-(2-(4-(3-aminopropyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione hydrochloride 	12.64 (s, 1 H) 11.50 (s, 1 H) 8.27 (s, 1 H) 7.85 (s, 1 H) 7.49 (t, 2 H) 7.24 (t, 2 H) 3.55 (d, 2 H) 3.32 - 3.16 (m, 8 H) 2.93 (d, 2 H) 2.18 - 2.07 (m, 2 H)	347	(Z)-5-(2-(4-(3-(1,3-dioxoisoindolin-2-yl)propyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione Method 74 
128	(Z)-3-amino-N-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-yl)propanamide hydrochloride 	12.34 (s, 1 H) 8.46 (d, 1 H) 7.86 (s, 3 H) 6.95 (s, 1 H) 6.63 (s, 1 H) 4.36 - 4.26 (m, 1 H) 3.84 (s, 3 H) 3.72 (s, 3 H), 3.32 - 3.21 (m, 3 H) 3.02 - 2.93 (m, 3 H) 2.18 (dd, 2 H) 1.86 (dd, 1 H)	421	(Z)-3-(1,3-dioxoisoindolin-2-yl)-N-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-yl)propanamide Method 75 

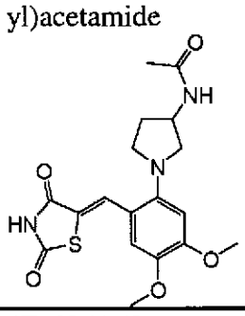
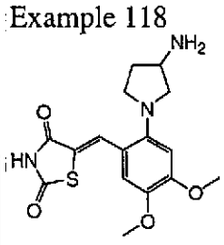
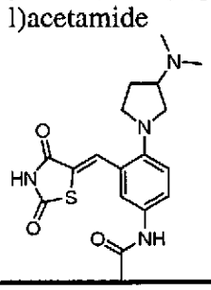
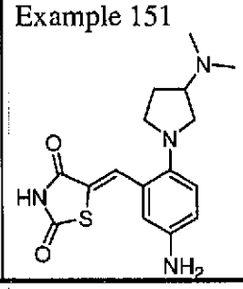
129A	(5Z)-5-{2-[4-(3-aminopropanoyl)piperazin-1-yl]benzylidene}-1,3-thiazolidine-2,4-dione hydrochloride 	12.59 (s, 1 H) 7.94 (s, 1 H) 7.82 (s, 2 H) 7.51 - 7.44 (m, 2 H) 7.26 - 7.17 (m, 2 H) 3.66 (m, 2 H) 3.59 (m, 2 H) 3.08 - 2.97 (m, 2 H) 2.96 - 2.86 (m, 4 H) 2.74 (m, 2 H)	361	(5Z)-(2-(4-(3-(1,3-dioxoisoindolin-2-yl)propanoyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione Method 76 
129B	(*R*,*Z*)-5-(2-(3-(3-aminopropylamino)piperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione 	12.69 (brs, 1 H) 9.31 (brs, 1 H) 8.05 (s, 3 H) 7.56 (d, 1 H) 7.49-7.41 (m, 1 H) 7.37 (t, 1 H) 3.76-3.65 (m, 3 H) 3.16 (brs, 1 H) 3.04 (brs, 2 H) 2.94-2.75 (m, 3 H) 2.33 (brs, 1 H) 2.04-1.92 (m, 2 H) 1.78 (d, 1 H) 1.65 (m, 1 H), 1.50 (m, 1 H)	395	(*R*,*Z*)-5-(3-chloro-2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)piperidin-1-yl)benzylidene)thiazolidine-2,4-dione Method 171 
129C	5-(2-(3-aminopropoxy)-5-methoxybenzylidene)thiazolidine-2,4-dione 	12.64 (brs, 1 H) 7.94 (brs, 4 H) 7.11 (m, 2 H) 6.93 (s, 1 H) 4.13 (m, 2 H) 3.77 (s, 3 H) 2.97 (m, 2 H) 2.06 (m, 2 H)	309	5-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-5-methoxybenzylidene)thiazolidine-2,4-dione Method 148 

Example 130:

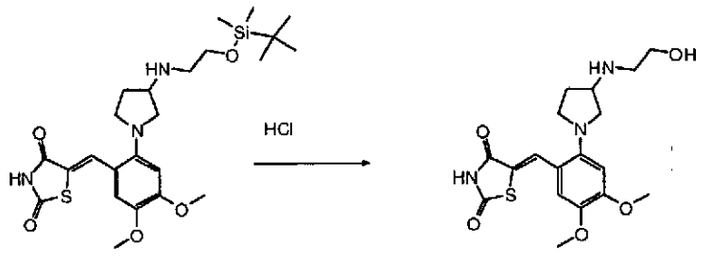


(5Z)-5-[2-(4-acetylpiperazin-1-yl)benzylidene]-1,3-thiazolidine-2,4-dione: To a mixture of (5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione (Example 115) and acetyl chloride (36.1 mg, 0.46 mmol) was added triethylamine (93 mg, 0.92 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight and was then treated with sat'd aqueous $NaHCO_3$ (~ 25 mL). This mixture was allowed to stir at room temperature for 10 min, and was then extracted with DCM (3 X 25 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered through a bed of Celite, and the filtrate was conc. *in vacuo* to afford the product which was purified via reverse phase HPLC (acetonitrile:water: 0.1 % TFA = 5 % to 70 %) to afford the title compound as a pale yellow solid (40.0 mg, 35.4 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12.58 (brs, 1 H) 7.94 (s, 1 H) 7.47 (d, 2 H) 7.30 - 7.07 (m, 2 H) 3.60 (brs, 4 H) 2.90 (brs, 2 H) 2.85 (brs, 2 H) 2.04 (s, 3 H); *m/z* 331.

The following examples were prepared by the procedure of Example 130, using the appropriate starting materials.

Ex.	Compound	^{1}H NMR	m/z	SM
131A	*N*-(1-{2-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-4,5-dimethoxyphenyl}pyrrolidin-3-yl)acetamide 	12.29 (brs, 1 H) 8.13 (d, 1 H) 7.85 (s, 1 H) 6.94 (s, 1 H) 6.61 (s, 1 H) 4.27 (d, 1 H) 3.83 (s, 3 H) 3.72 (s, 3 H) 3.43 - 3.14 (m, 4 H) 2.94 (dd, 1 H) 2.30 - 2.05 (m, 1 H) 1.82 (s, 3 H)	392	(5Z)-5-[2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene]-1,3-thiazolidine-2,4-dione Example 118 
131B	(Z)-*N*-(4-(3-(dimethylamino)pyrrolidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)acetamide 	9.86 (s, 1 H) 7.68 (s, 1 H) 7.56 (s, 1 H) 7.49-7.47 (d, 1 H) 6.96-6.94 (d, 1 H) 3.23 (m, 1 H) 3.00 (m, 4 H) 2.51 (s, 6 H) 2.15 (m, 1 H) 2.01 (s, 3 H) 1.55 (m, 1 H)	375	(Z)-5-(5-amino-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione Example 151 

Example 132:

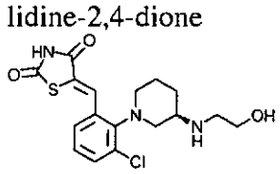
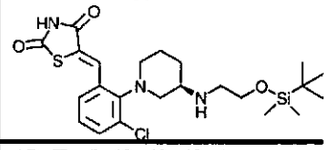
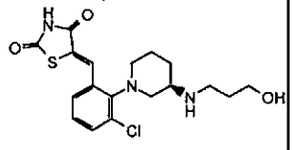
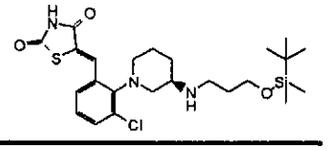


(Z)-5-(2-(3-(2-hydroxyethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione:

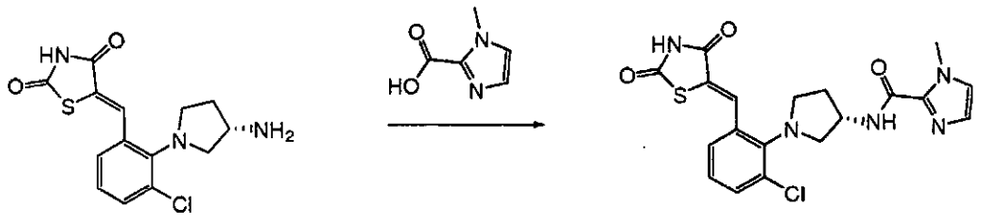
A mixture of (Z)-5-(2-(3-(2-(*tert*-butyldimethylsilyloxy)ethylamino)pyrrolidin-1-

yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione (Method 77) (120 mg, 0.24 mmol) in 5 mL of 1.25 M HCl in methanol was stirred at room temperature for 30 min. The mixture was then conc. *in vacuo* to afford the product which was purified via reverse phase HPLC (acetonitrile:water: 0.1 % NH_4OAc = 5 % to 55 %) to yield the title compound as a yellow solid (45.0 mg, 48.4 %). ^1H NMR (300 MHz, DMSO-D6) δ ppm 7.40 (s, 1 H) 7.07 (s, 1 H) 6.57 (s, 1 H) 3.78 (s, 3 H) 3.70 (s, 3 H) 3.45 (m, 2 H) 3.27 - 3.15 (m, 4 H) 2.92 (m, 1 H) 2.59 (m, 2 H) 2.08 (m, 1 H) 1.66 (m, 1 H); *m/z* 394.

The following examples were prepared by the procedure of Example 132 using the appropriate starting materials.

133	(*R,Z*)-5-(3-chloro-2-(3-(2-hydroxyethylamino)piperidin-1-yl)benzylidene)thiazolidine-2,4-dione 	8.81 (brs, 2 H) 7.96 (s, 1 H) 7.48 (d, 1 H) 7.40-7.32 (m, 1 H) 7.31-7.25 (m, 1 H) 3.63-3.55 (m, 2 H) 3.46-3.38 (m, 2 H) 3.08 (brs, 2 H) 2.96 (d, 2 H) 2.75 (brs, 1 H) 2.20 (m, 1H) 1.72 (brs, 1 H) 1.56 (brs, 1 H) 1.44 (brs, 1 H)	382	(*R,Z*)-5-(2-(3-(2-(*tert*-butyldimethylsilyloxy)ethylamino)piperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Method 169 
134	(*R,Z*)-5-(3-chloro-2-(3-(3-hydroxypropylamino)piperidin-1-yl)benzylidene)thiazolidine-2,4-dione 	12.69 (brs, 1 H) 8.84 (brs, 1 H) 8.04 (s, 1 H) 7.56 (d, 1 H) 7.49-7.39 (m, 1 H) 7.36 (t, 1 H) 3.69 (dd, 2 H) 3.17 (brs, 2 H) 3.00 (brs, 2 H) 2.83 (brs, 1 H) 2.26 (brs, 1 H) 1.93-1.72 (m, 4 H) 1.66 (brs, 1 H) 1.50 (brs, 1 H)		(*R,Z*)-5-(2-(3-(3-(*tert*-butyldimethylsilyloxy)propylamino)piperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Method 170 

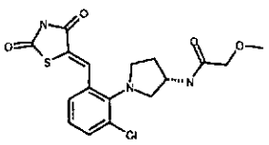
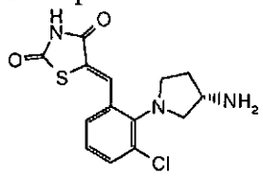
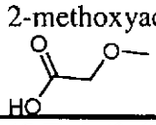
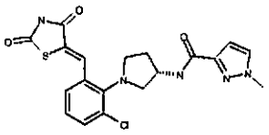
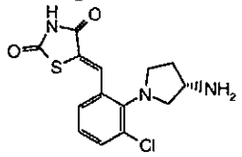
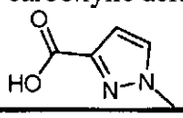
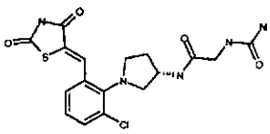
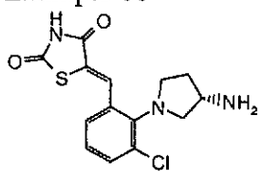
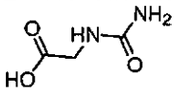
Example 135

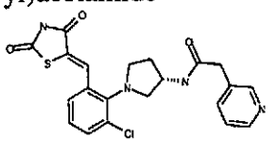
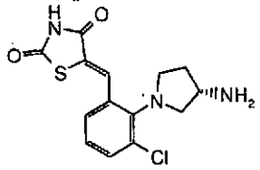
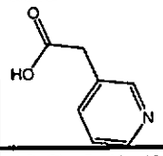
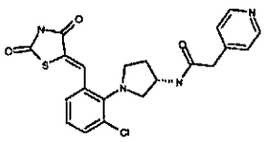
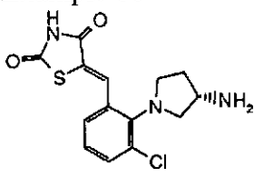
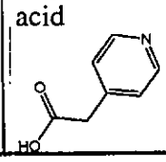


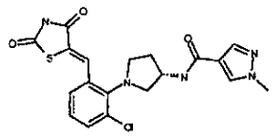
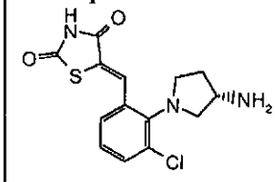
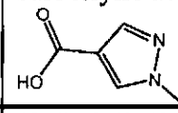
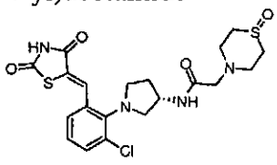
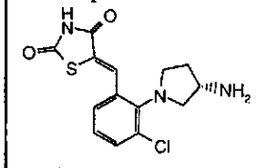
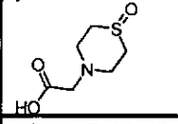
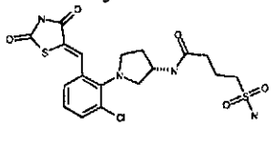
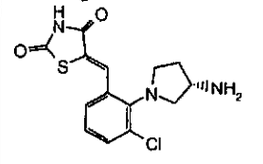
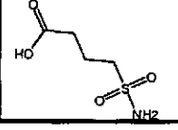
(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-1-methyl-1H-imidazole-2-carboxamide:

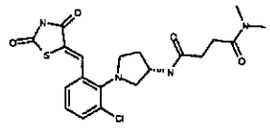
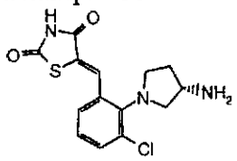
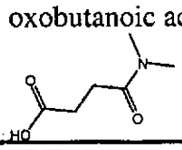
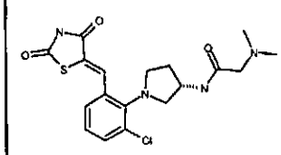
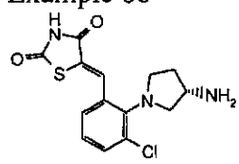
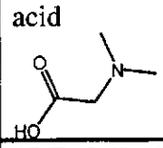
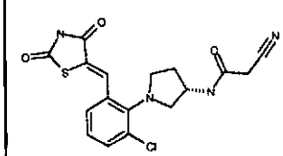
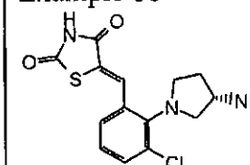
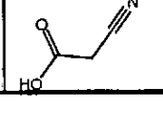
To a 50 mL vial charged with a magnetic stir bar was added (*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione (75 mg, 0.23 mmol) (Example 86), 1-methyl-1H-imidazole-2-carboxylic acid (87 mg, 0.69 mmol), HATU (220 mg, 0.58 mmol) and dichloromethane (5 mL). Hunig's base (0.202 mL, 1.16 mmol) was then added and the mixture was stirred at rt for 4 h. The reaction was then diluted with dichloromethane and washed with water. The mixture was separated with a phase separator tube and the organic phase was evaporated to dryness. The residue was purified by reverse phase chromatography to afford the title compound as a yellow solid (21 mg, 21 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.89 (s, 1 H) 7.51 (dd, 1 H) 7.41 (dd, 1 H) 7.18 – 7.27 (m, 2 H) 7.01 (s, 1 H) 4.67 – 4.77 (m, 1 H) 4.00 (s, 3 H) 3.63 – 3.75 (m, 2 H) 3.47 – 3.54 (m, 1 H) 3.36 – 3.47 (m, 1 H) 2.39 – 2.51 (m, 1 H) 2.14 (dd, 1 H); *m/z* 432.

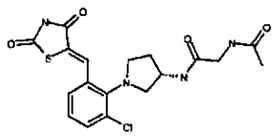
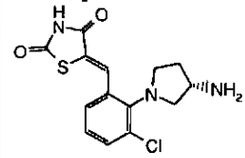
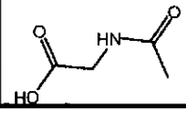
The following examples were prepared by the procedure of 135 using the appropriate starting materials.

136	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-2-methoxyacetamide 	7.89 (s, 1 H) 7.52 (dd, 1 H) 7.41 (dd, 1 H) 7.25 (t, 1 H) 4.58 – 4.67 (m, 1 H) 3.93 (s, 2 H) 3.65 (dd, 1 H) 3.36 – 3.46 (m, 5 H) 3.13 (dd, 1 H) 2.38 (dd, 1 H) 2.01 – 2.13 (m, 1 H)	396	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 2-methoxyacetic acid 
137	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-1-methyl-1H-pyrazole-3-carboxamide 	7.93 (s, 1 H) 7.61 (d, 1 H) 7.52 (dd, 1 H) 7.42 (dd, 1 H) 7.25 (t, 1 H) 6.73 (d, 1 H) 4.73 – 4.83 (m, 1 H) 3.92 – 3.99 (m, 3 H) 3.71 (dd, 1 H) 3.38 – 3.50 (m, 2 H) 3.23 (dd, 1 H) 2.38 – 2.50 (m, 1 H) 2.09 – 2.21 (m, 1 H)	432	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 1-methyl-1H-pyrazole-3-carboxylic acid 
138	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-2-ureidoacetamide 	7.93 (s, 1 H) 7.52 (dd, 1 H) 7.41 (dd, 1 H) 7.25 (t, 1 H) 4.53 (ddd, 1 H) 3.83 – 3.92 (m, 2 H) 3.65 – 3.70 (m, 1 H) 3.42 – 3.49 (m, 1 H) 3.35 – 3.42 (m, 1 H) 3.07 (dd, 1 H) 2.37 (dt, 1 H) 1.98 – 2.10 (m, 1 H)	424	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 2-ureidoacetic acid 

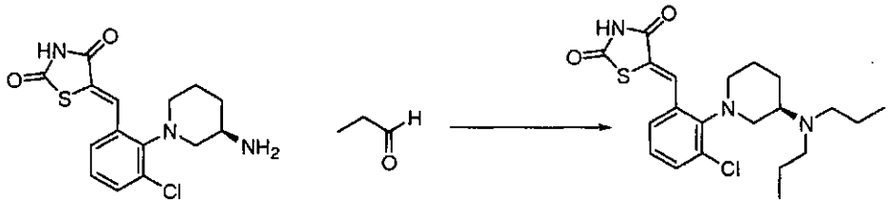
139	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-2-(pyridin-3-yl)acetamide 	8.44 (br. S., 2 H) 8.02 (s, 1 H) 7.83 (d, 1 H) 7.50 (dd, 1 H) 7.34 – 7.46 (m, 3 H) 7.25 (t, 1 H) 4.51 (t, 1 H) 3.60 – 3.69 (m, 3 H) 3.37 – 3.48 (m, 2 H) 3.08 (dd, 1 H) 2.31 – 2.43 (m, 1 H) 2.03 (dd, 1 H)	443	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 2-(pyridin-3-yl)acetic acid 
140	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-2-(pyridin-4-yl)acetamide 	8.47 (br. S., 1 H) 7.98 (s, 1 H) 7.53 (dd, 1 H) 7.41 (dd, 3 H) 7.25 (t, 1 H) 4.53 (t, 1 H) 3.64 – 3.71 (m, 3 H) 3.39 – 3.48 (m, 2 H) 3.07 (dd, 1 H) 2.32 – 2.44 (m, 1 H) 2.03 (dd, 1 H)	443	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 2-(pyridin-4-yl)acetic acid 

141	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-1-methyl-1H-pyrazole-4-carboxamide 	8.17 (s, 1 H) 8.07 (s, 1 H) 7.94 (s, 1 H) 7.47 (ddd, 2 H) 7.27 (t, 1 H) 4.67 – 4.78 (m, 1 H) 3.89 – 3.97 (m, 3 H) 3.73 (dd, 1 H) 3.44 (t, 2 H) 3.19 (dd, 1 H) 2.42 (dd, 1 H) 2.14 (dd, 1 H)	432	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 1-methyl-1H-pyrazole-4-carboxylic acid 
142	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-2-(oxidothiomorpholin-4-yl)acetamide 	7.91 (s, 1 H) 7.56 (dd, 1 H) 7.43 (dd, 1 H) 7.27 (t, 1 H) 4.62 (t, 1 H) 3.67 – 3.78 (m, 2 H) 3.41 – 3.48 (m, 2 H) 3.19 – 3.22 (m, 2 H) 3.10 – 3.17 (m, 5 H) 2.92 – 2.98 (m, 2 H) 2.81 – 2.86 (m, 1 H) 2.37 – 2.48 (m, 1 H) 2.02 – 2.13 (m, 1 H)	483	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and (1-oxidothiomorpholin-4-yl)acetic acid 
143	(*S,Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-4-sulfamoylbutanamide 	7.18 (s, 1 H) 6.70 (dd, 1 H) 6.62 (dd, 1 H) 6.45 (t, 1 H) 3.71 (s, 1 H) 2.84 (dd, 1 H) 2.56 – 2.66 (m, 2 H) 2.29 – 2.36 (m, 2 H) 2.26 (dd, 1 H) 1.64 (t, 2 H) 1.57 (d, 1 H) 1.25 – 1.37 (m, 2 H) 1.20 (d, 1 H)	473	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 4-sulfamoylbutanoic acid 

144	(*S*,*Z*)-*N*1-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-*N*4,*N*4-dimethylsuccinamide 	8.01 (s, 1 H) 7.50 (d, 1 H) 7.44 (d, 1 H) 7.26 (t, 1 H) 4.47 – 4.58 (m, 1 H) 3.62 (t, 1 H) 3.42 (t, 2 H) 3.02 – 3.15 (m, 4 H) 2.92 (s, 3 H) 2.67 (d, 2 H) 2.56 (t, 2 H) 2.36 (dd, 1 H) 2.02 (dd, 1 H)	451	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 4-(dimethylamino)-4-oxobutanoic acid 
145	(*S*,*Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-2-(dimethylamino)acetamide 	7.07 (s, 1 H) 6.69 – 6.74 (m, 1 H) 6.59 (dd, 1 H) 6.43 (t, 1 H) 3.76 (br. S., 1 H) 2.85 – 2.94 (m, 2 H) 2.84 (d, 1 H) 2.36 (br. S., 1 H) 2.29 (dd, 2 H) 1.52 – 1.64 (m, 7 H) 1.18 – 1.28 (m, 1 H)	409	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 2-(dimethylamino)acetic acid 
146	(*S*,*Z*)-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)-2-cyanoacetamide 	7.95 (s, 1 H) 7.52 (dd, 1 H) 7.42 (dd, 1 H) 7.26 (t, 1 H) 4.50 (ddd, 1 H) 3.68 – 3.78 (m, 1 H) 3.64 (dd, 1 H) 3.44 – 3.50 (m, 1 H) 3.40 (t, 1 H) 3.22 (q, 1 H) 3.09 (dd, 1 H) 2.39 (dt, 1 H) 2.03 (d, 1 H)	391	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 2-cyanoacetic acid 

147	(*S,Z*)-2-acetamido-*N*-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)acetamide 	7.89 (s, 1 H) 7.54 (dd, 1 H) 7.39 (dd, 1 H) 7.24 (t, 1 H) 4.49 – 4.60 (m, 1 H) 3.86 – 3.98 (m, 1 H) 3.65 (dd, 1 H) 3.36 – 3.48 (m, 2 H) 3.17 – 3.25 (m, 1 H) 3.07 – 3.16 (m, 1 H) 2.31 – 2.43 (m, 1 H) 1.96 – 2.09 (m, 4 H)	423	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione Example 86  and 2-acetamidoacetic acid 

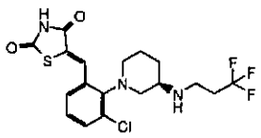
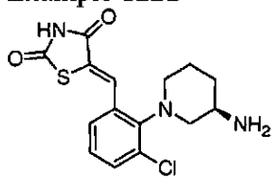
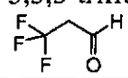
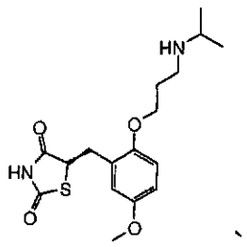
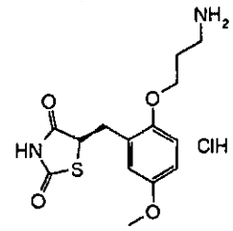
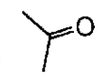
Example 148:



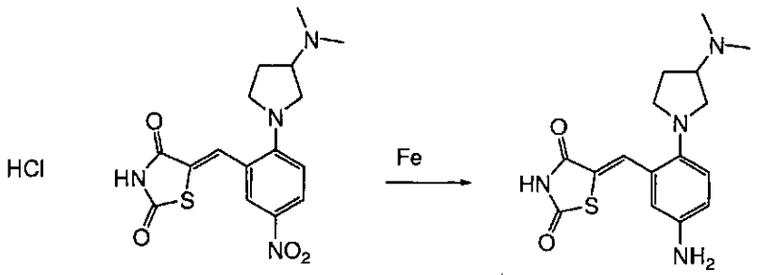
(*R,Z*)-5-(3-chloro-2-(3-(dipropylamino)piperidin-1-yl)benzylidene)thiazolidine-2,4-dione:

A mixture of (*R,Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione (122D) (100 mg, 0.27 mmol) and propionaldehyde (20.17 mg, 0.35 mmol) in CH_2Cl_2 (15 mL) was stirred at 50 °C for 20 min. before sodium triacetoxyborohydride (170 mg, 0.80 mmol) was added. The mixture was then stirred at 50 °C for 4 h. before sat'd aqueous K_2CO_3 (~ 50 mL) was added to the mixture. This solution was poured into a separatory funnel and extracted with $CHCl_3$/isopropanol (5/1) (2 x 50 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and conc. *in vacuo* affording the product. It was purified with Gilson (0.1% TFA in water:0.1% TFA in CAN=30% to 80%; UV absortion at 322) to yield the title compound as a yellow solid (94 mg, 77 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.96 (s, 1 H) 7.48 (d, 1 H) 7.41-7.34 (m, 1 H) 7.29 (t, 1 H) 3.67-3.58 (m, 2 H) 3.44-3.37 (m, 2 H) 3.03-2.78 (m, 5 H) 2.21 (brs, 1 H), 1.79 (d, 1 H) 1.61 (d, 6 H) 0.84-0.79 (m, 6 H). *m/z* 422.

He following examples were prepared by the procedure of 148, using the appropriate starting materials.

149	(*R*,*Z*)-5-(3-chloro-2-(3-(3,3,3-trifluoropropylamino) piperidin-1-yl)benzylidene)thiazolidine-2,4-dione 	12.65 (brs, 1 H) 9.35 (brs, 1H) 8.05 (s, 1 H) 7.56 (d, 1 H) 7.44 (brs, 1 H) 7.37 (t, 1 H) 3.75-3.63 (m, 2 H) 3.53-3.45 (m, 2 H) 3.23 (m, 1 H) 2.85-2.65 (m, 4 H) 2.30 (brs, 1 H) 1.85-1.76 (m, 1 H) 1.67 (brs, 1 H) 1.49 (brs, 1 H)	433	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride Example 122D  and 3,3,3-trifluoropropanal 
150	5-(2-(3-(isopropylamino)propoxy)-5-methoxybenzylidene) thiazolidine-2,4-dione 	12.65 (s, 1H), 8.91 (s, br, 2H), 7.91 (s, 1H), 7.10 (m, 2H), 7.85 (s, 1H), 4.17 (m, 2H), 3.65 (m, 4H), 3.05 (m, 2H), 2.14 (m, 2H), 1.22 (m, 6H)	351	5-(2-(3-aminopropoxy)-5-methoxybenzylidene)thiazolidine-2,4-dione hydrochloride Example 129C  And Acetone 

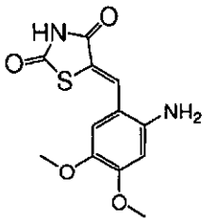
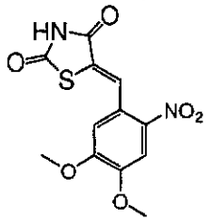
Example 151:



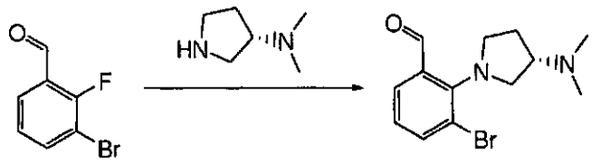
(Z)-5-(5-amino-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione

To a mixture of (Z)-5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-5-nitrobenzylidene)thiazolidine-2,4-dione (100 mg, 0.28 mmol) (Method 149) and iron (154 mg, 2.76 mmol) chip in MeOH (10 mL) was added 5 drops of conc. HCl and 5 drops of water. The mixture was stirred at 80 °C for 1hr. The mixture was loaded into silica gel, purified with ISCO (100% ethyl acetate to methanol/ethyl acetate=50%) to yield a red solid which was repurified with Gilson (acetonitrile:water:0.1%TFA=0% to 50% fro 7min) to yield a yellow solid as (Z)-5-(5-amino-2-(3-(dimethylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione (51.0 mg, 38.6 %). ^{1}H NMR (400 MHz, DMSO-d6) d ppm 12.55 (brs, 1 H), 11.32 (brs, 1 H), 10.30 (brs, 2 H), 7.80 (s, 1 H), 7.42 (m, 2 H), 7.19 (m, 1 H), 3.95 (m, 1 H), 3.39-3.27 (m, 4 H), 2.78 (s, 6 H), 2.30-2.10 (m, 2 H); *m/z* 333.

The following intermediates were prepared by the procedure of Example 151 using the appropriate starting materials.

Ex	Compound	^{1}H NMR	m/z	SM
152	(*Z*)-5-(2-amino-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione 	12.45 (brs, 1 H) 7.87 (s, 1 H) 6.80 (s, 1 H) 6.79 (s, 1 H) 3.78 (s, 3 H) 3.73 (s, 3 H)	280	(*Z*)-5-(4,5-dimethoxy-2-nitrobenzylidene)thiazolidine-2,4-dione Method 150 

Methods Section:

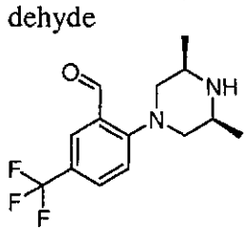
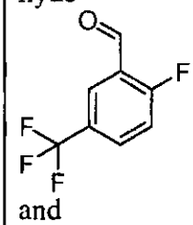
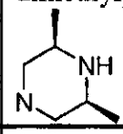
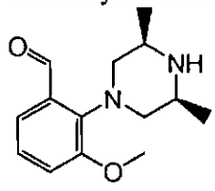
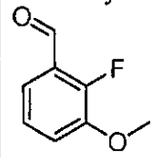
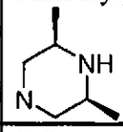
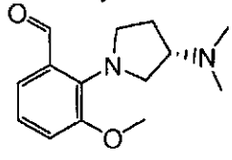
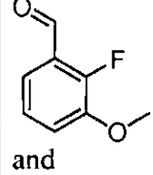
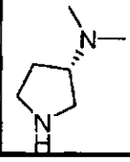


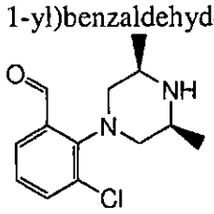
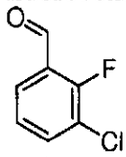
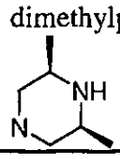
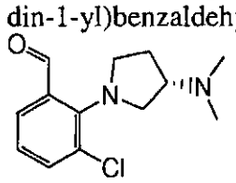
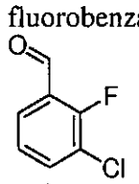
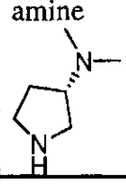
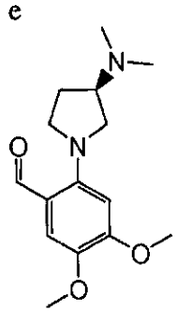
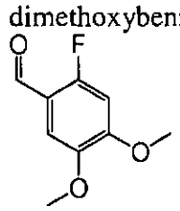
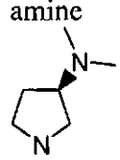
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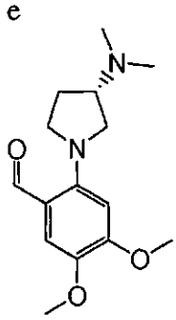
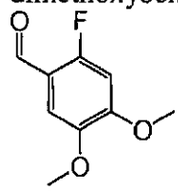
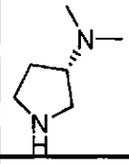
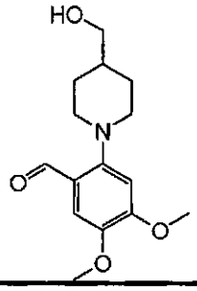
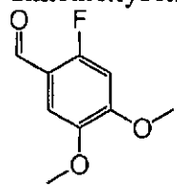
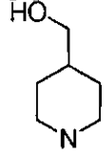
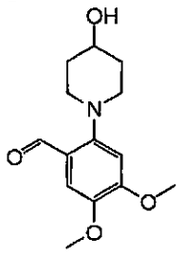
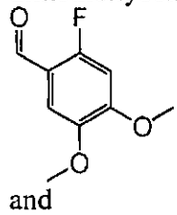
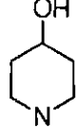
(*S*)-3-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde:

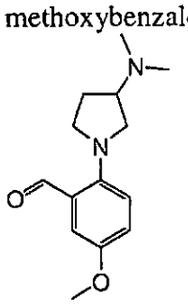
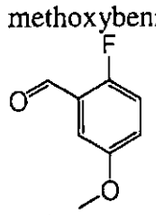
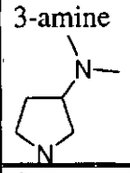
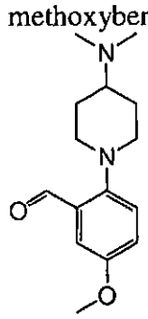
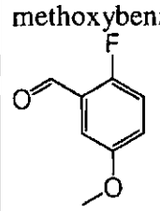
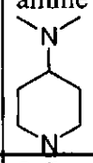
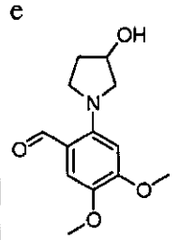
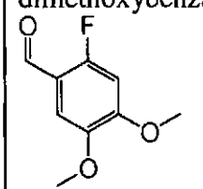
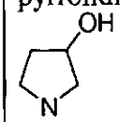
A 50 mL round bottom flask was charged with a magnetic stir bar, 3-bromo-2-fluorobenzaldehyde (0.555 g, 2.73 mmol), (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine (0.312 g, 2.73 mmol), DMSO (5.47 ml), and potassium carbonate (0.378 g, 2.73 mmol). The mixture was heated to 85 °C overnight with stirring. The reaction was allowed to cool to ambient temperature, was diluted with water, and extracted into methylene chloride. The combined organic extract was dried with $MgSO_4$, filtered, and conc. *in vacuo* to provide the product which was purified via silica gel chromatography (40 g) using ethyl acetate / MeOH (10 : 1) as eluent to afford (*S*)-3-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde (0.369 g, 45.4 %).

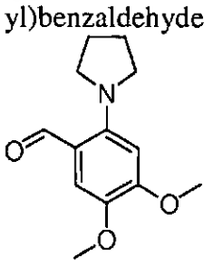
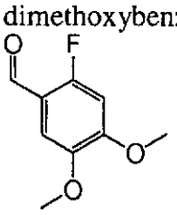
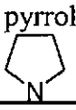
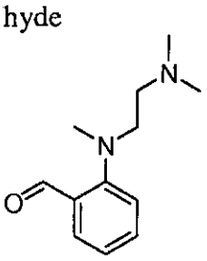
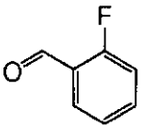
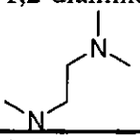
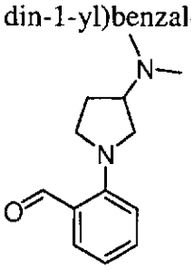
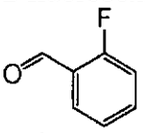
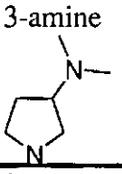
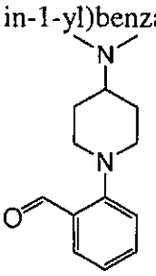
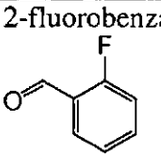
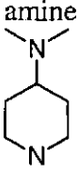
The following intermediates were prepared by the procedure of Method 1, using the appropriate starting materials.

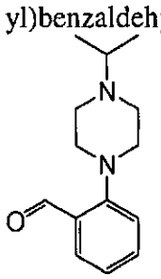
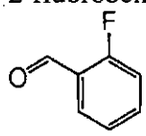
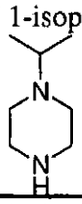
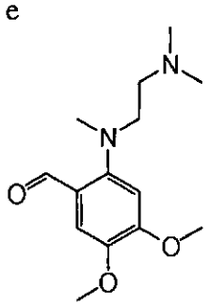
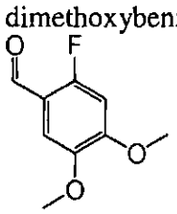
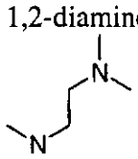
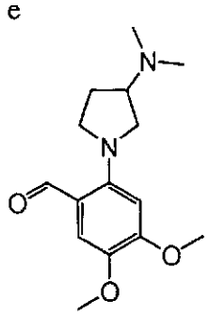
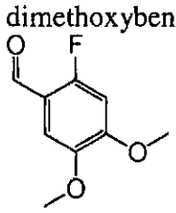
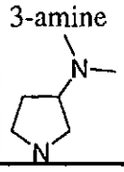
Method	Compound	^{1}H NMR	m/z	SM
2	2-((*3S,5R*)-3,5-dimethylpiperazin-1-yl)-5-(trifluoromethyl)benzaldehyde 		287	2-fluoro-5-(trifluoromethyl)benzaldehyde  and (*2R,6S*)-2,6-dimethylpiperazine 
3	2-((*3S,5R*)-3,5-dimethylpiperazin-1-yl)-3-methoxybenzaldehyde 		249	2-fluoro-3-methoxybenzaldehyde  and (*2R,6S*)-2,6-dimethylpiperazine 
4	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-3-methoxybenzaldehyde 		249	2-fluoro-3-methoxybenzaldehyde  and (*3S*)-*N,N*-dimethylpyrrolidin-3-amine 

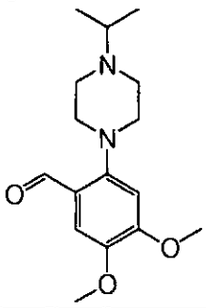
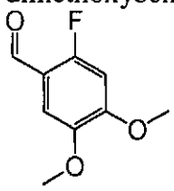
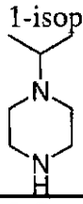
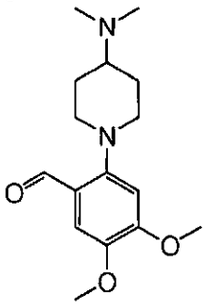
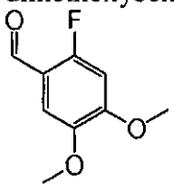
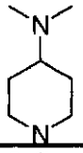
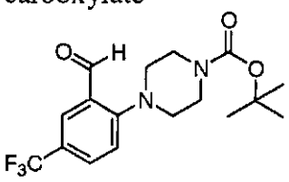
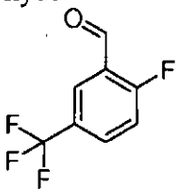
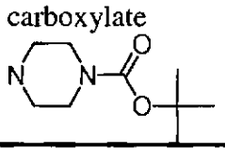
5	3-chloro-2-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzaldehyde 		254	3-chloro-2-fluorobenzaldehyde  and (2*R*,6*S*)-2,6-dimethylpiperazine 
6	(*S*)-3-chloro-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde 		253	3-chloro-2-fluorobenzaldehyde  and (*3S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
7	(*R*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde 		279	2-fluoro-4,5-dimethoxybenzaldehyde  and (3*R*)-*N*,*N*-dimethylpyrrolidin-3-amine 

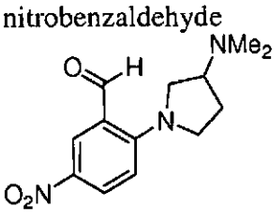
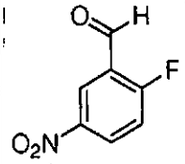
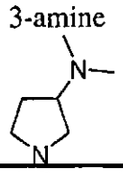
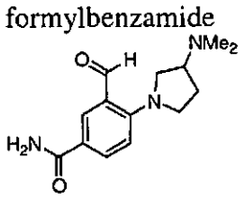
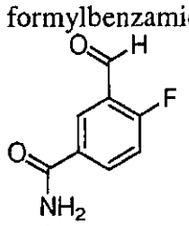
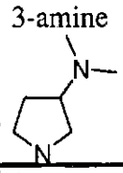
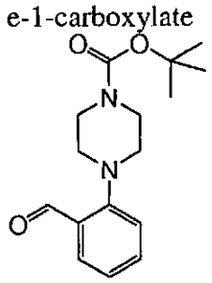
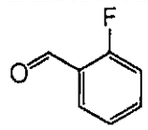
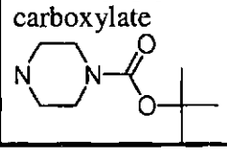
8	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde 		279	2-fluoro-4,5-dimethoxybenzaldehyde  and (*3S*)-*N,N*-dimethylpyrrolidin-3-amine 
9	2-(4-(hydroxymethyl)piperidin-1-yl)-4,5-dimethoxybenzaldehyde 		280	2-fluoro-4,5-dimethoxybenzaldehyde  and piperidin-4-ylmethanol 
10	2-(4-hydroxypiperidin-1-yl)-4,5-dimethoxybenzaldehyde 		266	2-fluoro-4,5-dimethoxybenzaldehyde  and piperidin-4-ol 

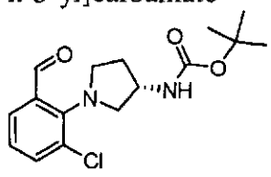
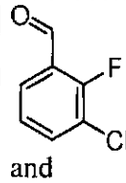
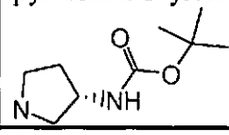
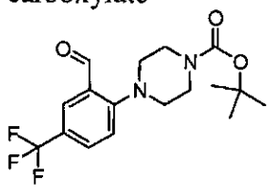
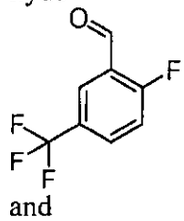
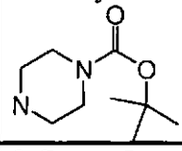
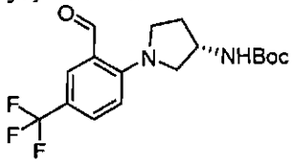
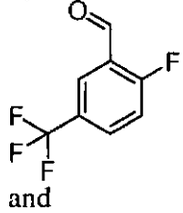
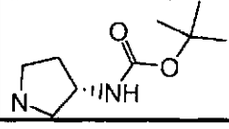
11	2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methoxybenzaldehyde 		249	2-fluoro-5-methoxybenzaldehyde  and *N,N*-dimethylpyrrolidin-3-amine 
12	2-(4-(dimethylamino)piperidin-1-yl)-5-methoxybenzaldehyde 		263	2-fluoro-5-methoxybenzaldehyde  and *N,N*-dimethylpiperidin-4-amine 
13	2-(3-hydroxypyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde 		253	2-fluoro-4,5-dimethoxybenzaldehyde  and pyrrolidin-3-ol 

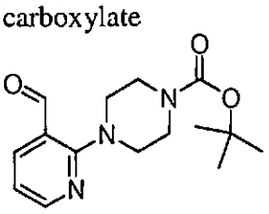
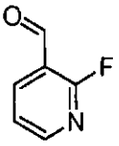
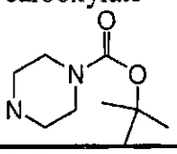
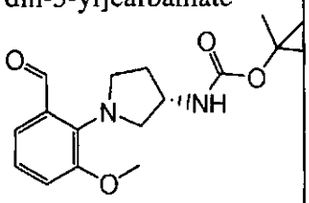
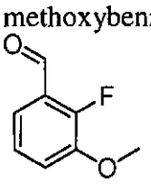
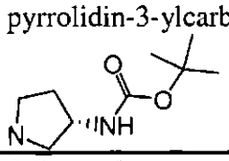
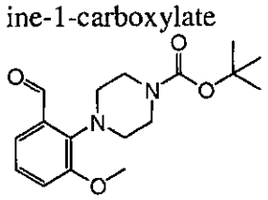
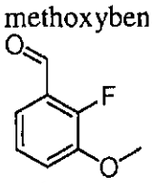
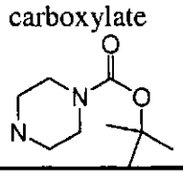
14	4,5-dimethoxy-2-(pyrrolidin-1-yl)benzaldehyde 		236	2-fluoro-4,5-dimethoxybenzaldehyde  and pyrrolidine 
15	2-((2-(dimethylamino)ethyl)(methyl)amino)benzaldehyde 		207	2-fluorobenzaldehyde  and *N,N,N'*-trimethylethane-1,2-diamine 
16	2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde 		219	2-fluorobenzaldehyde  and *N,N*-dimethylpyrrolidin-3-amine 
17	2-(4-(dimethylamino)piperidin-1-yl)benzaldehyde 		233	2-fluorobenzaldehyde  and *N,N*-dimethylpiperidin-4-amine 

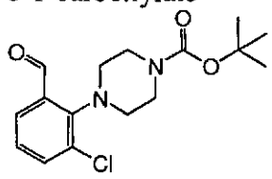
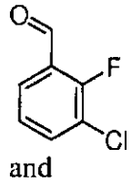
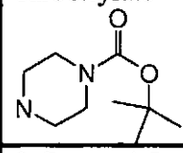
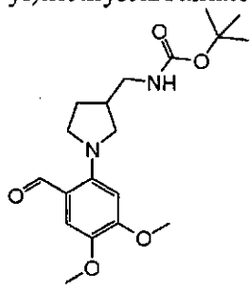
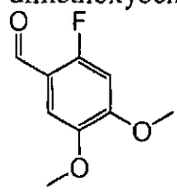
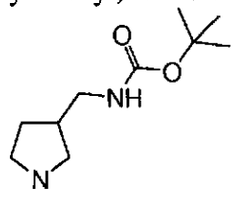
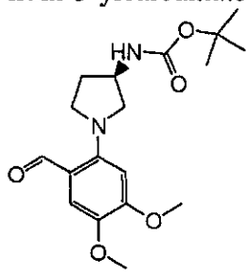
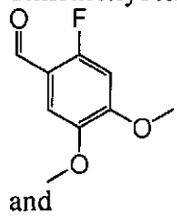
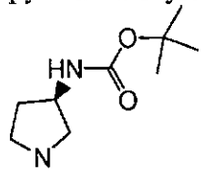
18	2-(4-isopropylpiperazin-1-yl)benzaldehyde 		233	2-fluorobenzaldehyde  and 1-isopropylpiperazine 
19	2-((2-(dimethylamino)ethyl)(methyl)amino)-4,5-dimethoxybenzaldehyde 		267	2-fluoro-4,5-dimethoxybenzaldehyde  and *N,N,N'*-trimethylethane-1,2-diamine 
20	2-(3-(dimethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzaldehyde 		279	2-fluoro-4,5-dimethoxybenzaldehyde  and *N,N*-dimethylpyrrolidin-3-amine 

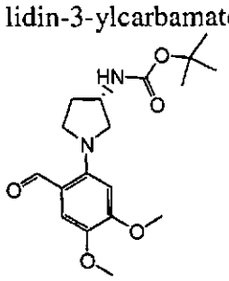
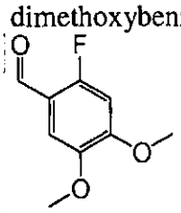
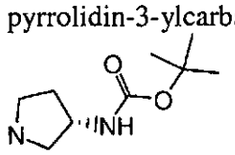
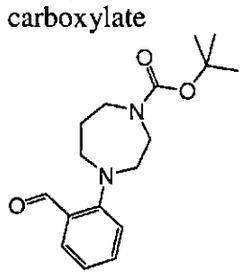
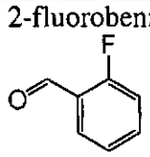
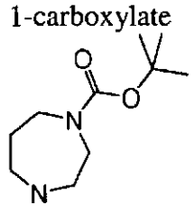
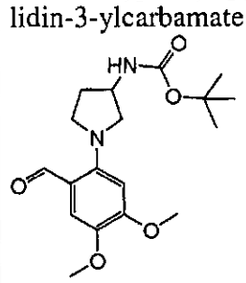
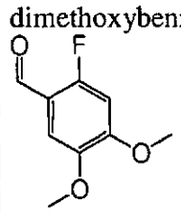
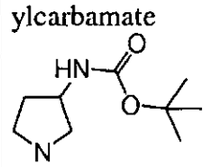
21	2-(4-isopropylpiperazin-1-yl)-4,5-dimethoxybenzaldehyde 		293	2-fluoro-4,5-dimethoxybenzaldehyde  and 1-isopropylpiperazine 
22	2-(4-(dimethylamino)piperidin-1-yl)-4,5-dimethoxybenzaldehyde 		293	2-fluoro-4,5-dimethoxybenzaldehyde  and *N,N*-dimethylpiperidin-4-amine 
23	*tert*-butyl 4-(2-formyl-4-(trifluoromethyl)phenyl)piperazine-1-carboxylate 		359	2-fluoro-5-(trifluoromethyl)benzaldehyde  and *tert*-butyl piperazine-1-carboxylate 

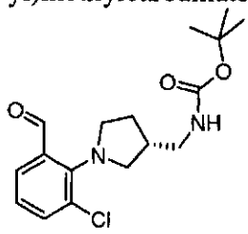
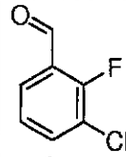
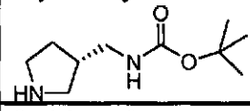
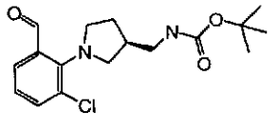
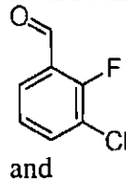
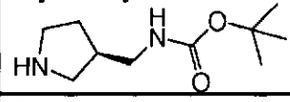
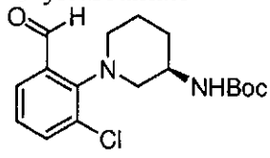
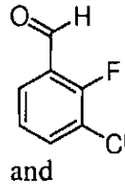
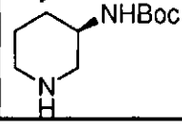
24	2-(3-(dimethylamino)pyrrolidin-1-yl)-5-nitrobenzaldehyde 		264	2-fluoro-5-nitrobenzaldehyde  and *N,N*-dimethylpyrrolidin-3-amine 
25	4-(3-(dimethylamino)pyrrolidin-1-yl)-3-formylbenzamide 		262	4-fluoro-3-formylbenzamide  and *N,N*-dimethylpyrrolidin-3-amine 
26	*tert*-butyl 4-(2-formylphenyl)piperazine-1-carboxylate 		291	2-fluorobenzaldehyde  and *tert*-butyl piperazine-1-carboxylate 

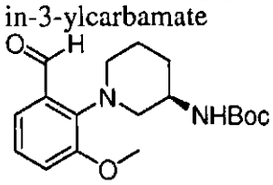
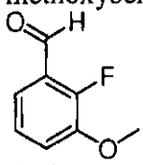
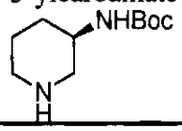
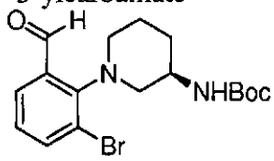
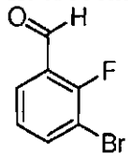
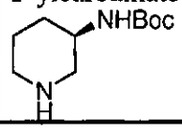
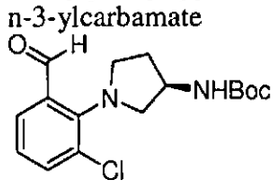
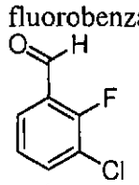
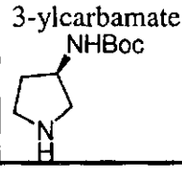
79	*tert*-butyl [(3*S*)-1-(2-chloro-6-formylphenyl)pyrrolidin-3-yl]carbamate 		326	3-chloro-2-fluorobenzaldehyde  and *tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate 
80	*tert*-butyl4-[2-formyl-4-(trifluoromethyl)phenyl]piperazine-1-carboxylate 		359	2-fluoro-5-(trifluoromethyl)benzaldehyde  and *tert*-butyl piperazine-1-carboxylate 
81	*tert*-butyl{(3*S*)-1-[2-formyl-4-(trifluoromethyl)phenyl]pyrrolidin-3-yl}carbamate 		359	2-fluoro-5-(trifluoromethyl)benzaldehyde  and *tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate 

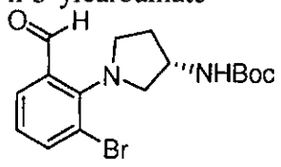
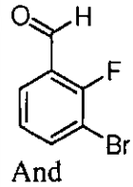
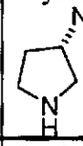
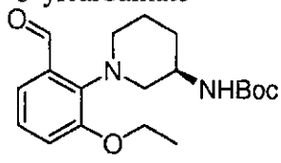
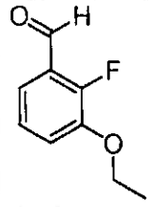
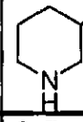
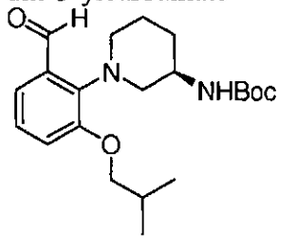
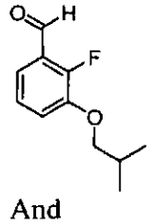
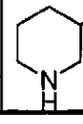
82	*tert*-butyl 4-(3-formylpyridin-2-yl)piperazine-1-carboxylate 		292	2-fluoronicotinaldehyde  and *tert*-butyl piperazine-1-carboxylate 
83	*tert*-butyl [(3*S*)-1-(2-formyl-6-methoxyphenyl)pyrrolidin-3-yl]carbamate 		322	2-fluoro-3-methoxybenzaldehyde  and *tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate 
84	*tert*-butyl 4-(2-formyl-6-methoxyphenyl)piperazine-1-carboxylate 		321	2-fluoro-3-methoxybenzaldehyde  and *tert*-butyl piperazine-1-carboxylate 

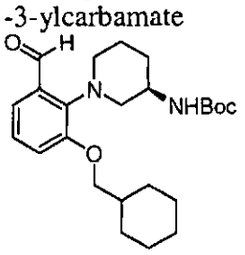
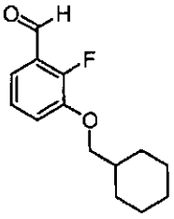
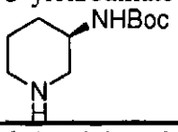
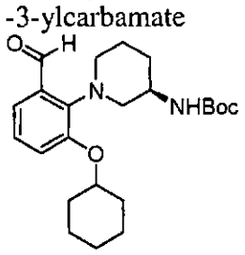
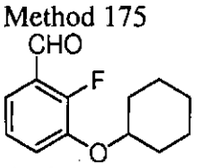
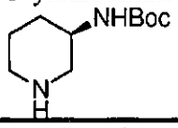
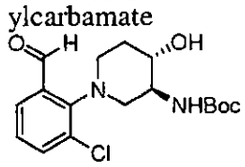
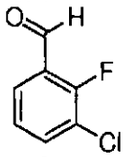
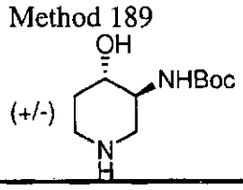
85	*tert*-butyl 4-(2-chloro-6-formylphenyl)piperazine-1-carboxylate 		326	3-chloro-2-fluorobenzaldehyde  and *tert*-butyl piperazine-1-carboxylate 
86	*tert*-butyl (1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-yl)methylcarbamate 		365	2-fluoro-4,5-dimethoxybenzaldehyde  and *tert*-butyl (pyrrolidin-3-ylmethyl)carbamate 
87	(*R*)-*tert*-butyl 1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate 		351	2-fluoro-4,5-dimethoxybenzaldehyde  and *tert*-butyl (3*R*)-pyrrolidin-3-ylcarbamate 

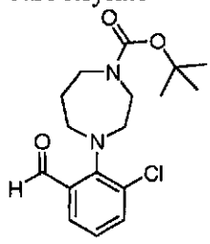
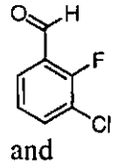
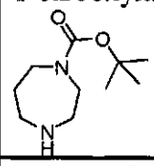
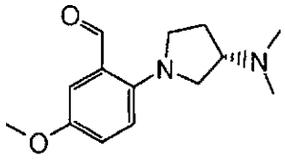
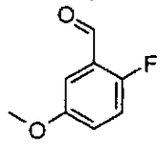
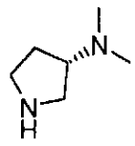
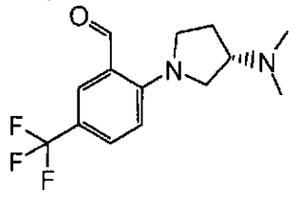
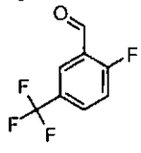
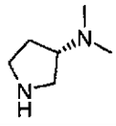
88	(*S*)-*tert*-butyl 1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate 		351	2-fluoro-4,5-dimethoxybenzaldehyde  and *tert*-butyl (3*S*)-pyrrolidin-3-ylcarbamate 
89	*tert*-butyl 4-(2-formylphenyl)-1,4-diazepane-1-carboxylate 		305	2-fluorobenzaldehyde  and *tert*-butyl 1,4-diazepane-1-carboxylate 
90	*tert*-butyl 1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate 		351	2-fluoro-4,5-dimethoxybenzaldehyde  and *tert*-butyl pyrrolidin-3-ylcarbamate 

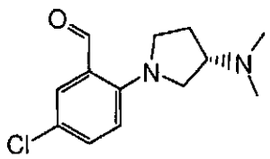
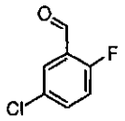
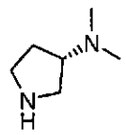
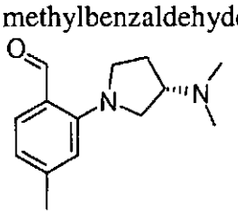
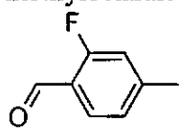
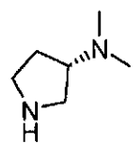
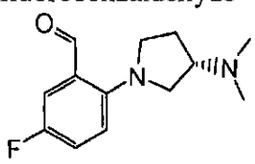
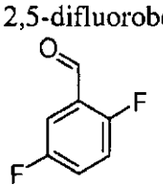
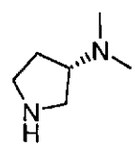
91	(*R*)-*tert*-butyl (1-(2-chloro-6-formylphenyl)pyrrolidin-3-yl)methylcarbamate 		339	3-chloro-2-fluorobenzaldehyde  and (*S*)-*tert*-butyl pyrrolidin-3-ylmethylcarbamate 
92	(*S*)-*tert*-butyl (1-(2-chloro-6-formylphenyl)pyrrolidin-3-yl)methylcarbamate 		339	3-chloro-2-fluorobenzaldehyde  and (*R*)-*tert*-butyl pyrrolidin-3-ylmethylcarbamate 
93	(*R*)-*tert*-butyl 1-(2-chloro-6-formylphenyl)piperidin-3-ylcarbamate 		339	3-chloro-2-fluorobenzaldehyde  and (*R*)-*tert*-butyl piperidin-3-ylcarbamate 

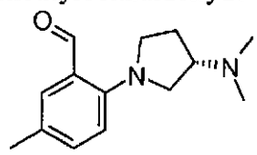
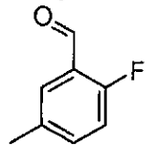
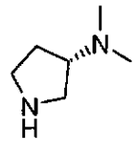
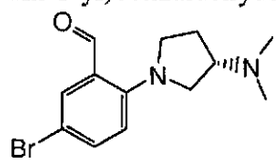
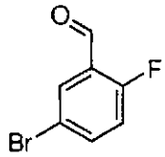
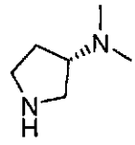
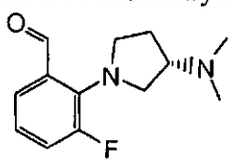
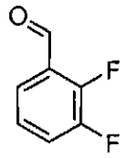
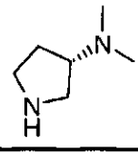
94	(*R*)-*tert*-butyl 1-(2-formyl-6-methoxyphenyl)piperidin-3-ylcarbamate 		335	2-fluoro-3-methoxybenzaldehyde  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
95	(*R*)-*tert*-butyl 1-(2-bromo-6-formylphenyl)piperidin-3-ylcarbamate 		385	3-bromo-2-fluorobenzaldehyde  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
96	(*R*)-*tert*-butyl 1-(2-chloro-6-formylphenyl)pyrrolidin-3-ylcarbamate 		325	3-chloro-2-fluorobenzaldehyde  and (*R*)-*tert*–butyl pyrrolidin-3-ylcarbamate 

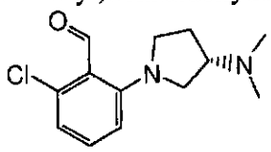
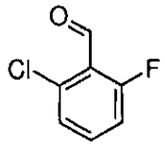
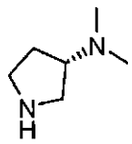
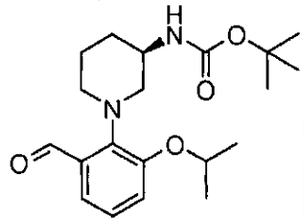
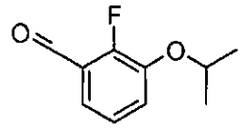
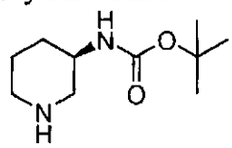
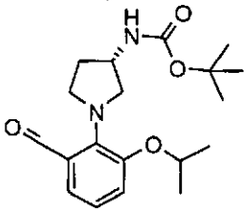
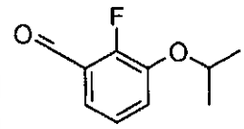
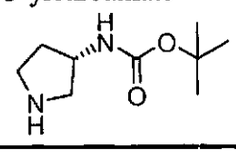
97	(*S*)-*tert*-butyl 1-(2-bromo-6-formylphenyl)pyrrolidin-3-ylcarbamate 		371	3-bromo-2-fluorobenzaldehyde  And (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate 
98	(*R*)-*tert*-butyl 1-(2-ethoxy-6-formylphenyl)piperidin-3-ylcarbamate 		349	3-ethoxy-2-fluorobenzaldehyde Method 172  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
99	(*R*)-*tert*-butyl 1-(2-formyl-6-isobutoxyphenyl)piperidin-3-ylcarbamate 		377	2-fluoro-3-isobutoxybenzaldehyde Method 173  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 

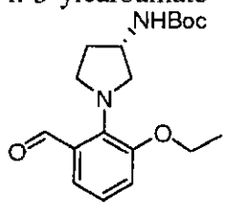
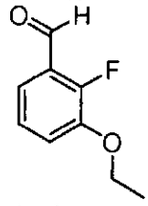
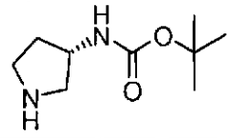
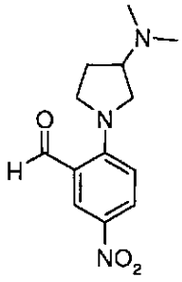
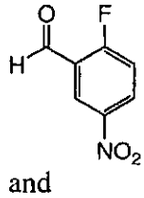
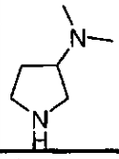
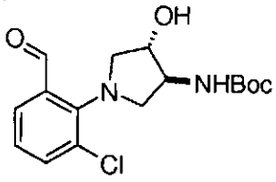
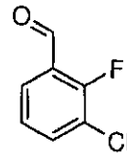
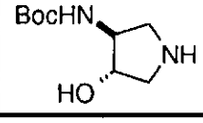
100	(*R*)-*tert*-butyl 1-(2-(cyclohexylmethoxy)-6-formylphenyl)piperidin-3-ylcarbamate 		417	3-(cyclohexylmethoxy)-2-fluorobenzaldehyde Method 174  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
101	(*R*)-*tert*-butyl 1-(2-(cyclohexyloxy)-6-formylphenyl)piperidin-3-ylcarbamate 		403	3-(cyclohexyloxy)-2-fluorobenzaldehyde Method 175  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
102	(±)-*tert*-butyl-1-(2-chloro-6-formylphenyl)-4-hydroxypiperidin-3-ylcarbamate 		354	3-chloro-2-fluorobenzaldehyde  and (±)-*tert*-butyl-4-hydroxypiperidin-3-ylcarbamate Method 189 

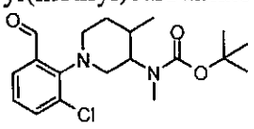
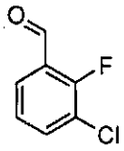
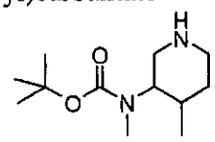
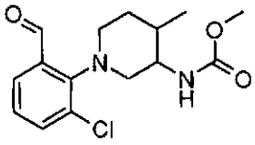
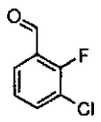
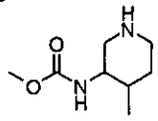
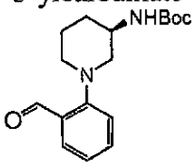
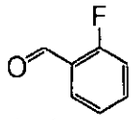
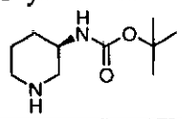
103	*tert*-butyl 4-(2-chloro-6-formylphenyl)-1,4-diazepane-1-carboxylate 	10.49 (s, 1 H), 7.75 (d, 1 H), 7.63 (d, 1 H), 7.25 (t, 1 H), 3.37 (brs, 4 H), 1.88 (brs, 2 H), 1.53 (s, 9 H)	339	3-chloro-2-fluorobenzaldehyde  and *tert*-butyl 1,4-diazepane-1-carboxylate 
104	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methoxybenzaldehyde 		249	2-fluoro-5-methoxybenzaldehyde  and (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
105	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-(trifluoromethyl)benzaldehyde 		287	2-fluoro-5-(trifluoromethyl)benzaldehyde  and (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 

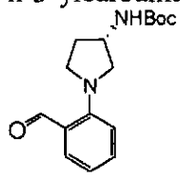
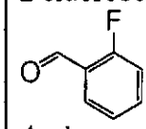
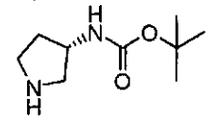
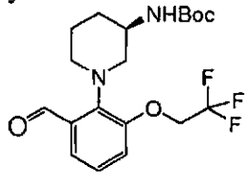
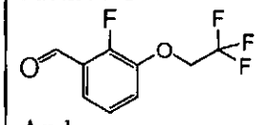
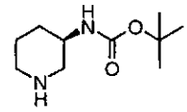
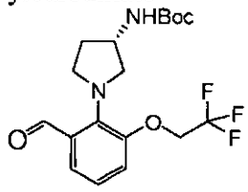
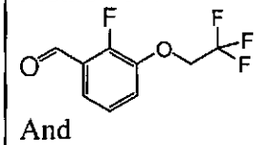
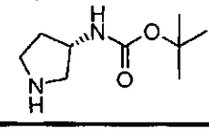
106	(*S*)-5-chloro-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehydeMethod 		253	5-chloro-2-fluorobenzaldehyde  and (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
107	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-4-methylbenzaldehyde 		233	2-fluoro-4-methylbenzaldehyde  And (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
108	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-fluorobenzaldehyde 		237	2,5-difluorobenzaldehyde  And (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 

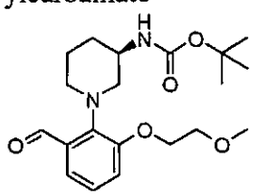
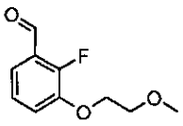
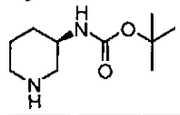
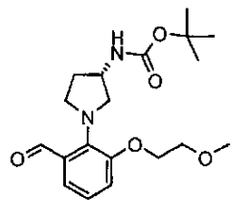
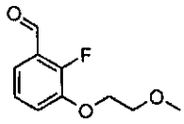
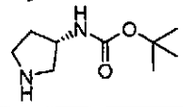
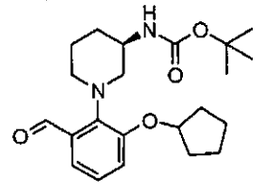
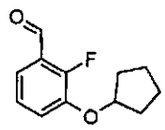
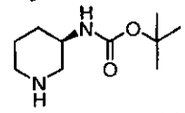
109	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-5-methylbenzaldehyde 		233	2-fluoro-5-methylbenzaldehyde  And (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
110	(*S*)-5-bromo-2-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde 		298	5-bromo-2-fluorobenzaldehyde  And (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
111	(*S*)-2-(3-(dimethylamino)pyrrolidin-1-yl)-3-fluorobenzaldehyde 		237	2,3-difluorobenzaldehyde  And (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 

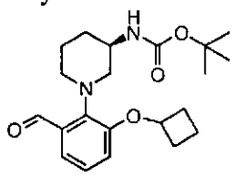
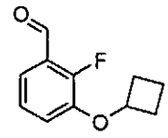
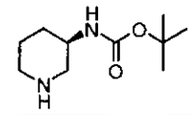
112	(S)-2-chloro-6-(3-(dimethylamino)pyrrolidin-1-yl)benzaldehyde 		253	2-chloro-6-fluorobenzaldehyde  And (*S*)-*N*,*N*-dimethylpyrrolidin-3-amine 
113	(*R*)-*tert*-butyl 1-(2-formyl-6-isopropoxyphenyl)piperidin-3-ylcarbamate 		363	2-fluoro-3-isopropoxybenzaldehyde Method 176  (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
114	(*S*)-*tert*-butyl 1-(2-formyl-6-isopropoxyphenyl)pyrrolidin-3-ylcarbamate 		349	2-fluoro-3-isopropoxybenzaldehyde Method 176  (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate 

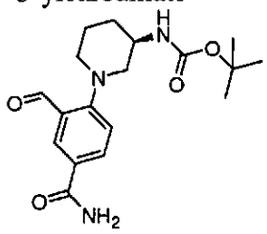
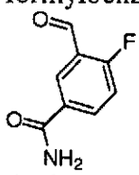
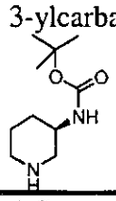
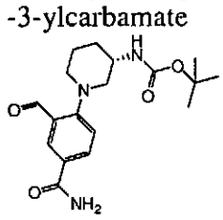
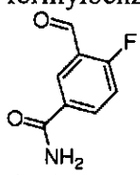
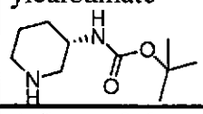
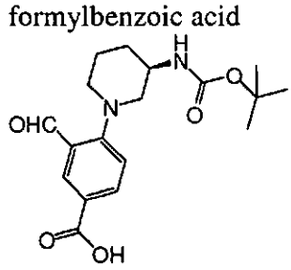
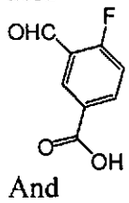
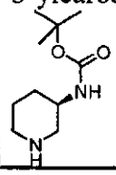
115	(*S*)-*tert*-butyl 1-(2-ethoxy-6-formylphenyl)pyrrolidin-3-ylcarbamate 		334	3-ethoxy-2-fluorobenzaldehyde Method 172  And (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate 
116	2-(3-(dimethylamino)pyrrolidin-1-yl)-5-nitrobenzaldehyde 		263	2-fluoro-5-nitrobenzaldehyde  and *N,N*-dimethylpyrrolidin-3-amine 
117	(±)-*tert*-butyl-1-(2-chloro-6-formylphenyl)-4-hydroxypyrrolidin-3-ylcarbamate 	10.30 (s, 1 H) 7.76 (dd, 1 H) 7.65 (dd, 1 H) 7.29-7.24(m, 1 H) 5.05 (brs, 1 H) 4.41 (brs, 1 H) 4.20 (brs, 1 H) 3.87 (dd, 1 H) 3.78 (dd, 1 H) 3.64-3.47 (m, 1 H) 3.36 (brs, 1 H) 3.21 (dd, 1 H) 1.50 (s, 9 H)	341	3-chloro-2-fluorobenzaldehyde  And (±)-*tert*-butyl-4-hydroxypyrrolidin-3-ylcarbamate Method 188 

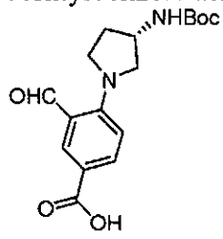
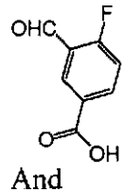
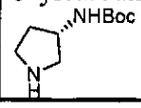
118	*tert*-butyl 1-(2-chloro-6-formylphenyl)-4-methylpiperidin-3-yl(methyl)carbamate 		367	3-chloro-2-fluorobenzaldehyde  *tert*-butyl methyl(4-methylpiperidin-3-yl)carbamate 
119	methyl 1-(2-chloro-6-formylphenyl)-4-methylpiperidin-3-ylcarbamate 		310	3-chloro-2-fluorobenzaldehyde  methyl 4-methylpiperidin-3-ylcarbamate 
120	*(R)-tert*-butyl 1-(2-formylphenyl)piperidin-3-ylcarbamate 		305	2-fluorobenzaldehyde  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 

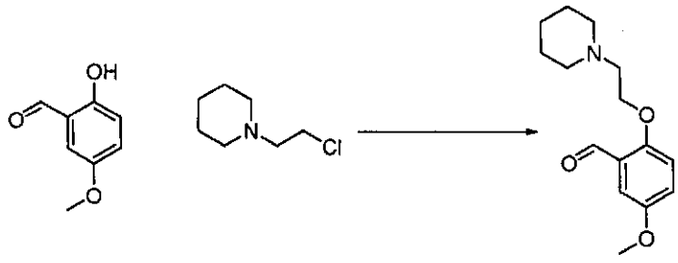
121	(*S*)-*tert*-butyl 1-(2-formylphenyl)pyrrolidin-3-ylcarbamate 		291	2-fluorobenzaldehyde  And (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate 
122	(*R*)-*tert*-butyl 1-(2-formyl-6-(2,2,2-trifluoroethoxy)phenyl) piperidin-3-ylcarbamate 		403	2-fluoro-3-(2,2,2-trifluoroethoxy)benzaldehyde Method 177  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
123	(*S*)-*tert*-butyl 1-(2-formyl-6-(2,2,2-trifluoroethoxy)phenyl) pyrrolidin-3-ylcarbamate 		389	2-fluoro-3-(2,2,2-trifluoroethoxy)benzaldehyde Method 177  And (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate 

124	(*R*)-*tert*-butyl 1-(2-formyl-6-(2-methoxyethoxy)phenyl)piperidin-3-ylcarbamate 		379	2-fluoro-3-(2-methoxyethoxy)benzaldehyde Method 178  and And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
125	(*S*)-*tert*-butyl 1-(2-formyl-6-(2-methoxyethoxy)phenyl)pyrrolidin-3-ylcarbamate 		365	2-fluoro-3-(2-methoxyethoxy)benzaldehyde Method 178  and (S)-tert-butyl pyrrolidin-3-ylcarbamate 
126	(*R*)-*tert*-butyl 1-(2-(cyclopentyloxy)-6-formylphenyl)piperidin-3-ylcarbamate 		389	3-(cyclopentyloxy)-2-fluorobenzaldehyde Method 179  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 

127	(*R*)-*tert*-butyl 1-(2-cyclobutoxy-6-formylphenyl)piperidin-3-ylcarbamate 		375	3-cyclobutoxy-2-fluorobenzaldehyde Method 180  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 

128	(*R*)-*tert*-butyl 1-(4-carbamoyl-2-formylphenyl)piperidin-3-ylcarbamate 		348	4-fluoro-3-formylbenzamide  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 
129	(*S*)-*tert*-butyl 1-(4-carbamoyl-2-formylphenyl)piperidin-3-ylcarbamate 		348	4-fluoro-3-formylbenzamide  And (*S*)-*tert*-butyl piperidin-3-ylcarbamate 
130	(*R*)-4-(3-(*tert*-butoxycarbonylamino) piperidin-1-yl)-3-formylbenzoic acid 		348	4-fluoro-3-formylbenzoic acid  And (*R*)-*tert*-butyl piperidin-3-ylcarbamate 

131	(*S*)-4-(3-(*tert*-butoxycarbonylamino) pyrrolidin-1-yl)-3-formylbenzoic acid 		334	4-fluoro-3-formylbenzoic acid  And (*S*)-*tert*-butyl pyrrolidin-3-ylcarbamate 



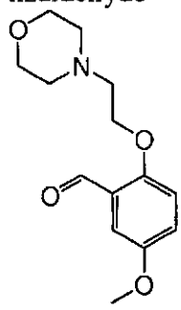
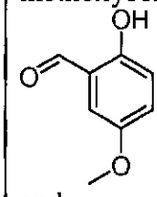
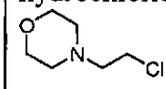
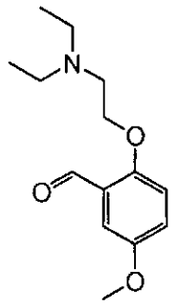
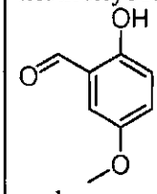
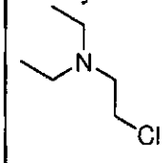
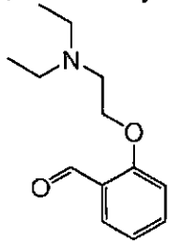
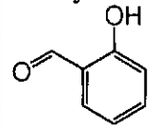
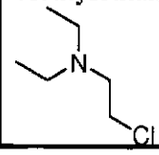
Method 27:

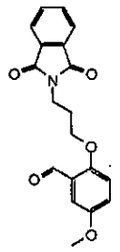
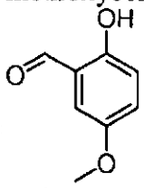
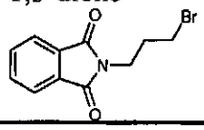
5-methoxy-2-(2-(piperidin-1-yl)ethoxy)benzaldehyde:

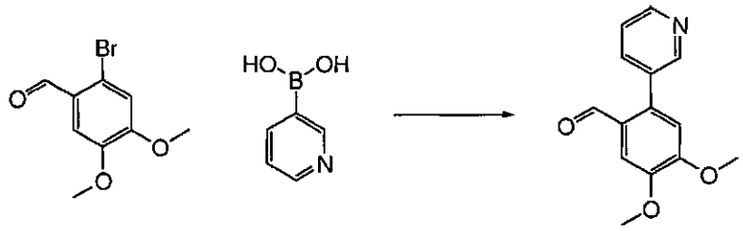
A mixture of 2-hydroxy-5-methoxybenzaldehyde (0.761 g, 5 mmol), 1-(2-chloroethyl)piperidine hydrochloride (0.921 g, 5.00 mmol), K_2CO_3 (2.07 g, 14.99 mmol), and sodium iodide (0.075 g, 0.50 mmol) in acetonitrile (40 mL) was stirred at 100 °C overnight. The reaction was allowed to cool to ambient temperature and sat'd aqueous K_2CO_3 was added to the reaction mixture. The mixture was poured into a separatory funnel and extracted with EtOAc. The organic phase was dried over anhydrous $MgSO_4$, filtered through a bed of Celite, and conc. *in vacuo* to yield the product which was purified via silica gel chromatography (80 g) using EtOAc/hexanes (4:1) as eluent to yield the title compound as a brown oil (0.551 g, 42 %); *m/z* 264.

The following intermediates were prepared by the procedure of Method 27, using the

appropriate starting materials.

Method	Compound	^{1}H NMR	m/z	SM
28	5-methoxy-2-(2-morpholinoethoxy)benzaldehyde 		266	2-hydroxy-5-methoxybenzaldehyde  and 4-(2-chloroethyl)morpholine hydrochloride 
29	2-(2-(diethylamino)ethoxy)-5-methoxybenzaldehyde 		252	2-hydroxy-5-methoxybenzaldehyde  and 2-chloro-*N*,*N*-diethylethanamine 
30A	2-(2-(diethylamino)ethoxy)benzaldehyde 		222	Salicylaldehyde  and 2-chloro-*N*,*N*-diethylethanamine 

30B	2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-5-methoxybenzaldehyde 	10.18 (s, 1 H) 7.69 (m, 4 H) 7.11 (m, 2 H) 6.97 (d, 1 H) 4.05 (m, 2 H) 3.83 (m, 2 H) 3.67 (s, 3 H) 2.12 (m, 2 H)	340	2-hydroxy-5-methoxybenzaldehyde  and 2-(3-bromopropyl)isoindoline-1,3-dione 

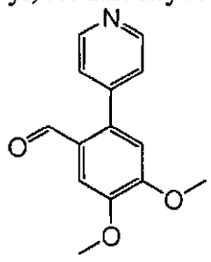
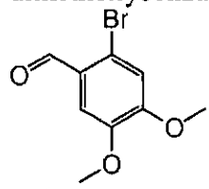
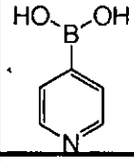
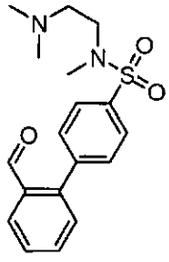
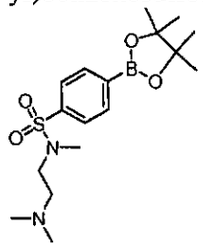
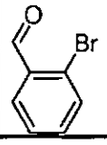


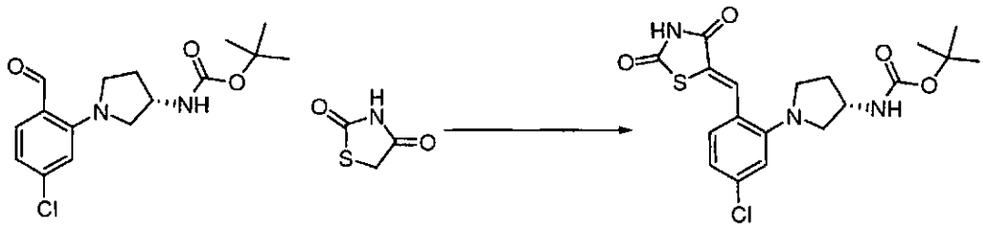
Method 31:

4,5-dimethoxy-2-(pyridin-3-yl)benzaldehyde:

A mixture of 2-bromo-4,5-dimethoxybenzaldehyde (0.368 g, 1.5 mmol), pyridin-3-ylboronic acid (0.246 g, 2.0 mmol), $Pd(PPh_3)_4$ (0.173 g, 0.150 mmol), and cesium carbonate (0.977 g, 3 mmol) were suspended in dioxane (4 mL) and water (1 mL). The mixture was heated to 140 °C in a microwave for 1 h. The reaction vessel was allowed to cool to ambient temperature, diluted with ethyl acetate (~ 25 mL), filtered through a bed of Celite, and conc. *in vacuo* to afford the aldehyde which was purified via SiO_2 chromatography (40 g) using ethyl acetate / hexanes (5:1) as eluent to afford the title compound as a white solid (0.340 g, 93 %); *m/z* 244.

The following intermediates were prepared by the procedure of Method 31, using the appropriate starting materials.

Method	Compound	^{1}H NMR	m/z	SM
32A	4,5-dimethoxy-2-(pyridin-4-yl)benzaldehyde 		244	2-bromo-4,5-dimethoxybenzaldehyde  and pyridin-4-ylboronic acid 
32B	*N*-(2-(dimethylamino)ethyl)-2'-formyl-*N*-methylbiphenyl-4-sulfonamide 	9.95 (s, 1 H), 8.05 (d, 1 H), 7.96 (d,2 H), 7.72 – 7.83 (m, 1 H), 7.57 – 7.72 (m, 3 H), 7.53 (d, 1 H), 3.24 (t, 2 H), 2.79 – 2.91 (m, 3 H), 2.65 (t, 2 H), 2.37 (s, 6 H)	346	*N*-(2-(dimethylamino)ethyl)-N-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide  And 2-bromobenzaldehyde 

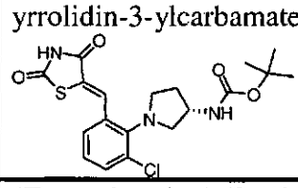
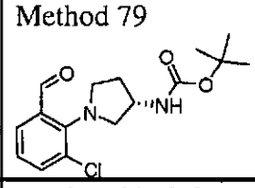
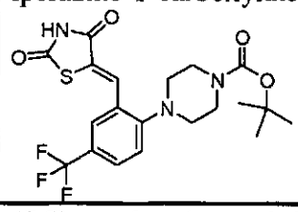
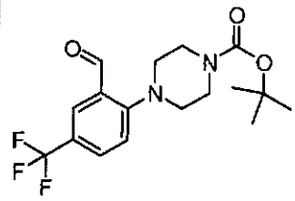
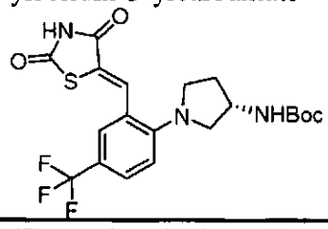
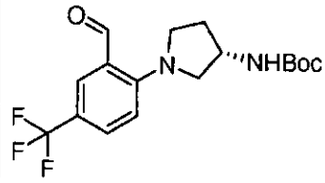
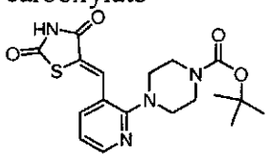
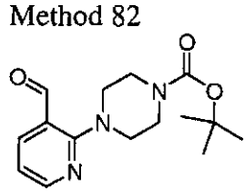


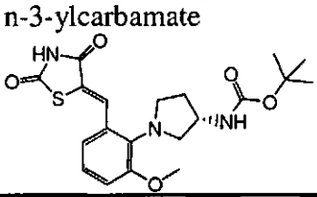
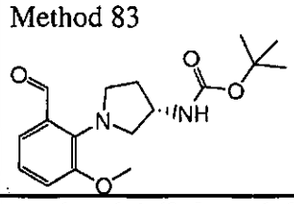
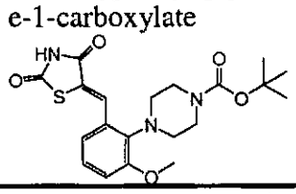
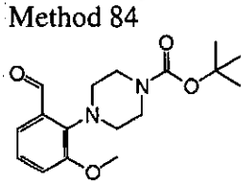
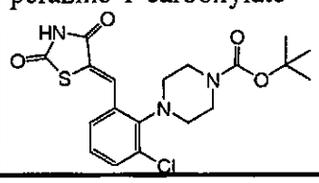
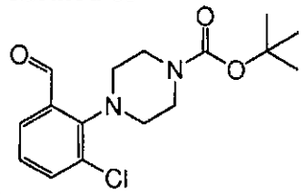
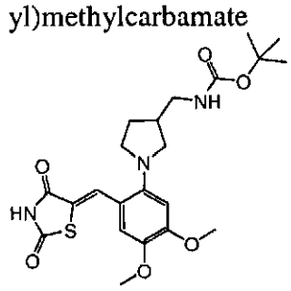
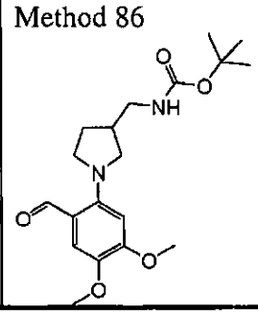
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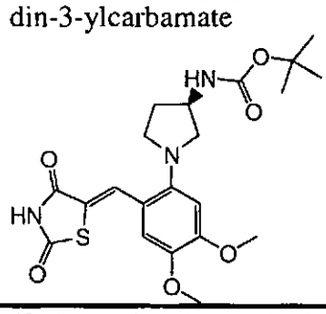
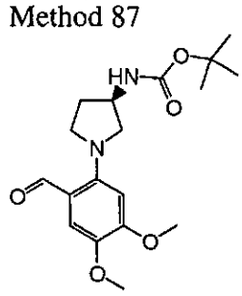
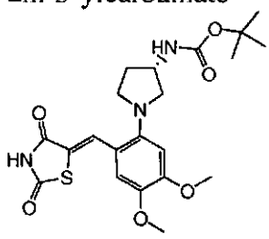
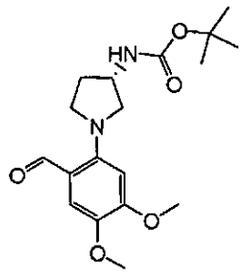
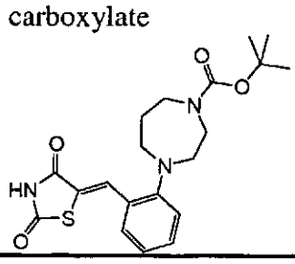
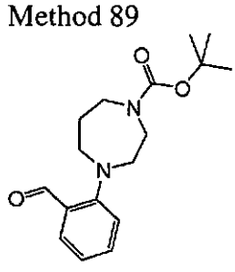
(*S,Z*)-*tert*-butyl 1-(5-chloro-2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate:

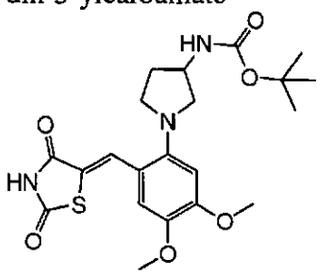
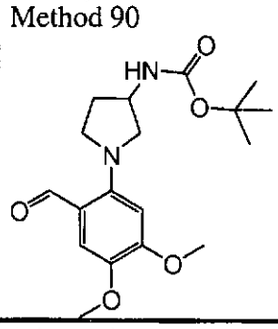
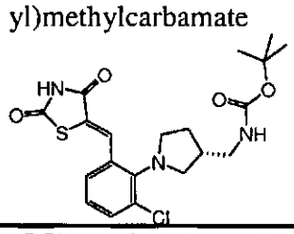
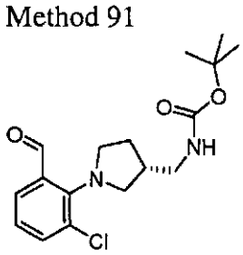
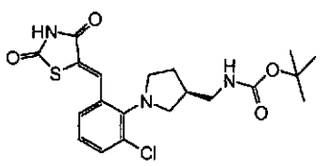
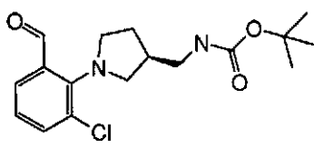
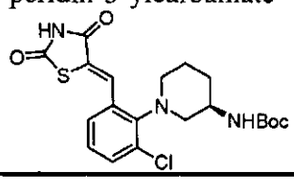
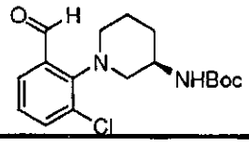
A 100 mL round bottom flask was charged with a magnetic stir bar, (*S*)-*tert*-butyl 1-(5-chloro-2-formylphenyl)pyrrolidin-3-ylcarbamate (Method 78) (1.100 g, 3.39 mmol), thiazolidine-2,4-dione (0.397 g, 3.39 mmol), and ethanol (11.29 ml). Piperidine (0.034 mL, 0.34 mmol) was added and the reaction was heated to reflux for 2 h. Once the reaction was judged to be complete by LCMS, it was allowed to cool to ambient temperature and conc. *in vacuo* to afford the title compound (1.310 g, 91 %) which was used in the next step without further purification.; *m/z* 425.

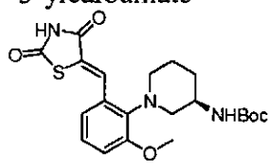
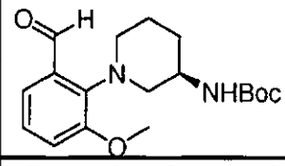
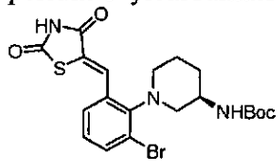
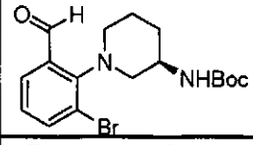
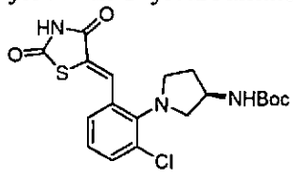
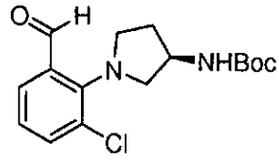
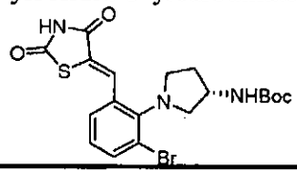
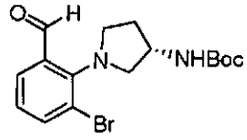
The following intermediates were prepared by the procedure of Method 33, using the appropriate starting materials.

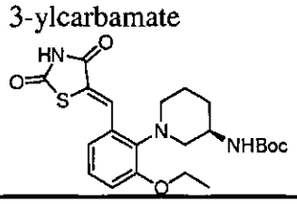
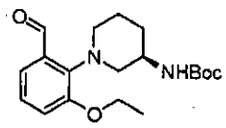
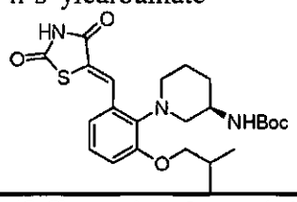
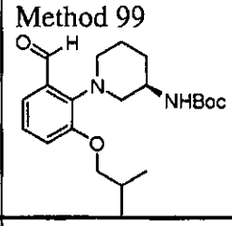
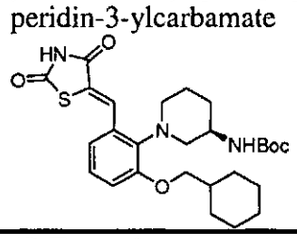
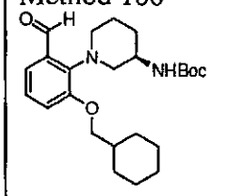
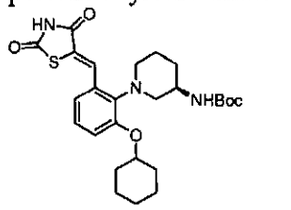
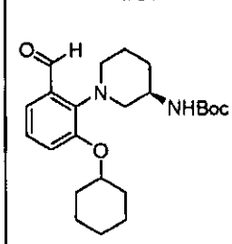
Method	Compound	^{1}H NMR	m/z	SM
34	(*S,Z*)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate 		425	*tert*-butyl [(3*S*)-1-(2-chloro-6-formylphenyl)pyrrolidin-3-yl]carbamate Method 79 
35	(*Z*)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)piperazine-1-carboxylate 		459	*tert*-butyl4-[2-formyl-4-(trifluoromethyl)phenyl]piperazine-1-carboxylate Method 80 
36	(*S,Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)pyrrolidin-3-ylcarbamate 		459	*tert*-butyl{(3*S*)-1-[2-formyl-4-(trifluoromethyl)phenyl]pyrrolidin-3-yl}carbamate Method 81 
37	(*Z*)-*tert*-butyl 4-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)pyridin-2-yl)piperazine-1-carboxylate 		391	*tert*-butyl 4-(3-formylpyridin-2-yl)piperazine-1-carboxylate Method 82 

44	(*S,Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)pyrrolidin-3-ylcarbamate 		421	*tert*-butyl [(3*S*)-1-(2-formyl-6-methoxyphenyl)pyrrolidin-3-yl]carbamate Method 83 
45	(*Z*)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)piperazine-1-carboxylate 		421	*tert*-butyl 4-(2-formyl-6-methoxyphenyl)piperazine-1-carboxylate Method 84 
46	(*Z*)-*tert*-butyl 4-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carboxylate 		425	*tert*-butyl 4-(2-chloro-6-formylphenyl)piperazine-1-carboxylate Method 85 
47	(*Z*)-*tert*-butyl (1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-yl)methylcarbamate 		465	*tert*-butyl (1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-yl)methylcarbamate Method 86 

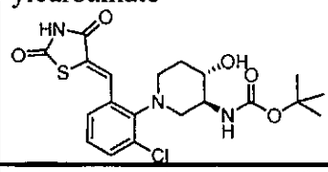
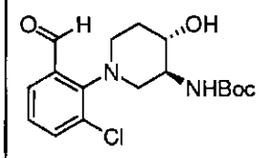
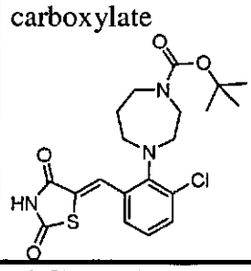
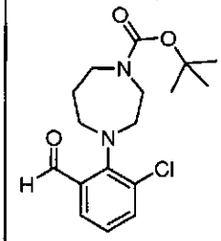
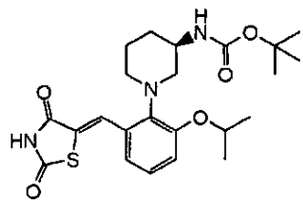
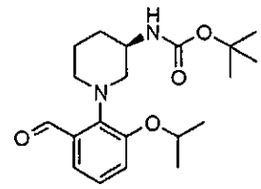
48	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate 		451	(*R*)-*tert*-butyl 1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate Method 87 
49	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate 		451	(*S*)-*tert*-butyl 1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate Method 88 
54	(*Z*)-*tert*-butyl 4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepane-1-carboxylate 		404	*tert*-butyl 4-(2-formylphenyl)-1,4-diazepane-1-carboxylate Method 89 

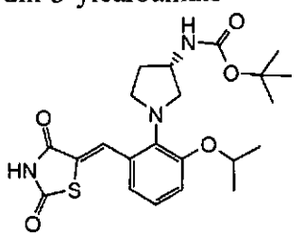
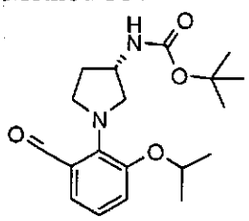
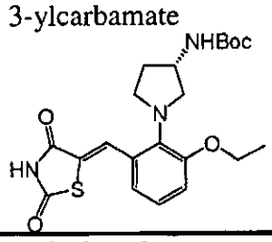
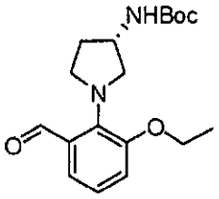
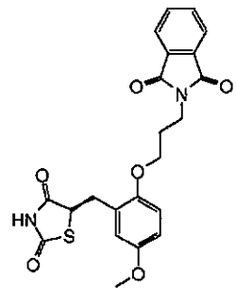
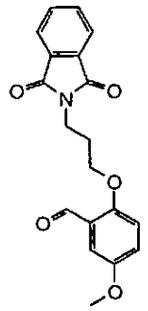
65	*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate 		451	*tert*-butyl 1-(2-formyl-4,5-dimethoxyphenyl)pyrrolidin-3-ylcarbamate Method 90 
132	(*R*,*Z*)-*tert*-butyl (1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)methylcarbamate 		439	(*R*)-*tert*-butyl (1-(2-chloro-6-formylphenyl)pyrrolidin-3-yl)methylcarbamate Method 91 
133	(*S*,*Z*)-*tert*-butyl (1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-yl)methylcarbamate 		439	(*S*)-*tert*-butyl (1-(2-chloro-6-formylphenyl)pyrrolidin-3-yl)methylcarbamate Method 92 
134	(*R*,*Z*)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		438	(*R*)-*tert*-butyl 1-(2-chloro-6-formylphenyl)piperidin-3-ylcarbamate Method 93 

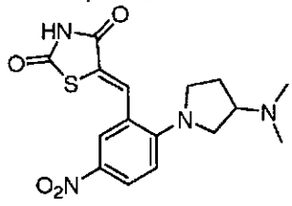
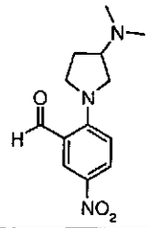
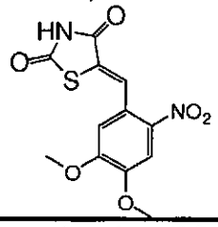
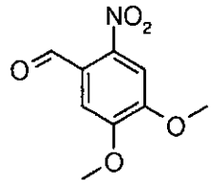
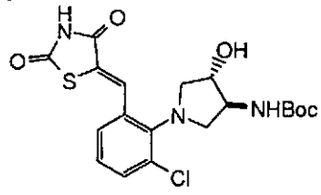
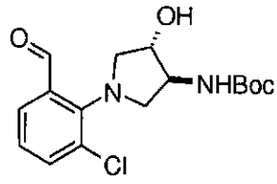
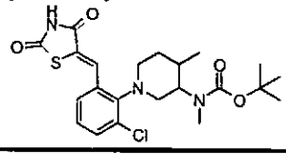
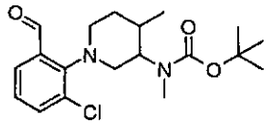
135	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)piperidin-3-ylcarbamate 		434	(*R*)-*tert*-butyl 1-(2-formyl-6-methoxyphenyl)piperidin-3-ylcarbamate Method 94 
136	(*R*,*Z*)-*tert*-butyl 1-(2-bromo-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		484	(*R*)-*tert*-butyl 1-(2-bromo-6-formylphenyl)piperidin-3-ylcarbamate Method 95 
137	(*R*,*Z*)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate 		424	(*R*)-*tert*-butyl 1-(2-chloro-6-formylphenyl)pyrrolidin-3-ylcarbamate Method 96 
138	(*S*,*Z*)-*tert*-butyl 1-(2-bromo-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate 		470	(*S*)-*tert*-butyl 1-(2-bromo-6-formylphenyl)pyrrolidin-3-ylcarbamate Method 97 

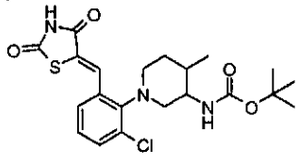
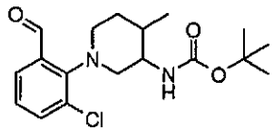
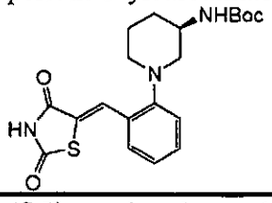
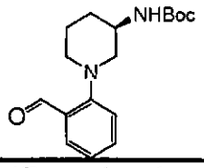
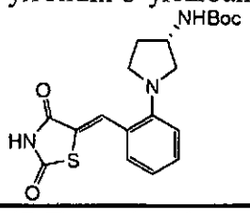
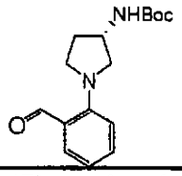
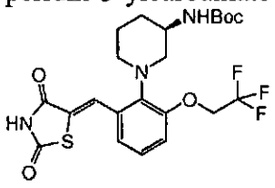
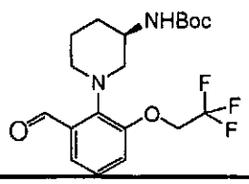
139	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-ethoxyphenyl)piperidin-3-ylcarbamate 		448	(*R*)-*tert*-butyl 1-(2-ethoxy-6-formylphenyl)piperidin-3-ylcarbamate Method 98 
140	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-isobutoxyphenyl)piperidin-3-ylcarbamate 		476	(*R*)-*tert*-butyl 1-(2-formyl-6-isobutoxyphenyl)piperidin-3-ylcarbamate Method 99 
141	(*R*,*Z*)-*tert*-butyl 1-(2-(cyclohexylmethoxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		516	(*R*)-*tert*-butyl 1-(2-(cyclohexylmethoxy)-6-formylphenyl)piperidin-3-ylcarbamate Method 100 
142	(*R*,*Z*)-*tert*-butyl 1-(2-(cyclohexyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		501	(*R*)-*tert*-butyl 1-(2-(cyclohexyloxy)-6-formylphenyl)piperidin-3-ylcarbamate Method 101 

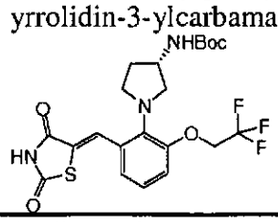
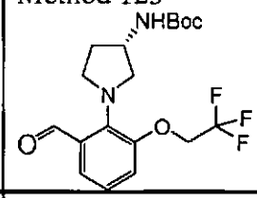
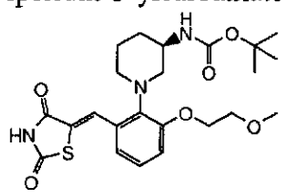
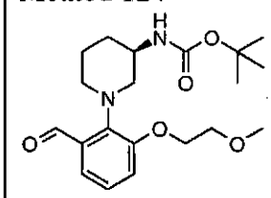
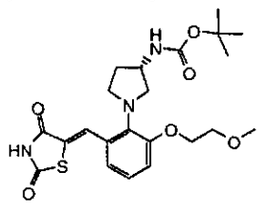
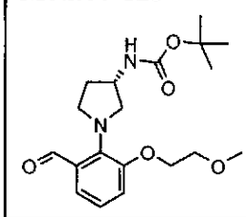
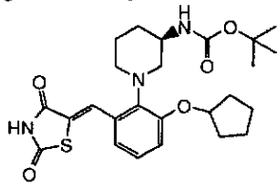
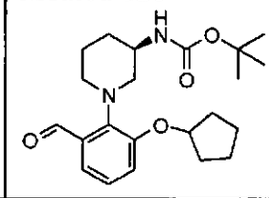
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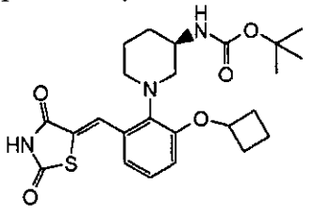
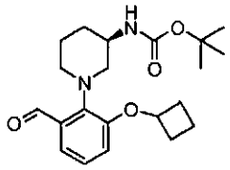
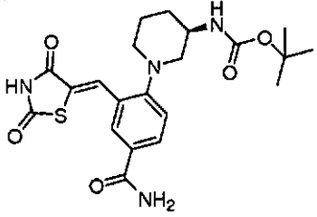
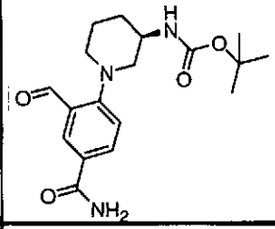
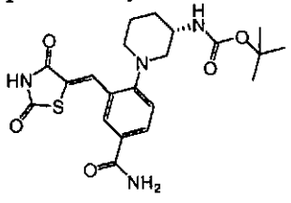
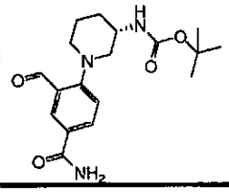
143	(±)-*tert*-butyl-1-(2-chloro-6-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-hydroxypiperidin-3-ylcarbamate 		454	(±)-*tert*-butyl-1-(2-chloro-6-formylphenyl)-4-hydroxypiperidin-3-ylcarbamate Method 102 
144	(Z)-*tert*-butyl 4-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepane-1-carboxylate 	8.66 (brs, 1 H), 8.36 (brs, 1 H), 7.47 (d, 1 H), 7.39 (d, 1 H), 7.22 (t, 1 H), 3.61 (brs, 3 H), 3.52 (brs, 2 H), 3.27 (brs, 3 H), 1.91 (brs, 2 H), 1.52 (s, 9 H)	438	*tert*-butyl 4-(2-chloro-6-formylphenyl)-1,4-diazepane-1-carboxylate Method 103 
145	(*R*,Z)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-isopropoxyphenyl)piperidin-3-ylcarbamate 		462	(*R*)-*tert*-butyl 1-(2-formyl-6-isopropoxyphenyl)piperidin-3-ylcarbamate Method 113 

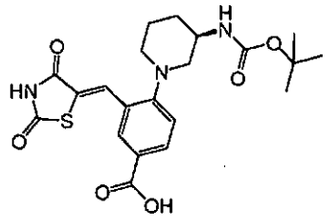
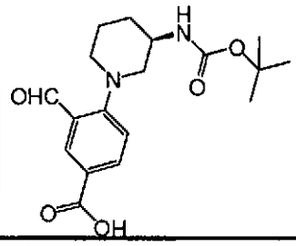
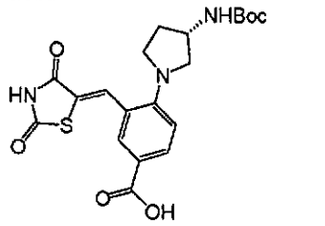
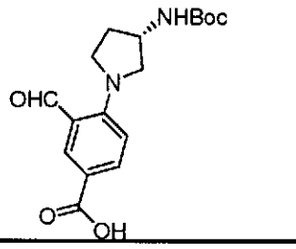
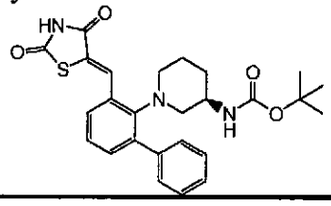
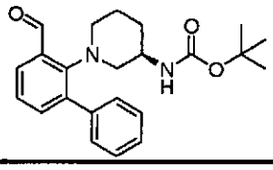
146	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-isopropoxyphenyl)pyrrolidin-3-ylcarbamate 		448	(*S*)-*tert*-butyl 1-(2-formyl-6-isopropoxyphenyl)pyrrolidin-3-ylcarbamate Method 114 
147	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-ethoxyphenyl)pyrrolidin-3-ylcarbamate 		334	(*S*)-*tert*-butyl 1-(2-ethoxy-6-formylphenyl)pyrrolidin-3-ylcarbamate Method 115 
148	5-(2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-5-methoxybenzylidene)thiazolidine-2,4-dione 	12.54 (s, 1 H) 7.83-7.79 (m, 5 H) 7.04 (s, 2 H) 6.86 (s, 1 H) 4.08 (m, 2 H) 3.80-3.75 (m, 5 H) 2.11 (m, 2 H)	438	2-(3-(1,3-dioxoisoindolin-2-yl)propoxy)-5-methoxybenzaldehyde Method 30B 

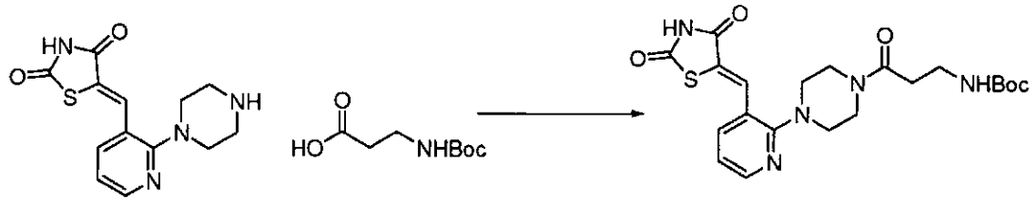
149	5-(2-(3-(dimethylamino)pyrrolidin-1-yl)-5-nitrobenzylidene)thiazolidine-2,4-dione 	8.20 (s, 1 H) 8.07 (d, 1 H) 7.82 (s, 1 H) 6.96 (d, 1H) 3.58-3.51 (m, 3H) 3.36 (m, 1 H) 3.04 (m, 1 H) 2.51 (s, 6 H), 2.40 (m, 1 H), 1.86 (m, 1 H)	363	2-(3-(dimethylamino)pyrrolidin-1-yl)-5-nitrobenzaldehyde Method 116 
150	(Z)-5-(4,5-dimethoxy-2-nitrobenzylidene)thiazolidine-2,4-dione 	8.32 (s, 1 H) 8.25 (brs, 1 H) 7.79 (s, 1 H) 7.02 (s, 1 H) 4.03 (s, 6 H)	309	4,5-dimethoxy-2-nitrobenzaldehyde 
151	*tert*-butyl (3*S*,4*S*)-1-(2-chloro-6-((Z)-(2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-hydroxypyrrolidin-3-ylcarbamate 	8.30 (s, 1 H) 7.49 (d, 1 H) 7.42 (d, 1 H) 7.28-7.20 (m, 1 H) 5.01 (d, 1 H) 4.39 (brs, 1 H) 4.27 (brs, 1 H) 4.05 (s, 1 H) 3.83 (dd, 1 H) 3.69 (dd, 1 H) 3.27 (brs, 1 H) 3.19 (dd, 1 H), 1.50 (s, 9 H)	439	*tert*-butyl (3*S*,4*S*)-1-(2-chloro-6-formylphenyl)-4-hydroxypyrrolidin-3-ylcarbamate Method 117 
152	(Z)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-methylpiperidin-3-yl(methyl)carbamate 		465	*tert*-butyl 1-(2-chloro-6-formylphenyl)-4-methylpiperidin-3-yl(methyl)carbamate Method 118 

153	(*Z*)-*tert*-butyl 1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-4-methylpiperidin-3-ylcarbamate 		451	*tert*-butyl 1-(2-chloro-6-formylphenyl)-4-methylpiperidin-3-ylcarbamate Method 119 
154	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		404	(*R*)-*tert*-butyl 1-(2-formylphenyl)piperidin-3-ylcarbamate Method 120 
155	(*S*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)pyrrolidin-3-ylcarbamate 		390	(*S*)-*tert*-butyl 1-(2-formylphenyl)pyrrolidin-3-ylcarbamate Method 121 
156	(*R*,*Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2,2,2-trifluoroethoxy)phenyl)piperidin-3-ylcarbamate 		502	(*R*)-*tert*-butyl 1-(2-formyl-6-(2,2,2-trifluoroethoxy)phenyl)piperidin-3-ylcarbamate Method 122 

157	(*S,Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2,2,2-trifluoroethoxy)phenyl)pyrrolidin-3-ylcarbamate 		488	(*S*)-*tert*-butyl 1-(2-formyl-6-(2,2,2-trifluoroethoxy)phenyl)pyrrolidin-3-ylcarbamate Method 123 
158	(*R,Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)phenyl)piperidin-3-ylcarbamate 		478	(*R*)-*tert*-butyl 1-(2-formyl-6-(2-methoxyethoxy)phenyl)piperidin-3-ylcarbamate Method 124 
159	(*S,Z*)-*tert*-butyl 1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-(2-methoxyethoxy)phenyl)pyrrolidin-3-ylcarbamate 		464	(*S*)-*tert*-butyl 1-(2-formyl-6-(2-methoxyethoxy)phenyl)pyrrolidin-3-ylcarbamate Method 125 
160	(*R,Z*)-*tert*-butyl 1-(2-(cyclopentyloxy)-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		488	(*R*)-*tert*-butyl 1-(2-(cyclopentyloxy)-6-formylphenyl)piperidin-3-ylcarbamate Method 126 

161	(*R*,*Z*)-*tert*-butyl 1-(2-cyclobutoxy-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		474	(*R*)-*tert*-butyl 1-(2-cyclobutoxy-6-formylphenyl)piperidin-3-ylcarbamate Method 127 
162	(*R*,*Z*)-*tert*-butyl 1-(4-carbamoyl-2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		447	(*R*)-*tert*-butyl 1-(4-carbamoyl-2-formylphenyl)piperidin-3-ylcarbamate Method 128 
163	(*S*,*Z*)-*tert*-butyl 1-(4-carbamoyl-2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylcarbamate 		447	(*S*)-*tert*-butyl 1-(4-carbamoyl-2-formylphenyl)piperidin-3-ylcarbamate Method 129 

164	(*R*,*Z*)-4-(3-(*tert*-butoxycarbonylamino)piperidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid 		447	(*R*)-4-(3-(*tert*-butoxycarbonylamino)piperidin-1-yl)-3-formylbenzoic acid Method 130 
165	(*S*,*Z*)-4-(3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl)-3-((2,4-dioxothiazolidin-5-ylidene)methyl)benzoic acid 		433	(*S*)-4-(3-(*tert*-butoxycarbonylamino)pyrrolidin-1-yl)-3-formylbenzoic acid Method 131 
166	(*R*,*Z*)-*tert*-butyl 1-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)biphenyl-2-yl)piperidin-3-ylcarbamate 		480	(*R*)-*tert*-butyl 1-(3-formylbiphenyl-2-yl)piperidin-3-ylcarbamate Method 201 



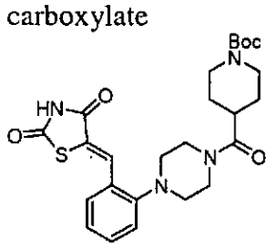
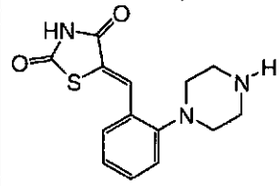
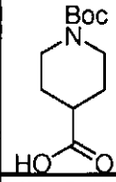
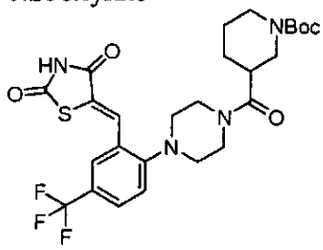
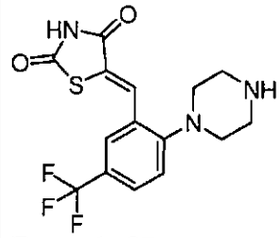
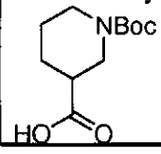
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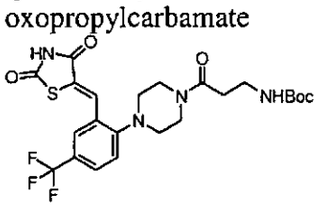
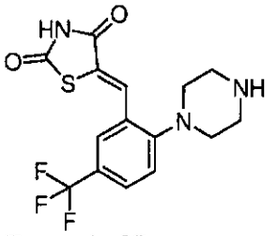
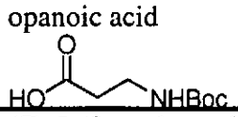
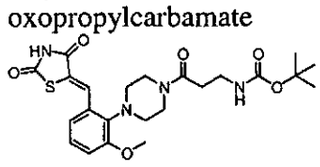
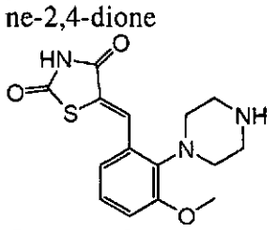
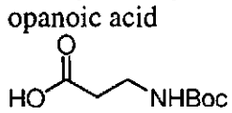
(Z)-*tert*-butyl 3-(4-(3-((2,4-dioxothiazolidin-5-ylidene)methyl)pyridin-2-yl)piperazin-1-yl)-3-oxopropylcarbamate:

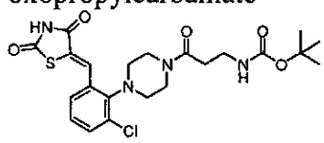
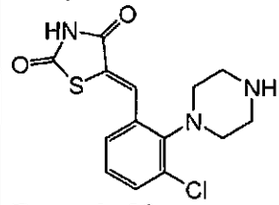
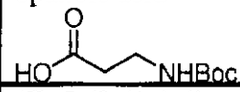
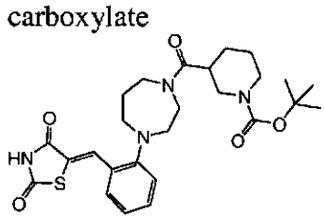
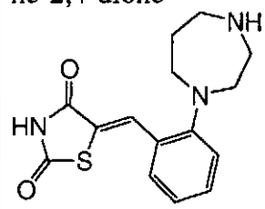
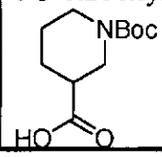
A 50 mL vial was charged with a magnetic spin bar, (Z)-5-((2-(piperazin-1-yl)pyridin-3-yl)methylene)thiazolidine-2,4-dione hydrochloride (Example 89) (0.125 g, 0.38 mmol), 3-(*tert*-butoxycarbonylamino)propanoic acid (0.109 g, 0.57 mmol), DMF (1.912 ml), and diisopropylethylamine (0.334 ml, 1.91 mmol). With stirring, HATU (0.291 g, 0.76 mmol) was added and the reaction was warmed to 50 °C for 3 h. The reaction was then diluted with water and extracted with ethyl acetate (3 X 50 mL). The combined organic extract was dried with $MgSO_4$, filtered through a bed of Celite, and conc. *in vacuo* to yield the product which was purified via silica gel chromatography (80 g) using ethyl acetate/hexanes (1:1) as eluent to provide the title compound as an off white solid. (0.080 g, 45.3 %); *m/z* 462.

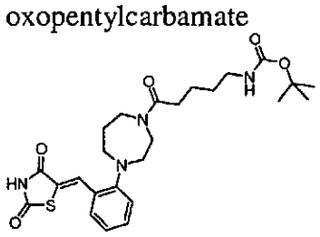
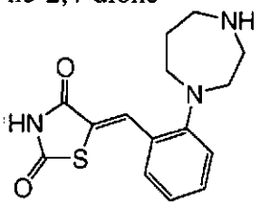
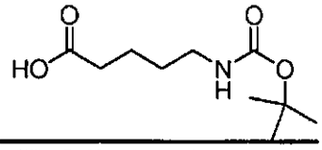
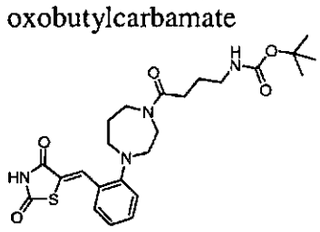
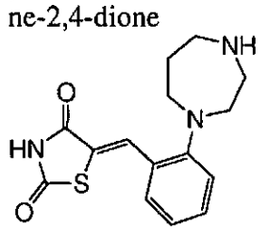
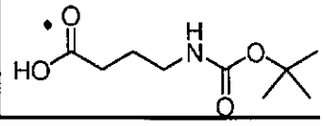
The following intermediates were prepared by the procedure of Method 38, using the appropriate starting materials.

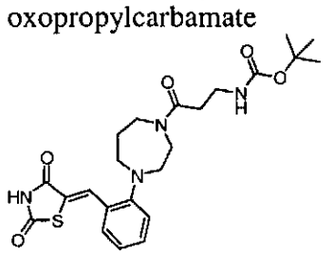
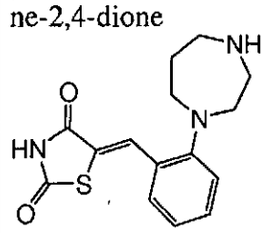
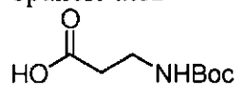
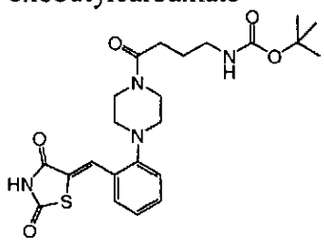
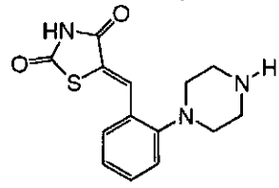
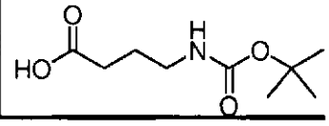
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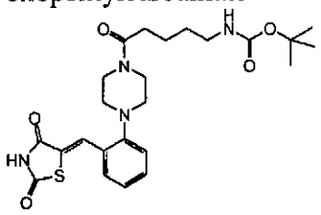
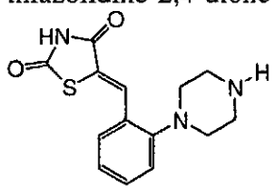
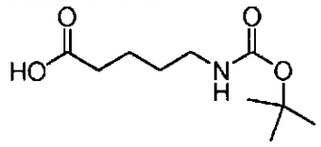
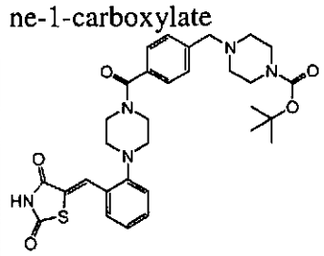
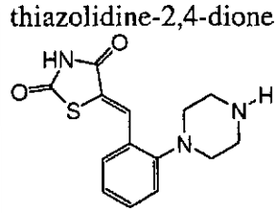
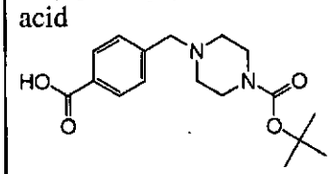
Method	Compound	^{1}H NMR	m/z	SM
39	(Z)-*tert*-butyl 4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)piperidine-1-carboxylate 		502	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid 
40	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)piperazine-1-carbonyl)piperidine-1-carboxylate 		560	(Z)-5-(2-(piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione  Example 87 and 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid 

41	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4-(trifluoromethyl)phenyl)piperazin-1-yl)-3-oxopropylcarbamate 		530	(Z)-5-(2-(piperazin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione  Example 87 and 3-[(*tert*-butoxycarbonyl)amino]propanoic acid 
42	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-6-methoxyphenyl)piperazin-1-yl)-3-oxopropylcarbamate 		492	(Z)-5-(3-methoxy-2-(piperazin-1-yl)benzylidene)thiazolidine-2,4-dione  Example 97 and 3-[(*tert*-butoxycarbonyl)amino]propanoic acid 

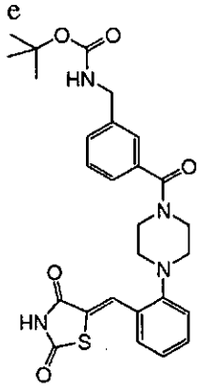
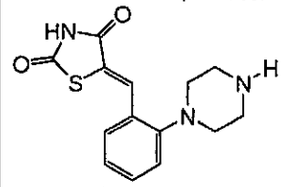
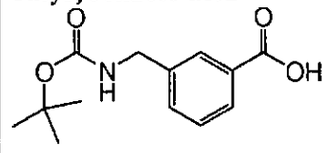
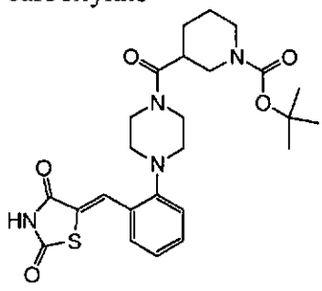
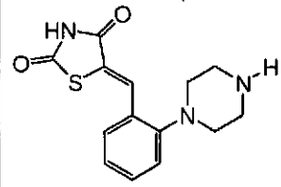
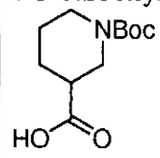
43	(Z)-*tert*-butyl 3-(4-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)-3-oxopropylcarbamate 		496	(Z)-5-(3-chloro-2-(piperazin-1-yl)benzylidene)thiazolidine-2,4-dione  Example 98 and 3-[(*tert*-butoxycarbonyl)amino]propanoic acid 
50	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepane-1-carbonyl)piperidine-1-carboxylate 		516	(Z)-5-(2-(1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione  Example 106 and 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid 

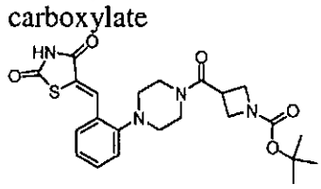
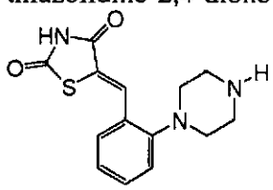
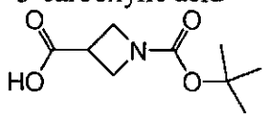
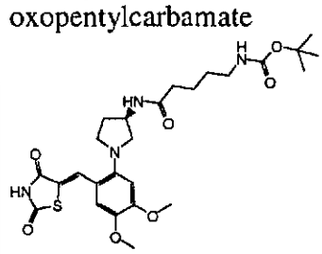
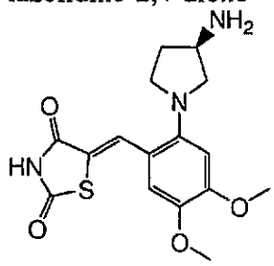
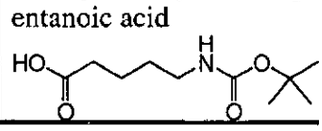
51	(Z)-*tert*-butyl 5-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepan-1-yl)-5-oxopentylcarbamate 		504	(Z)-5-(2-(1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione  Example 106 and 5-[(*tert*-butoxycarbonyl)amino]pentanoic acid 
52	(Z)-*tert*-butyl 4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepan-1-yl)-4-oxobutylcarbamate 		490	(Z)-5-(2-(1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione  Example 106 and 4-[(*tert*-butoxycarbonyl)amino]butanoic acid 

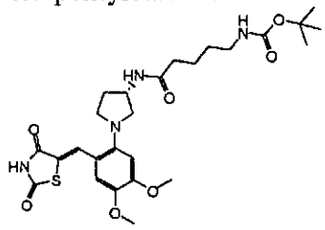
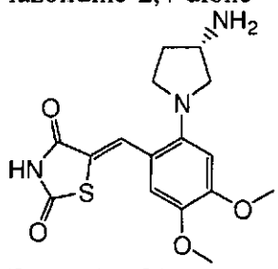
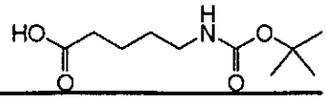
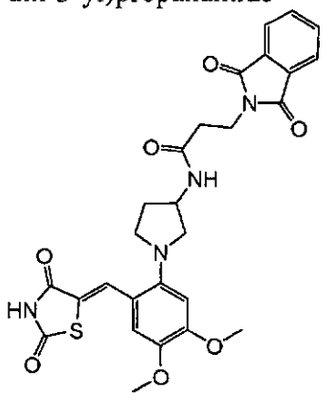
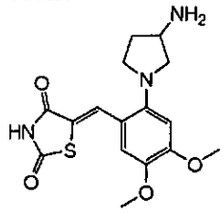
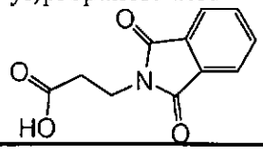
53	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)-1,4-diazepan-1-yl)-3-oxopropylcarbamate 		475	(Z)-5-(2-(1,4-diazepan-1-yl)benzylidene)thiazolidine-2,4-dione  Example 106 and 3-[(*tert*-butoxycarbonyl)amino]propanoic acid 
55	(Z)-*tert*-butyl 4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)-4-oxobutylcarbamate 		476	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and 4-[(*tert*-butoxycarbonyl)amino]butanoic acid 

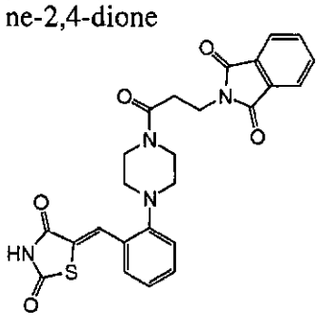
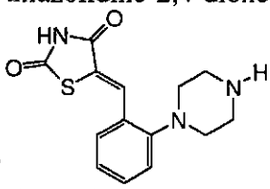
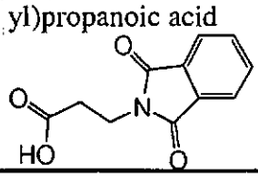
56	(Z)-*tert*-butyl 5-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)-5-oxopentylcarbamate 		490	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and nd 5-[(*tert*-butoxycarbonyl)amino]pentanoic acid 
57	(Z)-*tert*-butyl 4-(4-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)benzyl)piperazine-1-carboxylate 		593	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and 4-{[4-(*tert*-butoxycarbonyl)piperazin-1-yl]methyl}benzoic acid 

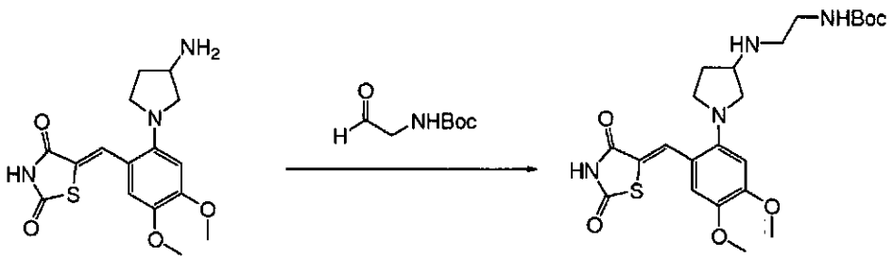
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58	(Z)-*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)benzylcarbamate 		524	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and 3-{[(*tert*-butoxycarbonyl)amino]methyl}benzoic acid 
63	*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)piperidine-1-carboxylate 		501	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 And 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid 

64	*tert*-butyl 3-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazine-1-carbonyl)azetidine-1-carboxylate 		473	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 And 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid 
66	(*R*,*Z*)-*tert*-butyl 5-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)-5-oxopentylcarbamate 		550	(*R*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione  Example 100 And 5-[(*tert*-butoxycarbonyl)amino]pentanoic acid 

67	(*S,Z*)-*tert*-butyl 5-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)-5-oxopentylcarbamate 		550	(*S,Z*)-5-(2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione  Example 101 And 5-[(*tert*-butoxycarbonyl)amino]pentanoic acid 
75	(*Z*)-3-(1,3-dioxoisoindolin-2-yl)-N-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-yl)propanamide 		552	(5*Z*)-5-[2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene]-1,3-thiazolidine-2,4-dione  Example 118 and 3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid 

76	5Z)-(2-(4-(3-(1,3-dioxoisoindolin-2-yl)propanoyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione 			(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and 3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoic acid 

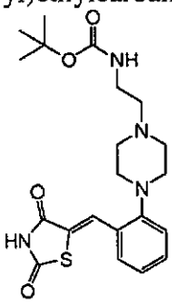
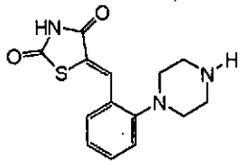
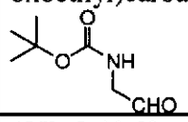
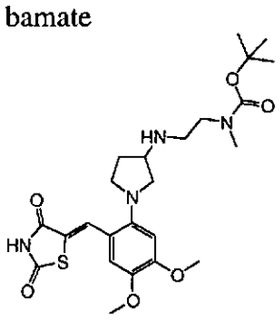
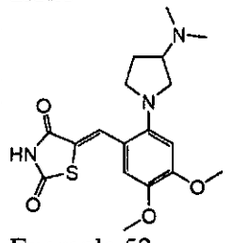
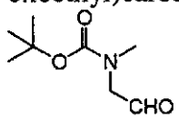


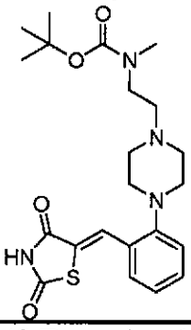
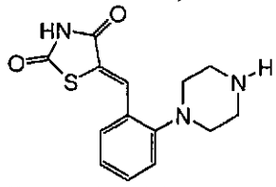
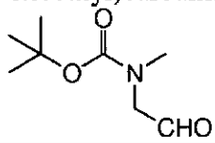
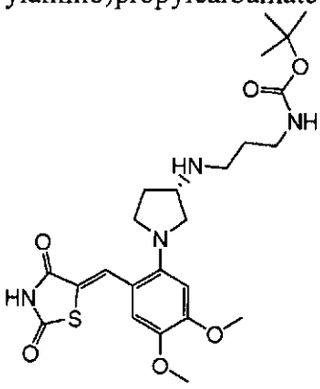
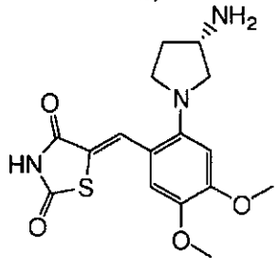
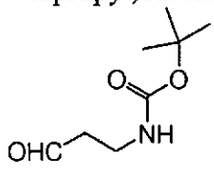
Method 59:

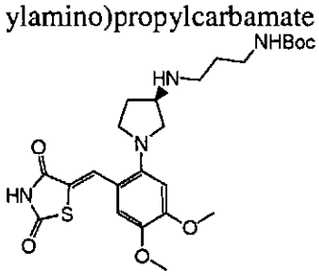
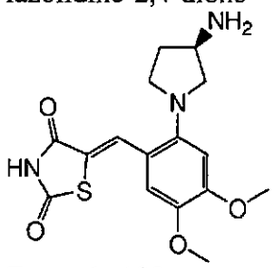
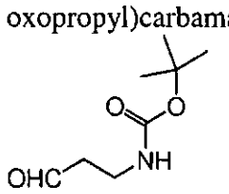
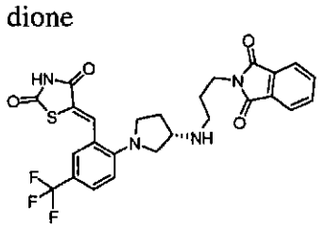
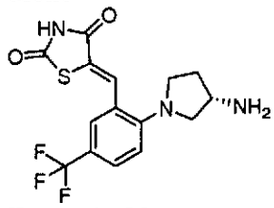
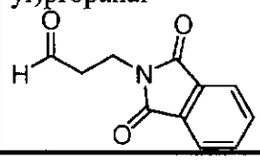
(Z)-*tert*-butyl 2-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)ethylcarbamate:

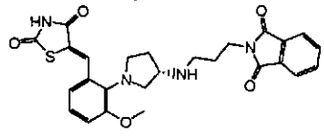
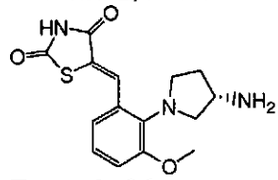
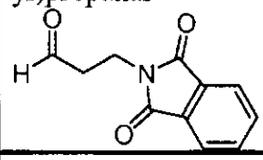
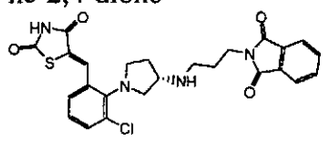
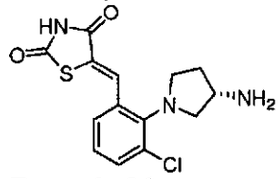
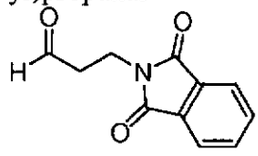
A mixture of (5Z)-5-{2-[3-(dimethylamino)pyrrolidin-1-yl]-4,5-dimethoxybenzylidene}-1,3-thiazolidine-2,4-dione (Example 52)(120 mg, 0.31 mmol) and *tert*-butyl 2-oxoethylcarbamate (198 mg, 1.24 mmol) in CH_2Cl_2 (20 mL) were heated to reflux for 15 min followed by the addition of sodium triacetoxyhydroborate (65.9 mg, 0.31 mmol). The reaction mixture was refluxed overnight before being allowed to cool to ambient temperature. Water (~ 0.5 mL) was added and the mixture was allowed to stir for 15 min before being loaded onto a silica gel column which was eluted with ethyl acetate/hexane (10:1) to yield the title compound as an orange solid as (60.0 mg, 39.2 %); *m/z* 493.

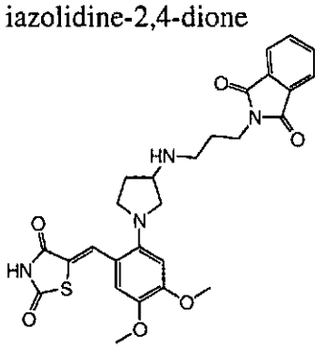
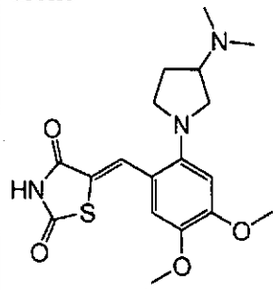
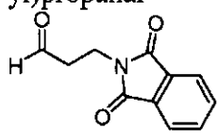
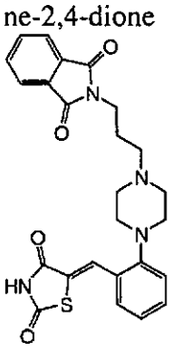
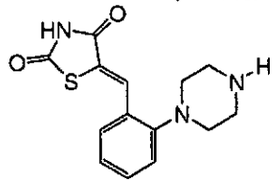
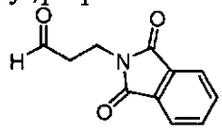
The following intermediates were prepared by the procedure of Method 59, using the appropriate starting materials.

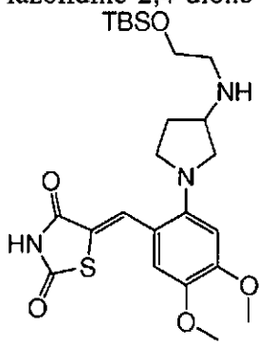
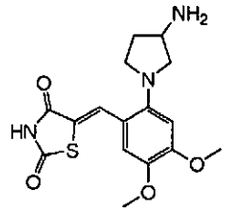
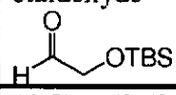
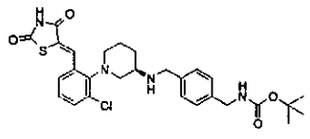
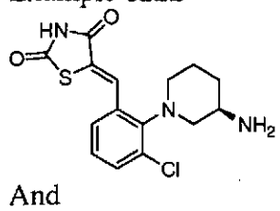
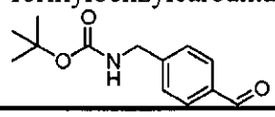
Method	Compound	^{1}H NMR	m/z	SM
60	(Z)-*tert*-butyl 2-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)ethylcarbamate 		433	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and *tert*-butyl (2-oxoethyl)carbamate 
61	(Z)-*tert*-butyl 2-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)ethyl(methyl)carbamate 		507	(5Z)-5-{2-[3-(dimethylamino)pyrrolidin-1-yl]-4,5-dimethoxybenzylidene}-1,3-thiazolidine-2,4-dione  Example 52 and *tert*-butyl methyl(2-oxoethyl)carbamate 

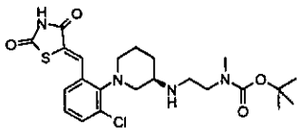
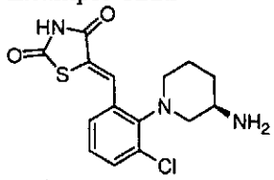
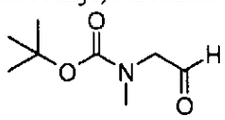
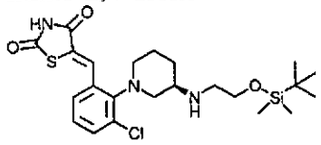
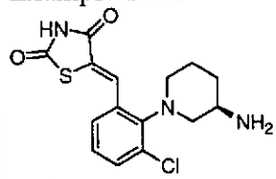
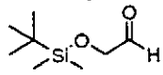
62	(*Z*)-*tert*-butyl 2-(4-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperazin-1-yl)ethyl(methyl)carbamate Method 62 		448	(5*Z*)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and *tert*-butyl methyl(2-oxoethyl)carbamate 
68	(*S*,*Z*)-*tert*-butyl 3-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)propylcarbamate 		507	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione  Example 101 and *tert*-butyl (3-oxopropyl)carbamate 

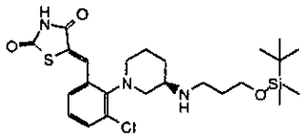
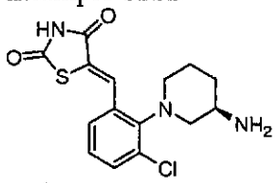
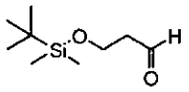
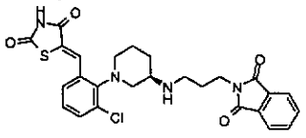
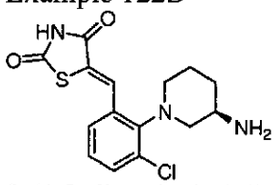
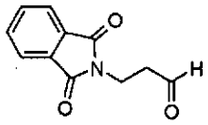
69	(*R*,*Z*)-*tert*-butyl 3-(1-(2-((2,4-dioxothiazolidin-5-ylidene)methyl)-4,5-dimethoxyphenyl)pyrrolidin-3-ylamino)propylcarbamate 		507	(*R*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione  Example 100 and *tert*-butyl (3-oxopropyl)carbamate 
70	(*S*,*Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione 		545	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-5-(trifluoromethyl)benzylidene)thiazolidine-2,4-dione  Example 88 and 3-(1,3-dioxoisoindolin-2-yl)propanal 

71	(*S*,*Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)-3-methoxybenzylidene)thiazolidine-2,4-dione 		508	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-methoxybenzylidene)thiazolidine-2,4-dione  Example 96 and 3-(1,3-dioxoisoindolin-2-yl)propanal 
72	(*S*,*Z*)-5-(3-chloro-2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)benzylidene)thiazolidine-2,4-dione 		512	(*S*,*Z*)-5-(2-(3-aminopyrrolidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione  Example 86 and 3-(1,3-dioxoisoindolin-2-yl)propanal 

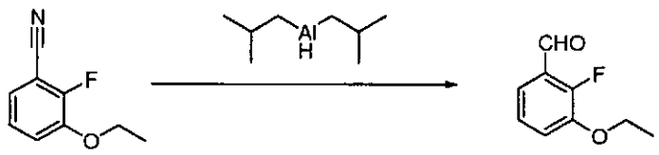
73	(Z)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione 		507	(5Z)-5-{2-[3-(dimethylamino)pyrrolidin-1-yl]-4,5-dimethoxybenzylidene}-1,3-thiazolidine-2,4-dione  Example 52 and 3-(1,3-dioxoisoindolin-2-yl)propanal 
74	(Z)-5-(2-(4-(3-(1,3-dioxoisoindolin-2-yl)propyl)piperazin-1-yl)benzylidene)thiazolidine-2,4-dione 		477	(5Z)-5-(2-piperazin-1-ylbenzylidene)-1,3-thiazolidine-2,4-dione  Example 115 and 3-(1,3-dioxoisoindolin-2-yl)propanal 

77	(*Z*)-5-(2-(3-(2-(*tert*-butyldimethylsilyloxy)ethylamino)pyrrolidin-1-yl)-4,5-dimethoxybenzylidene)thiazolidine-2,4-dione 		509	(5*Z*)-5-[2-(3-aminopyrrolidin-1-yl)-4,5-dimethoxybenzylidene]-1,3-thiazolidine-2,4-dione  Example 118 and 2-(*tert*-butyldimethylsilyloxy)acetaldehyde 
167	(*R*,*Z*)-*tert*-butyl 4-((1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylamino)methyl)benzylcarbamate 		557	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride Example 122D  And *tert*-butyl 4-formylbenzylcarbamate 

168	(*R*,*Z*)-*tert*-butyl 2-(1-(2-chloro-6-((2,4-dioxothiazolidin-5-ylidene)methyl)phenyl)piperidin-3-ylamino)ethyl(methyl)carbamate 		496	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride Example 122D  and *tert*-butyl methyl (2-oxoethyl)carbamate 
169	(*R*,*Z*)-5-(2-(3-(2-(*tert*-butyldimethylsilyloxy)ethylamino)piperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione 		496	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride Example 122D  and 2-(*tert*-butyldimethylsilyloxy)acetaldehyde 

170	(*R*,*Z*)-5-(2-(3-(3-(*tert*-butyldimethylsilyloxy)propylamino)piperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione 		510	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride Example 122D  and 3-(*tert*-butyldimethylsilyloxy)propanal 
171	(*R*,*Z*)-5-(3-chloro-2-(3-(3-(1,3-dioxoisoindolin-2-yl)propylamino)piperidin-1-yl)benzylidene)thiazolidine-2,4-dione 		525	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-yl)-3-chlorobenzylidene)thiazolidine-2,4-dione hydrochloride Example 122D  3-(1,3-dioxoisoindolin-2-yl)propanal 

Method 172

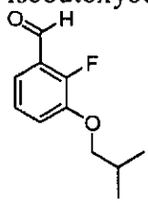
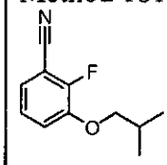
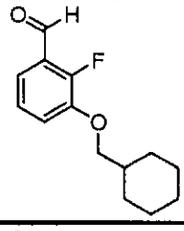
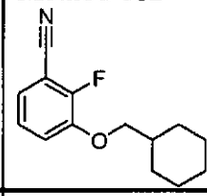
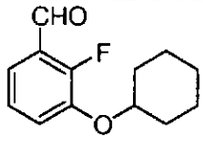
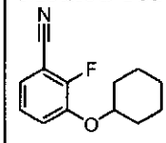
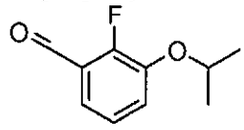
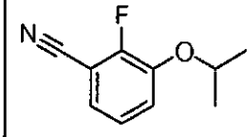
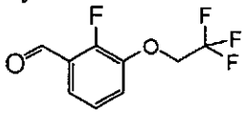
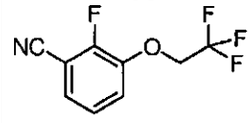


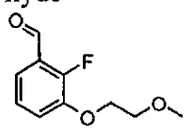
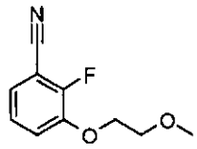
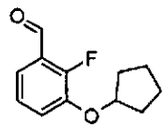
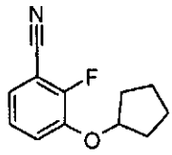
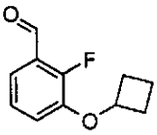
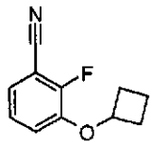
3-ethoxy-2-fluorobenzaldehyde:

A 200 mL round bottom flask was charged with a magnetic stir bar, 3-ethoxy-2-fluorobenzonitrile (1.000 g, 6.05 mmol), and anhydrous toluene (12.92 ml). The sol'n

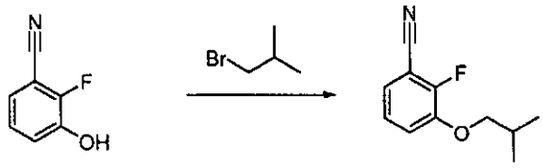
was placed under argon and cooled to 0 °C with an ice bath. DIBAL-H (7.27 ml, 7.27 mmol) (1M in PhMe) was then added drop wise via syringe and the reaction was allowed to stir to rt overnight. To this mixture was added 10 % HCl until the sol'n reached a pH of ~ 2. The resulting mixture was then left to stir for 0.5 h. and was then poured into a separatory funnel and extracted with ethyl acetate (2 x 200 mL). The combined organic extract was dried with $MgSO_4$, filtered, and conc. *in vacuo* to yield the crude product which was purified via silica gel chromatography (80 g) using ethyl acetate/hexanes (1:4) as eluent to provide pure 3-ethoxy-2-fluorobenzaldehyde (0.810 g, 80 %). *m/z* 196.

The following intermediates were prepared by the procedure of Method 172, using the appropriate starting materials.

173	2-fluoro-3-isobutoxybenzaldehyde 		197	2-fluoro-3-isobutoxybenzonitrile Method 181 
174	3-(cyclohexylmethoxy)-2-fluorobenzaldehyde 		237	3-(cyclohexylmethoxy)-2-fluorobenzonitrile Method 182 
175	3-(cyclohexyloxy)-2-fluorobenzaldehyde 		223	3-(cyclohexyloxy)-2-fluorobenzonitrile Method 183 
176	2-fluoro-3-isopropoxybenzaldehyde 		183	2-fluoro-3-isopropoxybenzonitrile Method 184 
177	2-fluoro-3-(2,2,2-trifluoroethoxy)benzaldehyde 		223	2-fluoro-3-(2,2,2-trifluoroethoxy)benzonitrile Method 200 

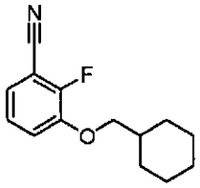
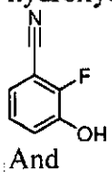
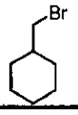
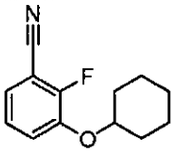
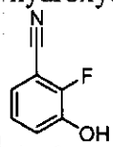
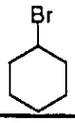
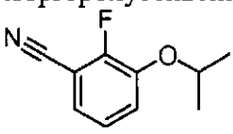
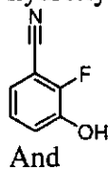
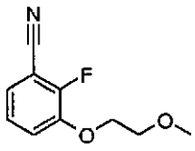
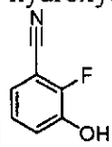
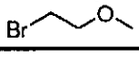
178	2-fluoro-3-(2-methoxyethoxy)benzaldehyde 	10.32 (s, 1 H) 7.56-7.35 (m, 2 H) 7.13-6.96 (m, 1 H) 4.33-4.22 (m, 2 H) 3.84-3.77 (m, 2 H) 3.42 (s, 3 H)	199	2-fluoro-3-(2-methoxyethoxy)benzonitrile Method 185 
179	3-(cyclopentyloxy)-2-fluorobenzaldehyde 		195	3-(cyclopentyloxy)-2-fluorobenzonitrile Method 187 
180	3-cyclobutoxy-2-fluorobenzaldehyde 	10.31 (s, 1 H) 7.41-7.36 (m, 2 H) 7.05-7.03 (m, 1 H) 4.94-4.85 (m, 1 H) 2.01-1.83 (m, 8 H)	209	3-cyclobutoxy-2-fluorobenzonitrile Method 186 

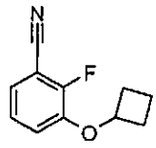
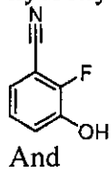
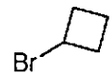
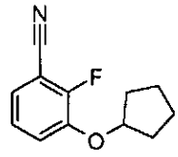
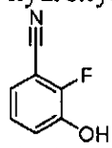
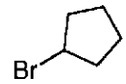
Method 181



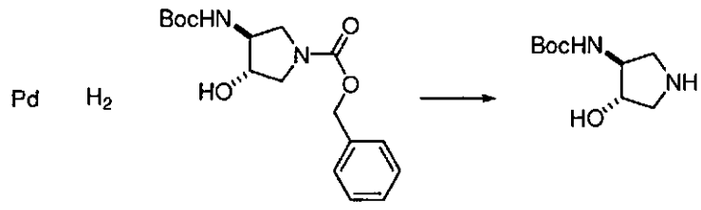
A 100 mL round bottom flask was charged with a magnetic stir bar, 2-fluoro-3-hydroxybenzonitrile (0.500 g, 3.65 mmol), MeCN (13.89 ml), 1-bromo-2-methylpropane (0.699 ml, 7.29 mmol), and K_2CO_3 (1.008 g, 7.29 mmol). The mixture was then placed in an oil bath and heated to 60 °C with stirring overnight. This mixture was then cooled to rt, filtered through a bed of Celite, and conc. *In vacuo*. The crude material was purified via silica gel chromatography (40 g) using ethyl acetate/hexanes (1:4) as eluent to afford pure 2-fluoro-3-isobutoxybenzonitrile (0.610 g, 87 %) as a colorless oil. *M/z* 194.

The following intermediates were prepared by the procedure of Method 181, using the appropriate starting materials.

182	3-(cyclohexylmethoxy)-2-fluorobenzonitrile 		234	2-fluoro-3-hydroxybenzonitrile  And (bromomethyl)cyclohexane 
183	3-(cyclohexyloxy)-2-fluorobenzonitrile 		220	2-fluoro-3-hydroxybenzonitrile  And Bromocyclohexane 
184	2-fluoro-3-isopropoxybenzonitrile 		179	2-fluoro-3-hydroxybenzonitrile  And 2-iodopropane 
185	2-fluoro-3-(2-methoxyethoxy)benzonitrile 		196	2-fluoro-3-hydroxybenzonitrile  And 1-bromo-2-methoxyethane 

186	3-cyclobutoxy-2-fluorobenzonitrile 		192	2-fluoro-3-hydroxybenzonitrile  And Bromocyclobutane 
187	3-(cyclopentyloxy)-2-fluorobenzonitrile 			2-fluoro-3-hydroxybenzonitrile  And bromocyclopentane 

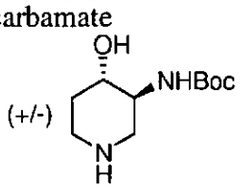
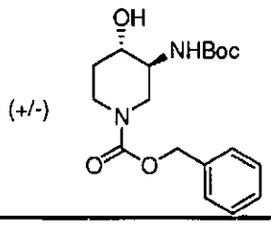
Method 188



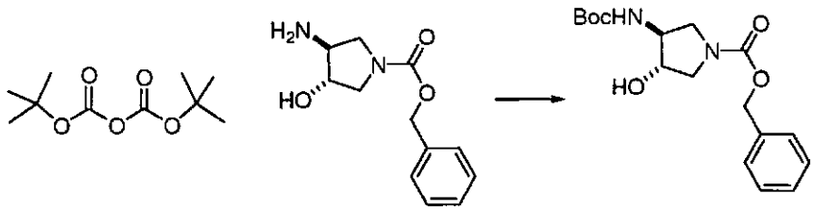
(±)-*tert*-butyl-4-hydroxypyrrolidin-3-ylcarbamate

A racemic mixture of *trans*-benzyl 3-(*tert*-butoxycarbonylamino)-4-hydroxypyrrolidine-1-carboxylate (3.36 g, 9.99 mmol) (Method 190) in MeOH (40 mL) was degassed, then 10 wt % Pd/C (3.19 g, 3.00 mmol) was added. The mixture was degassed, charged with H_2, and stirred overnight. The mixture was filtered through a bed of Celite, washed with methanol, the filtrate was dried over anhydrous Na_2SO_4, filtered and conc. *in vacuo* to yield a white solid as racemic *tert*-butyl-4-hydroxypyrrolidin-3-ylcarbamate (2.020 g, 100 %). ^{1}H NMR (400 MHz, MeOD) δ ppm 4.13 (dt, 1 H), 3.89-3.75 (m, 1 H), 3.35 (brs, 1 H), 3.14 (dd, 1 H), 2.93-2.73 (m, 2 H), 1.46 (s, 10 H); *m/z* 203.

The following intermediates were prepared by the procedure of Method 188, using the appropriate starting materials.

Method	Compound	^{1}H NMR	m/z	SM
189	(±)-*tert*-butyl-4-hydroxypiperidin-3-ylcarbamate 		216	(±)-benzyl 3-(*tert*-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate Method 191 

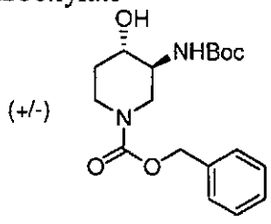
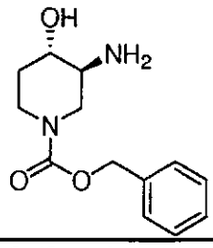
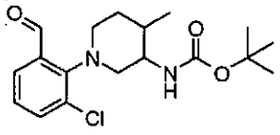
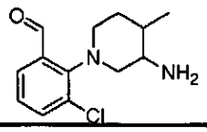
Method 190



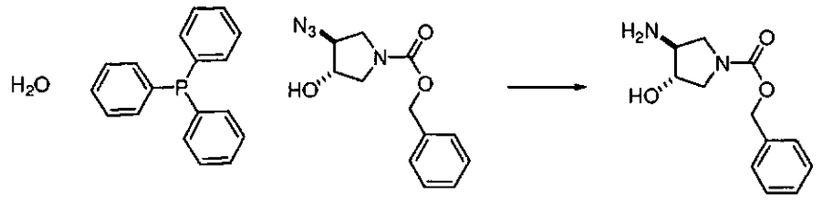
(±)-benzyl 3-(*tert*-butoxycarbonylamino)-4-hydroxypyrrolidine-1-carboxylate

To a mixture of racemic *trans*-benzyl 3-amino-4-hydroxypyrrolidine-1-carboxylate (2.67 g, 11.30 mmol)(Method 193) and di-*tert*-butyl dicarbonate (3.70 g, 16.95 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (4.73 mL, 33.90 mmol) at 0 °C. The mixture was then stirred at rt for 48 h. The reaction mixture was then conc. *in vacuo* giving a residue which was purified via silica gel chromatography (40% to 90% ethyl acetate/hexane) to yield a white solid as (±)-benzyl 3-(*tert*-butoxycarbonylamino)-4-hydroxypyrrolidine-1-carboxylate (3.36 g, 88 %). ^{1}H NMR (400 MHz, Dichloromethane-d2) δ ppm 7.48-7.32 (m, 5 H), 5.21-5.00 (m, 2 H), 4.78 (brs, 1 H), 4.29-4.18 (m, 1 H), 3.84 (dd, 1 H), 3.74 (d, 1 H), 3.41-3.12 (m, 2 H), 1.49-1.33 (m, 9 H); *m/z* 337

The following starting materials were prepared by the procedure of Method 190 using the appropriate starting materials.

Method	Compound	^{1}H NMR	m/z	SM
191	(±)-benzyl 3-(*tert*-butoxycarbonylamino)-4-hydroxypiperidine-1-carboxylate 		350	(±)-benzyl 3-amino-4-hydroxypiperidine-1-carboxylate Method 194 
192	*tert*-butyl 1-(2-chloro-6-formylphenyl)-4-methylpiperidin-3-ylcarbamate 		352	2-(3-amino-4-methylpiperidin-1-yl)-3-chlorobenzaldehyde Method 199 

Method 193

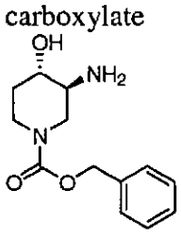
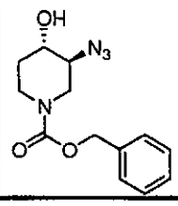


(±)-benzyl 3-amino-4-hydroxypyrrolidine-1-carboxylate:

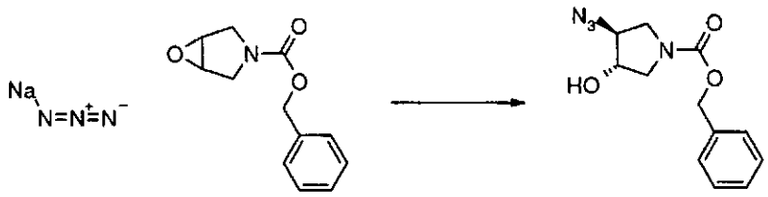
A mixture of racemic *trans*-benzyl 3-azido-4-hydroxypyrrolidine-1-carboxylate (2.96 g, 11.29 mmol) (Method 195) and triphenylphosphine (3.11 g, 11.85 mmol) in THF (25 mL) was stirred at rt for 7 h. Water (2 mL, 111 mmol) was then added and the mixture then stirred at 50 °C overnight. The mixture was then concentrated under reduced pressure, and the residue was purified via silica gel chromatography (100% DCM to 37:3:60/methanol:Et_3N:DCM) to yield the title compound (2.96 g, 11.29 mmol) as an oil.

^{1}H NMR (400 MHz, Dichloromethane-d2) δ ppm 7.38-7.19 (m, 5 H), 5.02 (s, 2 H), 3.89 (brs, 1 H), 3.62 (dd, 2 H), 3.29-3.15 (m, 2 H), 3.12-3.01 (m, 1 H); *m/z* 236.

The following starting materials were prepared by the procedure of Method 193 using the appropriate starting materials.

Method	Compound	^{1}H NMR	m/z	SM
194	(±)-benzyl 3-amino-4-hydroxypiperidine-1-carboxylate 		250	(±)-benzyl 3-azido-4-hydroxypiperidine-1-carboxylate Method 196 

Method 195

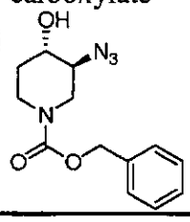
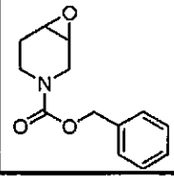


(±)-benzyl 3-azido-4-hydroxypyrrolidine-1-carboxylate

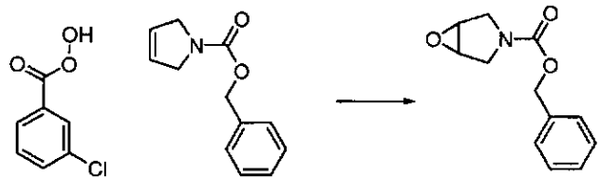
To a stirred mixture of benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (5.2 g, 23.72 mmol) (Method 197) in DMF (30 mL) was added sodium azide (2.313 g, 35.58 mmol) in a mixture of acetone (20.00 mL) and water (10.00 mL). The resulting mixture was stirred at 80 °C for 24 h. The mixture was then diluted with water and ether, separated, and the organic layer was washed with brine, dried and conc. invacuo. The resulting material was purified via silica gel chromatography (eluted with 15% to 35% ethyl acetate/hexane), yielding the title compound as a yellow solid (4.10 g, 65.9 %). ^{1}H NMR (400 MHz, dichloromethane-d2) δ ppm 7.50-7.25 (m, 5 H), 5.43-5.25 (m, 2 H),

4.31 (brs, 1 H), 4.00 (brs, 1 H), 3.77 (dd, 1 H), 3.69 (dd, 1 H), 3.53 (d, 1 H), 3.44 (dd, 1 H), 2.17 (brs, 1 H); *m/z* 263.

The following starting materials were prepared by the procedure of Method 195 using the appropriate starting materials.

Method	Compound	^{1}H NMR	m/z	SM
196	(±)-benzyl 3-azido-4-hydroxypiperidine-1-carboxylate 		276	benzyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate Method 198 

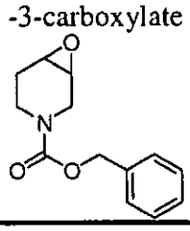
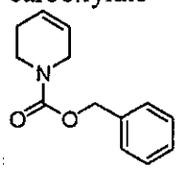
Method 197



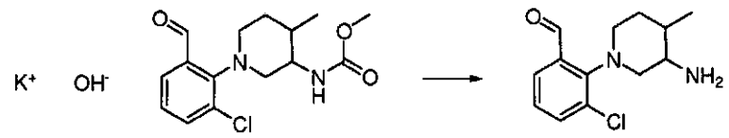
benzyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate

To a stirred mixture of benzyl 2,5-dihydro-1H-pyrrole-1-carboxylate (5 g, 24.60 mmol) in DCM (80 mL) was added 3-chlorobenzoperoxoic acid (6.89 g, 30.75 mmol) at 0 °C. The mixture was then stirred at rt overnight. The reaction mixture was then filtered through a bed of Celite and the filtrate was washed with sat'd aqueous Na_2CO_3 and brine. The organic was then separated and dried over anhydrous Na_2SO_4, filtered, and conc. *in vacuo* to yield the title compound that was used for next step without further purification.

The following starting materials were prepared by the procedure of Method 197 using the appropriate starting materials.

Method	Compound	^{1}H NMR	m/z	SM
198	benzyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate 		217	Benzyl 5,6-dihydropyridine-1(2H)-carboxylate 

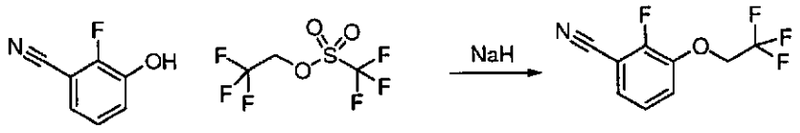
Method 199:



2-(3-amino-4-methylpiperidin-1-yl)-3-chlorobenzaldehyde

To a stirred solution of methyl 1-(2-chloro-6-formylphenyl)-4-methylpiperidin-3-ylcarbamate (220 mg, 0.71 mmol) (Method 119) in MeOH (3 ml) was added 40 % aqueous solution of KOH (10ml) drop wise, and the resulting mixture was heated at reflux for 16 h. The mixture was allowed to cool to rt, diluted with water, and extracted with DCM. The combined organic extract was dried over anhydrous Na_2SO_4, filtered, and conc. *in vacuo*. The resulting residue was purified via silica gel chromatography (100 % ethyl acetate to 10 % methanol in ethyl acetate) to yield the title compound as a light yellow gum (0.057 g, 31.9 %). ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.44 (s, 1 H), 7.40 (t, 2 H), 7.07 (t, 1 H), 4.29 (d, 1 H), 3.58 (ddd, 1 H), 3.38 (dd, 1 H), 3.11 (td, 1 H), 2.81 (d, 1 H), 2.20-1.91 (m, 1 H), 1.31-1.14 (m, 1 H), 1.08 (d, 3 H), 0.63-0.37 (m,1 H).

Method 200

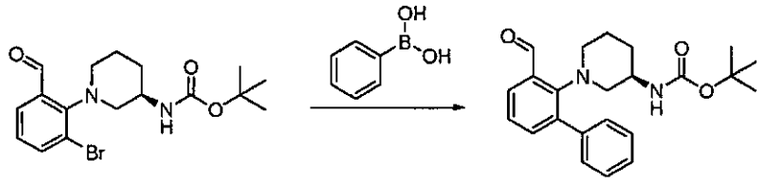


2-fluoro-3-(2,2,2-trifluoroethoxy)benzonitrile:

A stirred solution of 2-fluoro-3-hydroxybenzonitrile (800 mg, 5.83 mmol) in DMF (10 mL) at 0 °C was treated portionwise with NaH (280 mg, 7.00 mmol) (60% oil dispersion). The reaction mixture was then stirred for 0.5 h and 2,2,2-trifluoroethyl trifluoromethanesulfonate (1490 mg, 6.42 mmol) was added. The reaction was allowed to warm to rt overnight with stirring. The reaction mixture was then treated with water (40 mL) and brine (5 mL) and extracted with ethyl acetate (~ 50 mL). The organic extract was washed with water, dried over anhydrous Na_2SO_4, filtered and conc. *in vacuo* to afford a residue which was purified via silica gel chromatography (10 % to 30 % ethyl acetate/hexanes) to yield the title compound as a white solid (1040 mg, 81 %). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.56 (td, 1 H), 7.47-7.38 (m, 1 H), 7.38-7.24 (m, 1 H), 4.73 (q, 2 H); *m/z* 220.

Method 201:

(*R*)-*tert*-butyl 1-(3-formylbiphenyl-2-yl)piperidin-3-ylcarbamate:



A mixture of (*R*)-*tert*-butyl 1-(2-bromo-6-formylphenyl)piperidin-3-yl carbamate (Method 95) (300 mg, 0.78 mmol), phenylboronic acid (143 mg, 1.17 mmol), 1,1'-bis(di-*tert*-butyllphosphino)ferrocenedichloro palladium (II) complex (40.8 mg, 0.06 mmol), and Na_2CO_3 (124 mg, 1.17 mmol) was suspended in dioxane (5 mL) and water (1.50 mL) and stirred at 110 °C for overnight under an atmosphere of nitrogen. The reaction was cooled to rt and water (~ 50 mL) and ethyl acetate (~ 50 mL) was added to the mixture. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered, and conc. *in vacuo* affording a residue purified with via silica gel chromatography (40 g) using a gradient of 5% to 30% ethyl acetate/hexanes to yield the title compound as a low melting solid (168 mg, 56.4 %); *m/z* 381.

One may purify examples provided above by reverse-phase HPLC in a solvent

contain varying concentrations of trifluoroacetic acid or hydrochloric acid. Thus the examples above may be isolated as, the freebase, hydrochloride salt, or trifluoroacetate salt.

PIM 1 and 2 enzyme assay descriptions:

PIM1 in-vitro mobility shift assay

One may determine the activity of purified human His-PIM1 [2-313] enzyme *in-vitro* using a mobility shift assay on a Caliper LC3000 reader (Caliper, MA), which measures fluorescence of a phosphorylated and unphosphorylated FL-Ahx-Bad (FITC-(AHX)RSRHSSYPAGT-COOH, Primm 200606-00289, Primm Biotech, MA) and calculates a ratiometric value to determine percent turnover. One may express PIM1 (University of Dundee, Scotland) in baculovirus system with a typical yield of >85% purity.

One determines phosphorylation of the FL-Ahx-Bad in the presence and absence of the compound of interest. One preincubates 5ul of Enzyme/Substrate/adenosine triphosphate (ATP) mix consisting of 2.4nM PIM1, 3.6uM FL-Ahx-Bad, and 240uM ATP in 1.2x buffer with 2ul of compound for 20 minutes at 25 °C. One initiates reactions with 5ul of Metal mix consisting of 24mM $MgCl_2$ in 1.2x buffer and incubated at 25 °C for 90 minutes and stops the reactions by addition of 5ul of Stop mix consisting of 100mM HEPES, 121mM ethylenediamine tetraacetic acid, 0.8% Coatin Reagent 3 (Caliper, MA), and 0.01% Tween. One detects phosphorylated and unphosphorylated substrate by a Caliper LC3000 reader (Caliper, MA) in the presence of separation buffer consisting of 100mM HEPES, 16mM ethylenediamine tetraacetic acid, 0.1% Coatin Reagent 3 (Caliper, MA), 0.015% Brij-35, 5% DMSO, and 5.6mM $MgCl_2$. One may use the following separation conditions for a Caliper LC3000: -1.0 PSI, -2000 V upstream voltage, -400 V downstream voltage, 0.2 second sample sip, 45 second post sip, 10% laser strength.

PIM2 in-vitro mobility shift assay

One may determine the activity of purified human His-PIM2 [23-299] enzyme *in-vitro* using a mobility shift assay on a Caliper LC3000 reader (Caliper, MA), which measures fluorescence of a phosphorylated and unphosphorylated FL-Ahx-Bad (FITC-(AHX)RSRHSSYPAGT-COOH, Primm 200606-00289, Primm Biotech, MA) and calculates a ratiometric value to determine percent turnover. One may express PIM2 (produced at AstraZeneca, R&D Boston) in *E. coli* cells with a typical yield of >90% purity.

One determines phosphorylation of the FL-Ahx-Bad in the presence and absence of the compound of interest. One preincubates 5uL of Enzyme/Substrate/adenosine triphosphate (ATP) mix consisting of 2.4nM PIM1, 3.6uM FL-Ahx-Bad, and 12uM ATP in 1.2x buffer with 2ul of compound for 20 minutes at 25 °C. One initiates reactions with 5uL of Metal mix consisting of 24mM $MgCl_2$ in 1.2x buffer and incubates at 25 °C for 90 minutes. One stops reactions by addition of 5uL of Stop mix consisting of 100mM HEPES, 121mM ethylenediamine tetraacetic acid, 0.8% Coatin Reagent 3 (Caliper, MA), and 0.01% Tween. One detects phosphorylated and unphosphorylated substrate by a Caliper LC3000 reader (Caliper, MA) in the presence of separation buffer consisting of 100mM HEPES, 16mM ethylenediamine tetraacetic acid, 0.1% Coatin Reagent 3 (Caliper, MA), 0.015% Brij-35, 5% DMSO, and 5.6mM $MgCl_2$. One may use the following separation conditions for a Caliper LC3000: -1.0 PSI, -2000 V upstream voltage, -400 V downstream voltage, 0.2 second sample sip, 45 second post sip, 10% laser strength.

Using the above described assays, or appropriate modifications thereof, preferred compounds disclosed herein generally have an IC_{50} for PIM1 of less that 5 micromolar (uM), and even more preferred of less than 1 micromolar. The table 1 below provides the percent inhibition of PIM1 at 0.3 micromolar for Examples provided herein. Several examples were tested more than once. Variations in the experimental outcomes, negative values, or values over 100% inhibition are presumably due to experimental error inherent in the assay.

Table 1.

Example number	PIM1 %I at 0.3 uM	PIM2 %I at 0.3 uM
1	>95	77.7
2	>95	>95
3	>95	58.0
4	>95	79.6
5A	>95	79.9
5B	>95	>95
6	79.4	9.5
7	5.4	<5
8	16.3	<5
9	6.9	<5
10	>95	50.1
11	89.4	17.9
12	80.2	<5
13	<5	<5
14	>95	69.9
15	12.9	<5
16	13.9	<5
17	29.8	<5
18	<5	<5
19	>95	38.3

20	86.5	19.1
21	82.9	15.8
22	81.9	8.5
23	87.6	19.7
24	>95	44.3
25	>95	68.4
26	>95	49.6
27	90.8	25.1
28	90.0	27.4
29	92.8	
30	90.8	15.6
31	92.8	23.3
32	94.0	31.9
33	>95	>95
34	>95	39.3
35	<5	<5
36	>95	>95
37	89.7	69.4
38	>95	92.9
39	89.4	57.3
40	>95	89.8
41	74.0	25.1

42	58.8	23.3
43	55.4	14.7
44	83.8	46.7
45	40.1	14.3
46	13.4	15.7
47	50.0	26.3
48	84.4	41.3
49	>95	86.3
50	93.7	45.4
51	85.5	80.6
52	>95	93.5
53	92.3	82.1
54	88.1	73.1
55	11.0	<5
56	90.7	33.5
57	53.3	42.6
58	16.0	7.1
59	<5	6.6
60	35.4	11.3
61	81.8	28.1
62	62.1	17.5
63	79.2	21.5

64	86.5	25.7
65	45.3	18.9
66	50.3	20.9
67		<5
68	41.9	9.0
69	<5	16.3
70	<5	<5
71	<5	<5
72	<5	<5
73	<5	<5
74		
75	>95	69.5
76	59.6	27.6
77	51.2	22.7
78	71.4	30.0
79	90.0	60.7
80	<5	
81	<5	
82	87.4	58.2
83	34.0	
84A	92.9	54.3
84B		

84C	47.8	29.6
84D	27.8	<5
84E	11.7	6.1
84F	87.4	52.4
84G	92.0	63.0
84H	>95	67.0
84I	>95	82.7
84J	93.3	40.4
84K	>95	90.8
84L	>95	55.2
84M	>95	80.9
84N	92.8	81.4
84O	<5	<5
85	>95	82.4
86	>95	>95
87	>95	84.2
88	>95	88.4
89	48.4	21.5
90	78.2	86.3
91	6.6	16.4
92	>95	81.5
93	>95	66.3

94	>95	>95
95	>95	>95
96	>95	>95
97	>95	86.4
98	>95	81.4
99	>95	>95
100	93.0	93.9
101	>95	>95
102	93.3	91.9
103	>95	88.7
104	>95	92.4
105	>95	92.4
106	>95	92.8
107	>95	>95
108	>95	>95
109	64.2	65.8
110	90.9	90.7
111	>95	>95
112	>95	>95
113	>95	>95
114	>95	>95
115	93.3	76.1

116	>95	>95
117	>95	>95
118	>95	>95
119	56.2	20.1
120	58.9	22.2
121	>95	87.4
122A	88.2	55.0
122B	>95	92.3
122C	>95	>95
122D	>95	>95
122E	>95	>95
122F	>95	>95
122G	>95	92.1
122H	>95	>95
122I	>95	>95
122J	>95	>95
122K	>95	>95
122L	>95	>95
122M	>95	>95
122N	>95	>95
1220	>95	>95
122P	>95	>95

122Q	>95	>95
122R	>95	89.6
122S	>95	>95
122T	>95	>95
122U	>95	>95
122V	>95	>95
122W	>95	>95
122X	>95	67.1
122Y	>95	>95
122Z	>95	>95
122AA	>95	>95
122AB	>95	>95
122AC	>95	>95
122AD	>95	>95
122AE	>95	>95
122AF	83.9	87.9
122AG	68.9	86.7
122AH	19.0	14.0
122AI	>95	>95
123	>95	>95
124	>95	>95
125	>95	>95

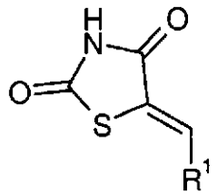
126	>95	>95
127	>95	>95
128	81.2	49.0
129A	>95	>95
129B	>95	>95
129C	85.0	52.1
130	66.2	45.5
131A	27.1	<5
131B	<5	<5
132	93.0	88.1
133	>95	93.4
134	>95	85.2
135	42.5	10.8
136	82.8	44.6
137	55.1	18.6
138	87.9	63.2
139	58.1	15.1
140	73.3	52.0
141	34.9	<5
142	86.1	75.2
143	85.9	49.8
144	63.2	21.2

145	>95	80.1
146	88.9	48.5
147	74.3	36.4
148	91.5	60.8
149	>95	75.4
150	79.8	31.7
151	31.5	13.5
152	10.8	16.7

CLAIMS

1. A method of treating or preventing cancer comprising,

a) providing a pharmaceutical composition comprising a compound of formula I,



formula I,

or salts thereof, functioning to inhibit a PIM kinase, wherein

R^1 is selected from a carbocyclyl, aryl, and heterocyclyl, wherein R^1 is optionally substituted with one or more, the same or different, R^2;

R^2 is selected from halogen, C_{1-6}alkyl, halogenated C_{1-6}alkyl, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, and heterocyclyl, wherein R^2 is optionally substituted with one or more, the same or different, R^3;

R^3 is selected from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^3 is optionally substituted with one or more, the same or different, R^4;

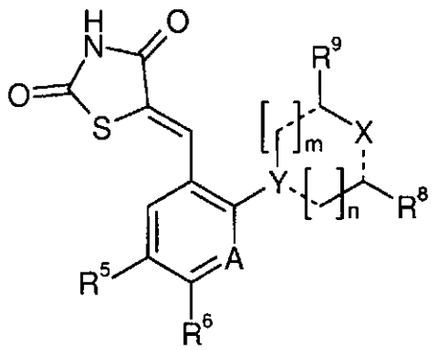
R^4 is selected from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^4 is optionally substituted with one or more, the same or different, R^5; and

R^5 is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl,

N-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl; and

b) administering said pharmaceutical composition to a subject diagnosed with, exhibiting symptoms of, or at risk for cancer.

2. A compound of formula IA,



formula IA,

or salts thereof, wherein,

--- is individually at each occurrence selected from a single and double bond;

n is selected from 0, 1, or 2;

m is selected from 0, 1, or 2;

A is selected from N and CR^7;

X is selected from O, S, CHR^{10} and NR^{11};

Y is selected from N, CH, and C;

R^5, R^6, and R^7 are each individually and independently from hydrogen, C_{1-6}alkyl, halogen, cyano, nitro, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, carbocyclyl, aryl, and heterocyclyl, wherein R^5, R^6, and R^7 are each optionally substituted with one or more, the same or different, R^{12};

R^8 and R^9 are each individually and independently selected from hydrogen, amino, hydroxyl, mercapto, C_{1-6}alkyl, C_{1-6}alkylamino, carbocyclyl, aryl, and heterocyclyl wherein R^8 and R^9 are each optionally substituted with one or more, the same or different, R^{15};

R^{10} is selected from hydrogen, C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{12};

R^{11} is selected from hydrogen, formyl, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, C_{1-6}alkoxycarbonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{11} is optionally substituted with one or more, the same or different, R^{12};

R^{12} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{12} is optionally substituted with one or more, the same or different, R^{16};

R^{15} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, and C_{1-6}alkoxycarbonyl wherein R^{15} is optionally substituted with one or more, the same or different, R^{12};

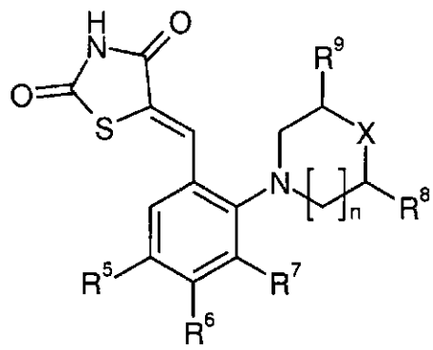
R^{16} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino,

aminomethyl, aminoethyl, aminopropyl, aminobutyl, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, and *N*-methyl-*N*-ethylsulfamoyl; and

provided that R^5, R^6, and R^7 are not all hydrogen and

provided the compound is not 5-((5-nitro-2-(1-piperidinyl)phenyl)methylene)-2,4-thiazolidinedione or 5-((2-(4-morpholinyl)-5-nitrophenyl)methylene)-2,4-thiazolidinedione.

3. A compound of formula IB,



formula IB,

or salts thereof, wherein,

n is selected from 0, 1, or 2;

X is selected from O, CHR^{10} and NR^{11};

R^5, R^6, and R^7 are each individually and independently from hydrogen, halogen, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl,

methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, and *N*-methyl-*N*-ethylsulfamoyl;

R^8 and R^9 are each individually and independently selected from hydrogen, amino, C_{1-6}alkyl, C_{1-6}alkylamino, wherein R^8 and R^9 are each optionally substituted with one or more, the same or different, R^{15};

R^{10} is selected from hydrogen, C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{12};

R^{11} is selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, C_{1-6}alkoxycarbonyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{11} is optionally substituted with one or more, the same or different, R^{12};

R^{12} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{12} is optionally substituted with one or more, the same or different, R^{16};

R^{15} is selected from C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, and C_{1-6}alkoxycarbonyl wherein R^{15} is optionally substituted with one or more, the same or different, R^{12};

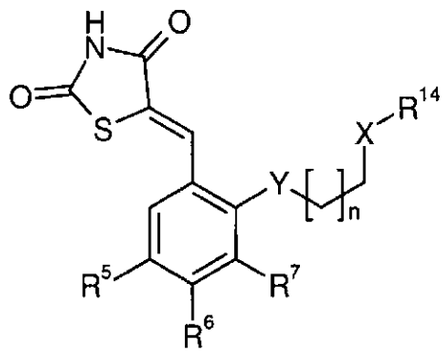
R^{16} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino,

dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, and *N*-methyl-*N*-ethylsulfamoyl.; and

provided that said compound is not,

5-[[2-(4-methyl-1-piperazinyl)phenyl]methylene]-2,4-thiazolidinedione or 5-[[2-[(2,6-dichloro-3-methylphenyl)amino]phenyl]methylene]-2,4-thiazolidinedione.

4. A compound of formula IC,



formula IC,

or salts thereof, wherein,

n is selected from 0, 1, 2, 3, 4, 5, 6, 7 or 8;

X is selected from O, S, CHR^{10} and NR^{11};

Y is selected from O, S, and NR^{13};

R^5, R^6, and R^7 are each individually and independently from C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylamino, C_{1-6}dialkylamino, carbocyclyl, aryl, and heterocyclyl, wherein R^5, R^6, and R^7 are each optionally substituted with one or more, the same or different, R^{12};

R^{10} is selected from hydrogen, C_{1-6}alkyl, halogen, nitro, cyano, hydroxy, amino, mercapto, formyl, carboxy, carbamoyl, C_{1-6}alkoxy, C_{1-6}alkylthio,

C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, C_{1-6}alkylsulfamoyl, arylsulfamoyl, carbocyclyl, aryl, and heterocyclyl, wherein R^{10} is optionally substituted with one or more, the same or different, R^{12};

R^{11}, R^{13}, and R^{14} are each individually and independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, arylsulfonyl, and C_{1-6}alkoxycarbonyl wherein R^{11} is optionally substituted with one or more, the same or different, R^{12};

or R^{11} and R^{14}, taken together with the atoms to which they are attached form a five, six, or seven membered heterocyclic ring optionally substituted with one or more, the same or different, R^{12};

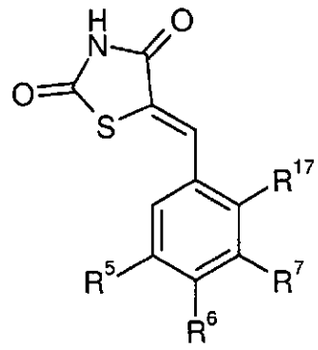
R^{12} is selected from halogen, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, formyl, carboxy, carbamoyl, mercapto, sulfamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, mesyl, ethylsulfonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulfamoyl, *N*-ethylsulfamoyl, *N,N*-dimethylsulfamoyl, *N,N*-diethylsulfamoyl, *N*-methyl-*N*-ethylsulfamoyl, carbocyclyl, aryl, and heterocyclyl.

5. A compound of formula IC as defined in Claim 4, or salts thereof, wherein Y is NR^{13}.

6. A compound of formula IA, IB, or IC, as defined in Claims 2-4, or salts thereof, wherein R^5 is a halogenated C_{1-6}alkyl.

7. A compound of formula IA, IB, or IC, as defined in Claims 2-4, or salts thereof, wherein R^7 is a halogen.

8. A compound of formula IX,



formula IX,

or salts thereof, wherein

R^5 is selected from hydrogen, C_{1-6}alkoxy, carbamoyl, and halogenated C_{1-6}alkyl;

R^6 is selected from hydrogen, halogen, C_{1-6}alkoxy, and 2-(1-piperidyl)ethoxy;

R^7 is selected from hydrogen, halogen, and C_{1-6}alkoxy;

R^{17} is a heterocarbocylcyl, wherein R^{17} is optionally substituted with one or more, the same or different, R^{18};

R^{18} is selected from halogen, formyl, amino, C_{1-6}alkyl, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, carbocyclyl, aryl, heterocyclyl, wherein R^{18} is optionally substituted with one or more, the same or different, R^{19};

R^{19} is selected from amino, C_{1-6}alkyl, hydroxy, carbocyclyl, and heterocyclyl wherein R^{19} is optionally substituted with one or more, the same or different, R^{20}; and

R^{20} is selected from amino, C_{1-6}alkyl, and halogen.

9. The compound of Claim 8, or salts thereof, wherein, R^{17} is selected from (3R)-3-aminopyrrolidin-1-yl, (3R)-3-dimethylaminopyrrolidin-1-yl, (3S)-3-(3-aminopropylamino)pyrrolidin-1-yl, (3S)-3-(5-aminopentanoylamino)pyrrolidin-1-yl, (3S)-3-amino-1-piperidyl, (3S)-3-aminopyrrolidin-1-yl, (3S)-3-dimethylaminopyrrolidin-1-yl, (3S,5R)-3,5-dimethylpiperazin-1-yl, 1,4-diazepan-1-yl, 2-(1-piperidyl)ethoxy, 2-diethylaminoethoxy, 2-dimethylaminoethyl-methyl-amino, 2-hydroxyethoxy, 2-morpholinoethoxy, 3-(2-aminoethylamino)pyrrolidin-1-yl, 3-(2-hydroxyethylamino)pyrrolidin-1-yl, 3-(2-methylaminoethylamino)pyrrolidin-1-yl, 3-(3-aminopropanoylamino)pyrrolidin-1-yl, 3-(3-aminopropylamino)pyrrolidin-1-yl, 3-(3-methyl-1,2,4-oxadiazol-5-yl)-1-piperidyl, 3-(aminomethyl)-1-piperidyl, 3-

(aminomethyl)pyrrolidin-1-yl, 3-acetamidopyrrolidin-1-yl, 3-aminopyrrolidin-1-yl, 3-dimethylaminopropoxy, 3-dimethylaminopropyl-methyl-amino, 3-dimethylaminopyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl, 3-pyridyl, 4-(1-methyl-4-piperidyl)piperazin-1-yl, 4-(1-piperidyl)-1-piperidyl, 4-(2-aminoethyl)piperazin-1-yl, 4-(2-hydroxyethyl)-1,4-diazepan-1-yl, 4-(2-hydroxyethyl)-1-piperidyl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-(2-methylaminoethyl)piperazin-1-yl, 4-(2-morpholinoethyl)piperazin-1-yl, 4-(3-aminopropanoyl)-1,4-diazepan-1-yl, 4-(3-aminopropanoyl)piperazin-1-yl, 4-(3-aminopropyl)piperazin-1-yl, 4-(3-hydroxypropyl)piperazin-1-yl, 4-(3-methyl-1,2,4-oxadiazol-5-yl)-1-piperidyl, 4-(4-aminobutanoyl)-1,4-diazepan-1-yl, 4-(4-aminobutanoyl)piperazin-1-yl, 4-(4-chloro-2-fluoro-phenyl)piperazin-1-yl, 4-(4-fluorophenyl)piperazin-1-yl, 4-(4-pyridylmethyl)piperazin-1-yl, 4-(5-aminopentanoyl)-1,4-diazepan-1-yl, 4-(5-aminopentanoyl)piperazin-1-yl, 4-(azetidine-3-carbonyl)piperazin-1-yl, 4-(benzo[1,3]dioxol-5-ylmethyl)piperazin-1-yl, 4-(cyclopropylmethyl)piperazin-1-yl, 4-(hydroxymethyl)-1-piperidyl, 4-(piperidine-3-carbonyl)-1,4-diazepan-1-yl, 4-(piperidine-3-carbonyl)piperazin-1-yl, 4-(piperidine-4-carbonyl)piperazin-1-yl, 4-[(2-chlorophenyl)methyl]piperazin-1-yl, 4-[3-(aminomethyl)benzoyl]piperazin-1-yl, 4-[4-(piperazin-1-ylmethyl)benzoyl]piperazin-1-yl, 4-acetylpiperazin-1-yl, 4-amino-1-piperidyl, 4-butyl-1,4-diazepan-1-yl, 4-cyclopentylpiperazin-1-yl, 4-dimethylamino-1-piperidyl, 4-hydroxy-1-piperidyl, 4-isobutylpiperazin-1-yl, 4-isopropylpiperazin-1-yl, 4-methylpiperazin-1-yl, 4-morpholino-1-piperidyl, 4-pyridyl, 4-pyrrolidin-1-yl-1-piperidyl, 4-tert-butoxycarbonylpiperazin-1-yl, 4-tert-butylpiperazin-1-yl, morpholino, piperazin-1-yl, and pyrrolidin-1-yl.

10. A compound selected from:

5-({2-[(3S)-3-aminopiperidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3R)-3-aminopiperidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[2-(4-aminopiperidin-1-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({2-[3-(aminomethyl)piperidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(1,4-diazepan-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-cyclopentylpiperazin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(4-fluorophenyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-pyrrolidin-1-ylpiperidin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(1-methylethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-methylpropyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-hydroxyethyl)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(4-chloro-2-fluorophenyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[3-(3-methyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-chlorobenzyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-morpholin-4-ylethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(cyclopropylmethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-morpholin-4-ylpiperidin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(3-hydroxypropyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(dimethylamino)piperidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-{[3-(dimethylamino)propyl](methyl)amino}-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-hydroxyethyl)-1,4-diazepan-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[2-(4-butyl-1,4-diazepan-1-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-chloro-2-[4-(2-hydroxyethyl)piperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-morpholin-4-yl-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[2-(4-tert-butylpiperazin-1-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[2-(1,4'-bipiperidin-1'-yl)-3-chloro-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-{[3-chloro-2-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

5-({3-bromo-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-chloro-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({3-[3-(4-methylpiperazin-1-yl)propoxy]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

2-{3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenoxy}acetamide;

(5Z)-5-{[3-(3-piperidin-1-ylpropoxy)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

(5Z)-5-({3-[(4-methylpiperazin-1-yl)methyl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

N-[2-(dimethylamino)ethyl]-2'-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-N-methylbiphenyl-4-sulfonamide;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-methoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-(trifluoromethyl)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({5-chloro-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-4-methylphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-fluorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-5-methylphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({5-bromo-2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-3-fluorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

5-({2-chloro-6-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-(aminomethyl)pyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-(aminomethyl)pyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-methoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-bromophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-bromophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-ethoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(2-methylpropoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclohexylmethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclohexyloxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R,4R)-3-amino-4-hydroxypiperidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-{[3-chloro-2-(1,4-diazepan-1-yl)phenyl]methylidene}-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(1-methylethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-(1-methylethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-ethoxyphenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-{[4-(aminomethyl)benzyl]amino}piperidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({3-chloro-2-[(3R)-3-{[2-(methylamino)ethyl]amino}piperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S,4S)-3-amino-4-hydroxypyrrolidin-1-yl]-3-chlorophenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({3-chloro-2-[4-methyl-3-(methylamino)piperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-{[2-(3-amino-4-methylpiperidin-1-yl)-3-chlorophenyl]methylidene}-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(2,2,2-trifluoroethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-(2,2,2-trifluoroethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(2-methoxyethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3S)-3-aminopyrrolidin-1-yl]-3-(2-methoxyethoxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclopentyloxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]-3-(cyclobutyloxy)phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

4-[(3R)-3-aminopiperidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide;

4-[(3S)-3-aminopiperidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzamide;

4-[(3R)-3-aminopiperidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzoic acid;

4-[(3S)-3-aminopyrrolidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]benzoic acid;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-yl]biphenyl-3-yl}methylidene)-1,3-thiazolidine-2,4-dione;

5-{[2-(3-aminopropoxy)-5-methoxyphenyl]methylidene}-1,3-thiazolidine-2,4-dione;

N-{4-[3-(dimethylamino)pyrrolidin-1-yl]-3-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}acetamide;

(5Z)-5-[(3-chloro-2-{(3R)-3-[(2-hydroxyethyl)amino]piperidin-1-yl}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

(5Z)-5-[(3-chloro-2-{(3R)-3-[(3-hydroxypropyl)amino]piperidin-1-yl}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-1-methyl-1H-imidazole-2-carboxamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-methoxyacetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-1-methyl-1H-pyrazole-3-carboxamide;

N^2-carbamoyl-N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]glycinamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-pyridin-3-ylacetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-pyridin-4-ylacetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-1-methyl-1H-pyrazole-4-carboxamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-(1-oxidothiomorpholin-4-yl)acetamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-4-sulfamoylbutanamide;

N'-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-N,N-dimethylbutanediamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-N~2~,N~2~-dimethylglycinamide;

N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]-2-cyanoacetamide;

N^2-acetyl-N-[(3S)-1-{2-chloro-6-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]phenyl}pyrrolidin-3-yl]glycinamide;

(5Z)-5-({3-chloro-2-[(3R)-3-(dipropylamino)piperidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione;

(5Z)-5-[(3-chloro-2-{(3R)-3-[(3,3,3-trifluoropropyl)amino]piperidin-1-yl}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

5-[(5-methoxy-2-{3-[(1-methylethyl)amino]propoxy}phenyl)methylidene]-1,3-thiazolidine-2,4-dione;

(5Z)-5-({5-amino-2-[3-(dimethylamino)pyrrolidin-1-yl]phenyl}methylidene)-1,3-thiazolidine-2,4-dione; and

5-[(2-amino-4,5-dimethoxyphenyl)methylidene]-1,3-thiazolidine-2,4-dione,

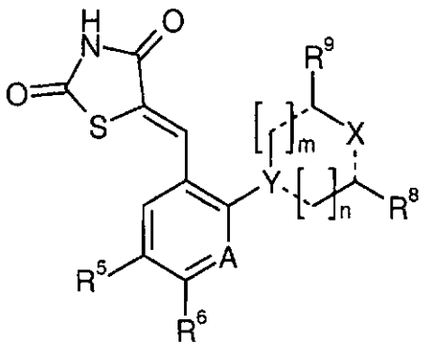
or salts thereof.

11. A pharmaceutical composition comprising a compound of formula I, IA, IB, IC, or IX, as defined in Claims 1-10, or a pharmaceutically acceptable salt thereof.

12. A method of inhibiting a PIM kinase comprising, providing a compound of formula I, IA, IB, IC, or IX, as defined in Claims 1-10 comprising mixing a PIM kinase and said compound under conditions such that PIM kinase phosphorylation is inhibited.

13. The use of a compound of the formula I, IA, IB, IC, or IX, or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1-10, for the manufacture of a medicament for the production of an anti-cancer effect in a subject.

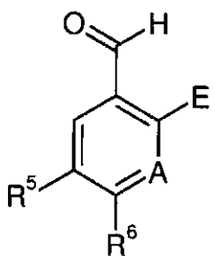
14. A method of making a compound of formula IA as defined in Claim 2,



formula IA,

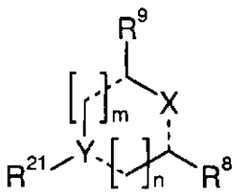
or salt thereof, comprising

a) mixing a compound of formula XI,



formula XI,

or salt thereof, wherein E is a halogen, and R^5, R^6, and A are defined in Claim 2, with a compound of formula XII,



formula XII,

or salt thereof, wherein

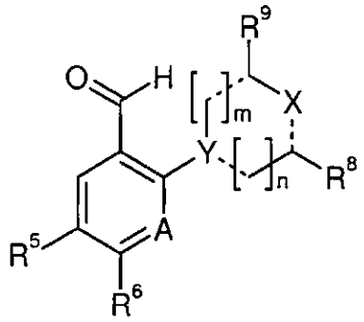
---, R^8, R^9, n, m, Y and X are defined in Claim 2,

if Y is N, then R^{21} is hydrogen,

if Y is C, then R^{21} is selected from boronic acid and a boronic ester, and

if Y is CH, then R^{21} is selected from a metal halide,

under conditions such that composition comprising a compound of formula XIII,

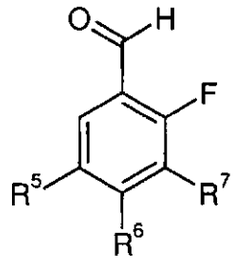


formula XIII,

or salt thereof, is formed; and

b) mixing the compound of formula XIII and thiazolidine-2,4-dione under conditions such that a compound of formula IA is formed.

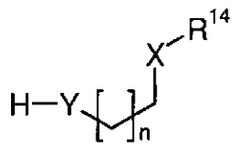
15. A method of making a compound of formula IC, or salt thereof comprising a) mixing a compound of formula V,



formula V,

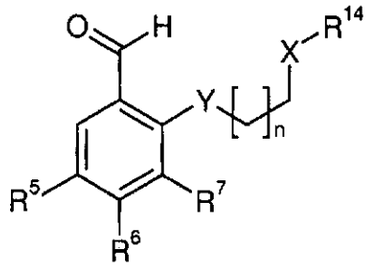
or salt thereof, wherein R^5, R^6, and R^7 are defined in Claim 4,

with a compound of formula VI,



formula VII,

or salt thereof, wherein R^{14}, n, X and Y are defined in Claim 4, under conditions such that a composition comprising a compound of formula VIII,



formula VIII

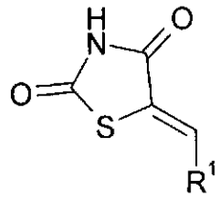
or salt thereof, is formed; and

b) mixing the compound of formula VIII and thiazolidine-2,4-dione under conditions such that a compound of formula IC is formed.

COMPUESTOS QUÍMICOS 251

CAMPO DE LA INVENCIÓN

La invención se refiere a compuestos químicos de fórmula I,



Fórmula I

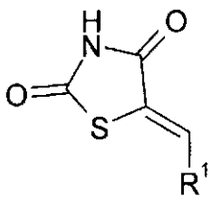
y sales de los mismos. En algunas realizaciones, la invención se refiere a inhibidores o moduladores de la actividad o función enzimática de la proteína quinasa PIM-1 y/o PIM-2 y/o PIM-3. En otras realizaciones adicionales, la invención se refiere a composiciones farmacéuticas que comprenden compuestos descritos en la presente y su uso en la prevención y tratamiento de afecciones y enfermedades relacionadas con la quinasa PIM, preferiblemente cáncer.

ANTECEDENTES

El gen PIM-1 se identificó primero como un sitio de inserción proviral en linfoma de células T inducido por virus de leucemia murina Moloney. El gen PIM-1 traduce una Ser/Thr proteína quinasa. La conocida familia de quinasas PIM también incluye las quinasas PIM-2 y PIM-3. Estudios en ratones sugieren que fisiológicamente las quinasas PIM participan en la señalización de factores de crecimiento y citoquinas. La expresión desregulada de la quinasa PIM se produce en un gran número de tumores hematopoyéticos, tales como leucemias y linfomas mieloides y linfoblásticos. Las quinasas PIM también se expresan en tumores sólidos tales como cáncer de próstata y cáncer pancreático y ratones transgénicos que expresan PIM-1 desarrollan linfoma de células T. Dhanasekaran et al., (2001). Nature 412: 822–826 y.Li et al., (2006) Cancer Res 66: 6741–6747. Por lo tanto, se cree que los inhibidores de quinasa PIM serán útiles en el tratamiento y/o prevención de cáncer. Por consiguiente, existe la necesidad de identificar inhibidores de quinasas PIM.

COMPENDIO DE LA INVENCIÓN

La invención se refiere a compuestos químicos de fórmula I,



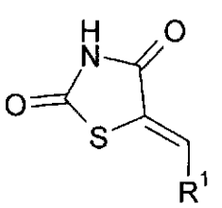
fórmula I

y sales de los mismos. En algunas realizaciones, la invención se refiere a inhibidores o moduladores de la actividad o función enzimática de la proteína quinasa PIM-1 y/o PIM-2 y/o PIM-3. En otras realizaciones adicionales, la invención se refiere a composiciones farmacéuticas que comprenden compuestos descritos en la presente y su uso en la prevención y tratamiento de afecciones y enfermedades relacionadas con la quinasa PIM, preferiblemente cáncer.

DESCRIPCIÓN DETALLADA

La invención se refiere a un método para tratar o prevenir cáncer que comprende,

a) proporcionar una composición farmacéutica que comprende un compuesto de fórmula I,



fórmula I,

o sales farmacéuticamente aceptables del mismo, que funciona para inhibir una quinasa PIM, en donde

R^1 se selecciona de un carbociclilo, arilo y heterociclilo, en donde R^1 opcionalmente se sustituye por uno o más R^2, iguales o diferentes;

R^2 se selecciona de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-}

$_{6})_2$amino, alquilC_{1-6}sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^2 opcionalmente se sustituye por uno o más R^3, iguales o diferentes;

R^3 se selecciona de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquil$C_{1-6})_2$amino, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, carbociclilo, arilo y heterociclilo, en donde R^3 opcionalmente se sustituye por uno o más R^4, iguales o diferentes;

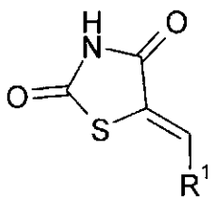
R^4 se selecciona de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquil$C_{1-6})_2$amino, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, carbociclilo, arilo y heterociclilo, en donde R^4 opcionalmente se sustituye por uno o más R^5, iguales o diferentes; y

R^5 se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo; y

b) administrar dicha composición farmacéutica a un sujeto al que se le ha diagnosticado, que exhibe síntomas o que corre el riesgo de padecer cáncer con la condición de que dicho compuesto de fórmula I no sea 5-[[2-[(2,6-dicloro-3-metilfenil)amino]fenil]metileno]-2,4-tiazolidinadiona.

En algunas realizaciones, la invención se refiere a un método para tratar o prevenir cáncer que comprende,

a) proporcionar una composición farmacéutica que comprende un compuesto de fórmula I,



fórmula I,

o sales del mismo, que funciona para inhibir una quinasa PIM, en donde

R^1 se selecciona de un carbociclilo, arilo y heterociclilo, en donde R^1 opcionalmente se sustituye por uno o más R^2, iguales o diferentes;

R^2 se selecciona de halógeno, alquiloC_{1-6}, alquiloC_{1-6} halogenado, amino, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino y heterociclilo, en donde R^2 opcionalmente se sustituye por uno o más R^3, iguales o diferentes;

R^3 se selecciona de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, carbociclilo, arilo y heterociclilo, en donde R^3 opcionalmente se sustituye por uno o más R^4, iguales o diferentes;

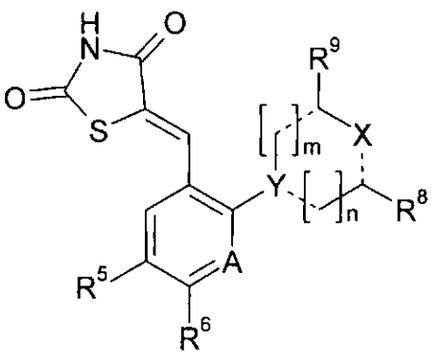
R^4 se selecciona de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, carbociclilo, arilo y heterociclilo, en donde R^4 opcionalmente se sustituye por uno o más R^5, iguales o diferentes; y

R^5 se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo; y

b) administrar dicha composición farmacéutica a un sujeto al que se le ha diagnosticado, que exhibe síntomas o que corre el riesgo de padecer cáncer bajo condiciones tales que se reduce o previene el cáncer.

En realizaciones adicionales, la invención se refiere a un método para tratar cáncer que comprende administrar a un individuo que lo necesite una composición farmacéutica que comprende un compuesto de la fórmula descrita en la presente, en donde dicho cáncer se selecciona de una leucemia, linfoma, cáncer de próstata, cáncer pancreático o otros tumores sólidos.

En realizaciones adicionales, la invención se refiere a un compuesto de fórmula IA,



fórmula IA,

o sales del mismo, en donde,

--- en cada caso se selecciona individualmente de un enlace simple y doble;

n se selecciona de 0, 1 o 2;

m se selecciona de 0, 1 o 2;

A se selecciona de N y CR^7;

X se selecciona de O, S, CHR^{10} y NR^{11};

Y se selecciona de N, CH y C;

R^5, R^6 y R^7 se seleccionan cada uno individualmente e independientemente de hidrógeno, alquiloC_{1-6}, halógeno, ciano, nitro, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, carbociclilo, arilo y heterociclilo, en donde R^5, R^6 y R^7 opcionalmente se sustituyen cada uno por uno o más R^{12} iguales o diferentes;

R^8 y R^9 se seleccionan cada uno individualmente e independientemente de hidrógeno, amino, hidroxilo, mercapto, alquiloC$_{1-6}$, alquilC$_{1-6}$amino, carbociclilo, arilo y heterociclilo en donde R^8 y R^9 opcionalmente se sustituyen cada uno por uno o más R^{15}, iguales o diferentes;

R^{10} se selecciona de hidrógeno, alquiloC$_{1-6}$, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC$_{1-6}$, alquilC$_{1-6}$tio, alquilC$_{1-6}$amino, (alquilC$_{1-6}$)$_2$amino, alquilC$_{1-6}$sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{10} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{11} se selecciona de hidrógeno, formilo, alquiloC$_{1-6}$, alcanoiloC$_{1-6}$, alquilC$_{1-6}$sulfinilo, alquilC$_{1-6}$sulfonilo, arilsulfonilo, alcoxiC$_{1-6}$carbonilo, carbociclilo, arilo y heterociclilo, en donde R^{11} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{12} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{12} opcionalmente se sustituye por uno o más R^{16}, iguales o diferentes;

R^{15} se selecciona de alquiloC$_{1-6}$, alcanoiloC$_{1-6}$, alquilC$_{1-6}$sulfinilo, alquilC$_{1-6}$sulfonilo, arilsulfonilo y alcoxiC$_{1-6}$carbonilo en donde R^{15} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

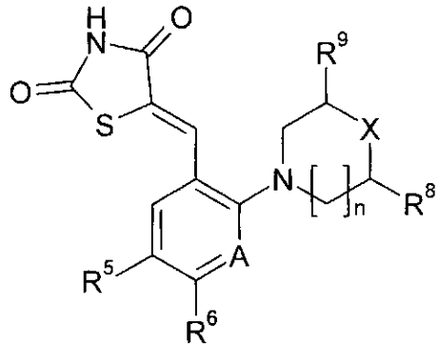
R^{16} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, aminometilo, aminoetilo, aminopropilo, aminobutilo, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo,

metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo y *N*-metil-*N*-etilsulfamoilo; y

siempre que R^5, R^6 y R^7 no sean todos hidrógeno y

siempre que el compuesto no sea 5-((5-nitro-2-(1-piperidinil)fenil)metileno)-2,4-tiazolidinadiona o 5-((2-(4-morfolinil)-5-nitrofenil)metileno)-2,4-tiazolidinadiona.

En algunas realizaciones, la invención se refiere a un compuesto de fórmula ID,



fórmula ID,

o sales del mismo, en donde,

n se selecciona de 0, 1 o 2;

A se selecciona de N y CR^7;

X se selecciona de O, S, CHR^{10} y NR^{11};

R^5, R^6 y R^7 se seleccionan cada uno individualmente e independientemente de hidrógeno, alquiloC_{1-6}, halógeno, ciano, nitro, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, carbociclilo, arilo y heterociclilo, en donde R^5, R^6 y R^7 opcionalmente se sustituyen cada uno por uno o más R^{12} iguales o diferentes;

R^8 y R^9 se seleccionan cada uno individualmente e independientemente de hidrógeno, amino, hidroxilo, mercapto, alquiloC_{1-6}, alquilC_{1-6}amino, carbociclilo, arilo y heterociclilo en donde R^8 y R^9 opcionalmente se sustituyen cada uno por uno o más R^{15}, iguales o diferentes;

R^{10} se selecciona de hidrógeno, alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{10} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{11} se selecciona de hidrógeno, formilo, alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, alcoxiC_{1-6}carbonilo, carbociclilo, arilo y heterociclilo, en donde R^{11} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{12} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{12} opcionalmente se sustituye por uno o más R^{16}, iguales o diferentes;

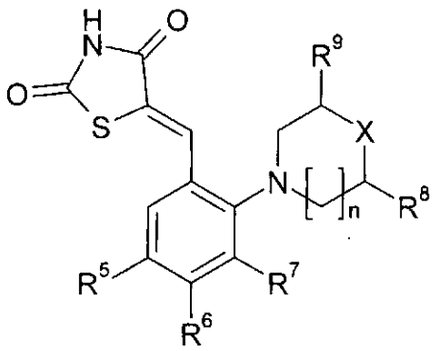
R^{15} se selecciona de alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo y alcoxiC_{1-6}carbonilo en donde R^{15} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{16} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, aminometilo, aminoetilo, aminopropilo, aminobutilo, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo y *N*-metil-*N*-etilsulfamoilo.

En algunas realizaciones con respecto a cualquiera de las fórmulas de compuesto proporcionadas en la presente, R^5, R^6 y R^7 no son todos hidrógeno.

En algunas realizaciones con respecto a cualquiera de las fórmulas de compuesto proporcionadas en la presente, R^5, R^6 y R^7 no son 5-((5-nitro-2-(1-piperidinil)fenil)metileno)-2,4-tiazolidinadiona o 5-((2-(4-morfolinil)-5-nitrofenil)metileno)-2,4-tiazolidinadiona.

En algunas realizaciones, la invención se refiere a un compuesto de fórmula IB,



fórmula IB,

o sales del mismo, en donde,

n se selecciona de 0, 1 o 2;

X se selecciona de O, CHR^{10} y NR^{11};

R^5, R^6 y R^7 se seleccionan cada uno individualmente e independientemente de hidrógeno, halógeno, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo y *N*-metil-*N*-etilsulfamoilo;

R^8 y R^9 se seleccionan cada uno individualmente e independientemente de hidrógeno, amino, alquiloC_{1-6}, alquilC_{1-6}amino, en donde R^8 y R^9 opcionalmente se sustituyen cada uno por uno o más R^{15}, iguales o diferentes;

R^{10} se selecciona de hidrógeno, alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{10} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{11} se selecciona de hidrógeno, alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, alcoxiC_{1-6}carbonilo, carbociclilo, arilo y heterociclilo, en donde R^{11} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{12} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo,

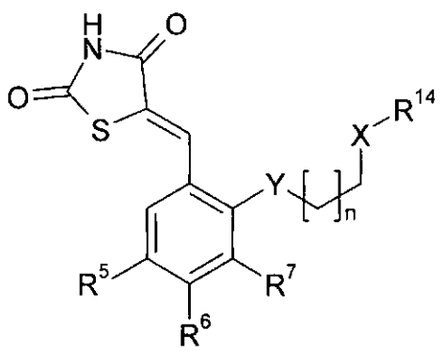
metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{12} opcionalmente se sustituye por uno o más R^{16}, iguales o diferentes;

R^{15} se selecciona de alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo y alcoxiC_{1-6}carbonilo en donde R^{15} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{16} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo y *N*-metil-*N*-etilsulfamoilo.

En algunas realizaciones, con respecto a cualquiera de las fórmulas de compuesto proporcionadas en la presente, dicho compuesto no es 5-[[2-(4-metil-1-piperazinil)fenil]metileno]-2,4-tiazolidinadiona o 5-[[2-[(2,6-dicloro-3-metilfenil)amino]fenil]metileno]-2,4-tiazolidinadiona.

En realizaciones adicionales, la invención se refiere a un compuesto de fórmula IC,



fórmula IC,

o sales del mismo, en donde,

n se selecciona de 0, 1, 2, 3, 4, 5, 6, 7 o 8;

X se selecciona de O, S, CHR^{10} y NR^{11};

Y se selecciona de O, S y NR^{13};

R^5, R^6 y R^7 se seleccionan cada uno individualmente e independientemente de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, dialquilC_{1-6}amino, carbociclilo, arilo y heterociclilo, en donde R^5, R^6 y R^7 opcionalmente se sustituyen cada uno por uno o más R^{12} iguales o diferentes;

R^{10} se selecciona de hidrógeno, alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{10} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{11}, R^{13} y R^{14} se seleccionan cada uno individualmente e independientemente de hidrógeno, alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo y alcoxiC_{1-6}carbonilo en donde R^{11} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

o R^{11} y R^{14}, tomados junto con los átomos a los que están unidos forman un anillo heterocíclico de cinco, seis o siete miembros opcionalmente sustituido por uno o más R^{12} iguales o diferentes;

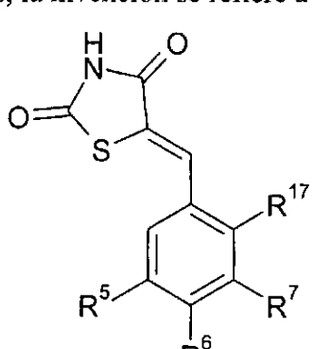
R^{12} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo.

En algunas realizaciones con respecto a cualquiera de las fórmulas de compuesto proporcionadas en la presente Y es NR^{13}, en donde R^{13} es un alquiloC_{1-6}.

En algunas realizaciones con respecto a cualquiera de las fórmulas de compuesto proporcionadas en la presente, R^5 es un alquiloC_{1-6} halogenado.

En algunas realizaciones con respecto a cualquiera de las fórmulas de compuesto proporcionadas en la presente, R^7 es un halógeno.

En algunas realizaciones, la invención se refiere a un compuesto de fórmula IX,



fórmula IX,

o sales del mismo, en donde

R^5 se selecciona de hidrógeno, alcoxiC_{1-6}, carbamoilo y alquiloC_{1-6} halogenado;

R^6 se selecciona de hidrógeno, halógeno, alcoxiC_{1-6} y 2-(1-piperidil)etoxi;

R^7 se selecciona de hidrógeno, halógeno y alcoxiC_{1-6};

R^{17} es un heterocarbociclilo, en donde R^{17} opcionalmente se sustituye por uno o más R^{18}, iguales o diferentes;

R^{18} se selecciona de halógeno, formilo, amino, alquiloC_{1-6}, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, carbociclilo, arilo, heterociclilo, en donde R^{18} opcionalmente se sustituye por uno o más R^{19}, iguales o diferentes;

R^{19} se selecciona de amino, alquiloC_{1-6}, hidroxi, carbociclilo y heterociclilo en donde R^{19} opcionalmente se sustituye por uno o más R^{20}, iguales o diferentes; y

R^{20} se selecciona de amino, alquiloC_{1-6} y halógeno.

En realizaciones adicionales, R^{17} se selecciona de (3R)-3-aminopirrolidin-1-ilo, (3R)-3-dimetilaminopirrolidin-1-ilo, (3S)-3-(3-aminopropilamino)pirrolidin-1-ilo, (3S)-3-(5-aminopentanoilamino)pirrolidin-1-ilo, (3S)-3-amino-1-piperidilo, (3S)-3-aminopirrolidin-1-ilo, (3S)-3-dimetilaminopirrolidin-1-ilo, (3S,5R)-3,5-dimetilpiperazin-1-ilo, 1,4-diazepan-1-ilo, 2-(1-piperidil)etoxi, 2-dietilaminoetoxi, 2-dimetilaminoetil-metil-amino, 2-hidroxietoxi, 2-morfolinoetoxi, 3-(2-aminoetilamino)pirrolidin-1-ilo, 3-

(2-hidroxietilamino)pirrolidin-1-ilo, 3-(2-metilaminoetilamino)pirrolidin-1-ilo, 3-(3-aminopropanoilamino)pirrolidin-1-ilo, 3-(3-aminopropilamino)pirrolidin-1-ilo, 3-(3-metil-1,2,4-oxadiazol-5-il)-1-piperidilo, 3-(aminometil)-1-piperidilo, 3-(aminometil)pirrolidin-1-ilo, 3-acetamidopirrolidin-1-ilo, 3-aminopirrolidin-1-ilo, 3-dimetilaminopropoxi, 3-dimetilaminopropil-metil-amino, 3-dimetilaminopirrolidin-1-ilo, 3-hidroxipirrolidin-1-ilo, 3-piridilo, 4-(1-metil-4-piperidil)piperazin-1-ilo, 4-(1-piperidil)-1-piperidilo, 4-(2-aminoetil)piperazin-1-ilo, 4-(2-hidroxietil)-1,4-diazepan-1-ilo, 4-(2-hidroxietil)-1-piperidilo, 4-(2-hidroxietil)piperazin-1-ilo, 4-(2-metilaminoetil)piperazin-1-ilo, 4-(2-morfolinoetil)piperazin-1-ilo, 4-(3-aminopropanoil)-1,4-diazepan-1-ilo, 4-(3-aminopropanoil)piperazin-1-ilo, 4-(3-aminopropil)piperazin-1-ilo, 4-(3-hidroxipropil)piperazin-1-ilo, 4-(3-metil-1,2,4-oxadiazol-5-il)-1-piperidilo, 4-(4-aminobutanoil)-1,4-diazepan-1-ilo, 4-(4-aminobutanoil)piperazin-1-ilo, 4-(4-cloro-2-fluoro-fenil)piperazin-1-ilo, 4-(4-fluorofenil)piperazin-1-ilo, 4-(4-piridilmetil)piperazin-1-ilo, 4-(5-aminopentanoil)-1,4-diazepan-1-ilo, 4-(5-aminopentanoil)piperazin-1-ilo, 4-(azetidina-3-carbonil)piperazin-1-ilo, 4-(benzo[1,3]dioxol-5-ilmetil)piperazin-1-ilo, 4-(ciclopropilmetil)piperazin-1-ilo, 4-(hidroximetil)-1-piperidilo, 4-(piperidina-3-carbonil)-1,4-diazepan-1-ilo, 4-(piperidina-3-carbonil)piperazin-1-ilo, 4-(piperidina-4-carbonil)piperazin-1-ilo, 4-[(2-clorofenil)metil]piperazin-1-ilo, 4-[3-(aminometil)benzoil]piperazin-1-ilo, 4-[4-(piperazin-1-ilmetil)benzoil]piperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-amino-1-piperidilo, 4-butil-1,4-diazepan-1-ilo, 4-ciclopentilpiperazin-1-ilo, 4-dimetilamino-1-piperidilo, 4-hidroxi-1-piperidilo, 4-isobutilpiperazin-1-ilo, 4-isopropilpiperazin-1-ilo, 4-metilpiperazin-1-ilo, 4-morfolino-1-piperidilo, 4-piridilo, 4-pirrolidin-1-il-1-piperidilo, 4-terc-butoxicarbonilpiperazin-1-ilo, 4-terc-butilpiperazin-1-ilo, morfolino, piperazin-1-ilo y pirrolidin-1-ilo.

En realizaciones adicionales, la invención se refiere a un compuesto que se selecciona de:

5-({2-[(3S)-3-aminopiperidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3R)-3-aminopiperidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[2-(4-aminopiperidin-1-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({2-[3-(aminometil)piperidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(1,4-diazepan-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-ciclopentilpiperazin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(4-fluorofenil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[4-(1,3-benzodioxol-5-ilmetil)piperazin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(3-metil-1,2,4-oxadiazol-5-il)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-pirrolidin-1-ilpiperidin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(1-metiletil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-metilpropil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-hidroxietil)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(4-cloro-2-fluorofenil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[3-(3-metil-1,2,4-oxadiazol-5-il)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(piridin-4-ilmetil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-clorobencil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(1-metilpiperidin-4-il)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-morfolin-4-iletil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(ciclopropilmetil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-morfolin-4-ilpiperidin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(3-hidroxipropil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(dimetilamino)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-{[3-(dimetilamino)propil](metil)amino}-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-hidroxietil)-1,4-diazepan-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[2-(4-butil-1,4-diazepan-1-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-hidroxietil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-morfolin-4-il-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[2-(4-terc-butilpiperazin-1-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[2-(1,4'-bipiperidin-1'-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-metilpiperazin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-bromo-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona; y

5-({2-[(3R,5S)-3,5-dimetilpiperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona,

(5Z)-5-({3-[3-(4-metilpiperazin-1-il)propoxi]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

2-{3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenoxi}acetamida;

(5Z)-5-{[3-(3-piperidin-1-ilpropoxi)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

(5Z)-5-({3-[(4-metilpiperazin-1-il)metil]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

N-[2-(dimetilamino)etil]-2'-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]-N-metilbifenil-4-sulfonamida;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-metoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({5-cloro-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-4-metilfenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-fluorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-metilfenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({5-bromo-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-3-fluorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-cloro-6-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-(aminometil)pirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-(aminometil)pirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-metoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-bromofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-bromofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-etoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(2-metilpropoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclohexilmetoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclohexiloxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R,4R)-3-amino-4-hidroxipiperidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-{[3-cloro-2-(1,4-diazepan-1-il)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(1-metiletoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-(1-metiletoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-etoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-{[4-(aminometil)bencil]amino}piperidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({3-cloro-2-[(3R)-3-{[2-(metilamino)etil]amino}piperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S,4S)-3-amino-4-hidroxipirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({3-cloro-2-[4-metil-3-(metilamino)piperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-{[2-(3-amino-4-metilpiperidin-1-il)-3-clorofenil]metilideno}-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(2,2,2-trifluoroetoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-(2,2,2-trifluoroetoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(2-metoxietoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-(2-metoxietoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclopentiloxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclobutiloxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

4-[(3R)-3-aminopiperidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzamida;

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4-[(3S)-3-aminopiperidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzamida;

ácido 4-[(3R)-3-aminopiperidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzoico;

ácido 4-[(3S)-3-aminopirrolidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzoico;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]bifenil-3-il}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[2-(3-aminopropoxi)-5-metoxifenil]metilideno}-1,3-tiazolidina-2,4-diona;

N-{4-[3-(dimetilamino)pirrolidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}acetamida;

(5Z)-5-[(3-cloro-2-{(3R)-3-[(2-hidroxietil)amino]piperidin-1-il}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

(5Z)-5-[(3-cloro-2-{(3R)-3-[(3-hidroxipropil)amino]piperidin-1-il}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-1-metil-1H-imidazol-2-carboxamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-metoxiacetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-1-metil-1H-pirazol-3-carboxamida;

N^2-carbamoil-N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]glicinamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-piridin-3-ilacetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-piridin-4-ilacetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-1-metil-1H-pirazol-4-carboxamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-(1-oxidotiomorfolin-4-il)acetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-4-sulfamoilbutanamida;

N'-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-N,N-dimetilbutanodiamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-N~2~,N~2~-dimetilglicinamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-cianoacetamida;

N^2-acetil-N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]glicinamida;

(5Z)-5-({3-cloro-2-[(3R)-3-(dipropilamino)piperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-[(3-cloro-2-{(3R)-3-[(3,3,3-trifluoropropil)amino]piperidin-1-il}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

5-[(5-metoxi-2-{3-[(1-metiletil)amino]propoxi}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

(5Z)-5-({5-amino-2-[3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona; y

5-[(2-amino-4,5-dimetoxifenil)metilideno]-1,3-tiazolidina-2,4-diona,

o sales del mismo.

En algunas realizaciones, la invención se refiere a cualquiera de los compuestos descritos en la presente que se encuentran en el isómero (Z).

En algunas realizaciones, la invención se refiere a cualquiera de los compuestos descritos en la presente que se encuentran en el isómero (E).

En algunas realizaciones, la invención se refiere a composiciones que comprenden una mezcla de los isómeros (Z) y (E).

En algunas realizaciones, la invención se refiere a una composición farmacéutica que comprende una 5-(3-halo-2-[piperidin-1-il]fenilmetilideno)-1,3-tiazolidina-2,4-diona sustituida que funciona para inhibir una quinasa PIM.

En realizaciones adicionales, la invención se refiere a una composición farmacéutica que comprende un compuesto de fórmula I, IA, IB, IC, ID, o IX o una sal farmacéuticamente aceptable del mismo.

En realizaciones adicionales, la invención se refiere a un método para inhibir una quinasa PIM que comprende proporcionar un compuesto de fórmula I, IA, IB, IC, ID, o IX, tal como se define en la presente y mezclar una quinasa PIM y dicho compuesto bajo condiciones tales que se inhibe la fosforilación de la quinasa PIM.

En realizaciones adicionales, dicho método es un método *in vitro*.

En realizaciones adicionales, dicho método es un método *in vivo*.

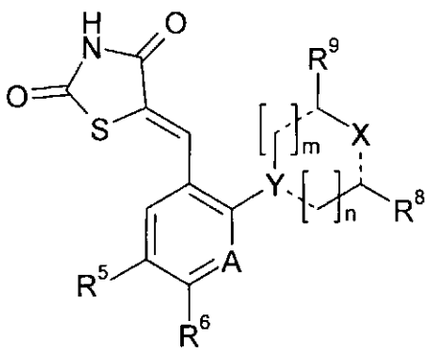
En realizaciones adicionales, la invención se refiere a un método para inhibir una quinasa PIM en un sujeto que comprende administrar al sujeto una cantidad terapéuticamente efectiva de un compuesto de cualquiera de las fórmulas descritas en la presente o una sal farmacéuticamente aceptable del mismo.

En realizaciones adicionales, dicho quinasa PIM se selecciona de PIM-1, PIM-2 y PIM-3.

En realizaciones adicionales, la invención se refiere al uso de un compuesto de la fórmula I, IA, IB, IC, ID, o IX, o una sal farmacéuticamente aceptable del mismo, tal como se define en la presente, para la fabricación de un medicamento para la producción de un efecto inhibitorio de la quinasa PIM en un sujeto.

En realizaciones adicionales, la invención se refiere al uso de un compuesto de la fórmula I, IA, IB, IC, ID, o IX, o una sal farmacéuticamente aceptable del mismo, como se describe en la presente, para la fabricación de un medicamento para la producción de un efecto anti-cáncer en un sujeto.

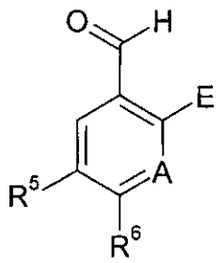
En algunas realizaciones, la invención se refiere a un método para preparar un compuesto de fórmula IA tal como se define en la presente,



fórmula IA,

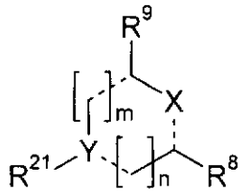
o sal del mismo, que comprende

a) mezclar un compuesto de fórmula XI,



fórmula XI,

o sal del mismo, en donde E es un halógeno y R^5, R^6 y A se definen en la presente, con un compuesto de fórmula XII,



fórmula XII,

o sal del mismo, en donde

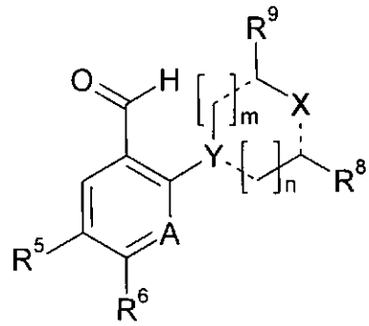
---, R^8, R^9, n, m, Y y X se definen en la presente,

si Y es N, entonces R^{21} es hidrógeno,

si Y es C, entonces R^{21} se selecciona de ácido borónico y un éster borónico y

si Y es CH, entonces R^{21} se selecciona de un haluro de metal,

bajo condiciones tales que se forma una composición que comprende un compuesto de fórmula XIII,



fórmula XIII,

o sal del mismo; y

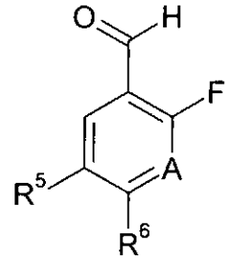
b) mezclar el compuesto de fórmula XIII y tiazolidina-2,4-diona bajo condiciones tales que se forma un compuesto de fórmula IA.

En realizaciones adicionales, dicho haluro de metal se selecciona de cloruro de litio y bromuro de magnesio.

En realizaciones adicionales, dicho éster borónico es un éster dialquilborónico, tal como éster dietil borónico, o un éster borónico cíclico, tal como el éster borónico de 1,2-alquildioles tales como 1,3,2-dioxaborolano, o cicloalquildioles que opcionalmente pueden sustituirse.

En realizaciones adicionales, la invención se refiere a un método para preparar un compuesto de fórmula ID, o sal del mismo que comprende

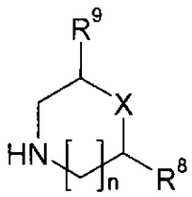
a) mezclar un compuesto de fórmula II,



fórmula II,

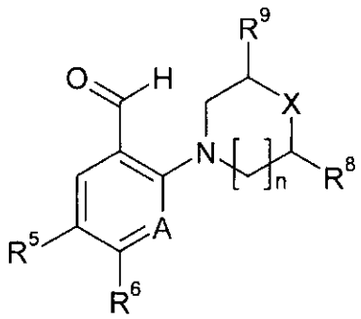
o sal del mismo, en donde R^5, R^6 y A se definen en la presente,

con un compuesto de fórmula III,



fórmula III,

o sal del mismo, en donde R^8, R^9, n y X se definen en la presente, bajo condiciones tales que se forma una composición que comprende un compuesto de fórmula IV,

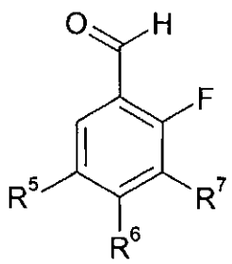


fórmula IV

o sal del mismo; y

b) mezclar el compuesto de fórmula IV y tiazolidina-2,4-diona bajo condiciones tales que se forma un compuesto de fórmula ID.

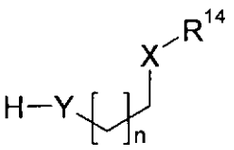
En realizaciones adicionales, la invención se refiere a un método para preparar un compuesto de fórmula IC, o sal del mismo, que comprende a) mezclar un compuesto de fórmula V,



fórmula V,

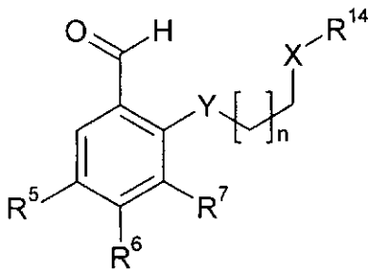
o sal del mismo, en donde R^5, R^6 y R^7 se definen en la presente,

con un compuesto de fórmula VI,



fórmula VII,

o sal del mismo, en donde R^{14}, n, X e Y se definen en la presente, bajo condiciones tales que se forma una composición que comprende un compuesto de fórmula VIII,



fórmula VIII

o sal del mismo; y

b) mezclar el compuesto de fórmula VIII y tiazolidina-2,4-diona bajo condiciones tales que se forma un compuesto de fórmula IC.

En algunas realizaciones, la invención se refiere a compuestos de fórmula I, IA, IB, IC, ID, o IX siempre que no se seleccionen de 5-((2-dipropilamino-5-nitrofenil)metileno)-2,4-tiazolidinadiona;

5-((5-nitro-2-(1-piperidinil)fenil)metileno)-2,4-tiazolidinadiona;

5-((2-(4-morfolinil)-5-nitrofenil)metileno)-2,4-tiazolidinadiona;

5-[[2-(4-metil-1-piperazinil)fenil]metileno]-2,4-tiazolidinadiona;

5-[[2-[(2,6-dicloro-3-metilfenil)amino]fenil]metileno]-2,4-tiazolidinadiona;

[2S-[2α(Z),4α]]-1-([1,1'-bifenil]-4-ilsulfonil)-N-[2-[(2,4-dioxo-5-tiazolidinilideno)metil]fenil]-4-(metiltio)-2-pirrolidinametanamina;

éster de 1,1-dimetiletilo de ácido [[2S-[2α(Z),4α]]-3-[[[1-([1,1'-bifenil]-4-ilsulfonil)-4-(metiltio)-2-pirrolidinil]metil]amino]-4-[(2,4-dioxo-5-tiazolidinilideno)metil]fenil]carbámico; y

[2S-[2α(Z),4α]]-N-[5-amino-2-[(2,4-dioxo-5-tiazolidinilideno)metil]fenil]-1-([1,1'-bifenil]-4-ilsulfonil)-4-(metiltio)-2-pirrolidinametanamina.

Los solicitantes entienden que el documento WO 2001002377 describe 5-((2-dipropilamino-5-nitrofenil)metileno)-2,4-tiazolidinadiona, 5-((5-nitro-2-(1-piperidinil)fenil)metileno)-2,4-tiazolidinadiona y 5-((2-(4-morfolinil)-5-nitrofenil)metileno)-2,4-tiazolidinadiona.

Los solicitantes entienden que el documento WO 9814433 describe 5-[[2-(4-metil-1-piperazinil)fenil]metileno]-2,4-tiazolidinadiona.

Los solicitantes entienden que la Patente de los Estados Unidos No. 6.211.209 describe 5-[[2-[(2,6-dicloro-3-metilfenil)amino]fenil]metileno]-2,4-tiazolidinadiona.

Los solicitantes entienden que el documento WO 9705135 describe [2S-[2α(Z),4α]]-1-([1,1'-bifenil]-4-ilsulfonil)-N-[2-[(2,4-dioxo-5-tiazolidinilideno)metil]fenil]-4-(metiltio)-2-pirrolidinametanamina, éster de 1,1-dimetiletilo de ácido [[2S-[2α(Z),4α]]-3-[[[1-([1,1'-bifenil]-4-ilsulfonil)-4-(metiltio)-2-pirrolidinil]metil]amino]-4-[(2,4-dioxo-5-tiazolidinilideno)metil]fenil]-carbámico y [2S-[2α(Z),4α]]-N-[5-amino-2-[(2,4-dioxo-5-tiazolidinilideno)metil]fenil]-1-([1,1'-bifenil]-4-ilsulfonil)-4-(metiltio)-2-pirrolidinametanamina.

Lo que los solicitantes entienden anteriormente no implica admisiones.

En algunas realizaciones, los compuestos descritos en la presente podrían usarse en la clínica, ya sea como un agente único en sí mismo o en combinación con otros agentes clínicamente relevantes. Este compuesto podría prevenir los posibles mecanismos de resistencia al cáncer que pueden originarse debido a mutaciones en un conjunto de genes.

El tratamiento anti-cáncer definido en la presente puede aplicarse como terapia única o puede implicar, además del compuesto de la invención, cirugía o radioterapia o quimioterapia convencionales. Dicha quimioterapia puede incluir una o más de las siguientes categorías de agentes antitumorales:

(i) fármacos antiproliferativos/antineoplásicos y combinaciones de los mismos, tal como se emplean en la oncología médica, como agentes alquilantes (por ejemplo cis-platina, carboplatina, ciclofosfamida, mostaza de nitrógeno, melfalán, clorambucil, busulfán y nitrosoureas); antimetabolitos (por ejemplo, antifolatos como fluoropirimidinas tal como 5-fluorouracilo y tegafur, raltitrexed, metotrexato, citosina arabinosida e hidroxiurea); antibióticos antitumorales (por ejemplo: antraciclinas como

adriamicina, bleomicina, doxorubicina, daunomicina, epirubicina, idarubicina, mitomicina-C, dactinomicina y mitramicina); agentes antimitóticos (por ejemplo alcaloides de la vinca como vincristina, vinblastina, vindesina y vinorelbina y taxoides como taxol y taxotere); e inhibidores de topoisomerasa (por ejemplo epipodofilotoxinas como etoposida y teniposida, amsacrina, topotecán y camptotecina); e inhibidores de proteosoma (por ejemplo, bortezomib [Velcade®]); y el agente anegrilida [Agrilin®]; y el agente alfa-interferón;

(ii) agentes citostáticos tales como antiestrógenos (por ejemplo tamoxifeno, toremifeno, raloxifeno, droloxifeno y yodoxifeno), reguladores hacia abajo del receptor de estrógenos (por ejemplo, fulvestrant), antiandrógenos (por ejemplo bicalutamida, flutamida, nilutamida y acetato de ciproterona), antagonistas de LHRH o agonistas de LHRH (por ejemplo goserelina, leuprorelina y buserelina), progestógenos (por ejemplo acetato de megestrol), inhibidores de aromatasa (por ejemplo anastrozol, letrozol, vorazol y exemestano) e inhibidores de 5α-reductasa como finasterida;

(iii) agentes que inhiben la invasión de células cancerosas (por ejemplo inhibidores de metaloproteinasa como marimastat e inhibidores del receptor de la función del activador plasminógeno de uroquinasa);

(iv) inhibidores de la función del factor de crecimiento, por ejemplo, dichos inhibidores incluyen anticuerpos del factor de crecimiento, anticuerpos del receptor del factor de crecimiento (por ejemplo el anticuerpo anti-erbB2 trastuzumab) [Herceptin™] y el anticuerpo anti erbB1 cetuximab [C225], inhibidores de farnesil transferasa, inhibidores de serina/treonina quinasa, por ejemplo, inhibidores de la familia del factor de crecimiento epidérmico (por ejemplo, inhibidores de la familia de la tirosina quinasa EGFR como:

N-(3-cloro-4-fluorofenil)-7-metoxi-6-(3-morfolinopropoxi)quinazolin-4-amina (gefitinib, ZD1839),

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),

por ejemplo, inhibidores de la familia del factor de crecimiento derivado de plaquetas y por ejemplo inhibidores de la familia del factor de crecimiento de

hepatocitos, por ejemplo inhibidores o fosfotidilinositol 3-quinasa (PI3K) y por ejemplo inhibidores de proteína quinasa activada por mitógenos (MEK1/2) y por ejemplo inhibidores de proteína quinasa B (PKB/Akt), por ejemplo inhibidores la familia de tirosinas quinasas Src y/o la familia de tirosinas quinasas Abelson (Abl) tales como AZD0530 y dasatinib (BMS-354825) y mesilato de imatinib (Gleevec™); y cualquier agente que modifique la señalización de STAT;

(v) agentes antiangiogénicos como los que inhiben los efectos del factor de crecimiento endotelial vascular, (por ejemplo el anticuerpo del factor de crecimiento endotelial anti-vascular bevacizumab [Avastin™], compuestos como los que se describen en las Solicitudes de Patente Internacionales WO 97/22596, WO 97/30035, WO 97/32856 y WO 98/13354) y compuestos que operan mediante otros mecanismos (por ejemplo: linomida, inhibidores de la función integrina αvβ3 y angiostatina);

(vi) agentes que producen daños vasculares como Combretastatina A4 y los compuestos revelados en las Solicitudes de Patente Internacionales WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 y WO 02/08213;

(vii) terapias anti-sentido, por ejemplo, aquellas dirigidas a los blancos mencionados anteriormente, como ISIS 2503, un anti-sentido anti-ras;

(viii) abordajes de terapia génica, incluyendo por ejemplo, el reemplazo de genes aberrantes como el aberrante p53 o los aberrantes BRCA1 o BRCA2, los enfoques de la GDEPT (terapia de pro-fármaco de enzimas dirigidas por genes) como los que emplean citosina deaminasa, timidina quinasa o una enzima nitrorreductasa bacterial y abordajes para incrementar la tolerancia de los pacientes a la quimioterapia o la radioterapia, como la terapia genética de resistencia a múltiples fármacos; y

(ix) abordajes de inmunoterapia, incluyendo, por ejemplo, abordajes ex-vivo e in-vivo para incrementar la inmunogenicidad de las células tumorales de los pacientes, como en la transfección con citoquinas como interleuquina 2, interleuquina 4 o el factor de estimulación de la colonia de granulocitos-macrófagos, abordajes para disminuir la anergia de las células T, abordajes que utilizan células inmunes transfectadas como células dendríticas transfectadas con citoquina, abordajes que emplean líneas de células tumorales transfectadas con citoquinas y abordajes que emplean anticuerpos anti-

idiotípicos y abordajes que utilizan los fármacos inmunomoduladores talidomida y lenalidomida [Revlimid®].

Dicho tratamiento conjunto puede lograrse mediante la dosificación simultánea, secuencial o separada de los componentes individuales del tratamiento. Dichos productos de combinación emplean los compuestos de esta invención dentro del rango de dosificación descrito anteriormente y los otros agentes farmacéuticamente activos dentro de su rango de dosificación aprobado.

La invención se refiere a inhibidores de fosforilación de quinasas PIM. En otras realizaciones adicionales, la invención se refiere a una composición farmacéutica que comprende compuestos descritos en la presente y su uso en la prevención y el tratamiento de cáncer.

Se comprenderá que las composiciones descritas en la presente pueden existir en tautómeros en forma sólida y en forma de solución. Por ejemplo, pueden dibujarse imidazol y heterociclos que contienen imidazol en una fórmula de forma tal que uno o el otro de los nitrógenos contenga un átomo de hidrógeno. Sin embargo, tal como se proporcionan en la presente, se considera que las realizaciones de dicha fórmula abarcan formas tautoméricas alternativas.

Tal como se utiliza en la presente, "alquilo" significa un hidrocarburo insaturado o saturado no cíclico de cadena recta o ramificada tal como los que contienen de 1 a 10 átomos de carbono, mientras que la expresión "alquilo inferior" o "alquilo C_{1-6}" tiene el mismo significado que alquilo pero contiene de 1 a 6 átomos de carbono. La expresión "alquilo superior" tiene el mismo significado que alquilo pero contiene de 7 a 10 átomos de carbono. Alquilos de cadena recta saturados representativos incluyen metilo, etilo, n-propilo, n-butilo, n-pentilo, n-hexilo, n-septilo, n-octilo, n-nonilo y similares; mientras que alquilos de cadena ramificada saturados incluyen isopropilo, sec-butilo, isobutilo, terc-butilo, isopentilo y similares. Los alquilos insaturados contienen al menos un doble o triple enlace entre átomos de carbono adyacentes (denominados "alquenilo" o "alquinilo", respectivamente). Alquenilos de cadena recta y ramificada representativos incluyen etilenilo, propilenilo, 1-butenilo, 2-butenilo, isobutilenilo, 1-pentenilo, 2-pentenilo, 3-metil-1-butenilo, 2-metil-2-butenilo, 2,3-dimetil-2-butenilo y similares; mientras que

alquinilos de cadena recta y ramificada representativos incluyen acetilenilo, propinilo, 1-butinilo, 2-butinilo, 1-pentinilo, 2-pentinilo, 3-metil-1-butinilo y similares.

Un "alquilo halogenado" se refiere a un grupo alquilo en el que uno o más o todos los hidrógenos están sustituidos por halógenos. Un alquilo halogenado representativo es trifluorometilo (es decir, $-CF_3$).

En la presente, los alquilos no aromáticos mono o policíclicos se denominan grupos "carbociclos" o "carbociclilos". Carbociclos saturados representativos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y similares; mientras que carbociclos insaturados incluyen ciclopentenilo y ciclohexenilo, arilos y similares.

Grupos "heterocarbociclos" o "heterocarbociclilo" son carbociclos que contienen de 1 a 4 heteroátomos seleccionados independientemente de nitrógeno, oxígeno y azufre que pueden ser saturados o insaturados (pero no aromáticos), monocíclicos o policíclicos, y en donde los heteroátomos de nitrógeno y azufre pueden oxidarse opcionalmente, y el heteroátomo de nitrógeno puede estar opcionalmente cuaternizado. Heterocarbociclos incluyen morfolinilo, pirrolidinonilo, pirrolidinilo, piperidinilo, hidantonilo, valerolactamilo, oxiranilo, oxetanilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidropiridinilo, tetrahidroprimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo, tetrahidropirimidinilo, tetrahidrotiofenilo, tetrahidrotiopiranilo y similares.

"Arilo" significa un anillo aromático carbocíclico monocíclico o policíclico tal como fenilo o naftilo.

Tal como se utiliza en la presente, "heteroarilo" se refiere a un heterocarbociclo aromático que tiene 1 a 4 heteroátomos seleccionados de nitrógeno, oxígeno y azufre y que contiene al menos 1 átomo de carbono, incluidos sistemas de anillos mono y policíclicos. Los sistemas de anillos policíclicos pueden contener, aunque no necesariamente, uno o más anillos no aromáticos, siempre que uno de los anillos sea aromático. Heteroarilos representativos son furilo, benzofuranilo, tiofenilo, benzotiofenilo, pirrolilo, indolilo, isoindolilo, azaindolilo, piridilo, quinolinilo, isoquinolinilo, oxazolilo, isooxazolilo, benzoxazolilo, pirazolilo, imidazolilo, benzimidazolilo, tiazolilo, benzotiazolilo, isotiazolilo, piridazinilo, pirimidinilo, pirazinilo, triazinilo, cinolinilo, ftalazinilo y quinazolinilo. Se prevé que el uso del

término "heteroarilo" incluya derivados N-alquilados tales como un sustituyente 1-metilimidazol-5-ilo.

Tal como se utiliza en la presente, "heterociclo" o "heterociclilo" se refieren a sistemas de anillos mono o policíclicos que tienen 1 a 4 heteroátomos seleccionados de nitrógeno, oxígeno y azufre y que contienen al menos 1 átomo de carbono. Los sistemas de anillos mono y policíclicos pueden ser aromáticos, no aromáticos o mezclas de anillos aromáticos y no aromáticos. Heterociclo incluye heterocarbociclos, heteroarilos y similares.

"Alquiltio" se refiere a un grupo alquilo, tal como se definió anteriormente, con el número de átomos de carbono indicado unidos a través de un puente de azufre. Un ejemplo de alquiltio es metiltio (es decir, -S-CH_3).

"Alcoxi" se refiere a un grupo alquilo, tal como se definió anteriormente, con el número de átomos de carbono indicado unidos a través de un puente de oxígeno. Ejemplos de alcoxi incluyen, a modo no taxativo, metoxi, etoxi, n-propoxi, i-propoxi, n-butoxi, s-butoxi, t-butoxi, n-pentoxi y s-pentoxi. Grupos alcoxi preferidos son metoxi, etoxi, n-propoxi, i-propoxi, n-butoxi, s-butoxi, t-butoxi.

"Alquilamino" se refiere a un grupo alquilo, tal como se definió anteriormente, con el número de átomos de carbono indicado unidos a través de un puente de amino. Un ejemplo de alquilamino es metilamino (es decir, -NH-CH_3).

"Alcanoilo" se refiere a un alquilo, tal como se definió anteriormente, con el número de átomos de carbono indicado unidos a través de un puente de carbonilo (es decir, -(C=O)alquilo).

"Alquilsulfonilo" se refiere a un alquilo, tal como se definió anteriormente, con el número de átomos de carbono indicado unidos a través de un puente de sulfonilo (es decir, -S(=O)$_2$alquilo) tal como mesilo y similares y "arilsulfonilo" se refiere a un arilo unido a través de un puente de sulfonilo (es decir, -S(=O)$_2$arilo).

"Alquilsulfamoilo" se refiere a un alquilo, tal como se definió anteriormente, con el número de átomos de carbono indicado unidos a través de un puente de sulfamoilo (es decir, -NHS(=O)$_2$alquilo) y "arilsulfamoilo" se refiere a un alquilo unido a través de un puente de sulfamoilo (es decir, -NHS(=O)$_2$arilo).

"Alquilsulfinilo" se refiere a un alquilo, tal como se definió anteriormente, con el número de átomos de carbono indicado unidos a través de un puente de sulfinilo (es decir, -S(=O)alquilo).

El término "sustituido" se refiere a una molécula en donde al menos un átomo de hidrógeno es reemplazado por un sustituyente. Cuando están sustituidos, uno o más de los grupos son "sustituyentes". La molécula puede estar múltiplemente sustituida. En caso de un sustituyente oxo ("=O"), los dos átomos de hidrógeno son reemplazados. Ejemplos de sustituyentes en este contexto pueden incluir halógeno, hidroxi, alquilo, alcoxi, nitro, ciano, oxo, carbociclilo, carbocicloalquilo, heterocarbociclilo, heterocarbocicloalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo, $-NR_aR_b$, $-NR_aC(=O)R_b$, $-NR_aC(=O)NR_aNR_b$, $-NR_aC(=O)OR_b$, $-NR_aSO_2R_b$, $-C(=O)R_a$, $-C(=O)OR_a$, $-C(=O)NR_aR_b$, $-OC(=O)NR_aR_b$, $-OR_a$, $-SR_a$, $-SOR_a$, $-S(=O)_2R_a$, $-OS(=O)_2R_a$ y $-S(=O)_2OR_a$. R_a y R_b en este contexto puede ser iguales o diferentes e independientemente hidrógeno, halógeno hidroxilo, alquilo, alcoxi, alquilo, amino, alquilamino, dialquilamino, carbociclilo, carbocicloalquilo, heterocarbociclilo, heterocarbocicloalquilo, arilo, arilalquilo, heteroarilo, heteroarilalquilo.

La expresión "opcionalmente sustituido", tal como se utiliza en la presente, significa que la sustitución es opcional y, por lo tanto, es posible que el átomo designado sea insustituido.

Tal como se utiliza en la presente, el término "prevenir" incluye la prevención de la reaparición, diseminación o inicio. No se pretende que la presente invención se limite a la prevención completa. En algunas realizaciones, el inicio es retrasado o la gravedad de la enfermedad es reducida.

Tal como se utiliza en la presente, el término "tratar" no se limita al caso en el que el sujeto (por ejemplo, el paciente) es curado y la enfermedad es erradicada. Por el contrario, realizaciones de la presente invención también contemplan el tratamiento que meramente reduce los síntomas y/o retrasa el avance de la enfermedad.

Tal como se utiliza en la presente, "sales" se refiere a derivados de los compuestos divulgados, en donde el compuesto base se modifica mediante la obtención de sales ácidas o básicas del mismo. Ejemplos de sales incluyen, a modo no taxativo, sales ácidas minerales u orgánicas de residuos básicos tales como aminas, alquilaminas o

dialquilaminas; sales alcalinas u orgánicas de residuos ácidos tales como ácidos carboxílicos; y similares. En una realización preferida, las sales son sales farmacéuticamente aceptables no tóxicas convencionales que incluyen las sales de amonio cuaternario del compuesto base formado y ácidos no tóxicos inorgánicos u orgánicos. Las sales preferidas incluyen aquellas derivadas de ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico, sulfámico, fosfórico, nítrico y similares; y las sales preparadas a partir de ácidos orgánicos tales como acético, propiónico, succínico, glicólico, esteárico, láctico, málico, tartárico, cítrico, ascórbico, pamoico, maleico, hidroximaleico, fenilacético, glutámico, benzoico, salicílico, sulfanílico, 2-acetoxibenzoico, fumárico, toluenosulfónico, metanosulfónico, etano disulfónico, oxálico, isetiónico y similares

Las sales farmacéuticamente aceptables de la presente invención pueden sintetizarse a partir del compuesto base que contiene un resto básico o ácido mediante métodos químicos convencionales. En general, dichas sales pueden prepararse haciendo reaccionar las formas de ácido o base libre de estos compuestos con una cantidad estequiométrica de la base o ácido apropiados en agua o en un disolvente orgánico, o una mezcla de ambos; generalmente se utilizan medios no acuosos tales como éter, acetato de etilo, etanol, isopropanol o acetonitrilo. Pueden encontrarse listas de sales adecuadas en Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, cuya divulgación se incorpora a la presente a modo de referencia.

"Sujeto" significa cualquier animal, preferiblemente un paciente humano, ganado o mascota doméstica.

"Cáncer" se refiere a cualquiera de las diversas enfermedades celulares con neoplasmas malignos caracterizados por la proliferación de las células. No se pretende que las células enfermas deban invadir el tejido circundante y producir metástasis en nuevos lugares del cuerpo. Cáncer puede implicar cualquier tejido del cuerpo y tener muchas formas diferentes en cada parte del cuerpo. En el contexto de ciertas realizaciones, el hecho de que el "cáncer se reduzca" podrá identificarse mediante una variedad de métodos de diagnóstico conocidos para el experto en la técnica, entre los que se incluyen, a modo no taxativo, observación de la reducción del tamaño o cantidad de las masas tumorales o de un aumento de la apoptosis de células cancerosas, por ejemplo,

un aumento superior al 5% de la apoptosis de células cancerosas para un compuesto de prueba en comparación con un testigo sin el compuesto. También puede identificarse por un cambio en el perfil de expresión de biomarcador o gen relevante, tal como PSA para el cáncer de próstata, her2 para el cáncer de mama u otros.

Las presentes composiciones farmacéuticas pueden tener forma de soluciones, suspensiones, emulsiones, comprimidos, pastillas, gránulos, cápsulas que contienen líquidos, polvos, formulaciones de liberación sostenida, supositorios, emulsiones, aerosoles, pulverizadores, suspensiones o cualquier otra forma adecuada para su uso.

La administración puede ser tópica, es decir, la sustancia se aplica directamente donde se desea, enteral u oral, es decir, la sustancia se administra a través del tracto digestivo, o parenteral, es decir, la sustancia se administra por otras vías diferentes del tracto digestivo, tal como mediante inyección.

En una realización preferida, el compuesto activo y opcionalmente otro agente terapéutico o profiláctico se formulan de acuerdo con procedimientos rutinarios como composiciones farmacéuticas adaptadas para la administración intravenosa a seres humanos. Típicamente, el compuesto activo para la administración intravenosa son soluciones en solución amortiguadora acuosa isotónica estéril. Cuando es necesario, las composiciones también pueden incluir un agente solubilizante. Las composiciones para la administración intravenosa pueden incluir opcionalmente un anestésico local tal como lignocaína para aliviar el dolor en el lugar de la inyección. Generalmente, los ingredientes se suministran separadamente o mezclados en una forma de dosificación unitaria, por ejemplo, como un polvo liofilizado seco o concentrado sin agua en un recipiente herméticamente sellado, tal como una ampolla. Cuando el compuesto activo ha de administrarse mediante infusión, el mismo puede dispensarse, por ejemplo, con una botella de infusión que contenga agua o solución salina estéril de grado farmacéutico. Cuando el compuesto activo se administra mediante inyección, puede proporcionarse una ampolla de agua estéril para inyección o solución salina para que los ingredientes puedan mezclarse antes de la administración.

Las composiciones para la administración oral pueden estar, por ejemplo, en forma de comprimidos, grageas, suspensiones acuosas u oleosas, gránulos, emulsiones, cápsulas, jarabes o elixires. Las composiciones administradas oralmente pueden contener

uno o más agentes opcionales, por ejemplo, agentes edulcorantes tales como fructosa, aspartamo o sacarina; agentes saborizantes tales como menta, esencia de gaulteria o cereza; agentes colorantes; y agentes conservantes para proporcionar una preparación farmacéuticamente agradable al paladar. También puede utilizarse un material de retardo del tiempo tal como monoestearato de glicerol o estearato de glicerol. Las composiciones orales pueden incluir vehículos estándar tales como manitol, lactosa, almidón, estearato de magnesio, sacarina sódica, celulosa, carbonato de magnesio y similares. Dichos vehículos son preferiblemente de grado farmacéutico.

Las composiciones para uso de acuerdo con la presente invención pueden formularse de manera convencional utilizando uno o más portadores o excipientes fisiológicamente aceptables. Por lo tanto, el compuesto y opcionalmente otro agente terapéutico o profiláctico y sus sales y solvatos fisiológicamente aceptables pueden formularse como composiciones farmacéuticas para la administración por inhalación o insuflación (a través de la boca o la nariz) o mediante administración oral, parenteral o a través de las mucosas (como bucal, vaginal, rectal, sublingual). En una realización, se utiliza la administración local o sistémica.

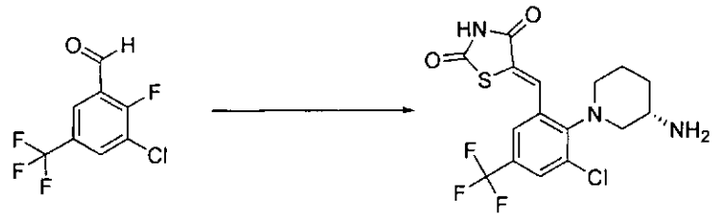
Para la administración oral, las composiciones pueden formularse, por ejemplo, como comprimidos o cápsulas preparadas por medios convencionales con excipientes farmacéuticamente aceptables tales como agentes aglutinantes (por ejemplo, almidón de maíz pregelatinizado, polivinilpirrolidona o hidroxipropilmetilcelulosa); cargas (por ejemplo, lactosa, celulosa microcristalina o hidrogenofosfato de calcio); lubricantes (por ejemplo, estearato de magnesio, talco o sílice); desintegrantes (por ejemplo, almidón de papa o glicolato de almidón sódico); o agentes humectantes (por ejemplo, laurilsulfato de sodio). Los comprimidos pueden recubrirse mediante procedimientos bien conocidos en la técnica. Las preparaciones líquidas para la administración oral pueden formularse como, por ejemplo, soluciones, jarabes o suspensiones, o pueden presentarse como un producto seco para reconstitución con agua u otro vehículo antes de su uso. Dichas preparaciones líquidas pueden prepararse de forma convencional con aditivos farmacéuticamente aceptables tales como agentes de suspensión (por ejemplo, jarabe de sorbitol, derivados de celulosa o grasas comestibles hidrogenadas); agentes emulsionantes (por ejemplo, lecitina o goma arábiga); vehículos no acuosos (por ejemplo,

aceite de almendras, ésteres oleosos, alcohol etílico o aceites vegetales fraccionados); y conservantes (por ejemplo, metil o propil-p-hidroxibenzoatos o ácido sórbico). Las preparaciones también pueden contener sales amortiguadoras, agentes saborizantes, colorantes y edulcorantes según sea apropiado.

SECCIÓN EXPERIMENTAL

A continuación se proporcionan ejemplos de métodos para preparar y utilizar realizaciones de la invención. No se pretende limitar el alcance de la invención.

Ejemplo 1:

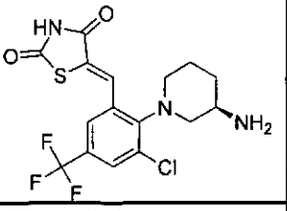
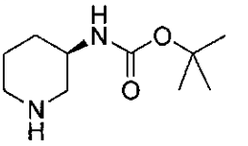
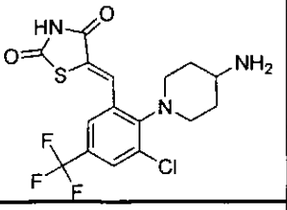
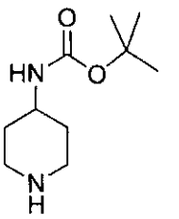
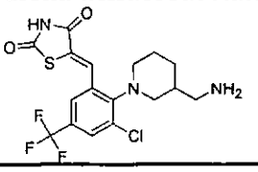
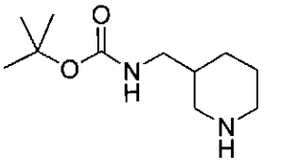


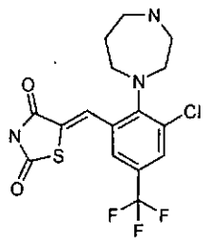
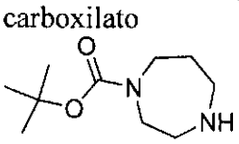
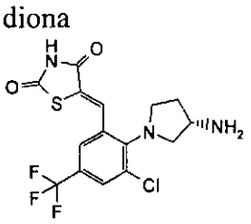
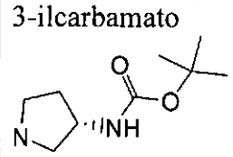
(*S,Z*)-5-(2-(3-aminopiperidin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona trifluoroacetato:

Se cargó un vial de 40 mL con una barra de agitación magnética, 3-cloro-2-fluoro-5-(trifluorometil)benzaldehído (0,134 ml, 1,10 mmol), acetonitrilo (2,76 ml), (*S*)-*terc*-butil piperidin-3-ilcarbamato (0,221 g, 1,10 mmol) y K_2CO_3 (0,229 g, 1,66 mmol). El vial se calentó hasta alcanzar 70°C con agitación durante 2 h. El recipiente se enfrió hasta alcanzar la TA y la mezcla se diluyó con DCM y se filtró. El filtrado se concentró al vacío para proporcionar el aldehído sustituido que se disolvió en EtOH (2,76 ml). Luego se agregaron tiazolidina-2,4-diona (0,155 g, 1,32 mmol) y piperidina (9,40 mg, 0,11 mmol). La mezcla se calentó hasta alcanzar reflujo durante 4 h antes de dejarse enfriar hasta alcanzar la TA y la mezcla se concentró al vacío. El producto se disolvió en DCM (2 mL) y TFA (1 mL) y se agitó a TA durante 1 h antes de concentrarse al vacío. El residuo se disolvió en DMSO (~ 2 mL) y se purificó mediante HPLC en fase inversa para proporcionar (*S,Z*)-5-(2-(3-aminopiperidin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona trifluoroacetato (0,214 g, 37,3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12,78 (s, 1 H) 7,95 (m, 3 H) 7,79 (s, 1 H) 7,62 (s, 1 H) 3,40-3,20 (s, 5 H) 2,12-2,06 (m, 1H) 1,79-1,70 (m 1H) 1,65-1,60 (m, 1 H) 1,52-1,41 (m, 1 H); *m/z* 406.

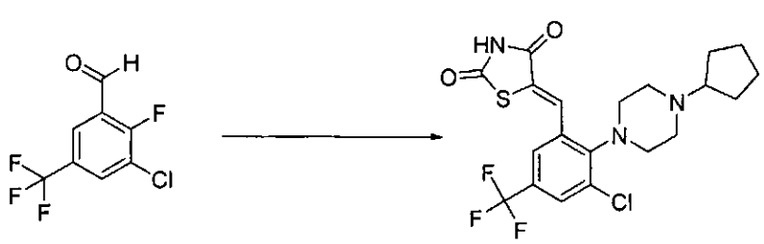
Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 1, utilizando los materiales de partida apropiados. Los siguientes compuestos base

obtenidos después de la cromatografía pueden convertirse en sus correspondientes sales clorhidrato utilizando el procedimiento en el Ejemplo 6 o un procedimiento similar.

Ej.	Compuesto	^{1}H NMR (300 MHz)	m/z	MP
2	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona trifluoroacetato 	12,79 (s, 1 H) 7,98 (s, 2 H) 7,95 (s, 1 H) 7,79 (s, 1 H) 7,62 (s, 1 H) 3,31-3,20 (m, 5 H) 2,12-2,09 (m, 1 H) 1,85 - 1,77 (m, 1 H) 1,66-1,63 (m, 1 H) 1,45-1,40 (m, 1 H)	406	(*R*)-*terc*-butil piperidin-3-ilcarbamato 
3	(*Z*)-5-(2-(4-aminopiperidin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona trifluoroacetato 	12,76 (s, 1 H) 7,99 (s, 1 H) 7,91 (s, 2 H) 7,78 (s, 1 H) 7,60 (s, 1 H) 3,33-3,18 (m, 5 H) 1,94 (d, 2 H) 1,71-1,60 (m, 2 H)	406	*terc*-butil piperidin-4-ilcarbamato 
4	(*Z*)-5-(2-(3-(aminometil)piperidin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona trifluoroacetato 	12,78 (s, 1 H) 7,93 (s, 1 H) 7,84 (s, 1 H) 7,75 (s, 1 H) 7,61 (s, 1 H) 3,31-3,05 (m, 6 H) 2,79-2,71 (m, 1 H) 1,95-1,89 (m, 2 H) 1,72-1,55 (m, 2 H) 1,29-1,10 (m, 1 H)	421	*terc*-butil piperidin-3-ilmetilcarbamato 

5A	(Z)-5-(3-cloro-2-(1,4-diazepan-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,83 (brs, 1 H) 9,20 (brs, 2 H) 8,05 (d, 1 H) 7,90 (s, 1 H) 7,66 (d,1 H) 3,51 (brs, 2 H) 3,35 (d, 2 H) 3,26 - 3,03 (m, 4 H) 2,27 – 1,99 (m, 2 H)	405	*terc*-butil 1,4-diazepan-1-carboxilato 
5B	(*S*,*Z*)-5-(2-(3-aminopirrolidin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona 	12,73 (brs, 1 H) 8,29 (brs, 3 H) 7,93 (s, 1 H) 7,83 (s, 1 H) 7,66 (s, 1 H) 3,88 (brs, 1 H) 3,66 (dd, 1 H), 3,52 - 3,27 (m, 3 H) 2,42-2,19 (m, 1 H) 2,12-1,88 (m, 1 H)	392	*terc*-butil (3*S*)-pirrolidin-3-ilcarbamato 

Ejemplo 6:

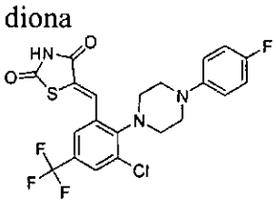
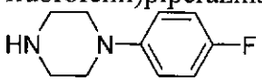
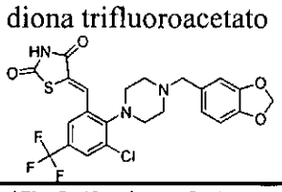
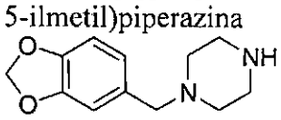
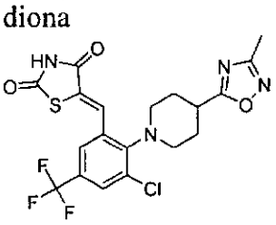
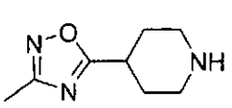


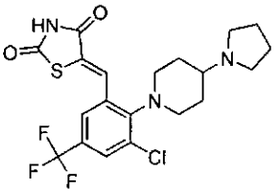
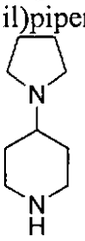
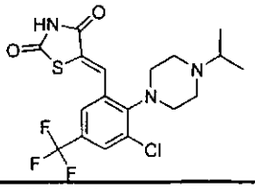
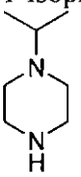
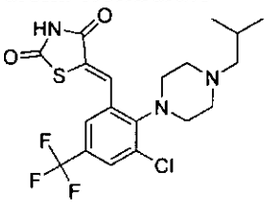
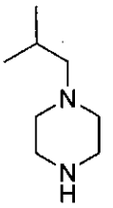
(Z)-5-(3-cloro-2-(4-ciclopentilpiperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato:

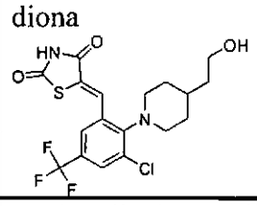
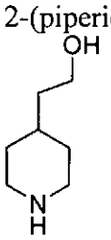
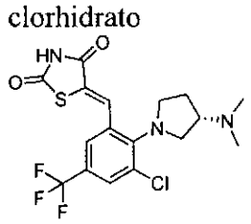
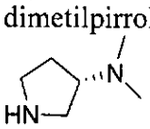
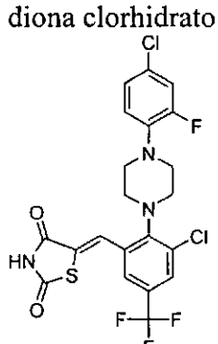
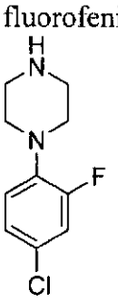
Se cargó un vial de 40 mL con una barra de agitación magnética, 3-cloro-2-fluoro-5-(trifluorometil)benzaldehído (0,134 ml, 1,10 mmol), acetonitrilo (2,76 ml), 1-ciclopentilpiperazina (0,213 g, 1,38 mmol) y K_2CO_3 (0,229 g, 1,66 mmol). El vial se calentó hasta alcanzar 70°C con agitación durante 2 h. El recipiente luego se enfrió hasta alcanzar la TA y la mezcla se diluyó con DCM y se filtró. El filtrado se concentró al

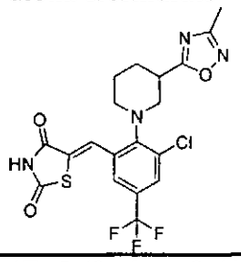
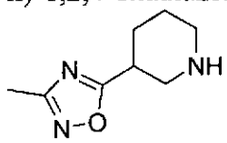
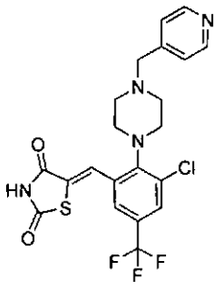
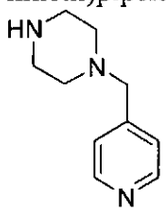
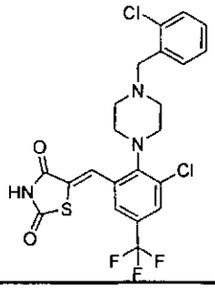
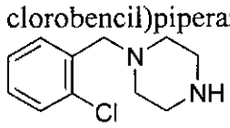
vacío para proporcionar el aldehído sustituido que se disolvió en EtOH (2,76 ml). Luego se agregaron tiazolidina-2,4-diona (0,155 g, 1,32 mmol) y piperidina (9,40 mg, 0,11 mmol) y la mezcla se calentó hasta alcanzar reflujo durante 4 h antes de dejarse enfriar hasta alcanzar la TA. La mezcla luego se concentró al vacío para proporcionar el producto que se disolvió en DMSO (~ 2 mL) y se purificó mediante HPLC en fase inversa para proporcionar fracciones que se concentraron al vacío, se suspendieron en metanol (~5 mL) y HCl 1N en éter dietílico (~2 mL). Esta mezcla se concentró al vacío para proporcionar (*Z*)-5-(3-cloro-2-(4-ciclopentilpiperazin-1-il)-5-(trifluorometil) bencilideno)tiazolidina-2,4-diona clorhidrato (0,215 g, 39,3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12,78 (s, 1 H) 7,96 (s, 1 H) 7,83 (s, 1 H) 7,63 (s, 1 H) 3,77-3,50 (m, 5 H) 3,30-3,22 (m, 2 H) 3,08-2,99 (m, 2 H) 2,03-1,99 (m, 2 H) 1,84-1,61 (m, 4 H) 1,60-1,50 (m, 2 H); *m/z* 461.

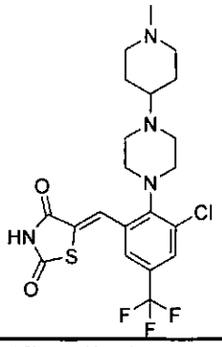
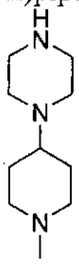
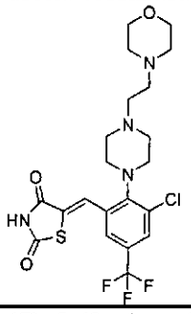
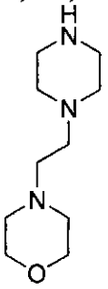
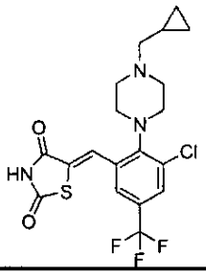
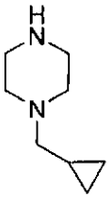
Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 6, utilizando los materiales de partida apropiados. Los siguientes compuestos base obtenidos después de la cromatografía pueden convertirse en su correspondiente sal clorhidrato de forma similar a la que se describe en el Ejemplo 6.

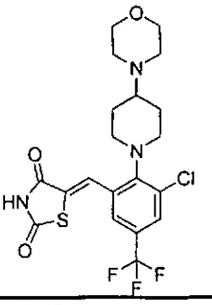
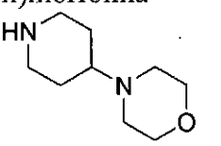
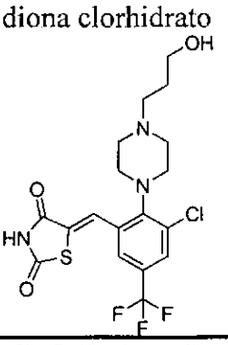
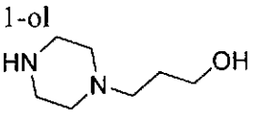
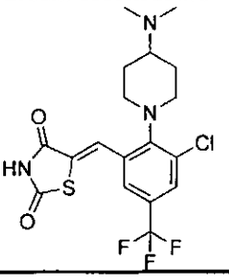
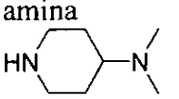
Ej.	Compuesto	^{1}H NMR	m/z	MP
7	(Z)-5-(3-cloro-2-(4-(4-fluorofenil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona 	12,74 (s, 1 H) 7,89 - 8,01 (m, 2 H) 7,62 (s, 1 H) 6,99 - 7,13 (m, 4 H) 3,34-3,23 (m, 8 H)	486	1-(4-fluorofenil)piperazina 
8	(Z)-5-(2-(4-(benzo[d][1,3]dioxol-5-ilmetil)piperazin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona trifluoroacetato 	12,77 (s, 1 H) 7,97 (d, 1 H) 7,97 (s, 1 H) 7,77 (s, 1 H) 7,63 (s, 1 H) 7,10 (s, 1 H) 7,02 (s, 2 H) 6,08 (s, 2 H) 4,34 (s, 2 H) 3,58-3,11 (m, 8 H)	526	1-(benzo[d][1,3]dioxol-5-ilmetil)piperazina 
9	(Z)-5-(3-cloro-2-(4-(3-metil-1,2,4-oxadiazol-5-il)piperidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona 	12,72 (s, 1 H) 7,91 (s, 1 H) 7,84 (s, 1 H) 7,61 (s, 1 H) 3,33-3,18 (m, 4 H) 2,79-2,71 (m, 1 H) 2,33 (s, 3 H) 2,06 (d, 2 H) 1,98-1,80 (m, 2 H)	473	3-metil-5-(piperidin-4-il)-1,2,4-oxadiazol 

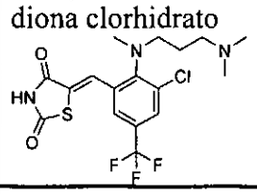
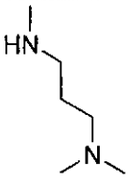
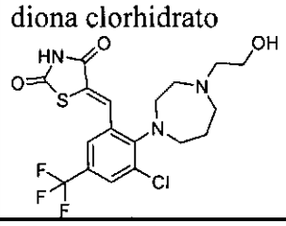
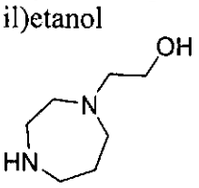
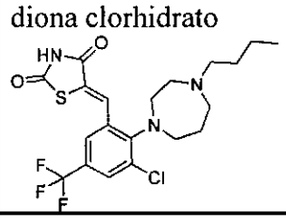
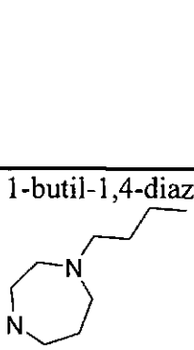
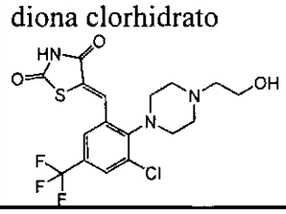
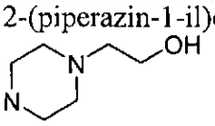
10	(Z)-5-(3-cloro-2-(4-(pirrolidin-1-il)piperidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,78 (s, 1 H) 7,92 (s, 1 H) 7,79 (s, 1 H) 7,60 (s, 1 H) 3,33 - 3,20 (m, 5 H) 3,12 - 3,03 (m, 4 H) 2,09 (d, 2 H) 1,97 - 1,78 (m, 6 H)	461	4-(pirrolidin-1-il)piperidina 
11	(Z)-5-(3-cloro-2-(4-isopropilpiperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,80 (s, 1 H) 7,96 (s, 1 H) 7,82 (s, 1 H) 7,62 (s, 1 H) 3,85 (t, 2 H) 3,55-3,52 (m, 1 H) 3,41 (d, 2 H) 3,26 (d, 2 H) 3,10 - 3,06 (m, 2 H) 1,32 (d, 6 H)	434	1-isopropilpiperazina 
12	(Z)-5-(3-cloro-2-(4-isobutilpiperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,80 (s, 1 H) 7,96 (d, 1 H) 7,80 (s, 1 H) 7,63 (s, 1 H) 3,87 (brs, 2 H) 3,52 (d, 2 H) 3,27 (brs, 2 H) 3,11 - 3,00 (m, 4 H) 2,10 (qq, 1 H) 1,00 (d, 6 H)	450	1-isobutilpiperazina 

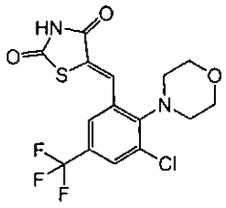
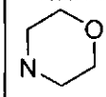
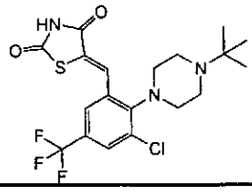
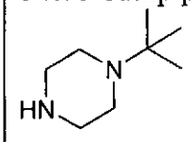
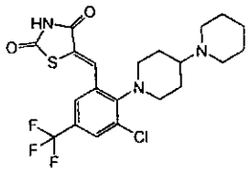
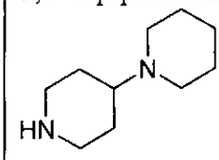
13	(*Z*)-5-(3-cloro-2-(4-(2-hidroxietil)piperidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona 	12,73 (s, 1 H) 7,87 (s, 1 H) 7,83 (s, 1 H) 7,59 (s, 1 H) 3,46 (t, 2 H) 3,23 (t, 2 H) 3,07 (brs, 2 H) 1,70 (d, 2 H) 1,61 - 1,52 (m, 1 H) 1,42 (q, 2 H) 1,33 - 1,20 (m, 2 H)	437	2-(piperidin-4-il)etanol 
14	(*S,Z*)-5-(3-cloro-2-(3-(dimetilamino)pirrolidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,65 (s, 1 H) 7,82 (s, 1 H) 7,72 (s, 1 H) 7,53 (s, 1 H) 3,59 - 3,50 (m, 1 H) 3,38 - 3,30 (m, 4 H) 2,56 (s, 6 H) 2,31 - 2,28 (m, 1 H) 2,09 - 2,01 (m, 1 H)	421	(*S*)-*N,N*-dimetilpirrolidin-3-amina 
15	(*Z*)-5-(3-cloro-2-(4-(4-cloro-2-fluorofenil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,75 (brs, 1 H) 8,06 – 7,90 (m, 2 H) 7,64 (d, 1 H) 7,38 (dd, 1 H) 7,23 (dd, 1 H) 7,11 (t, 1 H) 3,42 (m, 4 H) 3,15 (d, 4 H)	520	1-(4-cloro-2-fluorofenil)piperazina 

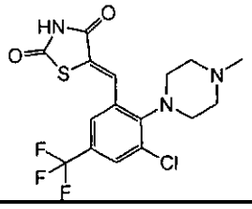
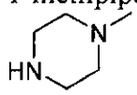
16	(*Z*)-5-(3-cloro-2-(3-(3-metil-1,2,4-oxadiazol-5-il)piperidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 		471	3-metil-5-(piperidin-3-il)-1,2,4-oxadiazol 
17	(*Z*)-5-(3-cloro-2-(4-(piridin-4-ilmetil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,75 (brs, 1H) 8,78 (d, 2 H) 7,98 (s, 1 H) 7,74 (brs, 1 H) 7,71 (s, 1 H) 7,64 (s, 1 H) 4,44 (brs, 2 H) 3,44 (brs, 4 H) 3,17 (s, 4 H)	483	1-(piridin-4-ilmetil)piperazina 
18	(*Z*)-5-(3-cloro-2-(4-(2-clorobencil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	7,98 (d, 1 H) 7,73 (dd, 1 H) 7,68 - 7,59 (m, 2 H) 7,58 - 7,42 (m, 3 H) 4,53 (brs, 2 H) 3,75-3,30 (m, 8 H)	517	1-(2-clorobencil)piperazina 

19	(Z)-5-(3-cloro-2-(4-(1-metilpiperidin-4-il)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	10,68 (brs, 1 H) 7,92 (d, 1 H) 7,78 (brs, 1 H) 7,58 (s, 1 H) 3,73 - 3,63 (m, 1 H) 3,61-3,41 (m, 6 H) 3,10 (brs, 3 H) 2,93 (brs, 3 H) 2,67 (s, 3 H) 2,39 - 2,18 (m, 2 H) 2,07 (brs, 2 H)	489	1-(1-metilpiperidin-4-il)piperazina 
20	(Z)-5-(3-cloro-2-(4-(2-morfolinoetil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	11,12 (brs, 1 H) 7,91 (d, 1 H) 7,79 (brs, 1 H) 7,59 (s, 1 H) 3,80-2,81 (m, 20 H)	505	4-(2-(piperazin-1-il)etil)morfolina 
21	(Z)-5-(3-cloro-2-(4-(ciclopropilmetil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,59 (brs, 1 H) 7,76 (d, 1 H) 7,61 (brs, 1 H) 7,43 (s, 1 H) 3,62 (brs, 2 H) 3,44 - 3,24 (m, 2 H) 3,10 (brs, 2 H) 2,87 (d, 4 H) 0,94 (brs, 1 H) 0,54 - 0,31 (m, 2 H) 0,32 - 0,08 (m, 2 H)	447	1-(ciclopropilmetil)piperazina 

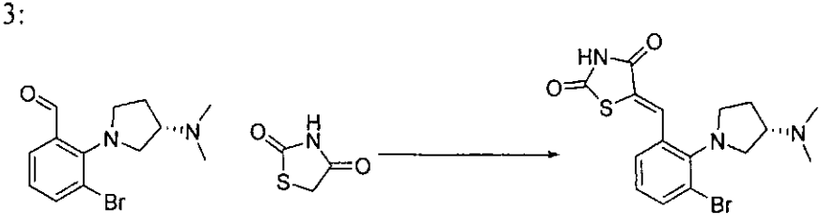
22	(*Z*)-5-(3-cloro-2-(4-morfolinopiperidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,92 (brs, 1 H) 8,08 (d, 1 H) 7,95 (brs, 1 H) 7,76 (s, 1 H) 4,14 (brs, 3 H) 3,98 (brs, 2 H) 3,58 (brs, 3 H) 3,53 - 3,34 (m, 3 H) 3,28 (brs, 2 H) 2,32 (brs, 2 H) 1,92 (d, 2 H)	476	4-(piperidin-4-il)morfolina 
23	(*Z*)-5-(3-cloro-2-(4-(3-hidroxipropil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,90 (brs, 1 H) 10,52 (brs, 1 H) 7,98 (d, 1 H) 7,84 (brs, 1 H) 7,65 (s, 1 H) 3,90 - 3,65 (m, 2 H) 3,57 - 3,41 (m, 5 H) 3,30 - 3,06 (m, 5 H) 1,96 - 1,73 (m, 2 H)	450	3-(piperazin-1-il)propan-1-ol 
24	(*Z*)-5-(3-cloro-2-(4-(dimetilamino)piperidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,79 (brs, 1 H) 7,94 (d, 1 H) 7,82 (s, 1 H) 7,61 (s, 1 H) 3,84 (brs, 1 H) 3,46 - 3,18 (m, 4 H) 2,75 (d, 6 H) 2,10 (d, 2 H) 1,74 (dd, 2 H)	434	*N,N*-dimetilpiperidin-4-amina 

25	(*Z*)-5-(3-cloro-2-((3-(dimetilamino)propil)(metil)amino)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,81 (brs, 1 H) 7,98 (d, 1 H) 7,81 (s, 1 H) 7,65 (d, 1 H) 3,15 (t, 2 H) 3,02 (brs, 2 H) 2,89 (s, 3 H) 2,72 (d, 6 H) 1,99 - 1,74 (m, 2 H)	422	*N1,N1,N3*-trimetilpropano-1,3-diamina 
26	(*Z*)-5-(3-cloro-2-(4-(2-hidroxietil)-1,4-diazepan-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	8,04 (brs, 1 H) 7,79 (d, 1 H) 7,63 (s, 1 H) 3,83 (t, 3 H) 3,71 (m, 2 H) 3,56 (m, 3 H) 3,33 (m, 6 H) 2,21 (m, 2 H)	451	2-(1,4-diazepan-1-il)etanol 
27	(*Z*)-5-(2-(4-butil-1,4-diazepan-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	10,76 (brs, 1 H) 8,06 (d, 1 H) 7,91 (brs, 1 H) 7,66 (d,1 H) 3,69 (m, 3 H) 3,57 (brs, 1 H) 3,46 (m, 3 H) 3,14 (m, 3 H) 2,34 (brs, 1 H) 2,16 (brs, 1 H) 1,73 (d, 2 H) 1,32 (m, 2 H) 0,93 (t, 3 H)	463	1-butil-1,4-diazepan 
28	(*Z*)-5-(3-cloro-2-(4-(2-hidroxietil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	7,98 (d, 1 H) 7,82 (brs, 1 H) 7,64 (d,1 H) 5,40 (brs, 1 H) 3,74 (m, 4 H) 3,56 (m, 3 H) 3,27 (m, 3 H) 3,18 (brs, 1 H) 3,11 (brs, 1 H)	436	2-(piperazin-1-il)etanol 

29	(Z)-5-(3-cloro-2-morfolino-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona 	12,76 (brs, 1 H) 7,94 (m, 2 H) 7,63 (d, 1 H) 3,71 (t, 4 H) 3,20 (brs, 4 H)	394	morfolina 
30	(Z)-5-(2-(4-*terc*-butilpiperazin-1-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,80 (brs, 1 H) 8,00 (d, 1 H) 7,85 (brs, 1 H) 7,65 (d, 1 H) 3,82 (m, 2 H) 3,56 (d, 2 H) 3,29 (dd, 2 H) 3,04 (m, 2 H) 1,39 (s, 9 H)	449	1-*terc*-butilpiperazina 
31	(Z)-5-(2-(1,4'-bipiperidin-1'-il)-3-cloro-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	9,75 (brs, 1 H) 7,94 (d, 1 H) 7,81 (brs, 1 H) 7,62 (s, 1 H) 3,29 (m, 7 H) 2,96 (m, 2 H) 2,14 (d, 2 H) 1,78 (m, 7 H) 1,44 (brs, 1 H)	474	1,4'-bipiperidina 

32	(*Z*)-5-(3-cloro-2-(4-metilpiperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	7,94 (brs, 1 H) 7,75 (d, 1 H) 7,63 (s, 1 H) 3,56 - 3,38 (m, 3 H) 3,31 - 3,21 (m, 5 H) 2,92 (s, 3 H)	406	1-metilpiperazina 

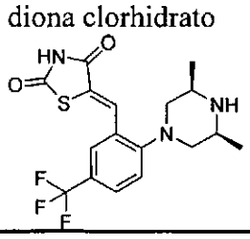
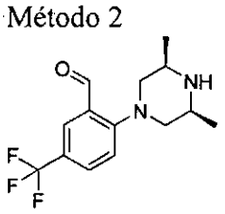
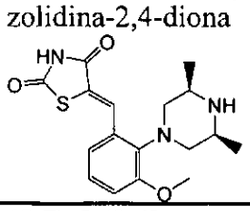
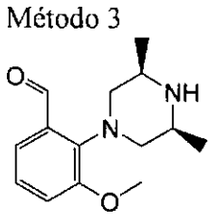
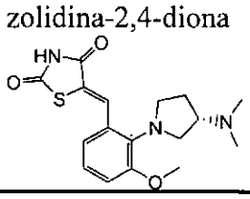
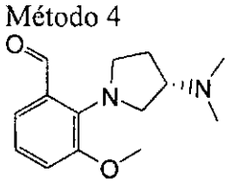
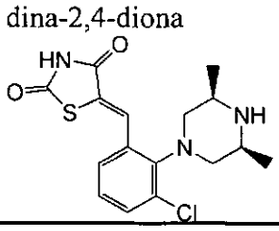
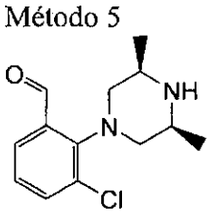
Ejemplo 33:



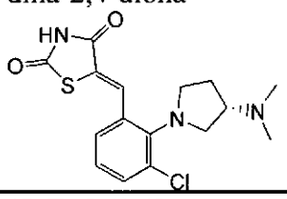
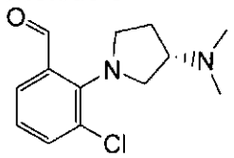
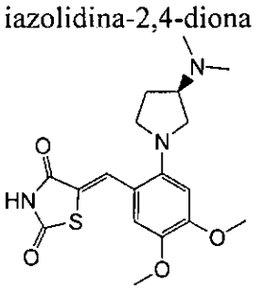
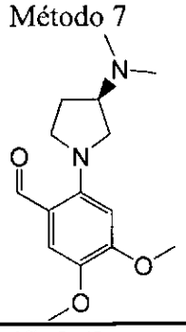
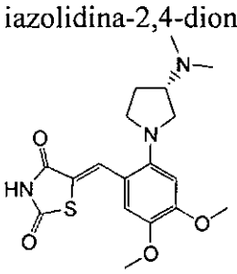
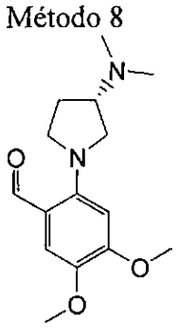
(*S,Z*)-5-(3-bromo-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato:

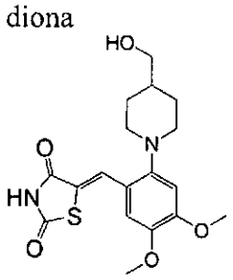
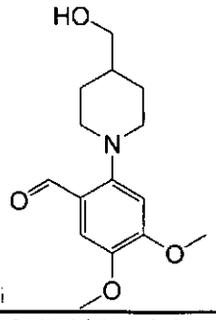
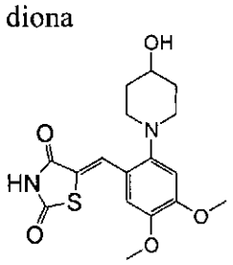
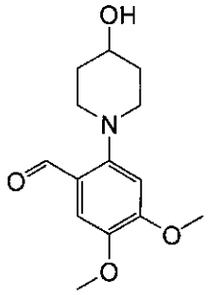
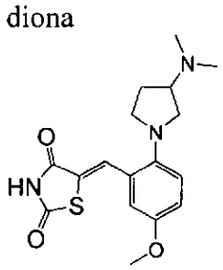
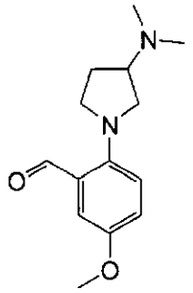
Un matraz de fondo redondo de 100 mL se cargó con una barra de agitación magnética, (*S*)-3-bromo-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído (Método 1) (0,370 g, 1,24 mmol), tiazolidina-2,4-diona (0,146 g, 1,24 mmol) y etanol (4,15 ml). Luego se agregó piperidina (0,012 ml, 0,12 mmol) y la reacción se calentó hasta alcanzar reflujo durante 2 h. Cuando se estimó que la reacción se había completado mediante LCMS, se dejó enfriar hasta alcanzar la TA y se concentró al vacío para proporcionar el producto que se purificó sobre 40 g de gel de sílice utilizando acetato de etilo / metanol (3:1) como eluyente para proporcionar la base libre que se suspendió en metanol (~ 5 mL) y HCl 1N en éter dietílico (2 mL) y se concentró al vacío para proporcionar (*S,Z*)-5-(3-bromo-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato (0,141 g, 26,2 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12,68 (s, 1 H) 7,91 (s, 1 H) 7,77 (d, 1 H) 7,48 (d, 1 H) 7,33 (t, 1 H) 4,10 - 4,02 (m, 1 H) 3,62 (t, 2 H) 3,50 - 3,45 (m, 2 H) 2,81 (s, 6 H) 2,42 - 2,38 (m, 1 H) 2,31 - 2,21 (m, 1 H); *m/z* 398.

Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 33, utilizando los materiales de partida apropiados. Los siguientes compuestos base obtenidos después de la cromatografía (en fase inversa o normal) pueden convertirse en su correspondiente sal clorhidrato como se describe en el Ejemplo 33, o mediante un procedimiento similar.

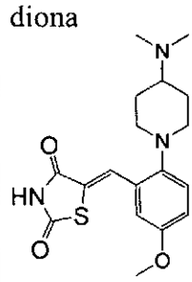
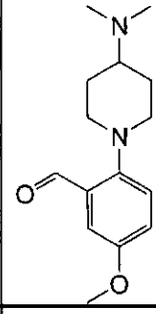
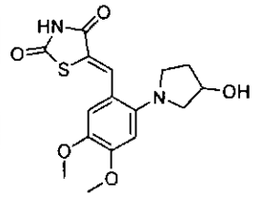
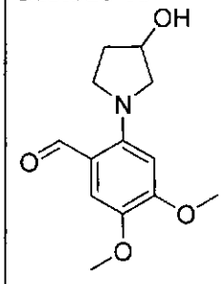
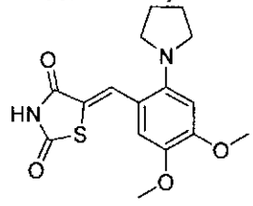
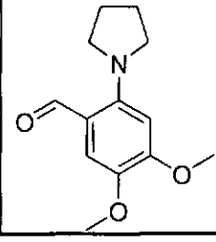
Ej.	Compuesto	^{1}H NMR	m/z	MP
34	(*Z*)-5-(2-((*3S,5R*)-3,5-dimetilpiperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,63 (s, 1 H) 8,99 - 8,94 (m, 1 H) 7,77 (d, 1 H) 7,72 (s, 2 H) 7,40 (d, 1 H) 3,49 - 3,43 (m, 2 H) 3,32 (d, 2 H) 2,92 (t, 2 H) 1,25 (d, 6 H)	387	2-((*3S,5R*)-3,5-dimetilpiperazin-1-il)-5-(trifluorometil)benzaldehído Método 2 
35	(*Z*)-5-(2-((*3S,5R*)-3,5-dimetilpiperazin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona 	7,87 (brs, 1 H) 7,24 (t, 1 H) 7,20 - 7,10 (m, 1 H) 7,02 (d, 1 H) 3,81 (s, 3 H) 3,48 - 3,23 (m, 2 H) 3,17 (t, 2 H) 2,89 (d, 2 H) 1,30 - 1,09 (m, 6 H)	348	2-((*3S,5R)*-3,5-dimetilpiperazin-1-il)-3-metoxibenzaldehído Método 3 
36	(*S,Z*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona 	7,89 (s, 1 H) 7,26 (m, 1 H) 7,10 (m, 2 H) 3,84 (s, 3 H) 3,41 - 3,29 (m, 7 H) 3,24 - 3,13 (m, 4 H) 2,18 (m, 1 H) 1,99 (m, 1 H)	348	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-3-metoxibenzaldehído Método 4 
37	(*Z*)-5-(3-cloro-2-((*3S,5R*)-3,5-dimetilpiperazin-1-il)bencilideno)tiazolidina-2,4-diona 	7,80 (s, 1 H) 7,50 (brs, 1 H) 7,38 (d, 1 H) 7,30 (brs, 1 H) 3,34-3,02 (m, 6 H) 1,26 - 1,09 (m, 6 H)	352	3-cloro-2-((3S,5R)-3,5-dimetilpiperazin-1-il)benzaldehído Método 5 

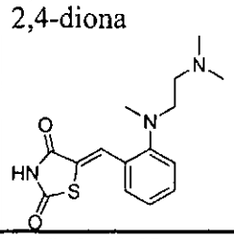
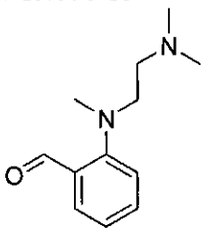
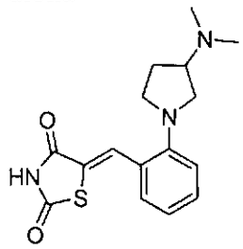
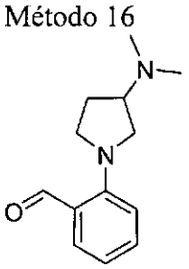
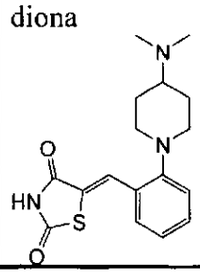
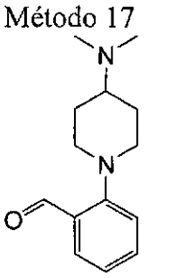
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38	(*S,Z*)-5-(3-cloro-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona 	7,73 (s, 1 H) 7,52 - 7,47 (m, 2 H) 7,47 (s, 1 H) 7,33 - 7,31 (m, 1 H) 3,58 - 3,52 (m, 1 H) 3,48 (m, 1 H) 3,37 - 3,27 (m, 3 H) 2,56 (s, 6 H) 2,26 - 2,35 (m, 1 H) 2,08 (m, 1 H)	352	(*S*)-3-cloro-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído Método 6 
39	(*R,Z*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona 	7,75 (s, 1 H) 6,98 (s, 1 H) 6,68 (s, 1 H) 3,83 (s, 3 H) 3,72 (s, 3 H) 3,24 - 3,06 (m, 4 H) 2,50 (m, 1 H) 2,32 (s, 6 H) 2,12 (m, 1 H) 1,84 (m, 1 H)	378	(*R*)-2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibenzaldehído Método 7 
40	(*S,Z*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona 	7,76 (s, 1 H) 6,98 (s, 1 H) 6,68 (s, 1 H) 3,83 (s, 3 H) 3,72 (s, 3 H) 3,26 – 3,01 (m, 5 H) 2,32 (s, 6 H) 2,15 – 2,09 (m, 1 H) 1,90 – 1,81 (m, 1 H)	378	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibenzaldehído Método 8 

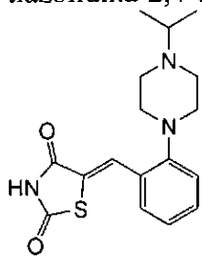
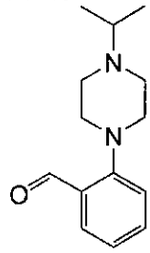
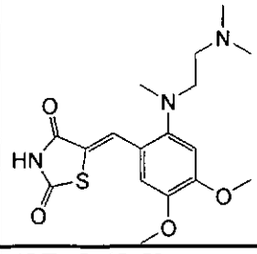
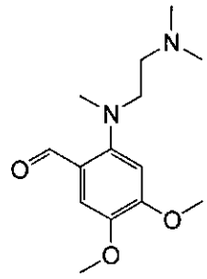
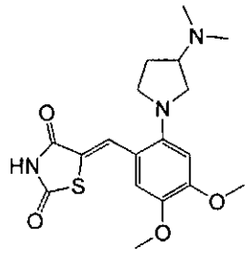
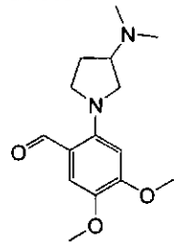
41	(5*Z*)-5-{2-[4-(hidroximetil)piperidin-1-il]-4,5-dimetoxibencilideno}-1-,3-tiazolidina-2,4-diona 	12,44 (brs, 1 H) 7,94 (s, 1 H) 7,05 - 6,87 (m, 1 H) 6,80 (s, 1 H) 4,54 (t, 1 H) 3,85 (s, 3 H) 3,76 (s, 3 H) 3,17 (d, 1 H) 3,03 (d, 2 H) 2,71 (t, 2 H) 1,75 (brs, 2 H) 1,56 - 1,26 (m, 3 H)	379	2-(4-(hidroximetil)piperidin-1-il)-4,5-dimetoxibenzaldehído Método 9 
42	(5*Z*)-5-[2-(4-hidroxipiperidin-1-il)-4,5-dimetoxibencilideno]-1,3-tiazolidina-2,4-diona 	12,50 (brs, 1 H) 8,02 (s, 1 H) 6,99 (s, 1 H) 6,92 - 6,82 (m, 1 H) 4,79 (d, 1 H) 3,90 (s, 3 H) 3,82 (s, 3 H) 3,74 - 3,58 (m, 1 H) 3,13 - 2,96 (m, 2 H) 2,88 - 2,71 (m, 2 H) 2,01 - 1,81 (m, 2 H) 1,78 - 1,58 (m, 2 H)	365	2-(4-hidroxipiperidin-1-il)-4,5-dimetoxibenzaldehído Método 10 
43	(5*Z*)-5-{2-[3-(dimetilamino)pirrolidin-1-il]-5-metoxibencilideno}-1,3-tiazolidina-2,4-diona 	7,51 (s, 1 H) 7,03 (d, 1 H) 6,99 (d, 1 H) 6,84 (dd, 1 H) 3,72 (s, 3 H) 3,09 - 3,21 (m, 1 H) 2,82 - 3,09 (m, 4 H) 2,23 (s, 6 H) 2,06 (d, 1 H) 1,73 - 1,85 (m, 1 H)	348	2-(3-(dimetilamino)pirrolidin-1-il)-5-metoxibenzaldehído Método 11 

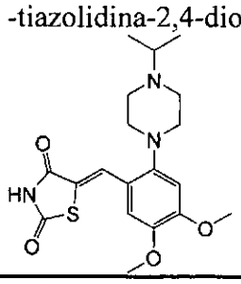
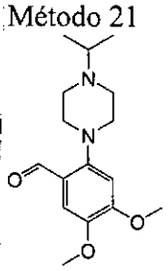
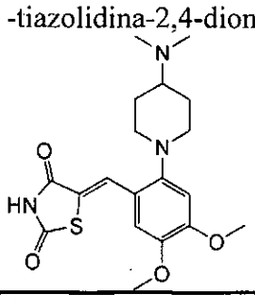
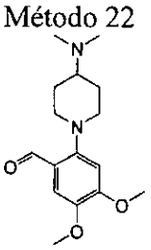
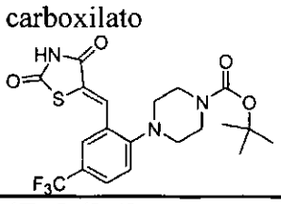
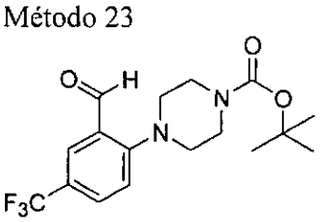
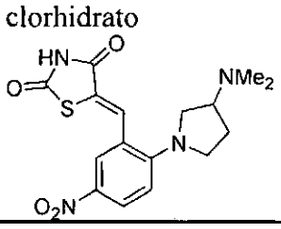
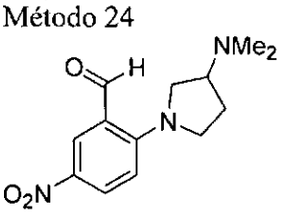
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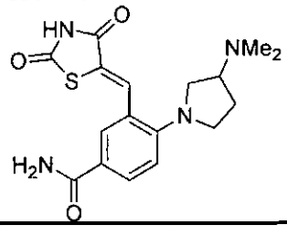
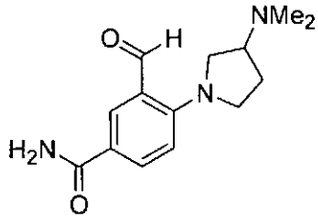
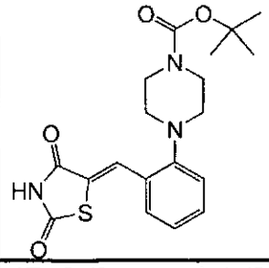
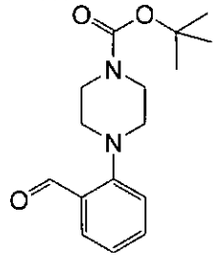
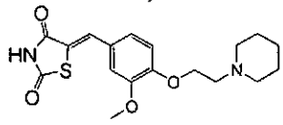
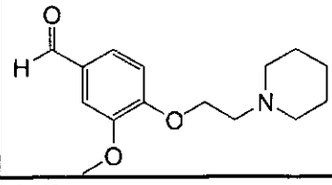
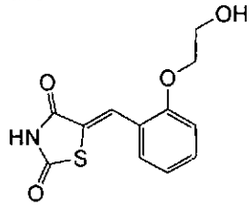
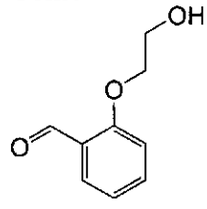
44	(5Z)-5-{2-[4-(dimetilamino)piperidin-1-il]-5-metoxibencilideno}-1,3-tiazolidina-2,4-diona 	7,59 (s, 1 H) 7,11 – 6,99 (m, 2 H) 6,85 (dd, 1 H) 3,75 (s, 3 H) 3,03 (m, 2 H) 2,64 - 2,54 (m, 2 H) 2,44 - 2,33 (m, 7 H) 1,91 (s, 2 H) 1,62 (dd, 2 H)	362	2-(4-(dimetilamino)piperidin-1-il)-5-metoxibenzaldehído Método 12 
45	(5Z)-5-[2-(3-hidroxipirrolidin-1-il)-4,5-dimetoxibencilideno]-1,3-tiazolidina-2,4-diona 	12,32 (brs, 1 H) 7,88 (s, 1 H) 6,93 (s, 1 H) 6,66 (s, 1 H) 4,34 (brs, 1 H) 3,83 (s, 3 H) 3,72 (s, 3 H) 3,55 - 3,29 (m, 3 H) 3,22 (brs, 1 H) 2,90 (d, 1 H) 2,16 - 1,94 (m, 1 H) 1,84 (d, 1 H)	351	2-(3-hidroxipirrolidin-1-il)-4,5-dimetoxibenzaldehído Método 13 
46	(5Z)-5-(4,5-dimetoxi-2-pirrolidin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona 	12,21 (brs, 1 H) 7,86 (s, 1 H) 6,94 (s, 1 H) 6,65 (s, 1 H) 3,83 (s, 3 H) 3,72 (s, 3 H) 3,12 (brs, 4 H) 1,90 (brs, 4 H)	335	4,5-dimetoxi-2-(pirrolidin-1-il)benzaldehído Método 14 

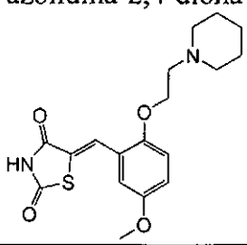
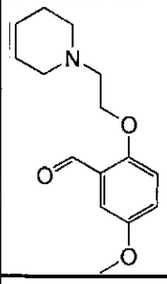
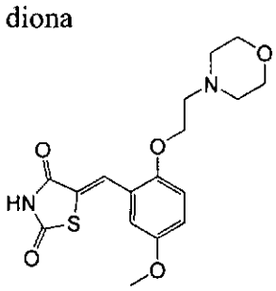
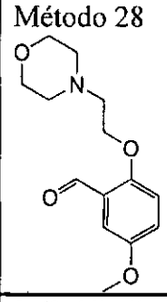
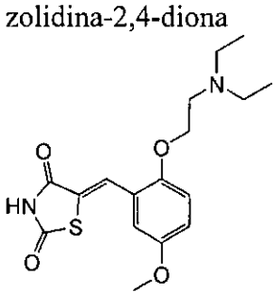
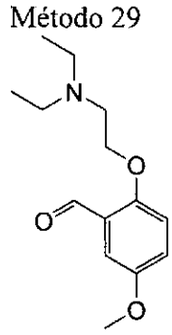
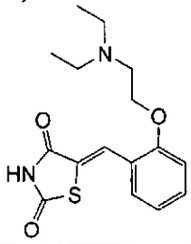
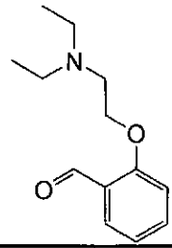
47	(5Z)-5-{2-[[2-(dimetilamino)etil](metil)amino]bencilideno}-1,3-tiazolidina-2,4-diona 	7,62 (s, 1 H) 7,48 (d, 1 H) 7,32 (t, 1 H) 7,17 (d, 1 H) 7,10 (t, 1 H) 3,06 (t, 2 H) 2,86 - 2,62 (m, 5 H) 2,36 (s, 6 H)	306	2-((2-(dimetilamino)etil)(metil)amino)benzaldehído Método 15 
48	(5Z)-5-{2-[3-(dimetilamino)pirrolidin-1-il]bencilideno}-1,3-tiazolidina-2,4-diona 	7,52 (s, 1 H) 7,27 - 7,21 (m, 1 H) 7,14 - 7,05 (m, 1 H) 6,84 (d, 1 H) 6,77 (t, 1 H) 3,17 (s, 1 H) 3,16 - 3,09 (m, 1 H) 3,06 - 2,94 (m, 2 H) 2,86 - 2,77 (m, 1 H) 2,16 - 2,11 (m, 6 H) 2,03 - 1,92 (m, 1 H) 1,66 (dd, 1 H)	318	2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído Método 16 
49	(5Z)-5-{2-[4-(dimetilamino)piperidin-1-il]bencilideno}-1,3-tiazolidina-2,4-diona 	7,64 (s, 1 H) 7,50 (d, 1 H) 7,35 - 7,27 (m, 1 H) 7,12 (t, 2 H) 3,22 (m, 2 H) 2,88 (m, 1 H) 2,68 (t, 2 H) 2,63 (s, 6 H) 2,04 (s, 2 H) 1,73 (td, 2 H)	332	2-(4-(dimetilamino)piperidin-1-il)benzaldehído Método 17 

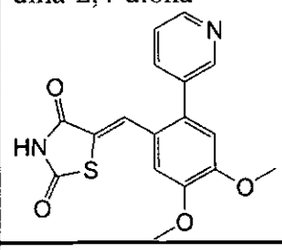
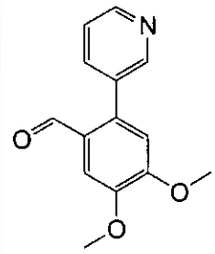
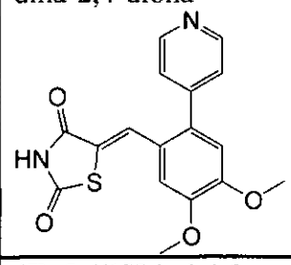
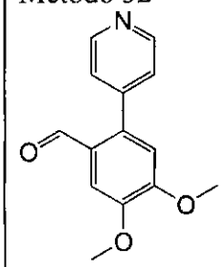
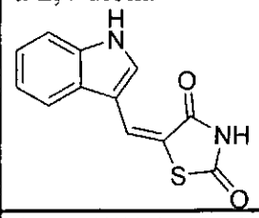
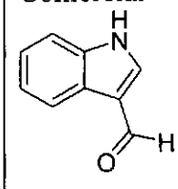
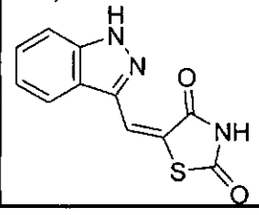
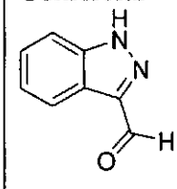
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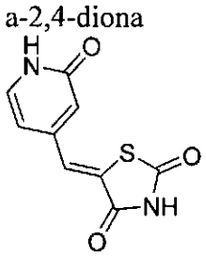
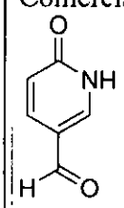
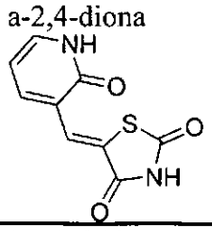
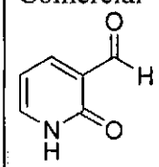
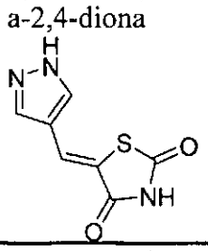
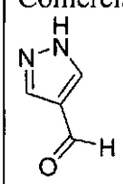
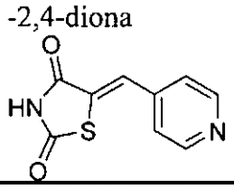
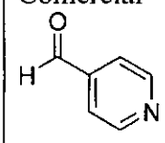
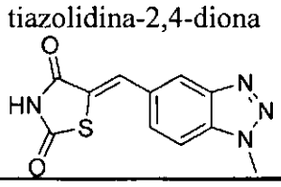
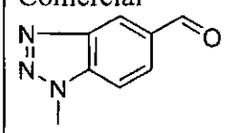
50	(5Z)-5-[2-(4-isopropilpiperazin-1-il)bencilideno]-1,3-tiazolidina-2,4-diona 	7,80 (s, 1 H) 7,49 - 7,43 (m, 1 H) 7,43 - 7,39 (m, 1 H) 7,22 - 7,13 (m, 2 H) 2,99 - 2,88 (m, 5 H) 2,80 (s, 4 H) 1,13 - 1,04 (m, 6 H)	332	2-(4-isopropilpiperazin-1-il)benzaldehído Método 18 
51	(5Z)-5-{2-[[2-(dimetilamino)etil](metil)amino]-4,5-dimetoxibencilideno}-1,3-tiazolidina-2,4-diona 	7,78 (s, 1 H) 7,02 (s, 1 H) 6,85 (s, 1 H) 3,83 (s, 3 H) 3,76 (s, 3 H) 3,11 - 2,98 (m, 2 H) 2,76 - 2,65 (m, 5 H) 2,37 (s, 6 H)	364	2-((2-(dimetilamino)etil)(metil)amino)-4,5-dimetoxibenzaldehído Método 19 
52	(5Z)-5-{2-[3-(dimetilamino)pirrolidin-1-il]-4,5-dimetoxibencilideno}-1,3-tiazolidina-2,4-diona 	7,76 (s, 1 H), 6,98 (s, 1 H), 6,68 (s, 1 H), 3,83 (s, 3 H), 3,72 (s, 3 H), 3,25 (m, 1 H), 3,13 (m, 2 H), 3,06 (m, 2 H), 2,32 (s, 6 H), 2,15 – 2,09 (m, 1 H) 1,90 – 1,81 (m, 1 H)	378	2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibenzaldehído Método 20 

53	(5*Z*)-5-{2-(4-isopropilpiperazin-1-il)-4,5-dimetoxibencilideno}-tiazolidina-2,4-diona 	7,86 (s, 1 H) 6,95 (s, 1 H) 6,77 (s, 1 H) 3,81 (s, 3 H) 3,76 - 3,67 (m, 3 H) 2,91 - 2,79 (m, 5 H) 2,71 (s, 4 H) 1,08 - 1,00 (m, 6 H)	392	2-(4-isopropilpiperazin-1-il)-4,5-dimetoxibenzaldehído Método 21 
54	(5*Z*)-5-{2-(4-(dimetilamino)piperidin-1-il)-4,5-dimetoxibencilideno}-tiazolidina-2,4-diona 	7,48 (s, 1 H) 6,82 (s, 1 H) 6,51 (s, 1 H) 3,58 (s, 3 H) 3,51 (s, 3 H) 2,87 (d, 2 H) 2,47 (m, 3 H) 2,35 (s, 6 H) 1,79 (d, 2 H) 1,49 (d, 2 H)	392	2-(4-(dimetilamino)piperidin-1-il)-4,5-dimetoxibenzaldehído Método 22 
55	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)piperazina-1-carboxilato 	12,65 (s, 1 H) 7,82 (s, 1 H) 7,72 (s, 1 H) 7,53 (s, 1 H) 3,59 - 3,50 (m, 1 H) 3,38 - 3,30 (m, 4 H) 2,56 (s, 6 H) 2,31 - 2,28 (m, 1 H) 2,09 - 2,01 (m, 1 H)	458	*terc*-butil 4-(2-formil-4-(trifluorometil)fenil)piperazina-1-carboxilato Método 23 
56	(*Z*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-5-nitrobencilideno)tiazolidina-2,4-diona clorhidrato 	12,64 (s, 1 H) 8,22 (d, 1 H) 8,12 (d, 1 H) 7,95 (d, 1 H) 7,04 (d, 1 H) 3,95 - 3,90 (m, 1 H) 3,70 - 3,65 (m, 2 H) 3,56 - 3,51 (m, 2 H) 2,79 (s, 6 H) 2,41 - 2,35 (m, 1 H) 2,34 - 2,22 (m, 1 H)	363	2-(3-(dimetilamino)pirrolidin-1-il)-5-nitrobenzaldehído Método 24 

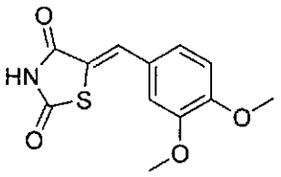
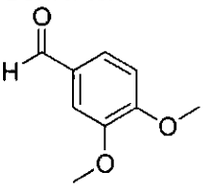
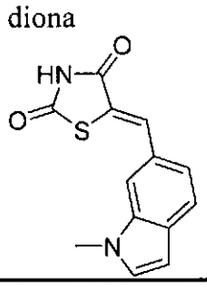
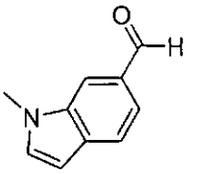
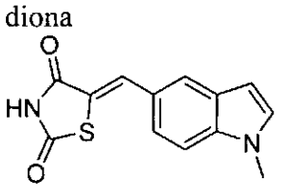
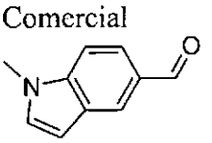
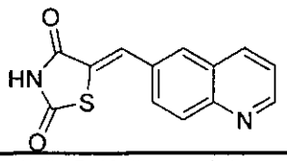
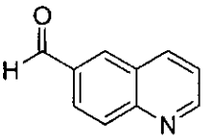
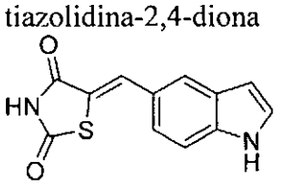
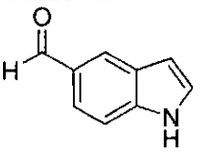
57	(*Z*)-4-(3-(dimetilamino)pirrolidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzamida clorhidrato 	12,47 (s, 1 H) 7,92 - 7,84 (m, 4 H) 7,23 (s, 1 H) 7,03 (d, 1 H) 3,98 - 3,91 (m, 1 H) 3,53 - 3,49 (m, 2 H) 3,46 - 3,39 (m, 2 H) 2,79 (s, 6 H) 2,34 - 2,19 (m, 2 H)	361	4-(3-(dimetilamino)pirrolidin-1-il)-3-formilbenzamida Método 25 
58	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carboxilato 	12,55 (s, 1 H) 7,92 (s, 1 H) 7,46 – 7,44 (m, 2 H) 7,21 –7,18 (m, 2 H) 3,48 (brs, 4 H) 2,86 (brs, 4 H) 1,43 (s, 9 H)	389	*terc*-butil 4-(2-formilfenil)piperazina-1-carboxilato Método 26 
59	(*Z*)-5-(3-metoxi-4-(2-(piperidin-1-il)etoxi)bencilideno)tiazolidina-2,4-diona 	7,78 (s, 1 H) 7,27 (s, 1 H) 7,21 (s, 2 H) 4,47 (t, 2 H) 3,84 (s, 3 H) 3,49 (t, 4 H) 3,04 (brs, 2 H) 1,80 (d, 4 H) 1,64 (brs, 1 H) 1,43 (brs, 1 H)	363	3-metoxi-4-(2-(piperidin-1-il)etoxi)benzaldehído Comercial 
60	(*Z*)-5-(2-(2-hidroxietoxi)bencilideno)tiazolidina-2,4-diona 	12,58 (brs, 1 H) 8,06 (s, 1 H) 7,57 - 7,32 (m, 2 H) 7,26 - 7,03 (m, 2 H) 4,95 (brs, 1 H) 4,13 (t, 2 H) 3,77 (brs, 2 H)	266	2-(2-hidroxietoxi)benzaldehído Comercial 

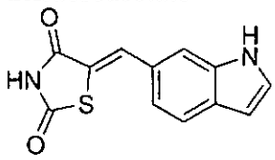
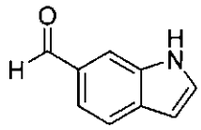
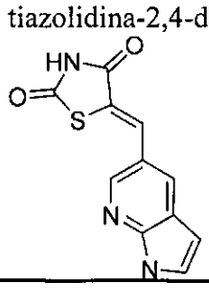
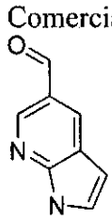
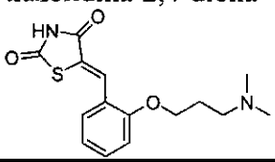
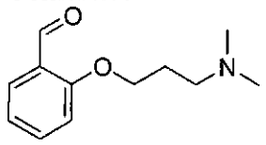
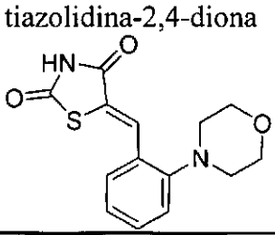
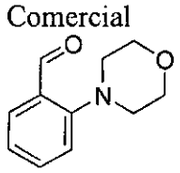
61	(Z)-5-(5-metoxi-2-(2-(piperidin-1-il)etoxi)bencilideno)tiazolidina-2,4-diona 	7,80 (s, 1 H) 7,10 (d, 1 H) 7,04 – 6,95 (m, 2 H) 4,22 (t, 2 H) 3,75 (s, 3 H) 3,07 (t, 2 H) 2,84 (s, 4 H) 1,62 (dq, 4 H) 1,46 (d, 2 H)	363	5-metoxi-2-(2-(piperidin-1-il)etoxi)benzaldehído Método 27 
62	(Z)-5-(5-metoxi-2-(2-morfolinoetoxi)bencilideno)tiazolidina-2,4-diona 	7,99 (s, 1 H) 7,22 - 7,10 (m, 1 H) 7,09 – 6,97 (m, 1 H) 6,91 (d, 1 H) 4,17 (t, 2 H) 3,76 (s, 3 H) 3,64 - 3,51 (m, 4 H) 2,75 (t, 2 H) 2,51 - 2,62 (m, 4 H)	365	5-metoxi-2-(2-morfolinoetoxi)benzaldehído Método 28 
63	(Z)-5-(2-(2-(dietilamino)etoxi)-5-metoxibencilideno)tiazolidina-2,4-diona 	7,77 (s, 1 H) 7,08 - 7,05 (m, 1 H) 7,03 – 6,95 (m, 2 H) 4,19 (t, 2 H) 3,75 (s, 3 H) 3,25 - 3,14 (m, 2 H) 2,95 (q, 4 H) 1,17 - 1,08 (m, 6 H)	352	2-(2-(dietilamino)etoxi)-5-metoxibenzaldehído Método 29 
64	(Z)-5-(2-(2-(dietilamino)etoxi)bencilideno)tiazolidina-2,4-diona 	7,84 (s, 1 H) 7,47 (d, 1 H) 7,43 - 7,35 (m, 1 H) 7,14 - 7,04 (m, 2 H) 4,24 (t, 2 H) 3,20 (m, 2 H) 2,90 (q, 4 H) 1,13 (t, 6 H)	321	2-(2-(dietilamino)etoxi)benzaldehído Método 30 

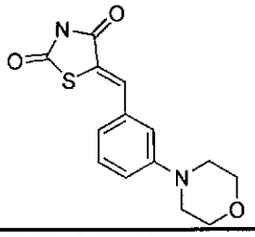
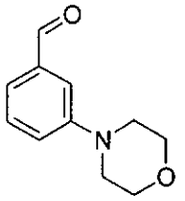
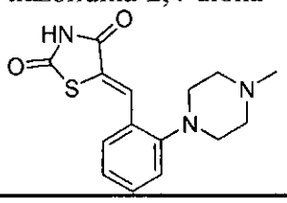
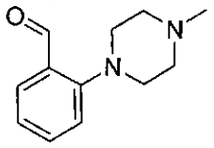
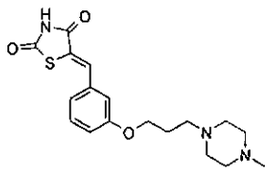
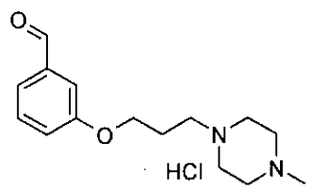
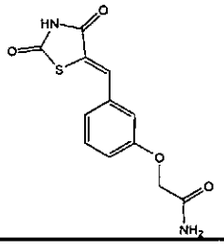
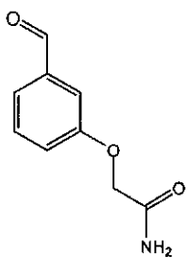
65	(Z)-5-(4,5-dimetoxi-2-(piridin-3-il)bencilideno)tiazolidina-2,4-diona 	12,55 (brs, 1 H) 8,73 - 8,61 (m, 1 H) 8,58 (brs, 1 H) 7,81 (dd, 1 H) 7,53 (dd, 1 H) 7,46 (s, 1 H) 7,13 (d, 2 H) 3,89 (d, 6 H)	343	4,5-dimetoxi-2-(piridin-3-il)benzaldehído Método 31 
66	(Z)-5-(4,5-dimetoxi-2-(piridin-4-il)bencilideno)tiazolidina-2,4-diona 	12,58 (brs, 1 H) 8,67 (d, 2 H) 7,48 (d, 1 H) 7,41 (d, 2 H) 7,12 (d, 2 H) 3,89 (s, 6 H)	343	4,5-dimetoxi-2-(piridin-4-il)benzaldehído Método 32 
67	(Z)-5-((1H-indol-3-il)metileno)tiazolidina-2,4-diona 	7,21 (dddd, 2 H) 7,50 (d, 1 H) 7,71 (d, 1 H) 7,87 (d, 1 H) 7,99 (s, 1 H) 12,07 (brs, 2 H)	245	1H-indol-3-carbaldehído Comercial 
68	(Z)-5-((1H-indazol-3-il)metileno)tiazolidina-2,4-diona 	7,28 (t, 1 H) 7,52 - 7,39 (m, 1 H) 7,64 (d, 1 H) 8,22 - 8,03 (m, 2 H) 12,41 (d, 1 H) 13,96 (s, 1 H)	246	1H-indazol-3-carbaldehído Comercial 

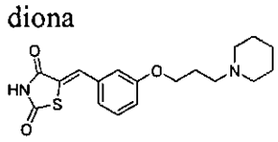
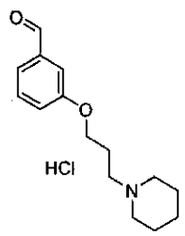
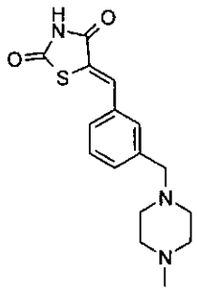
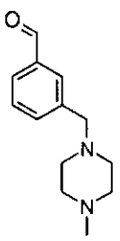
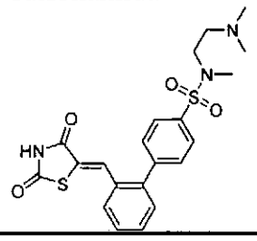
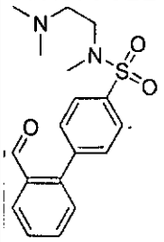
69	(*Z*)-5-((6-oxo-1,6-dihidropiridin-3-il)metileno)tiazolidina-2,4-diona 	11,99 (brs, 1 H) 7,74 (brs, 1 H) 7,69 - 7,58 (m, 1 H) 7,27 (s, 1 H) 6,43 (d, 1 H)	223	6-oxo-1,6-dihidropiridina-3-carbaldehído Comercial 
70	(*Z*)-5-((2-oxo-1,2-dihidropiridin-3-il)metileno)tiazolidina-2,4-diona 	12,43 (brs, 1 H) 12,16 (brs, 1 H) 7,73 (s, 1 H) 7,69 (dd, 1 H) 7,57 (d, 1 H) 6,38 (t, 1 H)	223	2-oxo-1,2-dihidropiridina-3-carbaldehído Comercial 
71	(*Z*)-5-((1H-pirazol-4-il)metileno)tiazolidina-2,4-diona 	13,51 (brs, 1 H) 12,37 (brs, 1 H) 8,20 (s, 1 H) 7,82 (s, 1 H) 7,74 (s, 1 H)	196	1*H*-pirazol-4-carbaldehído Comercial 
72	(*Z*)-5-(piridin-4-ilmetileno)tiazolidina-2,4-diona 	12,61 (brs, 1 H) 8,71 (d, 2 H) 7,74 (s, 1 H) 7,53 (d, 2 H)	207	4-piridinacarboxaldehído Comercial 
73	(5*Z*)-5-[(1-metil-1H-1,2,3-benzotriazol-5-il)metileno]-1,3-tiazolidina-2,4-diona 	12,65 (brs, 1 H) 8,28 (s, 1 H) 8,00-7,98 (m, 2 H) 7,76 (d, 1 H) 4,33 (s, 3 H)	259	1-metil-1H-benzo[d][1,2,3]triazol-5-carbaldehído Comercial 

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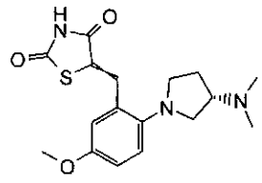
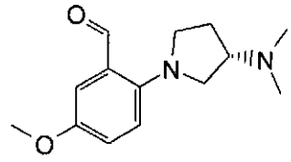
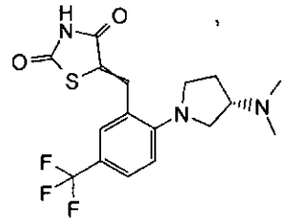
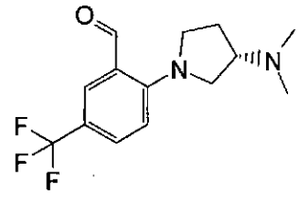
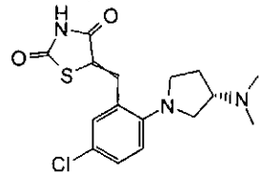
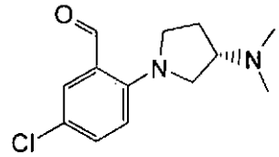
74	(5*Z*)-5-(3,4-dimetoxibencilideno)-1,3-tiazolidina-2,4-diona 	12,51 (brs, 1 H) 7,74 (s, 1 H) 7,19 – 7,09 (m, 3 H) 3,82 (s, 3 H) 3,80 (s, 3 H)	266	3,4-dimetoxibenzaldehído Comercial 
75	(5*Z*)-5-[(1-metil-1H-indol-6-il)metileno]-1,3-tiazolidina-2,4-diona 	12,49 (brs, 1 H) 7,92 (s, 1 H) 7,68 (d, 1 H) 7,54 (s 1 H) 7,25 (d, 1 H) 6,50 (s, 1 H) 3,84 (s, 3 H)		1-metil-1H-indol-6-carbaldehído Comercial 
76	(5*Z*)-5-[(1-metil-1H-indol-5-il)metileno]-1,3-tiazolidina-2,4-diona 	12,45 (brs, 1 H) 7,90 (s, 1 H) 7,84 (d, 1 H) 7,59 (d, 1 H) 7,44 (d, 1 H) 7,38 (d 1 H) 6,57 (d, 1 H) 3,82 (s, 3 H)	259	1-metil-1H-indol-5-carbaldehído Comercial 
77	(5*Z*)-5-(quinolin-6-ilmetileno)-1,3-tiazolidina-2,4-diona trifluoroacetato 	12,70 (brs, 1 H) 8,97 (d, 1 H) 8,51 (d, 1 H) 8,24 (s, 1 H) 8,12 (d, 1 H) 7,96 – 7,93 (m, 2 H) 7,64 – 7,61 (m, 1 H)	257	quinolina-6-carbaldehído Comercial 
78	(5*Z*)-5-(1*H*-indol-5-ilmetileno)-1,3-tiazolidina-2,4-diona 	12,43 (brs, 1 H) 11,44 (brs, 1 H) 7,85 (d, 1 H) 7,53 – 7,51 (m, 2 H) 7,45 – 7,44 (m, 1 H) 7,33 (d, 1 H) 6,56 (s, 1 H)	245	1*H*-indol-5-carbaldehído Comercial 

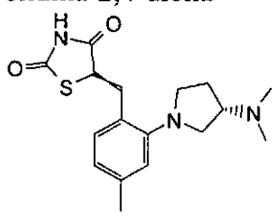
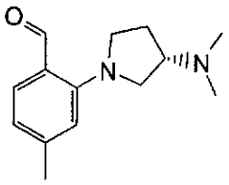
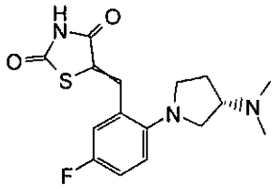
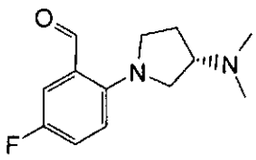
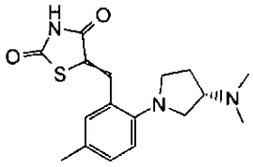
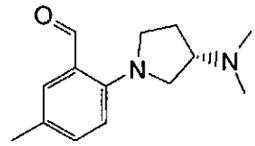
79	(5*Z*)-5-(1*H*-indol-6-ilmetileno)-1,3-tiazolidina-2,4-diona trifluoroacetato 	12,47 (brs, 1 H) 11,48 (brs, 1 H) 7,90 (s, 1 H) 7,69 – 7,66 (m, 2 H) 7,55 – 7,52 (m, 1 H) 7,23 (d, 1 H) 6,51 (s, 1 H)	245	1*H*-indol-6-carbaldehído Comercial 
80	(5*Z*)-5-(1H-pirrolo[2,3-b]piridin-5-ilmetileno)-1,3-tiazolidina-2,4-diona 	12,02 (brs, 1 H) 8,49 (d, 1 H) 8,15 (d, 1 H) 7,92 (s, 1 H) 7,58 (t, 1 H) 6,59 (brs, 1 H)	246	1*H*-pirrolo[2,3-b]piridina-5-carbaldehído Comercial 
81	(5*Z*)-5-{2-[3-(dimetilamino)propoxi]bencilideno}-1,3-tiazolidina-2,4-diona 	8,16 (s, 1 H) 7,76 (s, 1 H) 7,48 (d, 1 H) 7,34 (s, 1 H) 7,08 (d, 1 H) 4,11 (t, 2 H) 2,86 (t, 2 H) 2,53 (s, 6 H) 2,10 – 1,98 (m, 2 H)	307	2-[3-(dimetilamino)propoxi]benzaldehído Comercial 
82	(5*Z*)-5-(2-morfolin-4-ilbencilideno)-1,3-tiazolidina-2,4-diona 	7,89 (s, 1 H) 7,46 (d, 1 H) 7,45 - 7,41 (m, 1 H) 7,22 - 7,14 (m, 2 H) 3,80 - 3,69 (m, 4 H) 2,93 - 2,82 (m, 4 H)	291	2-morfolin-4-ilbenzaldehído Comercial 

83	(5Z)-5-(3-morfolin-4-ilbencilideno)-1,3-tiazolidina-2,4-diona trifluoroacetato 	12,58 (brs, 1 H) 7,74 (s, 1 H) 7,37 (t, 1 H) 7,12 (s, 1 H) 7,07 (dd, 1 H) 7,00 (d, 1 H) 3,79 - 3,69 (m, 4 H) 3,20 - 3,09 (m, 4 H)	290	3-morfolin-4-ilbenzaldehído Comercial 
84A	(5Z)-5-[2-(4-metilpiperazin-1-il)bencilideno]-1,3-tiazolidina-2,4-diona 	7,78 (s, 1 H) 7,46 (d, 1 H) 7,42 - 7,35 (m, 1 H) 7,19 - 7,11 (m, 2 H) 2,94 (t, 4 H) 2,70 (brs, 4 H) 2,40 (s, 3 H)	304	2-(4-metilpiperazin-1-il)benzaldehído Comercial 
84B	(Z)-5-(3-(3-(4-metilpiperazin-1-il)propoxi)benciliden o)tiazolidina-2,4-diona 	11,37 (brs, 1 H) 7,54 (s, 1 H) 7,38 (t, 1H) 7,12 (m, 2 H), 6,96 (m, 1 H) 4,58 (s, 3 H) 4,05 (t, 2 H) 3,00 - 2,55 (m, 10 H) 1,93 (m, 2 H)	362	3-(3-(4-metilpiperazin-1-il)propoxi)benzaldehído clorhidrato 
84C	(Z)-2-(3-((2,4-dioxotiazolidin-5-ilideno)metil)fenoxi)acetamida 	12,62 (s, 1 H) 7,73 (s, 1 H) 7,60 (s, 1 H) 7,44 (t, 1 H) 7,41 (s, 1 H) 7,19 (d, 1 H) 7,14 (m, 1 H) 7,05 (dd, 1 H) 4,48 (s, 2 H)	279	2-(3-formilfenoxi)acetamida 

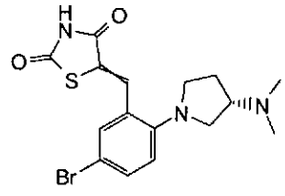
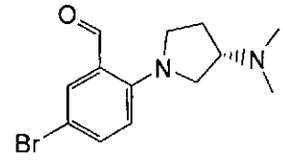
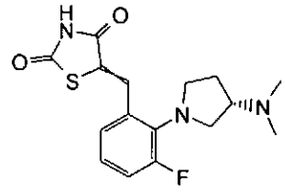
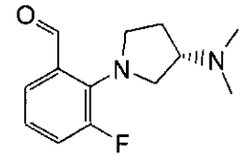
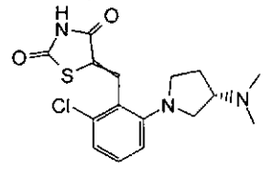
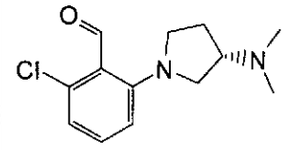
84D	(*Z*)-5-(3-(3-(piperidin-1-il)propoxi)benciliden o)tiazolidina-2,4-diona 	7,30 (t, 1 H) 7,24 (s, 1 H) 7,08 (m, 2 H) 6,85 (dd, 1 H) 4,01 (t, 2 H) 2,45 (t, 2 H) 2,40 (m, 4 H) 1,88 (m, 2 H) 1,50 (m, 4 H) 1,38 (m, 2 H)	347	3-(3-(piperidin-1-il)propoxi)benzaldehído clorhidrato 
84E	(*Z*)-5-(3-((4-metilpiperazin-1-il)metil)bencilideno)ti azolidina-2,4-diona 	7,59 (s, 1 H) 7,51 (s, 1 H) 7,46 (m, 2 H) 7,34 (m, 1 H) 3,59 (s, 2 H) 2,96 (m, 4 H) 2,59 (m, 4 H) 2,58 (s, 3 H)	318	3-((4-metilpiperazin-1-il)metil)benzaldehído 
84F	(*Z*)-*N*-(2-(dimetilamino)etil)-2'-((2,4-dioxotiazolidin-5-ilideno)metil)-*N*-metilbifenil-4-sulfonamida 	7,90 (d, 2 H) 7,69 (d, 1 H) 7,65-7,49 (m, 4 H) 7,49 - 7,40 (m, 1 H) 7,31 (s, 1 H) 3,24 (t, 2 H) 2,83 (t, 2 H) 2,78 (s, 3 H) 2,48 (s, 6 H)	445	*N*-(2-(dimetilamino)etil)-2'-formil-*N*-metilbifenil-4-sulfonamida Método 32B 

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84G	(*S*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-5-metoxibencilideno)tiazolidina-2,4-diona 		348	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-5-metoxibenzaldehído Método 104 
84H	(*S*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona 	12,55 (s, 1 H) 11,25 (brs, 1 H) 7,95 (s, 1 H) 7,78 (s, 1 H) 7,60 (m, 1 H), 7,15 (m, 1 H) 4,00 (m, 1 H) 3,65 (m, 2 H) 3,40 (m, 1 H) 3,32 (m, 1 H) 2,80 (s, 6 H) 2,35 (m, 1 H) 2,20 (m, 1 H)	386	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-5-(trifluorometil)benzaldehído Método 105 
84I	(*S*)-5-(5-cloro-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona 	12,55 (s, 1 H) 7,81 (s, 1H), 7,93 (m, 2H), 7,12 (m, 1H), 3,90(m, 1H), 3,45-3,30 (m, 2H), 3,29 (m, 1H), 3,15 (m, 1H), 2,80 (s, 6H), 2,35 (m, 1H), 2,20 (m, 1H)	352	(*S*)-5-cloro-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído Método 106 

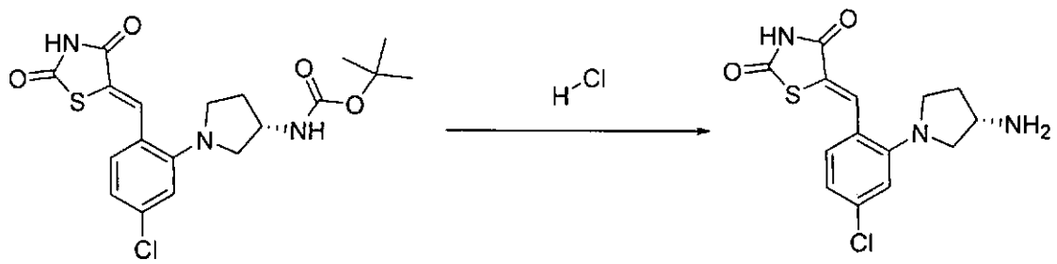
84J	(*S*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-4-metilbencilideno)tiazolidina-2,4-diona 		332	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-4-metilbenzaldehído Método 107 
84K	(*S*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-5-fluorobencilideno)tiazolidina-2,4-diona 	12,55 (s, 1 H) 11,40 (s, 1 H) 7,80 (s, 1 H) 7,30-7,15 (m, 3 H) 3,92 (m, 1 H) 3,45 (m, 1 H) 3,35 (m, 1 H) 3,18 (m, 1 H) 3,15 (m, 1 H) 3,80 (d, 6 H) 2,30 (m, 1 H), 2,20 (m, 1H)	336	(S)-2-(3-(dimetilamino)pirrolidin-1-il)-5-fluorobenzaldehído Método 108 
84L	(*S*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-5-metilbencilideno)tiazolidina-2,4-diona 		332	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-5-metilbenzaldehído Método 109 

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84M	(*S*)-5-(5-bromo-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona 		397	(*S*)-5-bromo-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído Método 110 
84N	(*S*)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-3-fluorobencilideno)tiazolidina-2,4-diona 	12,55 (s, 1 H) 10,34 (s, 1 H) 7,87 (d, 1H) 7,33-7,21 (m, 3 H) 3,93 (m, 1 H) 3,40 (m, 2 H) 3,25 (m, 1 H) 3,18 (m, 1 H) 2,79 (s, 6 H) 2,26 (m, 1H) 2,12 (m, 1H)	336	(S)-2-(3-(dimetilamino)pirrolidin-1-il)-3-fluorobenzaldehído Método 111 
84O	(*S*)-5-(2-cloro-6-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona 		352	(*S*)-2-cloro-6-(3-(dimetilamino)pirrolidin-1-il)benzaldehído Método 112 

Ejemplo 85:

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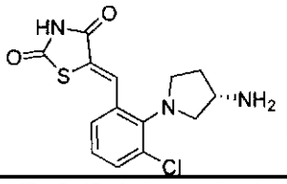
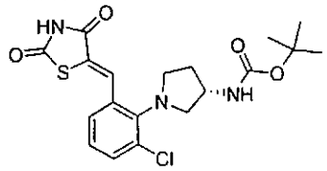
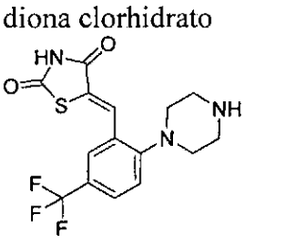
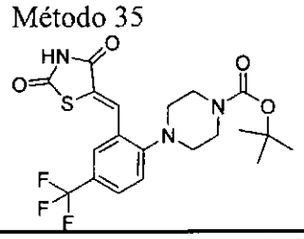
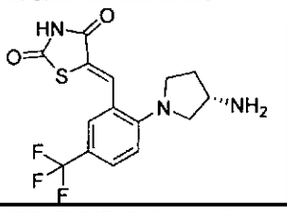
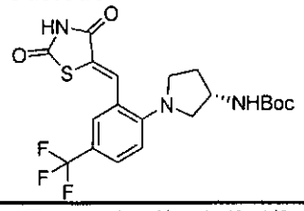
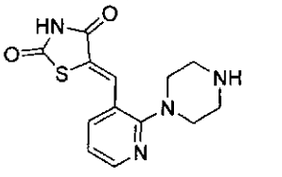
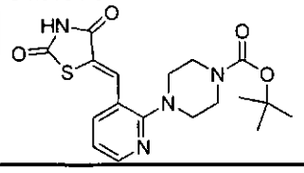


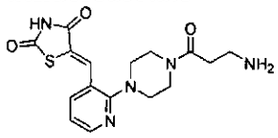
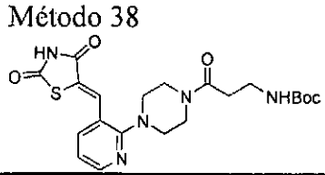
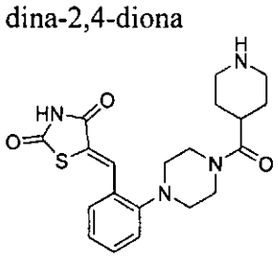
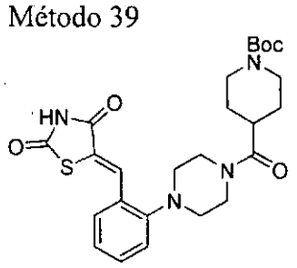
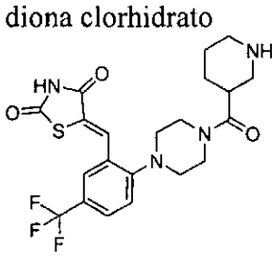
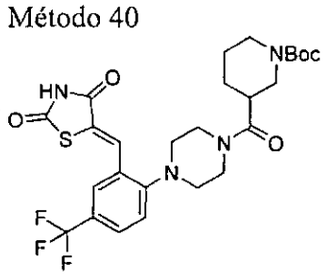
(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-4-clorobencilideno)tiazolidina-2,4-diona clorhidrato:

Un matraz de fondo redondo de 100 mL se cargó con una barra de agitación magnética, (*S,Z*)-*terc*-butil1-(5-cloro-2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato (Método 33) (1,300 g, 3,07 mmol), MeOH (10,22 ml) y una solución 1N de HCl en éter dietílico (2,294 ml, 46,00 mmol). La mezcla de reacción se dejó agitar durante toda la noche a TA antes de concentrarse al vacío para proporcionar el producto como su sal clorhidrato. Este material se disolvió en DMSO y se purificó mediante HPLC en fase inversa para proporcionar fracciones que se concentraron al vacío, se suspendieron en metanol (~ 5 mL) y HCl 1N en éter dietílico (~2 mL). Esta mezcla se concentró al vacío para proporcionar (*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-4-clorobencilideno)tiazolidina-2,4-diona clorhidrato (0,710 g, 64,3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12,51 (s, 1 H) 8,36 (s, 2 H) 7,85 (s, 1 H) 7,35 (d, 1 H) 6,96 (dd, 2 H) 3,90 - 3,75 (m, 1 H) 3,55- 3,47 (m, 1 H) 3,40 (dd, 1 H) 3,31 - 3,21 (m, 1 H) 3,18 - 3,10 (m, 1 H) 2,29 - 2,18 (m, 1 H) 2,10 - 1,96 (m, 1 H); *m/z* 325.

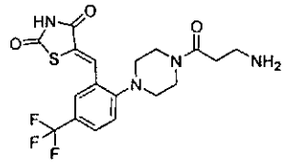
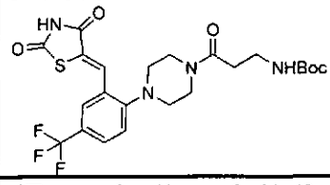
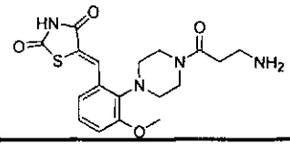
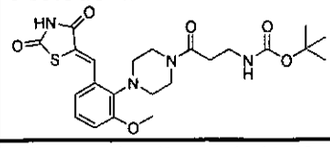
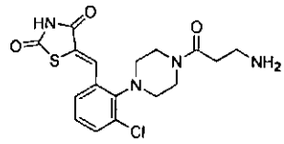
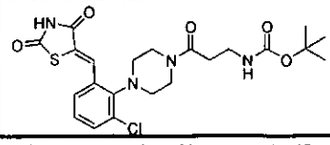
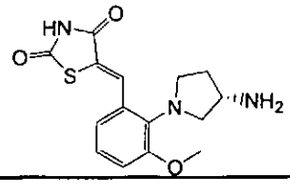
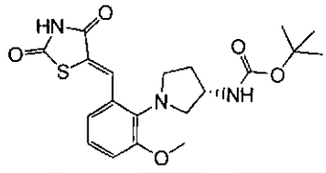
Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 85, utilizando los materiales de partida apropiados. Los siguientes compuestos base obtenidos después de la cromatografía pueden convertirse en su correspondiente sal clorhidrato de forma similar a la que se describe en el Ejemplo 85, o mediante un procedimiento similar.

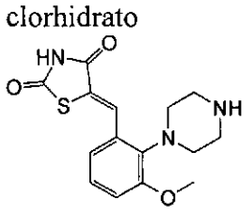
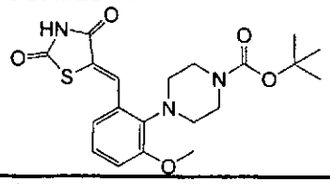
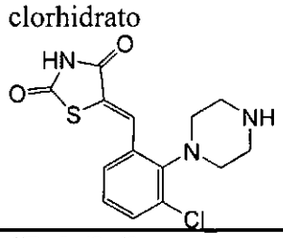
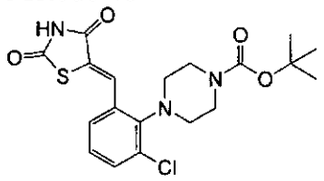
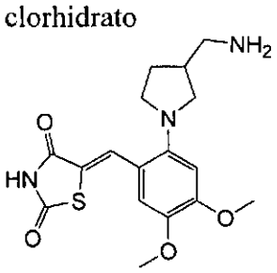
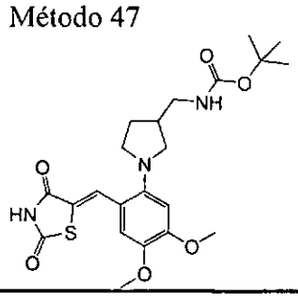
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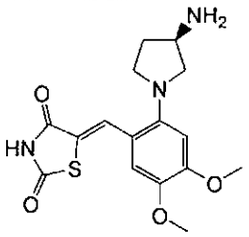
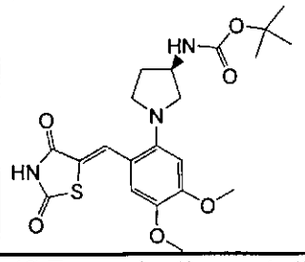
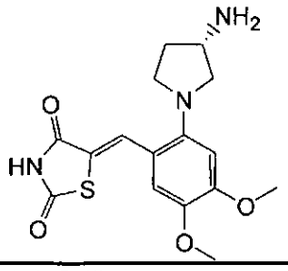
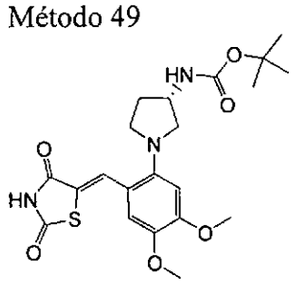
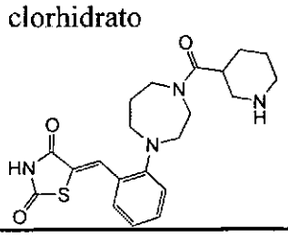
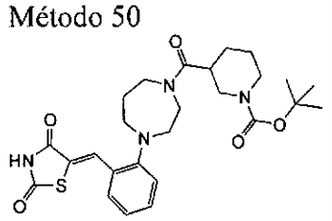
Ej.	Compuesto	^{1}H NMR	m/z	MP
86	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	12,69 (s, 1 H) 8,35 (brs, 2 H) 7,94 (s 1 H) 7,57 (d, 1 H) 7,41 - 7,35 (m, 2 H) 3,95 - 3,88 (m, 1 H) 3,53 - 3,26 (m, 4 H) 2,37 - 2,31 (m, 1 H) 2,08 - 2,01 (m, 1 H)	324	(*S,Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato Método 34 
87	(*Z*)-5-(2-(piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,69 (s, 1 H) 9,32 (brs, 2 H) 7,79 (d, 1 H) 7,71 (d, 2 H) 7,37 (d, 1 H) 3,23 (s, 8 H)	358	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)piperazina-1-carboxilato Método 35 
88	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,53 (s, 1 H) 8,17 (brs, 2 H) 7,95 (s, 1 H) 7,65 (s, 1 H) 7,59 (d 1 H) 7,05 (d, 1 H) 3,90 - 3,81 (m, 1 H) 3,56 (q, 1 H) 3,47 - 3,35 (m, 2 H) 3,18 (dd, 1 H) 2,33 - 2,18 (m, 1 H) 2,09 - 1,99 (m, 1 H)	358	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)pirrolidin-3-ilcarbamato Método 36 
89	(*Z*)-5-((2-(piperazin-1-il)piridin-3-il)metileno)tiazolidina-2,4-diona clorhidrato 	12,65 (s, 1 H) 8,39 (s, 1 H) 8,33 (d, 1 H) 7,83 (d, 1 H) 7,63 (s, 1 H) 7,15 (dd, 1 H) 3,41 (brs, 4 H) 3,17 (brs, 4 H)	291	(*Z*)-*terc*-butil 4-(3-((2,4-dioxotiazolidin-5-ilideno)metil)piridin-2-il)piperazina-1-carboxilato Método 37 

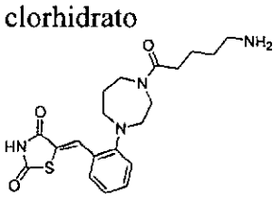
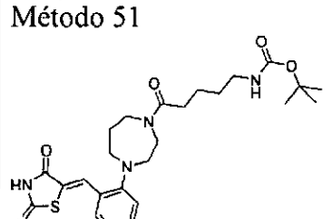
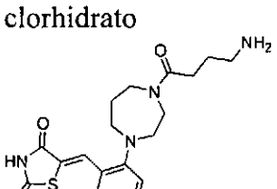
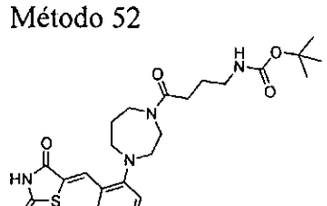
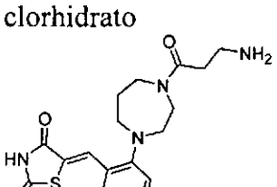
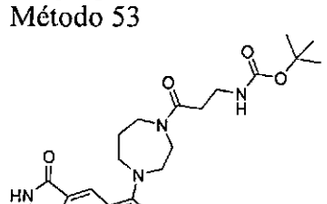
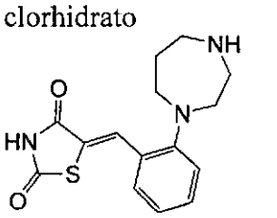
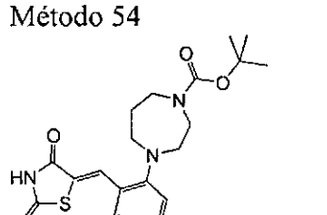
90	(*Z*)-5-((2-(4-(3-aminopropanoil)piperazin-1-il)piridin-3-il)metileno)tiazolidina-2,4-diona trifluoroacetato 	12,60 (s, 1 H) 8,32 (d, 1 H) 7,82 (s, 1 H) 7,68 (s, 1 H) 7,63 (brs, 2 H) 7,12 (dd, 1 H) 3,57 (d, 4 H) 3,17 (d, 4 H) 3,00 (q, 2 H) 2,70 (t, 2 H)	362	(*Z*)-*terc*-butil 3-(4-(3-((2,4-dioxotiazolidin-5-ilideno)metil)piridin-2-il)piperazin-1-il)-3-oxopropilcarbamato Método 38 
91	(*Z*)-5-(2-(4-(piperidina-4-carbonil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona 	9,00 (brs, 1 H) 8,67 (brs, 1 H) 8,18 (s, 1 H) 7,57 - 7,52 (m, 1 H) 7,30 -7,16 (m, 1 H) 3,71 (s, 1 H) 3,63 (s, 1 H) 3,34 (s, 3 H) 3,31 - 3,22 (m, 2 H) 3,13 (s, 3 H) 3,01 -2,87 (m, 5 H) 1,85 - 1,77 (m, 4 H)	401	(*Z*)-*terc*-butil 4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)piperidina-1-carboxilato Método 39 
92	(*Z*)-5-(2-(4-(piperidina-3-carbonil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,68 (s, 1 H) 8,87 (s, 1 H) 7,78 - 7,69 (m, 3 H) 7,32 (d, 1 H) 3,68 - 3,64 (m, 8 H) 3,38 (tt, 1 H) 3,13 - 2,98 (m, 4 H) 1,75 - 1,56 (m, 4 H)	469	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)piperazina-1-carbonil)piperidina-1-carboxilato Método 40 

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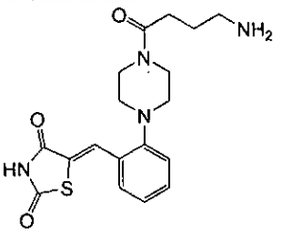
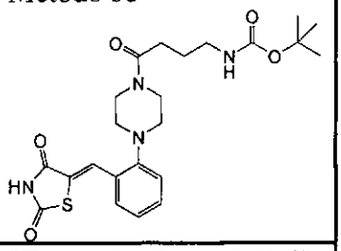
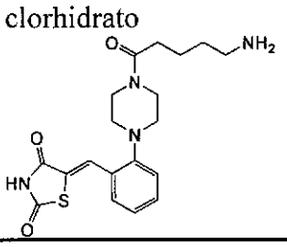
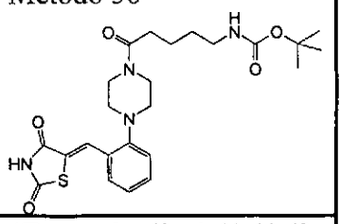
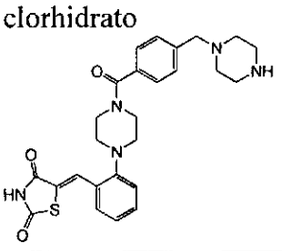
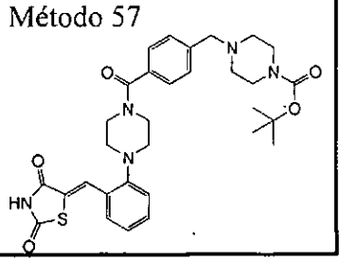
93	(*Z*)-5-(2-(4-(3-aminopropanoil)piperazin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,67 (s 1 H) 7,93 (brs, 2 H) 7,78 - 7,68 (m, 3 H) 7,32 (d, 1 H) 3,69 - 3,59 (m, 8 H) 3,00 - 2,74 (m, 4 H)	429	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)piperazin-1-il)-3-oxopropilcarbamato Método 41 
94	(*Z*)-5-(2-(4-(3-aminopropanoil)piperazin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,53 (brs, 1 H) 8,21 (s, 1 H), 7,58 (brs, 3 H), 7,24 (t, 1 H) 7,11 (d, 1 H) 7,00 (d, 1 H) 3,75 (s, 3 H) 3,35 (brs, 4 H) 3,09 - 2,85 (m, 4 H) 2,65 (brs, 2 H)	391	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)piperazin-1-il)-3-oxopropilcarbamato Método 42 
95	(Z)-5-(2-(4-(3-aminopropanoil)piperazin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	12,69 (brs, 1 H) 8,12 (s, 1 H) 7,67 (brs, 2 H) 7,55 (dd, 1 H) 7,49 - 7,40 (m, 1 H) 7,35 (t, 1 H) 4,17 (brs, 1 H) 3,75 (brs, 1 H) 3,35 (brs, 3 H) 3,13 - 2,84 (m, 5 H) 2,74 (brs, 2 H)	395	(*Z*)-*terc*-butil 3-(4-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)-3-oxopropilcarbamato Método 43 
96	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,43 (s, 1 H) 7,94 (s, 1 H) 7,86 (brs, 1 H) 7,16 (t, 1 H) 7,05 (d, 1 H) 6,91 (d, 1 H) 3,71 (s, 3 H) 3,30 (dd, 1 H) 3,17 - 3,08 (m, 1 H) 3,08 - 2,91 (m, 2 H) 2,23 - 2,06 (m, 2 H), 1,80 - 1,75 (m, 1 H)	320	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)pirrolidin-3-ilcarbamato Método 44 

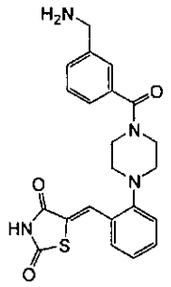
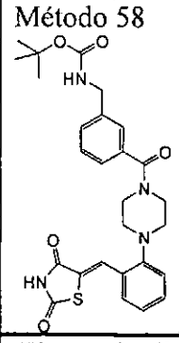
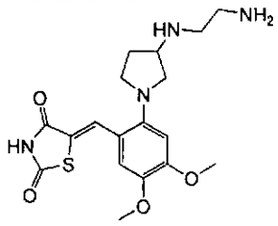
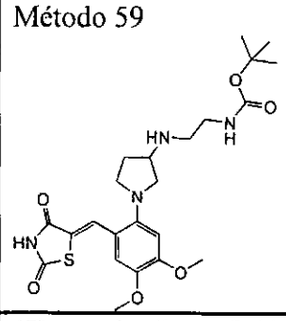
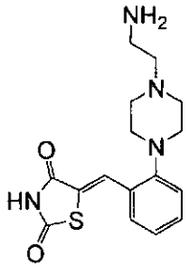
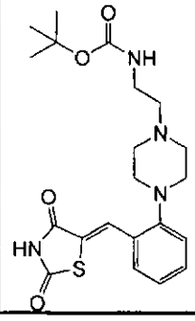
97	(*Z*)-5-(3-metoxi-2-(piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,45 (brs, 1 H) 8,59 (brs, 1 H) 7,99 (s, 1 H) 7,15 (t, 1 H) 7,02 (d, 1 H) 6,89 (d, 1 H) 3,67 (s, 3 H) 3,17 - 2,99 (m, 8 H)	320	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)piperazina-1-carboxilato Método 45 
98	(*Z*)-5-(3-cloro-2-(piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,72 (brs, 1 H) 9,19 (brs, 1 H) 8,01 (s, 1 H) 7,57 (dd, 1 H) 7,50 - 7,40 (m, 1 H) 7,36 (t, 1 H) 3,60 (brs, 2 H), 3,51 - 3,29 (m, 1 H) 3,29 - 3,12 (m, 2 H) 3,06 (brs, 3 H)	324	(*Z*)-*terc*-butil 4-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carboxilato Método 46 
99	(*Z*)-5-(2-(3-(aminometil)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,40 (s, 1 H) 9,25 (s, 1 H) 7,88 (s, 1 H) 6,97 (s, 1 H) 6,73 (s, 1 H) 3,85 (s, 3 H) 3,81 (m, 1 H) 3,74 (s, 3 H) 3,40 - 3,31 (m, 2 H) 3,25 - 3,13 (m, 2 H) 2,59 (t, 3 H) 2,31 (dd, 1 H) 2,08 (d, 1 H)	364	(*Z*)-*terc*-butil (1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-il)metilcarbamato Método 47 

100	(*R*,*Z*)-5-(2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,39 (s, 1 H) 8,06 (s, 2 H) 7,89 (s, 1 H) 6,96 (s, 1 H) 6,65 (s, 1 H) 3,84 (s, 4 H) 3,73 (s, 3 H) 3,35 (d, 2 H) 3,20 (s, 1 H) 3,07 (d, 1 H) 2,28 (s, 1 H) 1,97 (s, 1 H)	350	(*R*,*Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato Método 48 
101	(*S*,*Z*)-5-(2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,39 (s, 1 H) 8,08 (s, 2 H) 7,89 (s, 1 H) 6,96 (s, 1 H) 6,65 (s, 1 H) 3,84 (s, 4 H) 3,73 (s, 3 H) 3,45 - 3,30 (m, 2 H) 3,24 - 3,14 (m, 1 H) 3,12 - 3,00 (m, 1 H) 2,28 (s, 1 H) 1,98 (s, 1 H)	350	(*S*,*Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato Método 49 
102	(*Z*)-5-(2-(4-(piperidina-3-carbonil)-1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,49 (s, 1 H) 8,47 (s, 1 H) 7,82 (d, 1 H) 7,39 - 7,30 (m, 2 H) 7,16 (dd, 1 H) 7,06 (td, 1 H) 3,63 - 3,54 (m, 4 H) 3,29 - 3,06 (m, 9 H) 1,88 - 1,48 (m, 6 H)	415	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-carbonil)piperidina-1-carboxilato Método 50 

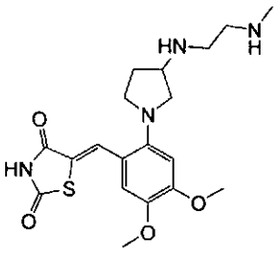
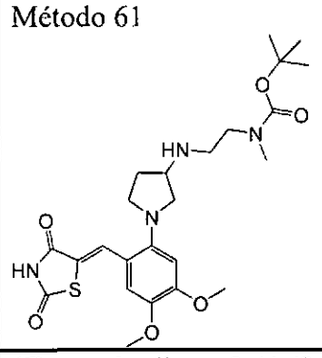
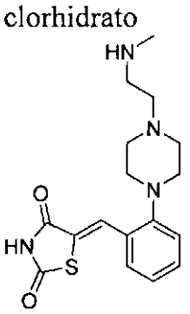
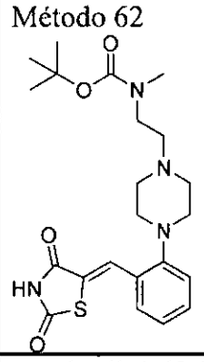
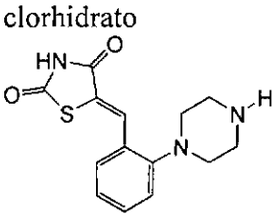
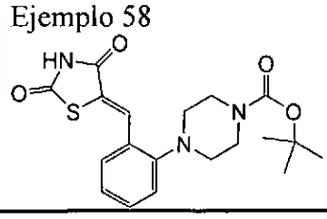
103	(*Z*)-5-(2-(4-(5-aminopentanoil)-1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,57 (s, 1 H) 7,90 (d, 1 H) 7,76 (s, 2 H) 7,47 - 7,36 (m, 2 H) 7,22 (t, 1 H) 7,12 (d, 1 H) 3,63 (d, 4 H) 3,22 (s, 1 H) 3,17 (s, 1 H) 3,05 (s, 2 H) 2,80 (s, 2 H) 2,41 (s, 1 H) 2,34 (s, 1 H) 1,91 (s, 1 H) 1,85 (s, 1 H) 1,57 (d, 4 H)	403	(*Z*)-*terc*-butil 5-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-il)-5-oxopentilcarbamato Método 51 
104	(*Z*)-5-(2-(4-(4-aminobutanoil)-1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,49 (s, 1 H) 7,83 (d, 1 H) 7,65 (s, 2 H) 7,39 - 7,30 (m, 2 H) 7,20 - 7,12 (m, 1 H) 7,09 - 7,01 (m, 1 H) 3,61 - 3,50 (m, 4 H) 3,18 - 3,07 (m, 2 H) 2,98 (d, 2 H) 2,77 (ddd, 2 H) 2,37 (t, 2 H) 1,85 - 1,66 (m, 4 H).	389	(*Z*)-*terc*-butil 4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-il)-4-oxobutilcarbamato Método 52 
105	(*Z*)-5-(2-(4-(3-aminopropanoil)-1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,50 (s, 1 H) 7,83 (s, 1 H) 7,63 (s, 2 H) 7,39 - 7,31 (m, 2 H) 7,16 (dd, 1 H) 7,10 - 7,01 (m, 1 H) 3,64 - 3,52 (m, 4 H) 3,20 - 3,09 (m, 2 H) 2,97 (dt, 4 H) 2,65 (dt, 2 H) 1,87-1,81 (m, 2 H)	375	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-il)-3-oxopropilcarbamato Método 53 
106	(*Z*)-5-(2-(1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,57 (s, 1 H) 9,31 (s, 1 H) 7,91 (s, 1 H) 7,46 - 7,40 (m, 2 H) 7,26 (d, 1 H) 7,18 - 7,09 (m, 1 H) 3,36 (d, 2 H) 3,27 (d, 4 H) 3,19 (dd, 2 H) 2,10 - 2,01 (m, 2 H)	304	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-carboxilato Método 54 

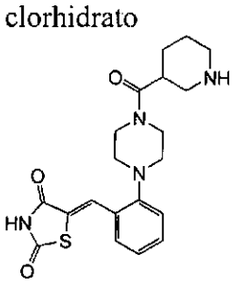
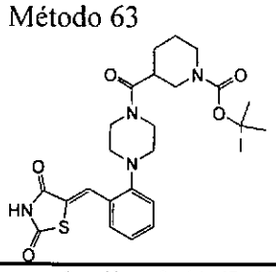
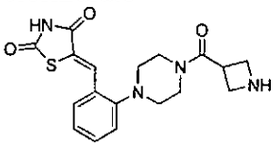
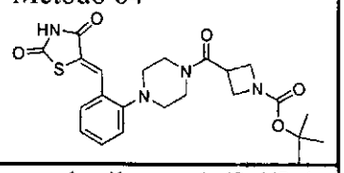
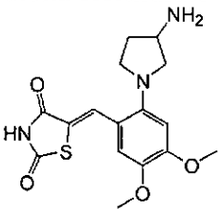
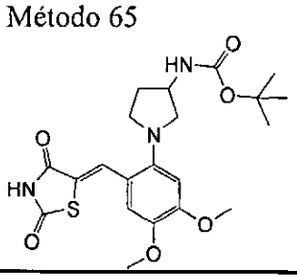
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107	(*Z*)-5-(2-(4-(4-aminobutanoil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,60 (s, 1 H) 7,95 (s, 4 H) 7,53 - 7,44 (m, 2 H) 7,26 - 7,17 (m, 2 H) 3,66 - 3,57 (m, 5 H) 2,89 (m, 4 H) 2,85 - 2,76 (m, 3 H) 1,85 - 1,76 (m, 2 H)	375	(*Z*)-*terc*-butil 4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)-4-oxobutilcarbamato Método 55 
108	(*Z*)-5-(2-(4-(5-aminopentanoil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,66 (s, 1 H) 8,10 (s, 2 H) 7,99 (s, 1 H) 7,52 (s, 1 H) 7,51 - 7,47 (m, 1 H) 7,25 (t, 2 H) 3,67 (s, 4 H) 2,92 - 2,81 (m, 6 H) 2,44 (t, 2 H) 1,62 (s, 4 H)	389	(*Z*)-*terc*-butil 5-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)-5-oxopentilcarbamato Método 56 
109	(*Z*)-5-(2-(4-(4-(piperazin-1-ilmetil)benzoil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,57 (brs, 1 H) 9,70 (brs, 1 H) 7,94 (s, 1 H) 7,75 (d, 2 H) 7,52 (m, 2 H) 7,49 - 7,41 (m, 2 H) 7,21 (t, 2 H) 4,45 (brs, 2 H) 3,81 (brs, 2 H) 3,54 - 3,35 (m, 8 H) 3,27 (brs, 2 H) 2,89 (brs, 4 H)	492	(*Z*)-*terc*-butil 4-(4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)bencil)piperazina-1-carboxilato Método 57 

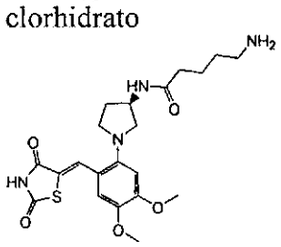
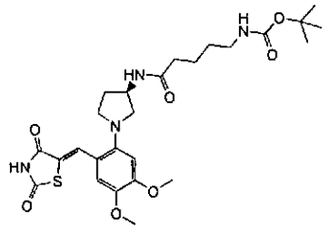
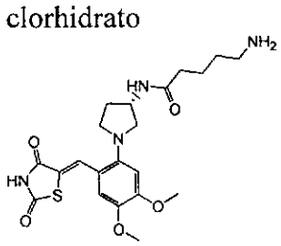
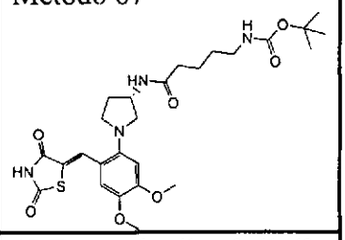
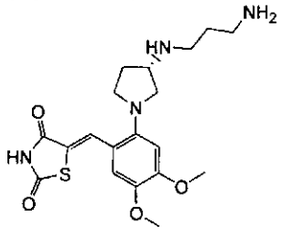
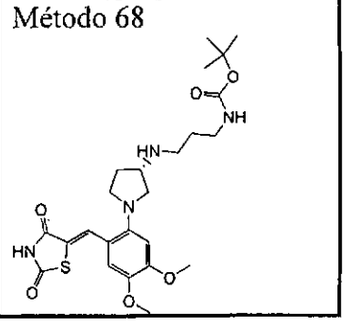
110	(*Z*)-5-(2-(4-(3-(aminometil)benzoil) piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,56 (s, 1 H) 8,18 (brs, 2 H) 7,95 (s, 1 H) 7,64 - 7,38 (m, 6 H) 7,36 - 7,11 (m, 2 H) 4,19 - 4,02 (m, 2 H) 3,82 (brs, 2 H) 3,52 (brs, 2 H) 2,92 (brs, 4 H)	423	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)bencilcarbamato Método 58 
111	(*Z*)-5-(2-(3-(2-aminoetilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,38 (s, 1 H) 9,99 (s, 1 H) 8,44 (s, 2 H) 7,86 (s, 1 H) 6,96 (s, 1 H) 6,76 (s, 1 H) 3,93 (s, 1 H) 3,84 (s, 3 H) 3,73 (s, 3 H) 3,45 - 3,33 (m, 2 H) 3,28 - 3,16 (m, 6 H) 2,32 (s, 1 H) 2,15 (s, 1 H)	393	(*Z*)-*terc*-butil 2-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)etilcarbamato Método 59 
112	(*Z*)-5-(2-(4-(2-aminoetil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,70 (s, 1 H) 11,43 (s, 1 H) 8,38 (s, 3 H) 7,86 (s, 1 H) 7,49 (m, 2 H) 7,25 (m, 2 H) 3,67 (m, 2 H) 3,42 - 3,30 (m, 8 H)	333	(*Z*)-*terc*-butil 2-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)etilcarbamato Método 60 

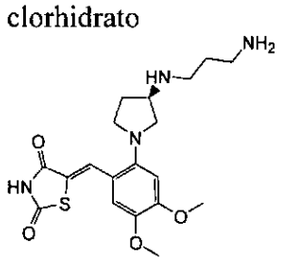
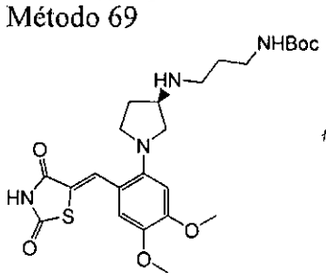
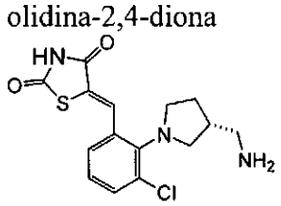
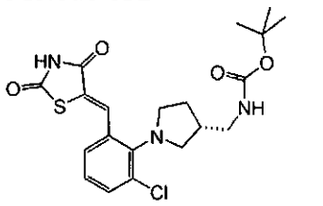
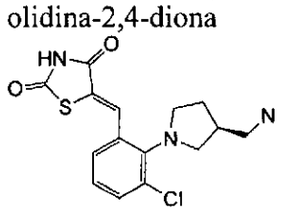
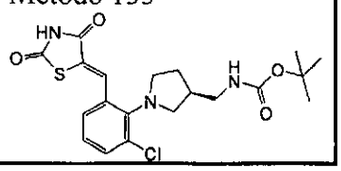
166

113	(*Z*)-5-(4,5-dimetoxi-2-(3-(2-(metilamino)etilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,39 (s, 1 H) 9,93 (brs, 1 H) 9,42 (brs, 1 H) 7,87 (s, 1 H) 6,98 (s, 1 H) 6,77 (s, 1 H) 4,00 – 3,91 (m, 1 H) 3,85 (s, 3 H) 3,74 (s, 3 H) 3,44 – 3,16 (m, 8 H) 2,62 (s, 3 H) 2,40 – 2,31 (m, 1 H) 2,20 – 2,14 (m, 1 H)	407	(*Z*)-*terc*-butil 2-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)etil(metil)carbamato Método 61 
114	(*Z*)-5-(2-(4-(2-(metilamino)etil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,62 (s, 1 H) 11,28 (s, 1 H) 9,28 (s, 1 H) 7,87 (s, 1 H) 7,50 (t, 1 H) 7,26 (t, 1 H) 3,71 (m, 4 H) 3,57 (m, 2 H) 3,45 (m, 2 H) 3,26 (m, 4 H) 2,62 (s, 3 H)	347	(*Z*)-*terc*-butil 2-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)etil(metil)carbamato Método 62 
115	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona clorhidrato 	12,61 (s, 1 H) 9,21 (s, 1 H) 7,86 (s, 1 H) 7,49 (t, 2 H) 7,24 (t, 2 H), 3,25 (s, 4 H) 3,12 (s, 4 H)	290	*terc*-butil-4-{2-[(*Z*)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}piperazina-1-carboxilato Ejemplo 58 

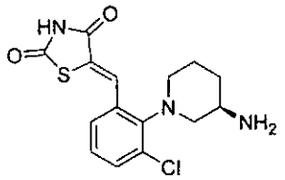
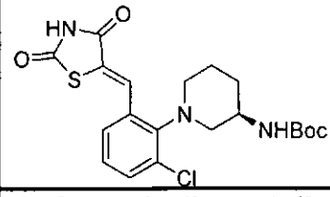
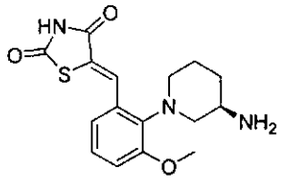
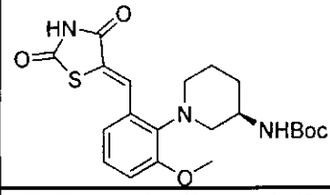
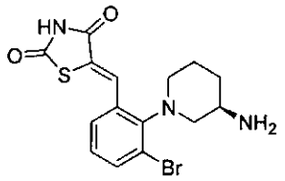
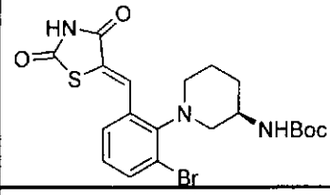
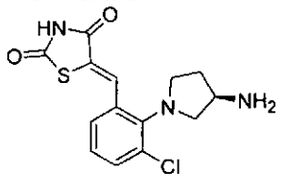
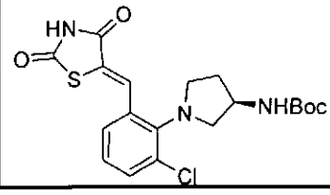
116	5-(2-(4-(piperidina-3-carbonil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,60 (s, 1 H) 9,10 (s, 1 H) 8,90 (s, 1 H) 7,94 (s, 1 H) 7,51 - 7,43 (m, 1 H) 7,21 (t, 2 H) 5,14 (m, 4 H) 3,67 (m, 3 H) 3,17 (m, 2 H) 2,91 - 2,88 (m, 4 H) 1,86 (s, 1 H) 1,81 - 1,71 (m, 2 H) 1,57 (d, 1 H)	401	*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)piperidina-1-carboxilato Método 63 
117	(5*Z*)-5-{2-[4-(azetidin-3-ilcarbonil)piperazin-1-il]bencilideno}-1,3-tiazolidina-2,4-diona clorhidrato 	12,59 (s, 1 H) 9,15 (s, 1 H) 8,86 (s, 1 H) 7,93 (s, 1 H) 7,47 (ddd, 2 H) 7,25 - 7,16 (m, 1 H) 4,15 - 4,05 (m, 4 H) 4,01 - 3,91 (m, 1 H) 3,71 (m, 2 H) 3,42 (s, 2 H) 2,89 (d, 4 H)	373	*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)azetidina-1-carboxilato Método 64 
118	(5*Z*)-5-[2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno]-1,3-tiazolidina-2,4-diona clorhidrato 	12,38 (s, 1 H) 8,34 (s, 2 H) 7,90 (s, 1 H) 6,96 (s, 1 H) 6,68 (s, 1 H) 3,89 - 3,80 (m, 4 H) 3,73 (s, 3 H) 3,46 - 3,34 (m, 2 H) 3,23 - 3,13 (m, 1 H) 3,10 (dd, 1 H) 2,28 (dd, 1 H) 2,01 (d, 1 H)	351	*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato Método 65 

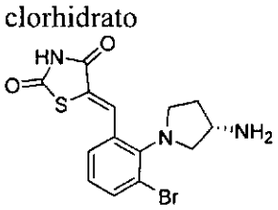
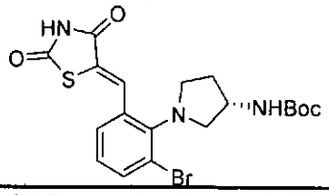
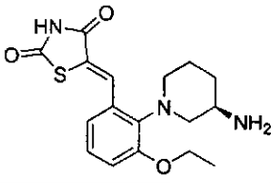
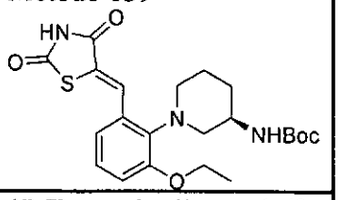
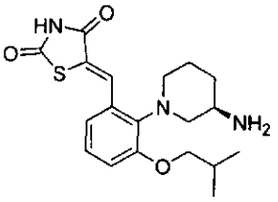
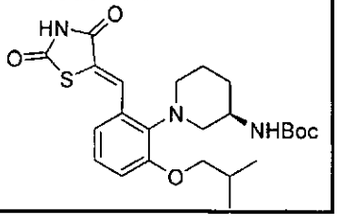
168

119	(*R,Z*)-5-amino-N-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-il)pentanamida clorhidrato 	12,24 (s, 1 H) 8,07 (d, 1 H) 7,79 (s, 1 H) 7,60 (brs, 2 H) 6,88 (s, 1 H) 6,55 (s, 1 H) 4,22 (d, 1 H) 3,76 (s, 3 H) 3,65 (s, 3 H) 3,30 - 3,15 (m, 2 H) 3,15 - 2,98 (m, 1 H) 2,86 (dd, 1 H) 2,70 (d, 2 H) 2,17-1,92 (m, 3 H) 1,76 (brs, 1 H) 1,52 - 1,25 (m, 4 H)	449	(*R,Z*)-*terc*-butil 5-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)-5-oxopentilcarbamato Método 66 
120	(*S,Z*)-5-amino-N-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-il)pentanamida clorhidrato 	12,24 (s, 1 H) 8,07 (d, 1 H) 7,79 (s, 1 H) 7,60 (brs, 2 H) 6,88 (s, 1 H) 6,55 (s, 1 H) 4,22 (d, 1 H) 3,76 (s, 3 H) 3,65 (s, 3 H) 3,30 - 3,15 (m, 2 H) 3,15 - 2,98 (m, 1 H) 2,86 (dd, 1 H) 2,70 (d, 2 H) 2,17-1,92 (m, 3 H) 1,76 (brs, 1 H) 1,52 - 1,25 (m, 4 H)	449	(*S,Z*)-*terc*-butil 5-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)-5-oxopentilcarbamato Método 67 
121	(*S,Z*)-5-(2-(3-(3-aminopropilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,50 (s, 1 H) 9,78 (s, 1 H) 7,92 (s, 1 H) 7,05 (s, 1 H) 6,85 (s, 1 H) 4,21 - 4,11 (m, 1 H) 3,93 (s, 3 H) 3,83 (s, 3 H) 3,42 - 3,25 (m, 8 H) 2,45 (m, 1 H) 2,20 (m, 1 H) 1,32 (m, 2 H)	407	(*S,Z*)-*terc*-butil 3-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)propilcarbamato Método 68 

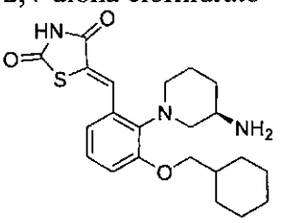
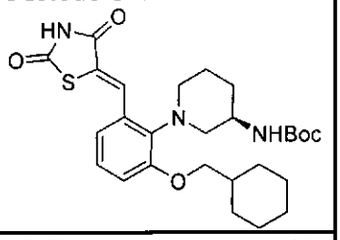
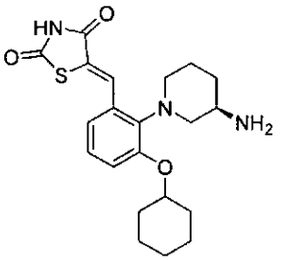
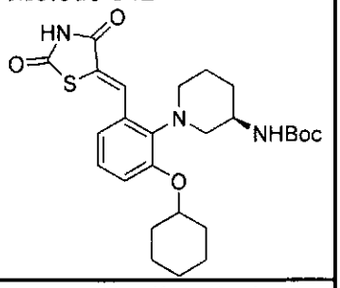
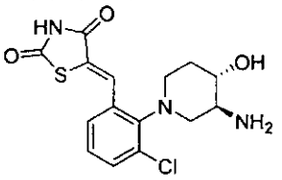
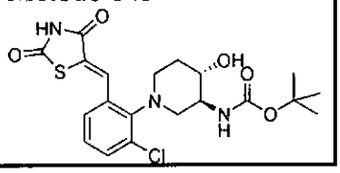
122A	(*R,Z*)-5-(2-(3-(3-aminopropilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,44 (s, 1 H) 9,78 (s, 1 H) 7,92 (s, 1 H) 7,05 (s, 1 H) 6,85 (s, 1 H) 4,21 - 4,11 (m, 1 H) 3,93 (s, 3 H) 3,83 (s, 3 H) 3,42 - 3,25 (m, 8 H) 2,45 (m, 1 H) 2,20 (m, 1 H) 1,32 (m, 2 H)	407	(*R,Z*)-*terc*-butil 3-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)propilcarbamato Método 69 
122B	(*R,Z*)-5-(2-(3-(aminometil)pirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona 	(400 MHz, MeOD) ppm 8,08 (s, 1 H) 7,49 (dd, 2 H) 7,31 (t, 1 H) 3,56 (t, 1 H) 3,42 – 3,51 (m, 1 H) 3,38 (td, 1 H) 3,09 – 3,15 (m, 2 H) 2,71 – 2,78 (m, 1 H) 2,26 – 2,36 (m, 1 H) 1,86 – 1,96 (m, 1 H) 1,31 (dd, 1 H)	338	(*R,Z*)-*terc*-butil (1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)metilcarbamato Método 132 
122C	(*S,Z*)-5-(2-(3-(aminometil)pirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona 	(400 MHz, MeOD) ppm 8,07 (s, 1 H) 7,49 (dd, 2 H) 7,31 (t, 1 H) 3,56 (t, 1 H) 3,42 – 3,51 (m, 2 H) 3,38 (td, 1 H) 3,07 – 3,16 (m, 2 H) 2,67 – 2,79 (m, 1 H) 2,24 – 2,36 (m, 1 H) 1,90 (dd, 1 H)	338	(*S,Z*)-*terc*-butil (1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)metilcarbamato Método 133 

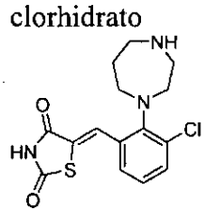
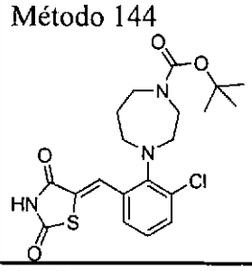
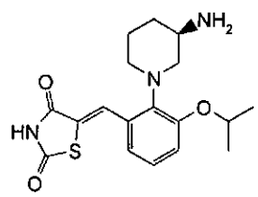
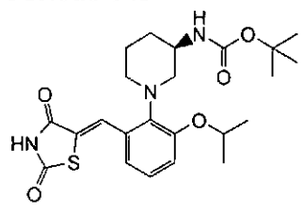
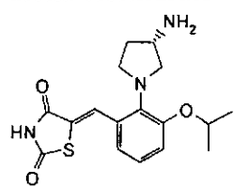
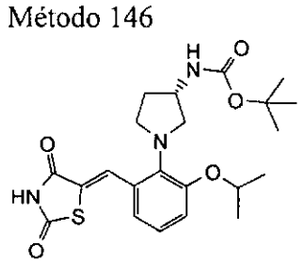
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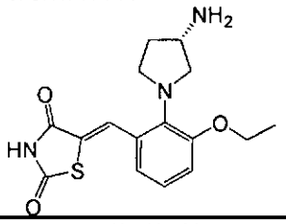
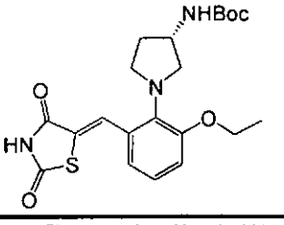
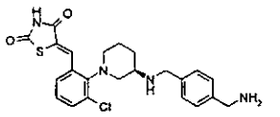
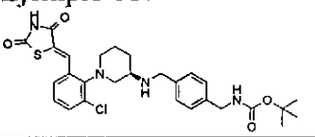
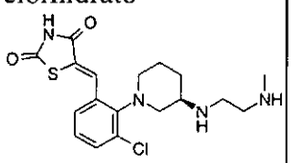
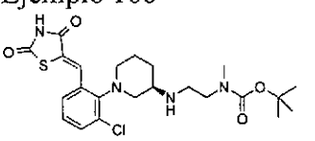
122D	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	12,70 (s, 1 H) 8,17 (brs, 3 H) 8,01 (s, 1 H) 7,52 (d, 1 H) 7,41-7,31 (m, 2 H) 3,40-3,10 (m, 4 H) 2,84-2,81 (m, 1 H) 2,12-2,10 (m, 1 H) 1,80-1,58 (m, 3 H)	338	(*R,Z*)-terc-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 134 
122E	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,60 (s, 1 H) 8,12 (brs, 4 H) 7,28-7,02 (m, 3 H) 3,82 (s, 3 H) 3,18-2,87 (m, 5 H) 2,10-2,07 (m, 1 H) 1,75-1,38 (m, 3 H)	334	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)piperidin-3-ilcarbamato Método 135 
122F	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-bromobencilideno)tiazolidina-2,4-diona clorhidrato 	12,70 (s, 1 H) 8,15 (brs, 3 H) 8,01 (s, 1 H) 7,74-7,69 (m, 1 H) 7,46 (d, 1 H) 7,26 (t, 1 H) 3,27-2,99 (m, 4 H) 2,82-2,80 (m, 1 H) 2,12-2,10 (m, 1 H) 1,76-1,40 (m, 3 H)	383	*(R,Z)-terc*-butil 1-(2-bromo-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 136 
122G	(*R,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	12,67 (brs, 1 H) 8,30 (brs, 3 H) 7,93 (s, 1 H) 7,55 (d, 1 H) 7,41-7,31 (m, 2 H) 3,87 (brs, 1 H) 3,50-3,27 (m, 4 H) 2,40-2,28 (m, 1 H) 2,08-1,95 (m, 1 H)	324	(*R,Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato Método 137 

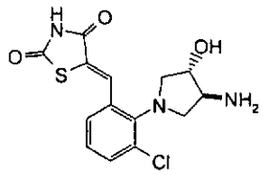
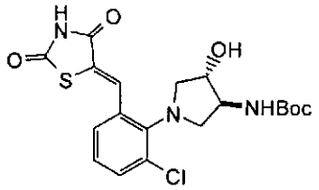
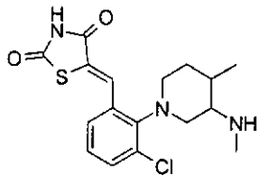
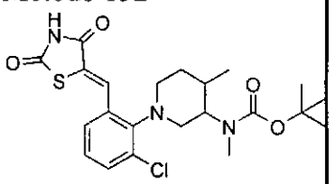
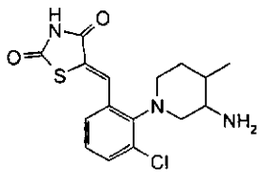
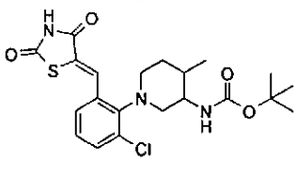
122H	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-bromobencilideno)tiazolidina-2,4-diona clorhidrato 	12,68 (brs, 1 H) 8,31 (brs, 3 H) 7,90 (s, 1 H) 7,75 (d, 1 H) 7,46 (d, 1 H) 7,29 (t, 1 H) 3,75 (brs, 1 H) 3,55 (t, 1 H) 3,38-3,25 (m, 3 H) 2,40-2,32 (m, 1 H) 2,12-2,02 (m, 1 H)	370	(*S,Z*)-*terc*-butil 1-(2-bromo-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato Método 138 
122I	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-etoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,58 (s, 1 H) 8,13-8,09 (m, 4 H) 7,26-7,24 (m, 1 H) 7,16-7,14 (m, 1 H) 7,03-7,01 (m, 1 H) 4,07 (q, 2 H) 3,78-3,67 (m, 2 H) 3,22-3,07 (m, 3 H) 2,10-2,07 (m, 1 H) 1,76-1,55 (m, 3 H) 1,38 (t, 3 H)	348	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-etoxifenil)piperidin-3-ilcarbamato Método 139 
122J	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-isobutoxifenil)piperidin-3-ilcarbamato clorhidrato 	12,60 (s, 1 H) 8,18 (brs, 3 H) 8,15 (s, 1 H) 7,26 (t, 1 H) 7,15 (d, 1 H) 7,02 (d, 1 H) 3,84-3,74 (m, 2 H) 3,20-3,02 (m, 4 H) 2,74 (d, 1 H) 2,14–2,07 (m, 2 H) 1,73-1,21 (m, 3 H) 1,03 (d, 6 H)	376	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-isobutoxifenil)piperidin-3-ilcarbamato Método 140 

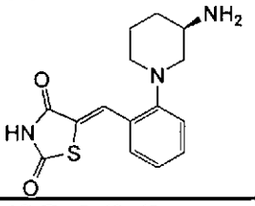
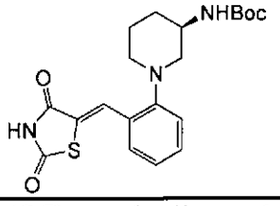
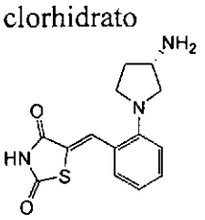
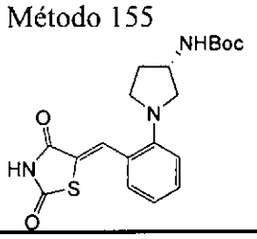
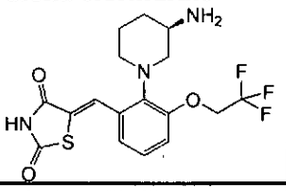
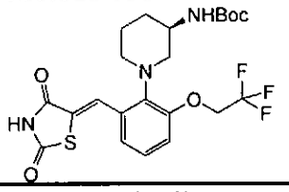
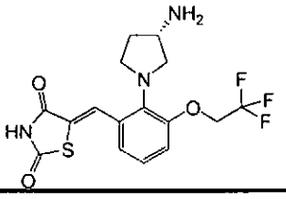
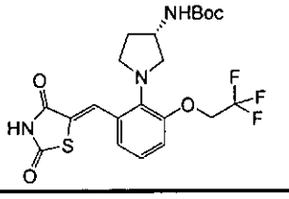
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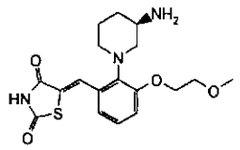
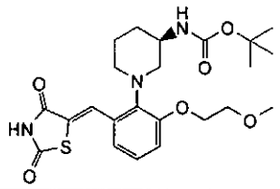
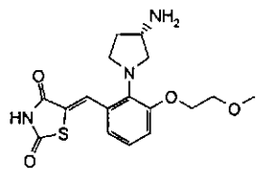
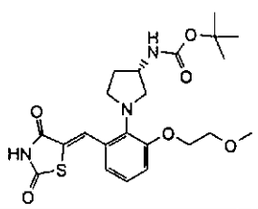
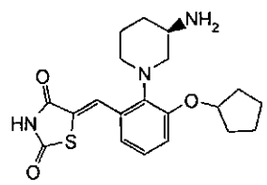
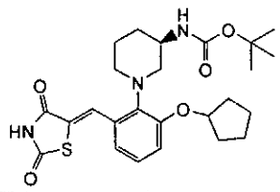
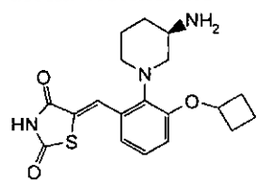
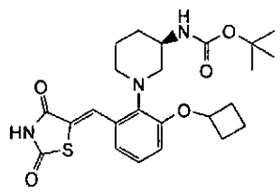
122K	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-(ciclohexilmetoxi)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,60 (s, 1 H) 8,14 (brs, 4 H) 7,25 (t, 1 H) 7,14 (d, 1 H) 7,00 (d, 1 H) 3,82 (brs, 2 H) 3,29-3,00 (m, 4 H) 2,75-2,72 (m, 1 H) 2,12-2,10 (m, 1 H) 1,86-1,50 (m, 8 H) 1,35-1,03 (m, 6 H)	416	(*R*,*Z*)-*terc*-butil 1-(2-(ciclohexilmetoxi)-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 141 
122L	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-(ciclohexiloxi)bencilideno)tiazolidina-2,4-diona clorhidrato 		402	(*R*,*Z*)-*terc*-butil 1-(2-(ciclohexiloxi)-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 142 
122M	(±)-(*Z*)-5-(2-3-amino-4-hidroxipiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	12,68 (s, 1 H) 8,01 (brs, 4 H) 7,53 (d, 1 H) 7,44-7,42 (m, 1 H) 7,35 (t, 1 H) 5,72-5,70 (m, 1 H) 3,32-3,22 (m, 2 H) 3,20-3,11 (m, 3 H) 1,96-1,94 (m, 1 H) 1,40-1,37 (m, 1 H)	354	(±)-*terc*-butil-1-(2-cloro-6-((*Z*)-(2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-hidroxipiperidin-3-ilcarbamato Método 143 

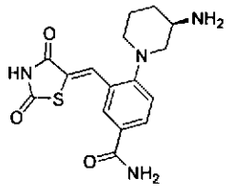
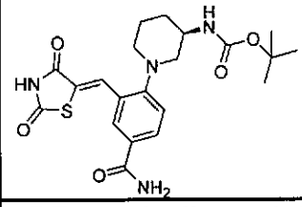
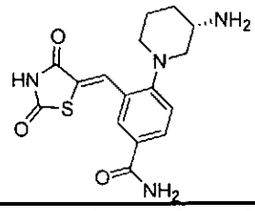
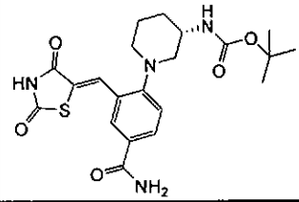
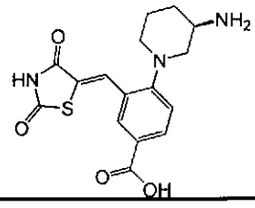
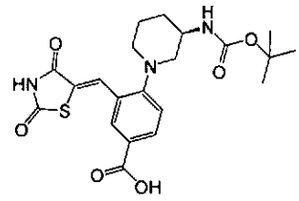
122N	(*Z*)-5-(3-cloro-2-(1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,73 (brs, 1 H), 9,18 (brs, 2 H), 8,04 (s, 1 H), 7,62 (d, 1 H), 7,41 (dt, 2 H), 3,65 (brs, 1 H), 3,34 - 3,30 (m, 5 H), 3,04 (brs, 2 H), 2,14 (brs, 2 H)	338	(*Z*)-*terc*-butil 4-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-carboxilato Método 144 
122O	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-isopropoxibenciliden o)tiazolidina-2,4-diona clorhidrato 	12,61 (brs, 1 H) 8,33 (brs, 3 H) 8,15 (brs, 1 H) 7,34-7,09 (m, 2 H) 6,99 (d, 1 H) 4,67 (ddd 1 H) 3,28 (brs, 1 H) 3,07 (brs, 3 H) 2,70 (brs, 1 H) 2,12 (brs, 1 H) 1,73 (brs, 1 H) 1,57 (brs, 1 H) 1,51 - 1,21 (m, 7 H)	362	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-isopropoxifenil)piperidin -3-ilcarbamato Método 145 
122P	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-isopropoxibenciliden o)tiazolidina-2,4-diona clorhidrato 	12,58 (brs, 1 H) 8,52 (brs, 3 H) 8,08 (s, 1 H) 7,39-7,10 (m, 2 H) 6,99 (d, 1 H) 4,70 (d, 1 H) 3,78 (brs, 1 H) 3,52-3,33 (m, 1 H) 3,33 - 3,03 (m, 3 H) 2,28 (brs, 1 H) 2,00 (d, 1 H) 1,32 (d, 6 H)	348	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-isopropoxifenil)pirrolidin -3-ilcarbamato Método 146 

122Q	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-etoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,58 (brs, 1 H) 8,48 (brs, 3 H) 8,09 (s, 1 H) 7,26 (t, 1 H) 7,16 (d, 1 H) 7,02 (d, 1 H) 4,09 (q, 2 H) 3,80 (d, 1 H) 3,47 (dd, 1 H) 3,28 (m, 1 H) 3,21 (dd, 1 H) 2,29 (d, 1 H) 2,01 (dd, 1 H) 1,40 (t, 3 H)	334	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-etoxifenil)pirrolidin-3-ilcarbamato Método 147 
122R	(*R,Z*)-5-(2-(3-(4-(aminometil)bencilamino)piperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	9,62 (brs, 1 H) 8,46 (brs, 3 H) 7,66-7,49 (m, 5 H) 7,47-7,34 (m, 2 H) 4,26-4,12 (m, 2 H) 4,09-3,94 (m, 2 H) 3,42-3,25 (m, 4 H) 2,83 (brs, 1 H) 2,36 (s, 1 H) 1,85 (m, 1 H) 1,62 (d, 2 H)	457	(*R,Z*)-*terc*-butil 4-((1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilamino)metil)bencilcarbamato Ejemplo 167 
122S	(*R,Z*)-5-(3-cloro-2-(3-(2-(metilamino)etilamino)piperidin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,68 (brs, 1 H) 9,68 (brs, 2 H) 9,21 (brs, 2 H) 8,05 (s, 1 H) 7,56 (d, 1 H) 7,50-7,42 (m, 1 H) 7,37 (t, 1 H) 3,75-3,65 (m, 5 H) 3,63-3,57 (m, 2 H) 3,16 (d, 1 H) 2,82 (brs, 1 H) 2,60 (brs, 3 H) 2,37-2,28 (m, 1 H) 1,80 (d, 1 H) 1,65 (m, 1H) 1,54 (brs, 1 H)	395	(*R,Z*)-*terc*-butil 2-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilamino)etil(metil)carbamato Ejemplo 168 

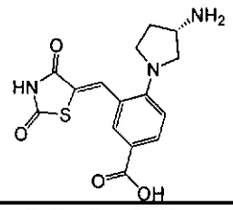
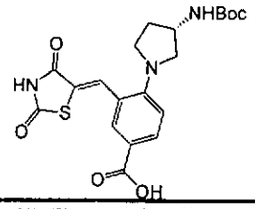
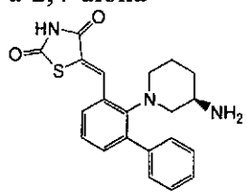
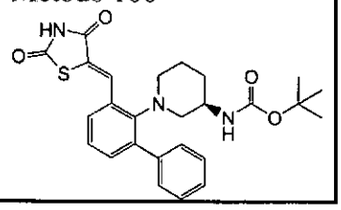
122T	(*Z*)-5-(2-((3S,4S)-3-amino-4-hidroxipirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	12,68 (brs, 1 H) 8,50 (brs, 3 H) 8,10-7,81 (m, 1 H) 7,58 (dd, 1 H) 7,51-7,27 (m, 2 H) 4,56-4,28 (m, 1 H) 3,84 (brs, 1 H) 3,66-3,40 (m, 4 H) 3,39-3,23 (m, 1 H)	339	*terc*-butil (3*S*,4*S*)-1-(2-cloro-6-((*Z*)-(2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-hidroxipirrolidin-3-ilcarbamato Método 151 
122U	(*Z*)-5-(3-cloro-2-(4-metil-3-(metilamino)piperidin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,69 (brs, 1 H) 8,63 (brs, 2 H) 8,02 (s, 1 H) 7,57 (d, 1 H) 7,47-7,31 (m, 2 H) 3,58 (m, 1 H) 3,07 (m, 1 H) 2,67 (brs, 1 H) 2,58 (brs, 3 H) 2,40 (m, 1 H) 1,87 (m, 1 H) 1,68 (m, 1 H) 1,29 (m, 1 H) 1,07 (d, 3 H) 0,87 (d, 1 H)	365	(*Z*)-terc-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-metilpiperidin-3-il(metil)carbamato Método 152 
122V	(*Z*)-5-(2-(3-amino-4-metilpiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 		351	(*Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-metilpiperidin-3-ilcarbamato Método 153 

122W	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,58 (s, 1 H), 8,44 (brs, 3 H) 7,89 (s, 1 H) 7,54-7,34 (m, 2 H) 7,27-7,05 (m, 2 H) 3,26 (d, 2 H) 2,94 (d, 1 H), 2,87-2,61 (m, 2 H) 2,05 (brs, 1 H) 1,85 (brs, 1 H) 1,75-1,47 (m, 2 H)	304	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 154 
122X	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,49 (s, 1 H) 8,50 (brs, 3 H) 7,91 (s, 1 H) 7,44-7,22 (m, 2 H) 7,07-6,79 (m, 2 H) 3,83 (d, 1 H) 3,51-3,29 (m, 2 H) 3,28-3,17 (m, 2 H) 2,27 (dd, 1 H), 2,11-1,94 (m, 1 H)	290	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato Método 155 
122Y	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-(2,2,2-trifluoroetoxi)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,57 (brs, 1 H) 8,03 (brs, 1 H) 7,90 (brs, 3 H) 7,36-7,13 (m, 2 H) 7,07 (d, 1 H) 4,85-4,55 (m, 2 H) 2,98 (brs, 4 H) 2,74 (brs, 1 H) 2,02 (d, 1 H) 1,69 (d, 1 H) 1,54 (d, 1 H) 1,30 (brs, 1 H)	402	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2,2,2-trifluoroetoxi)fenil)piperidin-3-ilcarbamato Método 156 
122Z	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-(2,2,2-trifluoroetoxi)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,52 (brs, 1 H) 8,21-7,91 (m, 4 H) 7,34-7,14 (m, 2 H) 7,07 (d, 1 H) 4,88-4,72 (m, 2 H) 3,74 (d, 1 H) 3,40 (dd, 1 H) 3,22 (td, 1 H) 3,18-3,10 (m, 1 H) 3,06 (dd, 1 H) 2,30-2,10 (m, 1 H) 1,90 (dd, 1 H)	388	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2,2,2-trifluoroetoxi)fenil)pirrolidin-3-ilcarbamato Método 157 

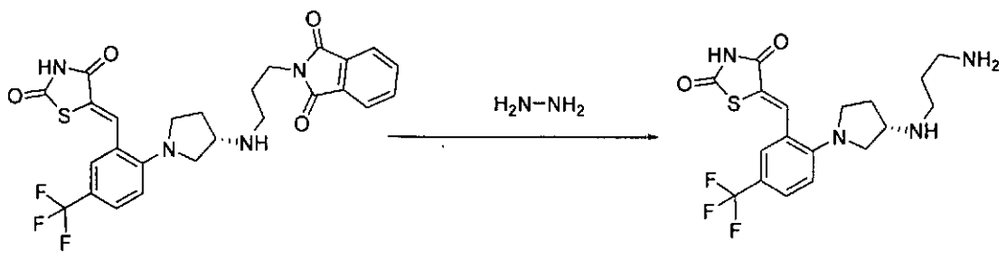
122AA	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-(2-metoxietoxi)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,67 (brs, 1 H) 8,30 (brs, 3 H) 8,20 (brs, 1 H) 7,33 (brs, 1 H) 7,25 (brs, 1 H) 7,10 (d, 1 H) 4,68 (brs, 3 H) 4,22 (t, 2 H) 3,91-3,65 (m, 2 H) 3,42 (s, 3 H) 3,29 (brs, 1 H) 2,80 (brs, 1 H) 2,18 (brs, 1 H) 1,81 (brs, 1 H) 1,68 (brs, 1 H) 1,48 (brs, 1 H)	378	(*R*,*Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2-metoxietoxi)fenil)piperidin-3-ilcarbamato Método 158 
122AB	(*S*,*Z*)-5-(2-(3-aminopirrolidin-1-il)-3-(2-metoxietoxi)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,58 (brs, 1 H) 8,42 (brs, 3 H) 8,10 (s, 1 H) 7,28 (t, 1 H) 7,23-7,11 (m, 1 H) 7,04 (d, 1 H) 4,27-3,97 (m, 2 H) 3,85 (d, 1 H) 3,78-3,63 (m, 2 H) 3,49 (dd, 1 H) 3,34 (s, 3 H) 3,27 (td, 1 H) 3,22-3,06 (m, 2 H) 2,30 (dd, 1 H) 2,02 (dd, 1 H)	364	(*S*,*Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2-metoxietoxi)fenil)pirrolidin-3-ilcarbamato Método 159 
122AC	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-(ciclopentiloxi)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,37 (brs, 1 H) 8,00 (brs, 3H) 7,93 (s, 1 H) 7,02 (d, 1 H) 6,91 (d, 1 H) 6,77 (d, 1 H) 3,02-2,91 (m, 1 H) 2,82 (d, 3 H) 2,48 (brs, 1 H) 1,89-1,40 (m, 12 H) 1,16 (brs, 1 H)	388	(*R*,*Z*)-*terc*-butil 1-(2-(ciclopentiloxi)-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 160 
122AD	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-ciclobutoxibenciliden o)tiazolidina-2,4-diona clorhidrato 	12,60 (brs, 1 H) 8,14 (brs, 4 H) 7,23 (d, 1 H) 7,00 (dd, 2 H), 4,86-4,67 (m, 1 H) 3,25 (m, 1H) 3,05 (m, 2H) 2,74 (brs, 1 H) 2,49-2,35 (m, 2 H) 2,21-1,95 (m, 3 H) 1,93-1,76 (m, 2 H) 1,67 (td, 3 H) 1,42 (brs, 1 H)	374	(*R*,*Z*)-*terc*-butil 1-(2-ciclobutoxi-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 161 

122AE	(*R,Z*)-4-(3-aminopiperidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzamida clorhidrato 		347	(*R,Z*)-*terc*-butil 1-(4-carbamoil-2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 162 
122AF	(*S,Z*)-4-(3-aminopiperidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzamida clorhidrato 		347	(*S,Z*)-*terc*-butil 1-(4-carbamoil-2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato Método 163 
122AG	clorhidrato de ácido (*R,Z*)-4-(3-aminopiperidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzoico 		348	ácido (*R,Z*)-4-(3-(*terc*-butoxicarbonilamino)piperidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzoico Método 164 

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122AH	ácido (*S,Z*)-4-(3-aminopirrolidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzoico 		333	ácido (*S,Z*)-4-(3-(*terc*-butoxicarbonilamino)pirrolidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzoico Método 165 
122AI	(*R,Z*)-5-((2-(3-aminopiperidin-1-il)bifenil-3-il)metileno)tiazolidina-2,4-diona 	12,64 (brs, 1 H) 8,09 (brs, 3 H) 7,92 (s, 1 H) 7,56-7,36 (m, 4 H) 7,36 - 7,16 (m, 4 H) 3,06 (brs, 1 H) 3,00 (brs, 1 H) 2,72 (d, 1 H) 2,35 (brs, 2 H) 2,05 (brs, 1 H) 1,58 (brs, 2 H) 1,32-1,15 (m, 1 H)	380	(*R,Z*)-*terc*-butil 1-(3-((2,4-dioxotiazolidin-5-ilideno)metil)bifenil-2-il)piperidin-3-ilcarbamato Método 166 

Ejemplo 123:

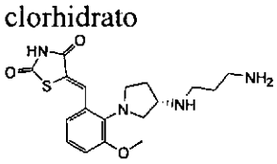
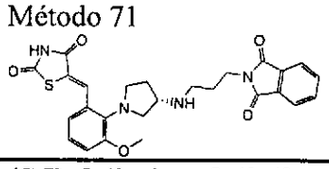
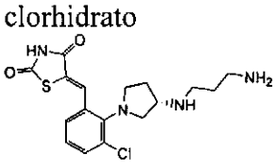
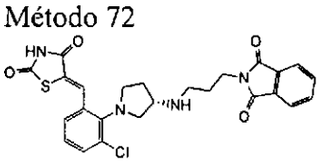
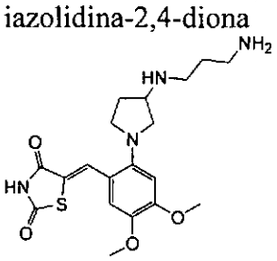
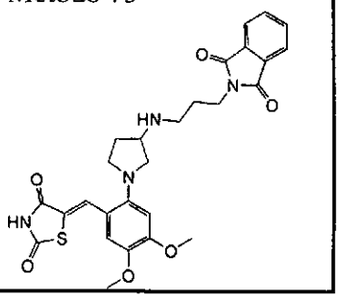


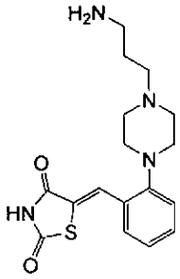
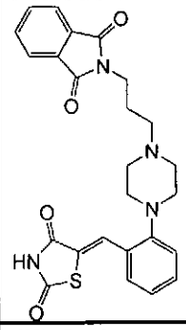
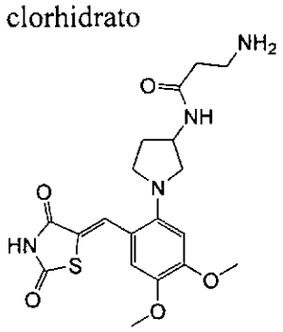
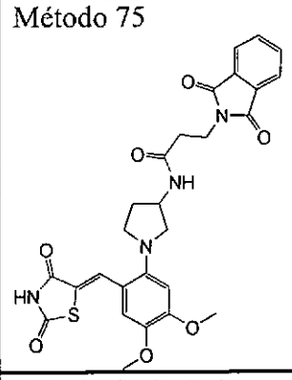
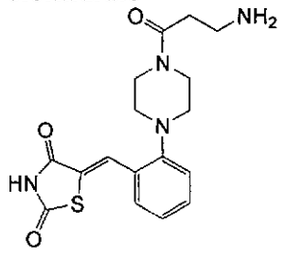
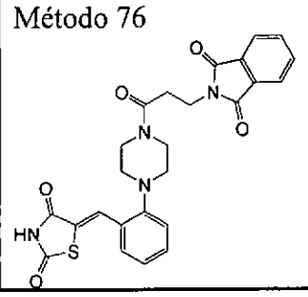
(*S,Z*)-5-(2-(3-(3-aminopropilamino)pirrolidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona clorhidrato:

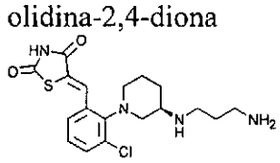
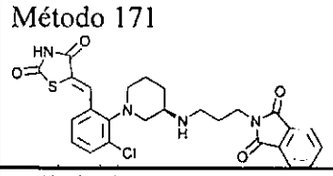
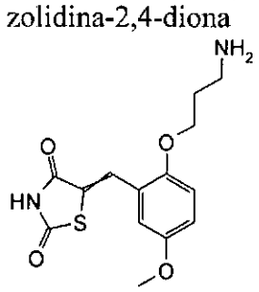
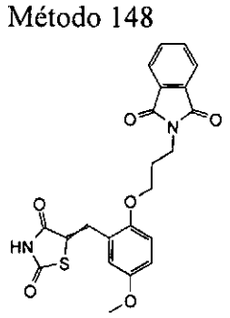
Un matraz de fondo redondo de 25 mL se cargó con una barra de agitación magnética, (*S,Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)-5-(trifluorometil)bencilideno)tiazolidina-2,4-diona (Método 70) (0,271 g, 0,50 mmol), EtOH (2,488 ml) e hidrazina (0,023 ml, 0,75 mmol). La reacción se agitó a TA durante 30 min y luego se filtró a través de un lecho de Celite. El filtrado se concentró al vacío y se purificó mediante HPLC en fase inversa (MeCN/agua) para proporcionar fracciones

que se concentraron al vacío, se suspendieron en metanol (~ 5 mL) y HCl 1N en éter dietílico (~2 mL) y se concentraron al vacío para proporcionar (*S,Z*)-5-(2-(3-(3-aminopropilamino)pirrolidin-1-il)-5-(trifluorometil) bencilideno)tiazolidina-2,4-diona clorhidrato (0,071 g, 29,3 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12,52 (s, 1 H) 9,49 (s, 1 H) 8,08 (brs, 2 H) 7,93 (s, 1 H) 7,67 (s, 1 H) 7,61 (d, 1 H) 7,08 (d, 1 H) 3,88 - 3,81 (m, 1 H) 3,53 - 3,33 (m, 4 H) 3,08 - 3,05 (m, 2 H) 2,92 - 2,89 (m, 2 H) 2,33 - 2,19 (m, 2 H) 2,04 - 1,96 (m, 2 H); *m/z* 415.

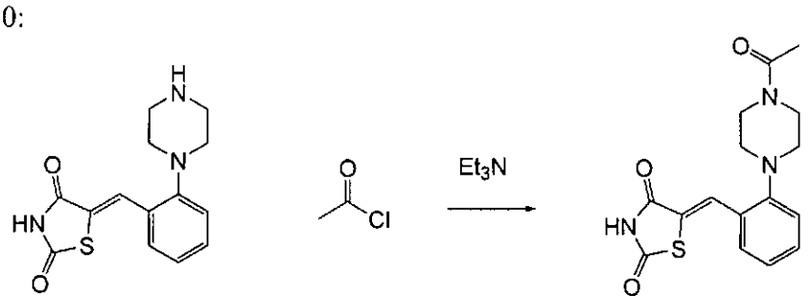
Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 123, utilizando los materiales de partida apropiados. Los siguientes compuestos base obtenidos después de la cromatografía pueden convertirse en su correspondiente sal clorhidrato de forma similar a la que se describe en el Ejemplo 123.

Ej.	Compuesto	^{1}H NMR	m/z	MP
124	(*S,Z*)-5-(2-(3-(3-aminopropilamino)pirrolidin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona clorhidrato 	12,59 (brs, 1 H) 9,30 (brs, 1 H) 8,09 (s, 1 H) 8,07 (brs, 1 H) 7,32 (t, 1 H) 7,21 (d, 1 H) 7,08 (d, 1 H) 3,87 (s, 3 H) 3,46 – 3,44 (m, 1 H) 3,39 – 3,25 (m, 2 H) 3,17 – 2,99 (m, 4 H) 2,96 – 2,91 (m 2 H) 2,19 – 2,10 (m, 2 H) 2,08-1,99 (m, 2 H)	377	(*S,Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona Método 71 
125	(*S,Z*)-5-(2-(3-(3-aminopropilamino)pirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato 	12,72 (brs, 1 H) 9,50 (brs, 1 H) 8,10 (brs, 2 H) 7,96 (s, 1 H) 7,60 (d, 1 H) 7,46 – 7,39 (m 2 H) 3,95 – 3,91 (m, 1 H) 3,51 – 3,20 (m, 4 H) 2,99 – 2,92 (m, 2 H) 2,44 – 2,38 (m, 2 H) 2,21 – 2,11 (m, 2 H) 2,08 – 1,99 (m, 2 H)	382	(*S,Z*)-5-(3-cloro-2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona Método 72 
126	(*Z*)-5-(2-(3-(3-aminopropilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona 	12,40 (s, 1 H) 9,78 (s, 1 H) 7,92 (s, 1 H) 7,05 (s, 1 H) 6,85 (s, 1 H) 4,21 - 4,11 (m, 1 H) 3,93 (s, 3 H) 3,83 (s, 3 H) 3,42 - 3,25 (m, 8 H) 2,45 (m, 1 H) 2,20 (m, 1 H) 1,32 (m, 2 H)	407	(*Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona Método 73 

127	(Z)-5-(2-(4-(3-aminopropil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona clorhidrato 	12,64 (s, 1 H) 11,50 (s, 1 H) 8,27 (s, 1 H) 7,85 (s, 1 H) 7,49 (t, 2 H) 7,24 (t, 2 H) 3,55 (d, 2 H) 3,32 - 3,16 (m, 8 H) 2,93 (d, 2 H) 2,18 - 2,07 (m, 2 H)	347	(Z)-5-(2-(4-(3-(1,3-dioxoisoindolin-2-il)propil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona Método 74 
128	(Z)-3-amino-N-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-il)propanamida clorhidrato 	12,34 (s, 1 H) 8,46 (d, 1 H) 7,86 (s, 3 H) 6,95 (s, 1 H) 6,63 (s, 1 H) 4,36 - 4,26 (m, 1 H) 3,84 (s, 3 H) 3,72 (s, 3 H), 3,32 - 3,21 (m, 3 H) 3,02 - 2,93 (m, 3 H) 2,18 (dd, 2 H) 1,86 (dd, 1 H)	421	(Z)-3-(1,3-dioxoisoindolin-2-il)-N-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-il)propanamida Método 75 
129A	(5Z)-5-{2-[4-(3-aminopropanoil)piperazin-1-il]bencilideno}-1,3-tiazolidina-2,4-diona clorhidrato 	12,59 (s, 1 H) 7,94 (s, 1 H) 7,82 (s, 2 H) 7,51 - 7,44 (m, 2 H) 7,26 - 7,17 (m, 2 H) 3,66 (m, 2 H) 3,59 (m, 2 H) 3,08 - 2,97 (m, 2 H) 2,96 - 2,86 (m, 4 H) 2,74 (m, 2 H)	361	(5Z)-(2-(4-(3-(1,3-dioxoisoindolin-2-il)propanoil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona Método 76 

129B	(*R*,*Z*)-5-(2-(3-(3-aminopropilamino)piperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona 	12,69 (brs, 1 H) 9,31 (brs, 1 H) 8,05 (s, 3 H) 7,56 (d, 1 H) 7,49-7,41 (m, 1 H) 7,37 (t, 1 H) 3,76-3,65 (m, 3 H) 3,16 (brs, 1 H) 3,04 (brs, 2 H) 2,94-2,75 (m, 3 H) 2,33 (brs, 1 H) 2,04-1,92 (m, 2 H) 1,78 (d, 1 H) 1,65 (m, 1 H), 1,50 (m, 1 H)	395	(*R*,*Z*)-5-(3-cloro-2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)piperidin-1-il)bencilideno)tiazolidina-2,4-diona Método 171 
129C	5-(2-(3-aminopropoxi)-5-metoxibencilideno)tiazolidina-2,4-diona 	12,64 (brs, 1 H) 7,94 (brs, 4 H) 7,11 (m, 2 H) 6,93 (s, 1 H) 4,13 (m, 2 H) 3,77 (s, 3 H) 2,97 (m, 2 H) 2,06 (m, 2 H)	309	5-(2-(3-(1,3-dioxoisoindolin-2-il)propoxi)-5-metoxibencilideno)tiazolidina-2,4-diona Método 148 

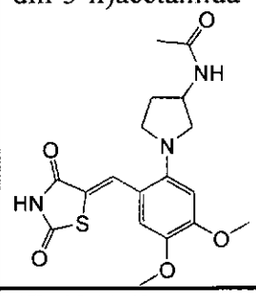
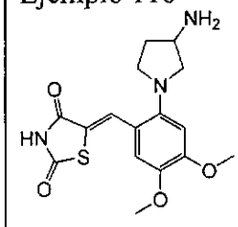
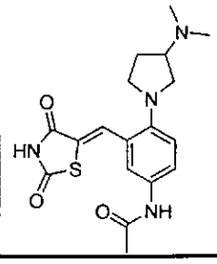
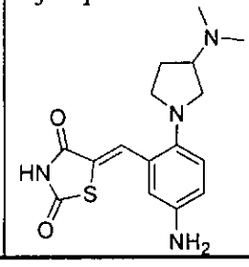
Ejemplo 130:



(5Z)-5-[2-(4-acetilpiperazin-1-il)bencilideno]-1,3-tiazolidina-2,4-diona: A una mezcla de (5Z)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona (Ejemplo 115) y cloruro de acetilo (36,1 mg, 0,46 mmol) se agregó trietilamina (93 mg, 0,92 mmol) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante toda la noche y luego se trató con $NaHCO_3$ acuoso saturado (~ 25 mL). Esta mezcla se dejó agitar a temperatura ambiente durante 10 min y luego se extrajo con DCM (3 X 25 mL). El extracto orgánico combinado se secó sobre Na_2SO_4 anhidro, se filtró a través de

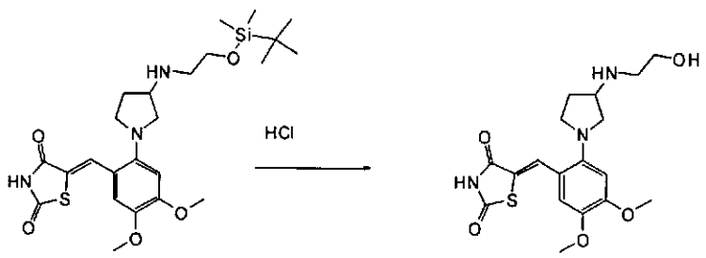
un lecho de Celite y el filtrado se concentró al vacío para proporcionar el producto que se purificó mediante HPLC en fase inversa (acetonitrilo:agua: 0,1 % TFA = 5 % a 70 %) para proporcionar el compuesto del título como un sólido amarillo claro (40,0 mg, 35,4 %). ^{1}H NMR (300 MHz, DMSO-D6) δ ppm 12,58 (brs, 1 H) 7,94 (s, 1 H) 7,47 (d, 2 H) 7,30 - 7,07 (m, 2 H) 3,60 (brs, 4 H) 2,90 (brs, 2 H) 2,85 (brs, 2 H) 2,04 (s, 3 H); *m/z* 331.

Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 130, utilizando los materiales de partida apropiados.

Ej.	Compuesto	^{1}H NMR	m/z	MP
131A	*N*-(1-{2-[(*Z*)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]-4,5-dimetoxifenil}pirrolidin-3-il)acetamida 	12,29 (brs, 1 H) 8,13 (d, 1 H) 7,85 (s, 1 H) 6,94 (s, 1 H) 6,61 (s, 1 H) 4,27 (d, 1 H) 3,83 (s, 3 H) 3,72 (s, 3 H) 3,43 - 3,14 (m, 4 H) 2,94 (dd, 1 H) 2,30 - 2,05 (m, 1 H) 1,82 (s, 3 H)	392	(5*Z*)-5-[2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno]-1,3-tiazolidina-2,4-diona Ejemplo 118 
131B	(*Z*)-*N*-(4-(3-(dimetilamino)pirrolidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)acetamida 	9,86 (s, 1 H) 7,68 (s, 1 H) 7,56 (s, 1 H) 7,49-7,47 (d, 1 H) 6,96-6,94 (d, 1 H) 3,23 (m, 1 H) 3,00 (m, 4 H) 2,51 (s, 6 H) 2,15 (m, 1 H) 2,01 (s, 3 H) 1,55 (m, 1 H)	375	(Z)-5-(5-amino-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona Ejemplo 151 

Ejemplo 132:

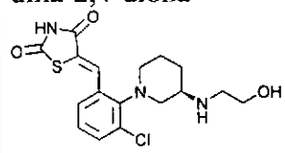
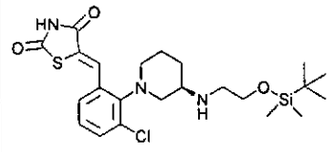
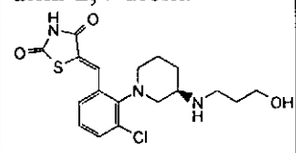
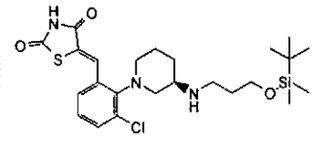
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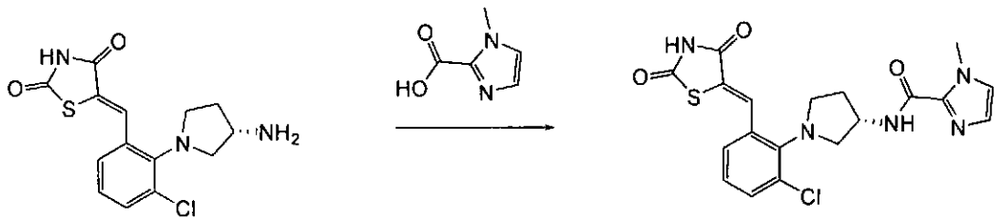
(*Z*)-5-(2-(3-(2-hidroxietilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona:

Una mezcla de (*Z*)-5-(2-(3-(2-(*terc*-butildimetilsililoxi)etilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona (Método 77) (120 mg, 0,24 mmol) en 5 mL de HCl 1,25 M en metanol se agitó a temperatura ambiente durante 30 min. La mezcla luego se concentró al vacío para proporcionar el producto que se purificó mediante HPLC en fase inversa (acetonitrilo:agua: 0,1 % NH_4OAc = 5 % a 55 %) para proporcionar el compuesto del título como un sólido amarillo (45,0 mg, 48,4 %). ^1H NMR (300 MHz, DMSO-D6) δ ppm 7,40 (s, 1 H) 7,07 (s, 1 H) 6,57 (s, 1 H) 3,78 (s, 3 H) 3,70 (s, 3 H) 3,45 (m, 2 H) 3,27 - 3,15 (m, 4 H) 2,92 (m, 1 H) 2,59 (m, 2 H) 2,08 (m, 1 H) 1,66 (m, 1 H); *m/z* 394.

Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 132 utilizando los materiales de partida apropiados.

133	(*R,Z*)-5-(3-cloro-2-(3-(2-hidroxietilamino)piperidin-1-il)bencilideno)tiazolidina-2,4-diona 	8,81 (brs, 2 H) 7,96 (s, 1 H) 7,48 (d, 1 H) 7,40-7,32 (m, 1 H) 7,31-7,25 (m, 1 H) 3,63-3,55 (m, 2 H) 3,46-3,38 (m, 2 H) 3,08 (brs, 2 H) 2,96 (d, 2 H) 2,75 (brs, 1 H) 2,20 (m, 1H) 1,72 (brs, 1 H) 1,56 (brs, 1 H) 1,44 (brs, 1 H)	382	(*R,Z*)-5-(2-(3-(2-(*terc*-butildimetilsililoxi)etilamino)piperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Método 169 
134	(*R,Z*)-5-(3-cloro-2-(3-(3-hidroxipropilamino)piperidin-1-il)bencilideno)tiazolidina-2,4-diona 	12,69 (brs, 1 H) 8,84 (brs, 1 H) 8,04 (s, 1 H) 7,56 (d, 1 H) 7,49-7,39 (m, 1 H) 7,36 (t, 1 H) 3,69 (dd, 2 H) 3,17 (brs, 2 H) 3,00 (brs, 2 H) 2,83 (brs, 1 H) 2,26 (brs, 1 H) 1,93-1,72 (m, 4 H) 1,66 (brs, 1 H) 1,50 (brs, 1 H)		(*R,Z*)-5-(2-(3-(3-(*terc*-butildimetilsililoxi)propilamino)piperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Método 170 

Ejemplo 135

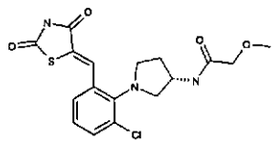
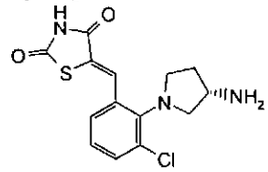
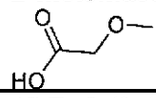
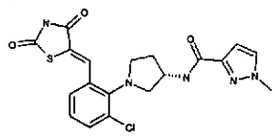
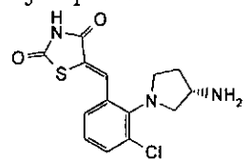
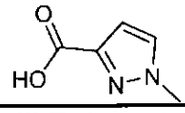
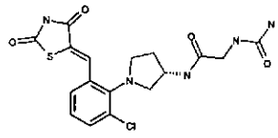
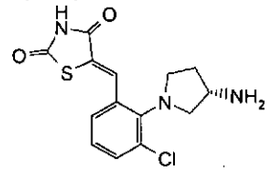
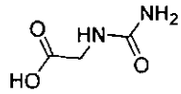


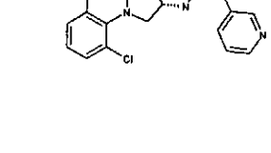
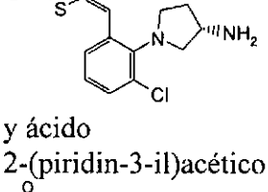
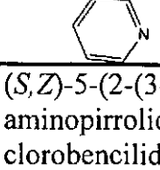
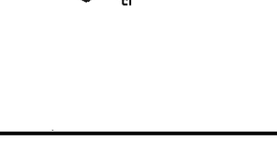
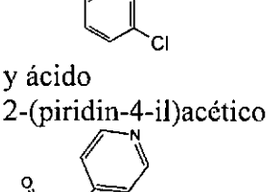
(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-1-metil-1H-imidazol-2-carboxamida:

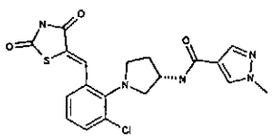
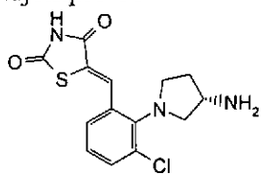
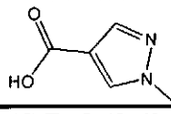
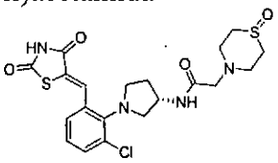
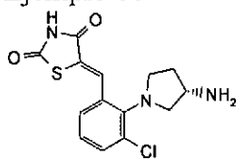
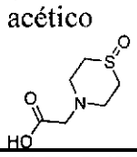
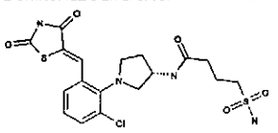
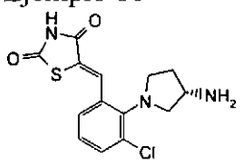
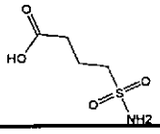
A un vial de 50 mL cargado con una barra de agitación magnética se agregó (*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona (75 mg, 0,23 mmol) (Ejemplo 86), ácido 1-metil-1H-imidazol-2-carboxílico (87 mg, 0,69 mmol), HATU (220 mg, 0,58 mmol) y diclorometano (5 mL). Luego se agregó base de Hunig (0,202 mL, 1,16 mmol) y la mezcla se agitó a TA durante 4 h. La reacción luego se diluyó con diclorometano y se lavó con agua. La mezcla se separó con un tubo separador de fases y la fase orgánica se evaporó hasta secarse. El residuo se purificó mediante cromatografía en fase inversa para proporcionar el compuesto del título como un sólido

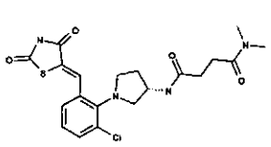
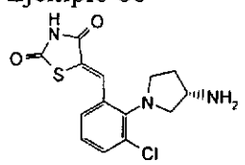
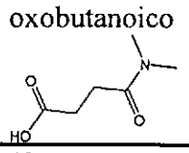
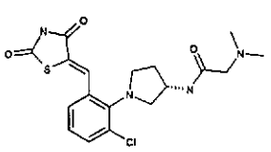
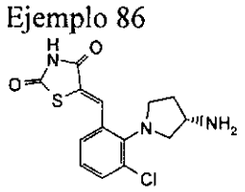
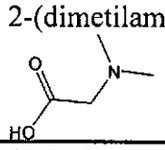
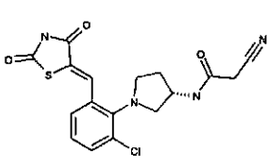
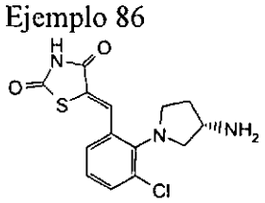
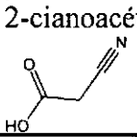
amarillo (21 mg, 21 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7,89 (s, 1 H) 7,51 (dd, 1 H) 7,41 (dd, 1 H) 7,18 – 7,27 (m, 2 H) 7,01 (s, 1 H) 4,67 – 4,77 (m, 1 H) 4,00 (s, 3 H) 3,63 – 3,75 (m, 2 H) 3,47 – 3,54 (m, 1 H) 3,36 – 3,47 (m, 1 H) 2,39 – 2,51 (m, 1 H) 2,14 (dd, 1 H); *m/z* 432.

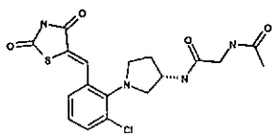
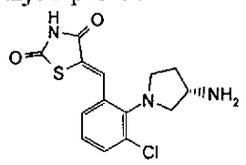
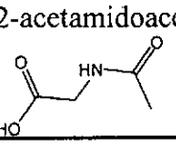
Los siguientes ejemplos se prepararon mediante el procedimiento del Ejemplo 135 utilizando los materiales de partida apropiados.

136	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-2-metoxiacetamida 	7,89 (s, 1 H) 7,52 (dd, 1 H) 7,41 (dd, 1 H) 7,25 (t, 1 H) 4,58 – 4,67 (m, 1 H) 3,93 (s, 2 H) 3,65 (dd, 1 H) 3,36 – 3,46 (m, 5 H) 3,13 (dd, 1 H) 2,38 (dd, 1 H) 2,01 – 2,13 (m, 1 H)	396	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 2-metoxiacético 
137	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-1-metil-1H-pirazol-3-carboxamida 	7,93 (s, 1 H) 7,61 (d, 1 H) 7,52 (dd, 1 H) 7,42 (dd, 1 H) 7,25 (t, 1 H) 6,73 (d, 1 H) 4,73 – 4,83 (m, 1 H) 3,92 – 3,99 (m, 3 H) 3,71 (dd, 1 H) 3,38 – 3,50 (m, 2 H) 3,23 (dd, 1 H) 2,38 – 2,50 (m, 1 H) 2,09 – 2,21 (m, 1 H)	432	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 1-metil-1H-pirazol-3-carboxílico 
138	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-2-ureidoacetamida 	7,93 (s, 1 H) 7,52 (dd, 1 H) 7,41 (dd, 1 H) 7,25 (t, 1 H) 4,53 (ddd, 1 H) 3,83 – 3,92 (m, 2 H) 3,65 – 3,70 (m, 1 H) 3,42 – 3,49 (m, 1 H) 3,35 – 3,42 (m, 1 H) 3,07 (dd, 1 H) 2,37 (dt, 1 H) 1,98 – 2,10 (m, 1 H)	424	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 2-ureidoacético 

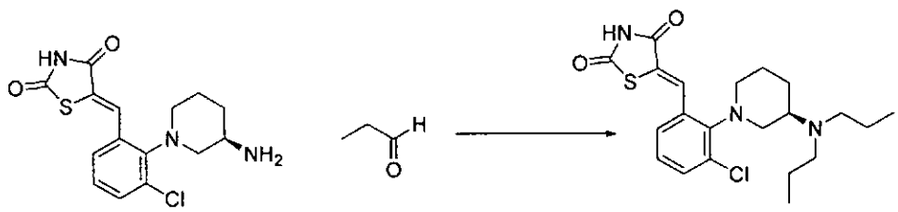
139	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-2-(piridin-3-il)acetamida 	8,44 (br. S., 2 H) 8,02 (s, 1 H) 7,83 (d, 1 H) 7,50 (dd, 1 H) 7,34 – 7,46 (m, 3 H) 7,25 (t, 1 H) 4,51 (t, 1 H) 3,60 – 3,69 (m, 3 H) 3,37 – 3,48 (m, 2 H) 3,08 (dd, 1 H) 2,31 – 2,43 (m, 1 H) 2,03 (dd, 1 H)	443	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 2-(piridin-3-il)acético 
140	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-2-(piridin-4-il)acetamida 	8,47 (br. S., 1 H) 7,98 (s, 1 H) 7,53 (dd, 1 H) 7,41 (dd, 3 H) 7,25 (t, 1 H) 4,53 (t, 1 H) 3,64 – 3,71 (m, 3 H) 3,39 – 3,48 (m, 2 H) 3,07 (dd, 1 H) 2,32 – 2,44 (m, 1 H) 2,03 (dd, 1 H)	443	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 2-(piridin-4-il)acético

141	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-1-metil-1H-pirazol-4-carboxamida 	8,17 (s, 1 H) 8,07 (s, 1 H) 7,94 (s, 1 H) 7,47 (ddd, 2 H) 7,27 (t, 1 H) 4,67 – 4,78 (m, 1 H) 3,89 – 3,97 (m, 3 H) 3,73 (dd, 1 H) 3,44 (t, 2 H) 3,19 (dd, 1 H) 2,42 (dd, 1 H) 2,14 (dd, 1 H)	432	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 1-metil-1H-pirazol-4-carboxílico 
142	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-2-(oxidotiomorfolin-4-il)acetamida 	7,91 (s, 1 H) 7,56 (dd, 1 H) 7,43 (dd, 1 H) 7,27 (t, 1 H) 4,62 (t, 1 H) 3,67 – 3,78 (m, 2 H) 3,41 – 3,48 (m, 2 H) 3,19 – 3,22 (m, 2 H) 3,10 – 3,17 (m, 5 H) 2,92 – 2,98 (m, 2 H) 2,81 – 2,86 (m, 1 H) 2,37 – 2,48 (m, 1 H) 2,02 – 2,13 (m, 1 H)	483	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido (1-oxidotiomorfolin-4-il) acético 
143	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-4-sulfamoilbutanamida 	7,18 (s, 1 H) 6,70 (dd, 1 H) 6,62 (dd, 1 H) 6,45 (t, 1 H) 3,71 (s, 1 H) 2,84 (dd, 1 H) 2,56 – 2,66 (m, 2 H) 2,29 – 2,36 (m, 2 H) 2,26 (dd, 1 H) 1,64 (t, 2 H) 1,57 (d, 1 H) 1,25 – 1,37 (m, 2 H) 1,20 (d, 1 H)	473	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 4-sulfamoilbutanoico 

144	(*S,Z*)-*N*1-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-*N*4,*N*4-dimetilsuccinamida 	8,01 (s, 1 H) 7,50 (d, 1 H) 7,44 (d, 1 H) 7,26 (t, 1 H) 4,47 – 4,58 (m, 1 H) 3,62 (t, 1 H) 3,42 (t, 2 H) 3,02 – 3,15 (m, 4 H) 2,92 (s, 3 H) 2,67 (d, 2 H) 2,56 (t, 2 H) 2,36 (dd, 1 H) 2,02 (dd, 1 H)	451	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 4-(dimetilamino)-4-oxobutanoico 
145	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-2-(dimetilamino)acetamida 	7,07 (s, 1 H) 6,69 – 6,74 (m, 1 H) 6,59 (dd, 1 H) 6,43 (t, 1 H) 3,76 (br. S., 1 H) 2,85 – 2,94 (m, 2 H) 2,84 (d, 1 H) 2,36 (br. S., 1 H) 2,29 (dd, 2 H) 1,52 – 1,64 (m, 7 H) 1,18 – 1,28 (m, 1 H)	409	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 2-(dimetilamino) acético 
146	(*S,Z*)-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)-2-cianoacetamida 	7,95 (s, 1 H) 7,52 (dd, 1 H) 7,42 (dd, 1 H) 7,26 (t, 1 H) 4,50 (ddd, 1 H) 3,68 – 3,78 (m, 1 H) 3,64 (dd, 1 H) 3,44 – 3,50 (m, 1 H) 3,40 (t, 1 H) 3,22 (q, 1 H) 3,09 (dd, 1 H) 2,39 (dt, 1 H) 2,03 (d, 1 H)	391	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 2-cianoacético 

147	(*S,Z*)-2-acetamido-*N*-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)acetamida 	7,89 (s, 1 H) 7,54 (dd, 1 H) 7,39 (dd, 1 H) 7,24 (t, 1 H) 4,49 – 4,60 (m, 1 H) 3,86 – 3,98 (m, 1 H) 3,65 (dd, 1 H) 3,36 – 3,48 (m, 2 H) 3,17 – 3,25 (m, 1 H) 3,07 – 3,16 (m, 1 H) 2,31 – 2,43 (m, 1 H) 1,96 – 2,09 (m, 4 H)	423	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona Ejemplo 86  y ácido 2-acetamidoacético 

Ejemplo 148:

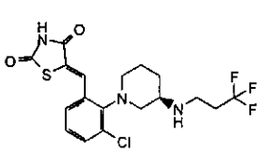
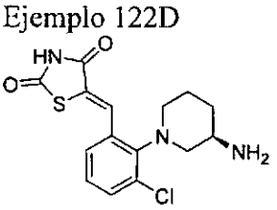
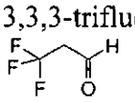
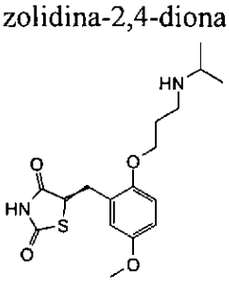
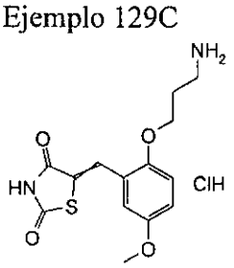
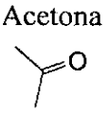


(*R,Z*)-5-(3-cloro-2-(3-(dipropilamino)piperidin-1-il)bencilideno)tiazolidina-2,4-diona:

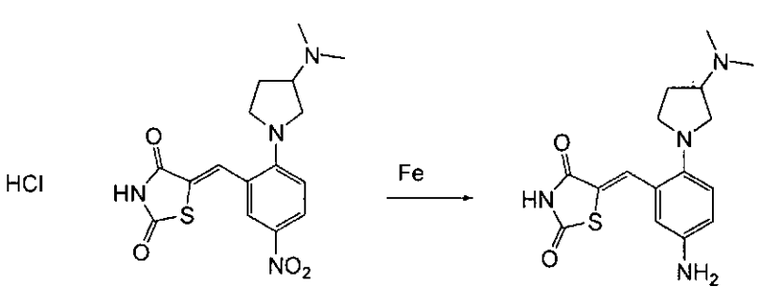
Una mezcla de (*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona (122D) (100 mg, 0,27 mmol) y propionaldehído (20,17 mg, 0,35 mmol) en CH_2Cl_2 (15 mL) se agitó a 50°C durante 20 min. antes de agregarse triacetoxiborohidruro de sodio (170 mg, 0,80 mmol). La mezcla luego se agitó a 50°C durante 4 h. antes de agregarse K_2CO_3 saturado acuoso (~ 50 mL) a la mezcla. Esta solución se vertió en un embudo de separación y se extrajo con $CHCl_3$/isopropanol (5/1) (2 x 50 mL). El extracto orgánico combinado se secó sobre Na_2SO_4 anhidro, se filtró y se concentró al vacío para proporcionar el producto. Esto se purificó con Gilson (0,1% TFA en agua:0,1% TFA en CAN = 30% a 80%; absorción UV a 322) para proporcionar el compuesto del título como un sólido amarillo (94 mg, 77 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7,96 (s, 1 H) 7,48 (d, 1 H) 7,41-7,34 (m, 1 H) 7,29 (t, 1 H) 3,67-3,58 (m, 2 H) 3,44-3,37 (m, 2 H) 3,03-2,78 (m, 5 H) 2,21 (brs, 1 H), 1,79 (d, 1 H) 1,61 (d, 6 H) 0,84-0,79 (m, 6 H). *m/z* 422.

Los siguientes ejemplos se prepararon mediante el procedimiento del 148, utilizando los

materiales de partida apropiados.

149	(*R,Z*)-5-(3-cloro-2-(3-(3,3,3-trifluoropropilamino) piperidin-1-il)bencilideno)tiazolidina-2,4-diona 	12,65 (brs, 1 H) 9,35 (brs, 1H) 8,05 (s, 1 H) 7,56 (d, 1 H) 7,44 (brs, 1 H) 7,37 (t, 1 H) 3,75-3,63 (m, 2 H) 3,53-3,45 (m, 2 H) 3,23 (m, 1 H) 2,85-2,65 (m, 4 H) 2,30 (brs, 1 H) 1,85-1,76 (m, 1 H) 1,67 (brs, 1 H) 1,49 (brs, 1 H)	433	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato Ejemplo 122D  y 3,3,3-trifluoropropanal 
150	5-(2-(3-(isopropilamino)propoxi)-5-metoxibencilideno)tiazolidina-2,4-diona 	12,65 (s, 1H), 8,91 (s, br, 2H), 7,91 (s, 1H), 7,10 (m, 2H), 7,85 (s, 1H), 4,17 (m, 2H), 3,65 (m, 4H), 3,05 (m, 2H), 2,14 (m, 2H), 1,22 (m, 6H)	351	5-(2-(3-aminopropoxi)-5-metoxibencilideno)tiazolidina-2,4-diona clorhidrato Ejemplo 129C  y Acetona 

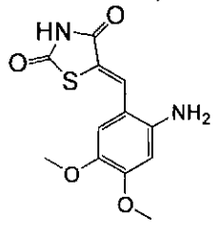
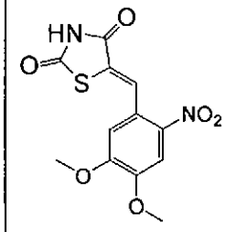
Ejemplo 151:



(Z)-5-(5-amino-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona

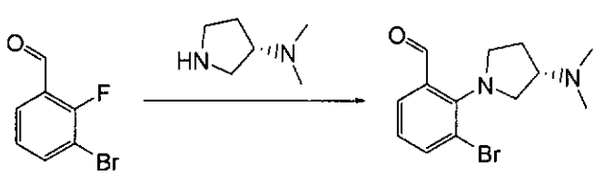
A una mezcla de (Z)-5-(2-(3-(dimetilamino)pirrolidin-1-il)-5-nitrobencilideno)tiazolidina-2,4-diona (100 mg, 0,28 mmol) (Método 149) y virutas de hierro (154 mg, 2,76 mmol) en MeOH (10 mL) se agregaron 5 gotas de HCl conc. y 5 gotas de agua. La mezcla se agitó a 80°C durante 1hr. La mezcla se cargó en gel de sílice, se purificó con ISCO (100% de acetato de etilo a metanol/acetato de etilo = 50%) para proporcionar un sólido rojo que se purificó nuevamente con Gilson (acetonitrilo:agua:0,1% TFA = 0% a 50% durante 7min) para proporcionar un sólido amarillo como (Z)-5-(5-amino-2-(3-(dimetilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona (51,0 mg, 38,6 %). ^{1}H NMR (400 MHz, DMSO-d6) d ppm 12,55 (brs, 1 H), 11,32 (brs, 1 H), 10,30 (brs, 2 H), 7,80 (s, 1 H), 7,42 (m, 2 H), 7,19 (m, 1 H), 3,95 (m, 1 H), 3,39-3,27 (m, 4 H), 2,78 (s, 6 H), 2,30-2,10 (m, 2 H); *m/z* 333.

Los siguientes intermediarios se prepararon mediante el procedimiento del Ejemplo 151 utilizando los materiales de partida apropiados.

Ej	Compuesto	^{1}H NMR	m/z	MP
152	(*Z*)-5-(2-amino-4,5-dimetoxibencilideno)tiazolidina-2,4-diona 	12,45 (brs, 1 H) 7,87 (s, 1 H) 6,80 (s, 1 H) 6,79 (s, 1 H) 3,78 (s, 3 H) 3,73 (s, 3 H)	280	(*Z*)-5-(4,5-dimetoxi-2-nitrobencilideno)tiazolidina-2,4-diona Método 150 

Sección de métodos:

103251

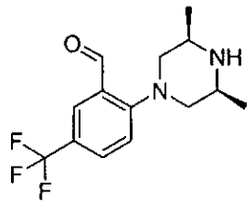
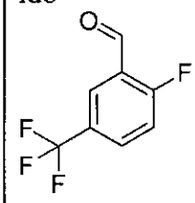
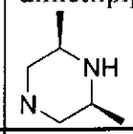
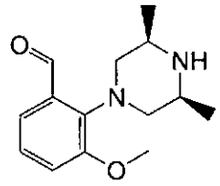
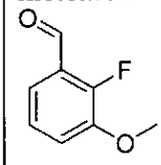
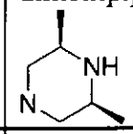
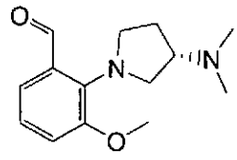
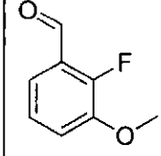
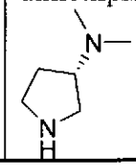


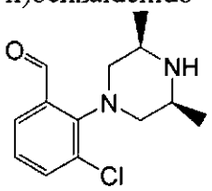
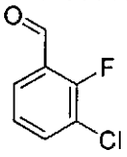
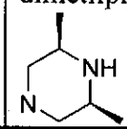
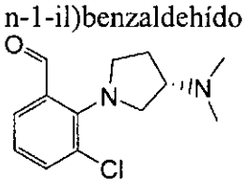
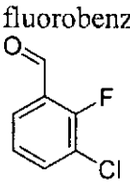
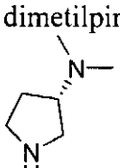
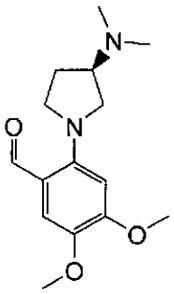
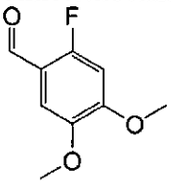
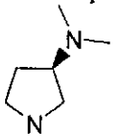
Método 1:

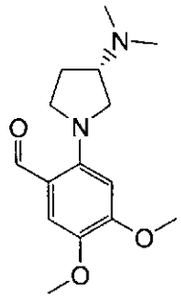
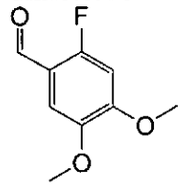
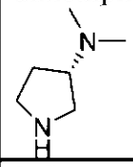
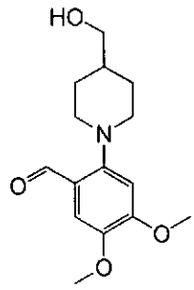
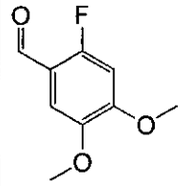
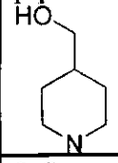
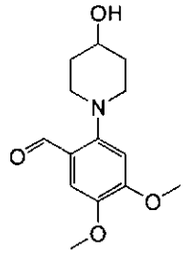
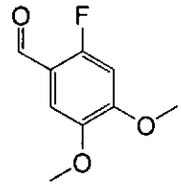
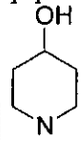
(*S*)-3-bromo-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído:

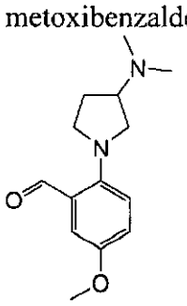
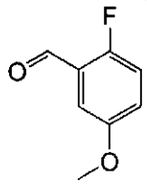
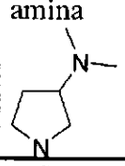
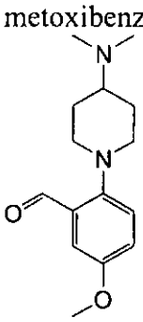
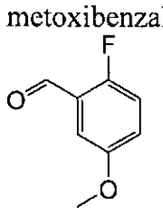
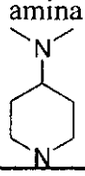
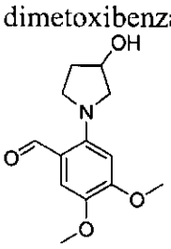
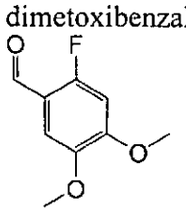
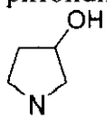
Un matraz de fondo redondo de 50 mL se cargó con una barra de agitación magnética, 3-bromo-2-fluorobenzaldehído (0,555 g, 2,73 mmol), (*S*)-*N,N*-dimetilpirrolidin-3-amina (0,312 g, 2,73 mmol), DMSO (5,47 ml) y carbonato de potasio (0,378 g, 2,73 mmol). La mezcla se calentó hasta alcanzar 85°C durante toda la noche con agitación. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente, se diluyó con agua y se extrajo y se colocó en cloruro de metileno. El extracto orgánico combinado se secó con $MgSO_4$, se filtró y se concentró al vacío para proporcionar el producto que se purificó mediante cromatografía en gel de sílice (40 g) utilizando acetato de etilo / MeOH (10 : 1) como eluyente para proporcionar (*S*)-3-bromo-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído (0,369 g, 45,4 %).

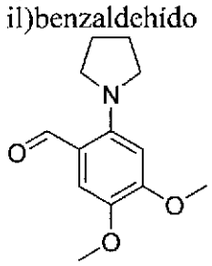
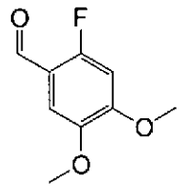
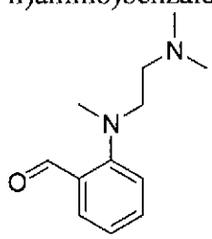
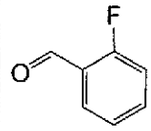
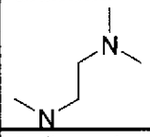
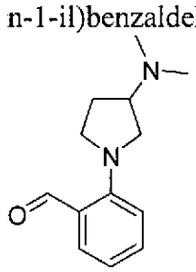
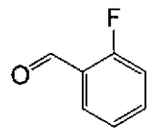
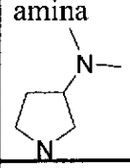
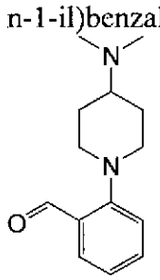
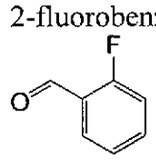
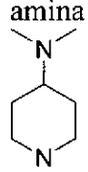
Los siguientes intermediarios se prepararon mediante el procedimiento del Método 1, utilizando los materiales de partida apropiados.

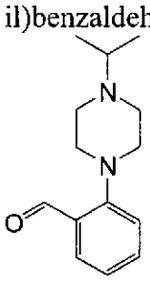
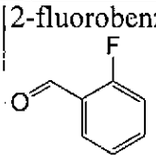
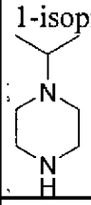
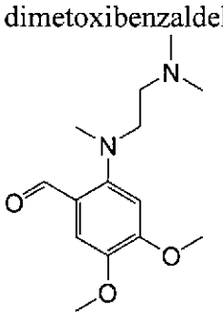
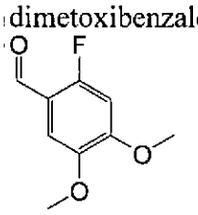
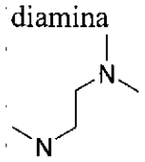
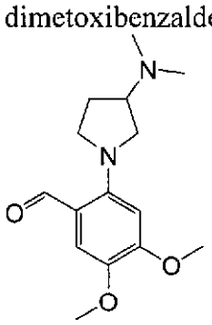
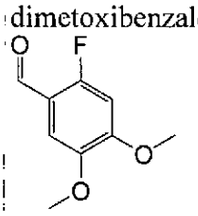
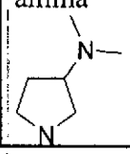
Método	Compuesto	^{1}H NMR	m/z	MP
2	2-((*3S,5R*)-3,5-dimetilpiperazin-1-il)-5-(trifluorometil)benzaldehído 		287	2-fluoro-5-(trifluorometil)benzaldehído  y (2*R*,6*S*)-2,6-dimetilpiperazina 
3	2-((*3S,5R)*-3,5-dimetilpiperazin-1-il)-3-metoxibenzaldehído 		249	2-fluoro-3-metoxibenzaldehído  y (2*R*,6*S*)-2,6-dimetilpiperazina 
4	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-3-metoxibenzaldehído 		249	2-fluoro-3-metoxibenzaldehído  y (*3S*)-*N,N*-dimetilpirrolidin-3-amina 

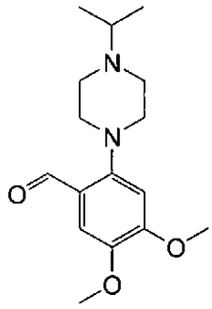
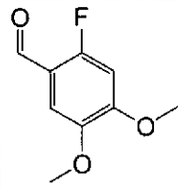
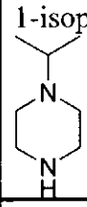
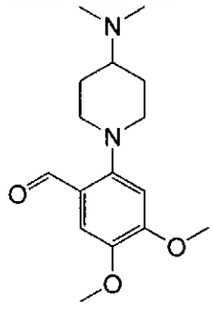
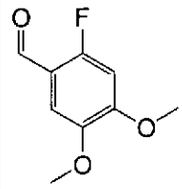
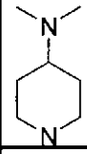
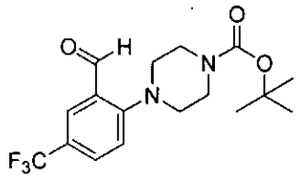
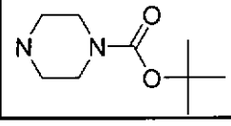
5	3-cloro-2-((3*S*,5*R*)-3,5-dimetilpiperazin-1-il)benzaldehído 		254	3-cloro-2-fluorobenzaldehído  y (2*R*,6*S*)-2,6-dimetilpiperazina 
6	(*S*)-3-cloro-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído 		253	3-cloro-2-fluorobenzaldehído  y (*3S*)-*N*,*N*-dimetilpirrolidin-3-amina 
7	(*R*)-2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibenzaldehído 		279	2-fluoro-4,5-dimetoxibenzaldehído  y (3*R*)-*N*,*N*-dimetilpirrolidin-3-amina 

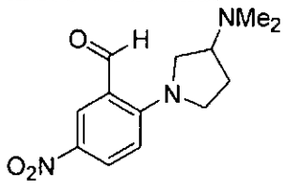
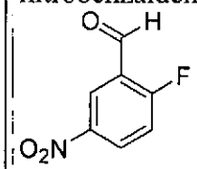
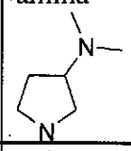
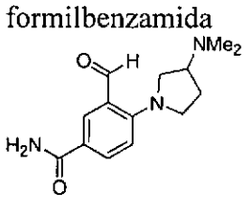
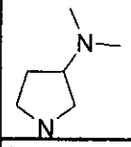
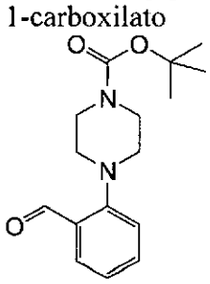
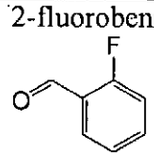
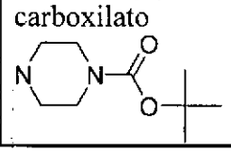
8	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibenzaldehído 		279	2-fluoro-4,5-dimetoxibenzaldehído  y (*3S*)-*N,N*-dimetilpirrolidin-3-amina 
9	2-(4-(hidroximetil)piperidin-1-il)-4,5-dimetoxibenzaldehído 		280	2-fluoro-4,5-dimetoxibenzaldehído  y piperidin-4-ilmetanol 
10	2-(4-hidroxipiperidin-1-il)-4,5-dimetoxibenzaldehído 		266	2-fluoro-4,5-dimetoxibenzaldehído  y piperidin-4-ol 

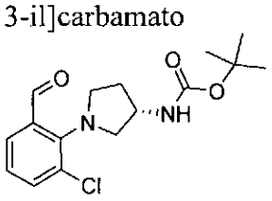
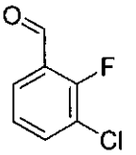
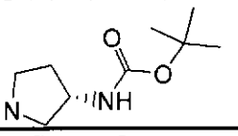
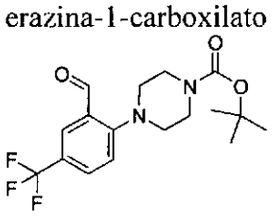
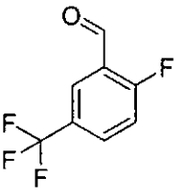
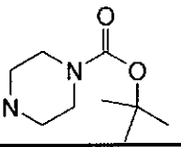
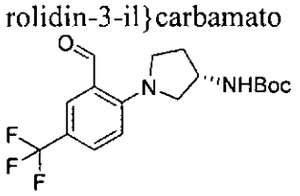
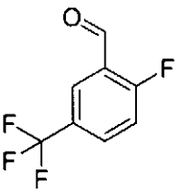
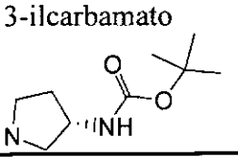
11	2-(3-(dimetilamino)pirrolidin-1-il)-5-metoxibenzaldehído 		249	2-fluoro-5-metoxibenzaldehído  y *N,N*-dimetilpirrolidin-3-amina 
12	2-(4-(dimetilamino)piperidin-1-il)-5-metoxibenzaldehído 		263	2-fluoro-5-metoxibenzaldehído  y *N,N*-dimetilpiperidin-4-amina 
13	2-(3-hidroxipirrolidin-1-il)-4,5-dimetoxibenzaldehído 		253	2-fluoro-4,5-dimetoxibenzaldehído  y pirrolidin-3-ol 

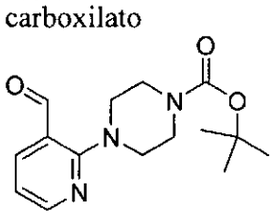
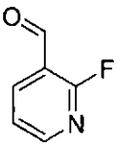
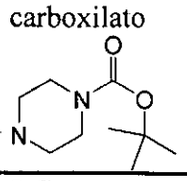
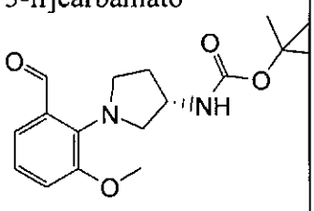
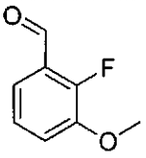
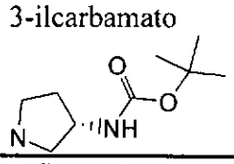
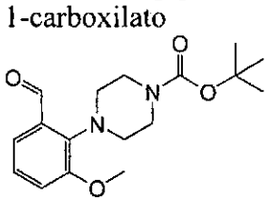
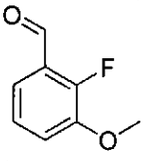
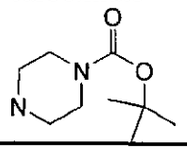
14	4,5-dimetoxi-2-(pirrolidin-1-il)benzaldehído 		236	2-fluoro-4,5-dimetoxibenzaldehído  y pirrolidina 
15	2-((2-(dimetilamino)etil)(metil)amino)benzaldehído 		207	2-fluorobenzaldehído  y *N,N,N'*-trimetiletano-1,2-diamina 
16	2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído 		219	2-fluorobenzaldehído  y *N,N*-dimetilpirrolidin-3-amina 
17	2-(4-(dimetilamino)piperidin-1-il)benzaldehído 		233	2-fluorobenzaldehído  y *N,N*-dimetilpiperidin-4-amina 

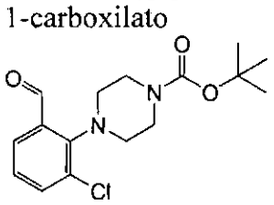
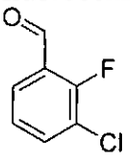
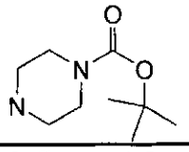
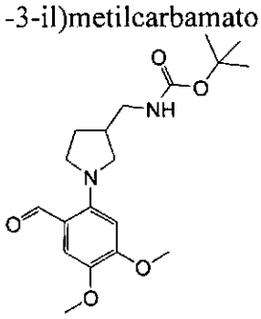
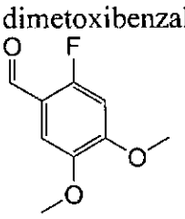
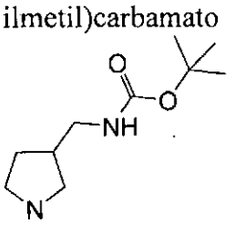
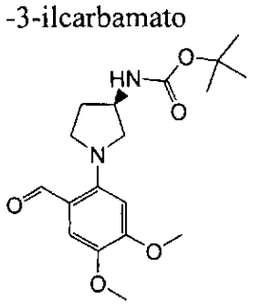
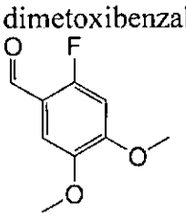
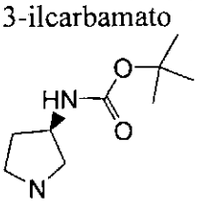
18	2-(4-isopropilpiperazin-1-il)benzaldehído 		233	2-fluorobenzaldehído  y 1-isopropilpiperazina 
19	2-((2-(dimetilamino)etil)(metil)amino)-4,5-dimetoxibenzaldehído 		267	2-fluoro-4,5-dimetoxibenzaldehído  y *N,N,N'*-trimetiletano-1,2-diamina 
20	2-(3-(dimetilamino)pirrolidin-1-il)-4,5-dimetoxibenzaldehído 		279	2-fluoro-4,5-dimetoxibenzaldehído  y *N,N*-dimetilpirrolidin-3-amina 

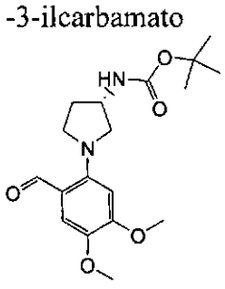
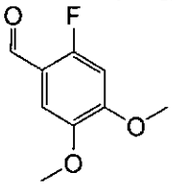
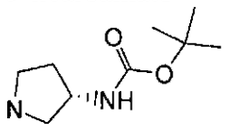
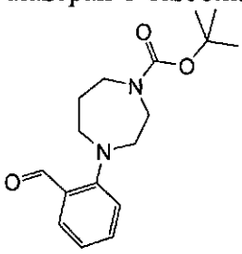
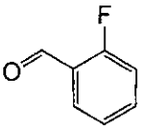
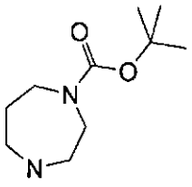
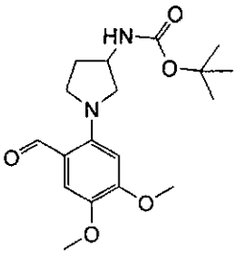
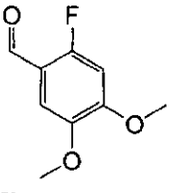
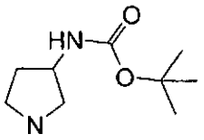
21	2-(4-isopropilpiperazin-1-il)-4,5-dimetoxibenzaldehído 		293	2-fluoro-4,5-dimetoxibenzaldehído  y 1-isopropilpiperazina 
22	2-(4-(dimetilamino)piperidin-1-il)-4,5-dimetoxibenzaldehído 		293	2-fluoro-4,5-dimetoxibenzaldehído  y *N,N*-dimetilpiperidin-4-amina 
23	*terc*-butil 4-(2-formil-4-(trifluorometil)fenil)piperazina-1-carboxilato 		359	2-fluoro-5-(trifluorometil)benzaldehído  y *terc*-butil piperazina-1-carboxilato 

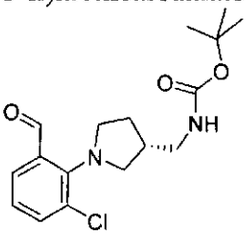
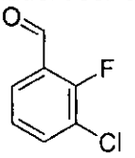
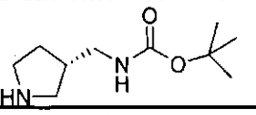
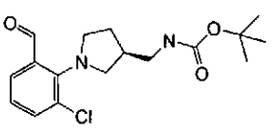
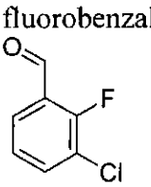
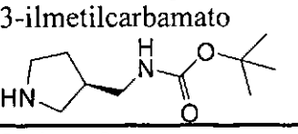
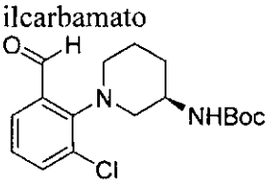
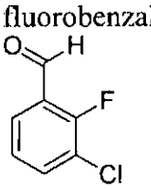
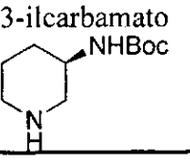
24	2-(3-(dimetilamino)pirrolidin-1-il)-5-nitrobenzaldehído 		264	2-fluoro-5-nitrobenzaldehído  y *N,N*-dimetilpirrolidin-3-amina 
25	4-(3-(dimetilamino)pirrolidin-1-il)-3-formilbenzamida 		262	4-fluoro-3-formilbenzamida  y *N,N*-dimetilpirrolidin-3-amina 
26	*terc*-butil 4-(2-formilfenil)piperazina-1-carboxilato 		291	2-fluorobenzaldehído  y *terc*-butil piperazina-1-carboxilato 

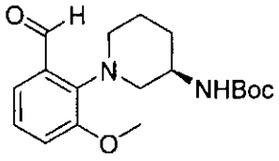
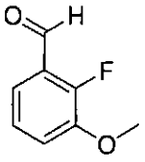
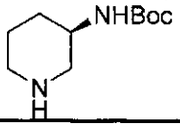
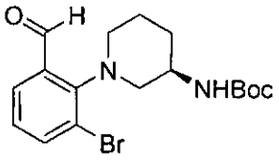
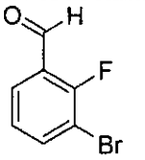
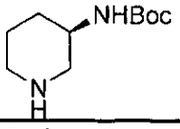
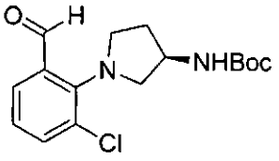
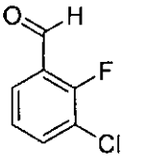
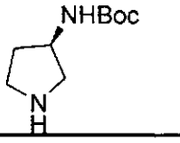
79	*terc*-butil [(3*S*)-1-(2-cloro-6-formilfenil)pirrolidin-3-il]carbamato 		326	3-cloro-2-fluorobenzaldehído  y *terc*-butil (3*S*)-pirrolidin-3-ilcarbamato 
80	*terc*-butil4-[2-formil-4-(trifluorometil)fenil]piperazina-1-carboxilato 		359	2-fluoro-5-(trifluorometil)benzaldehído  y *terc*-butil piperazina-1-carboxilato 
81	*terc*-butil{(3*S*)-1-[2-formil-4-(trifluorometil)fenil]pirrolidin-3-il}carbamato 		359	2-fluoro-5-(trifluorometil)benzaldehído  y *terc*-butil (3*S*)-pirrolidin-3-ilcarbamato 

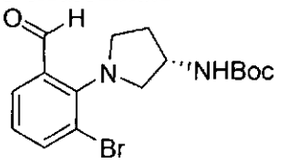
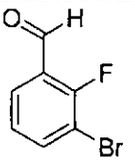
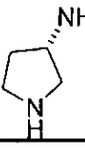
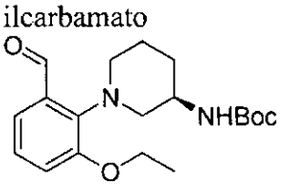
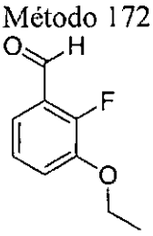
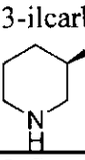
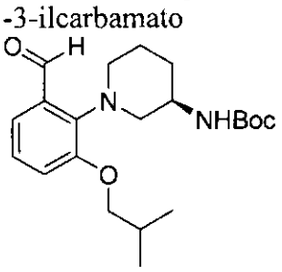
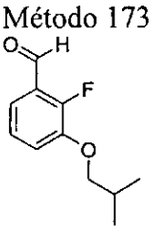
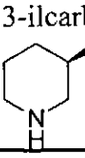
82	*terc*-butil 4-(3-formilpiridin-2-il)piperazina-1-carboxilato 		292	2-fluoronicotinaldehído  y *terc*-butil piperazina-1-carboxilato 
83	*terc*-butil [(3*S*)-1-(2-formil-6-metoxifenil)pirrolidin-3-il]carbamato 		322	2-fluoro-3-metoxibenzaldehído  y *terc*-butil (3*S*)-pirrolidin-3-ilcarbamato 
84	*terc*-butil 4-(2-formil-6-metoxifenil)piperazina-1-carboxilato 		321	2-fluoro-3-metoxibenzaldehído  y *terc*-butil piperazina-1-carboxilato 

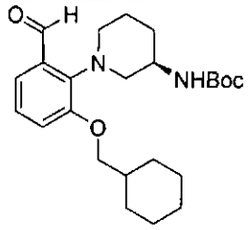
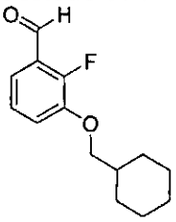
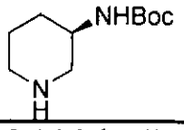
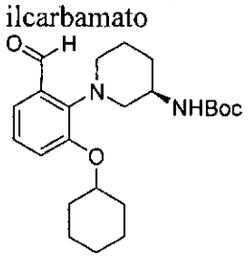
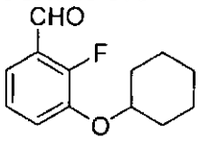
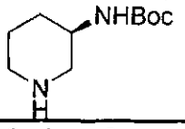
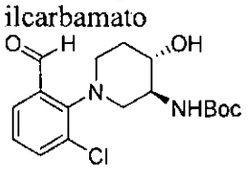
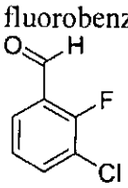
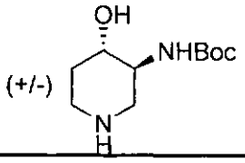
85	*terc*-butil 4-(2-cloro-6-formilfenil)piperazina-1-carboxilato 		326	3-cloro-2-fluorobenzaldehído  y *terc*-butil piperazina-1-carboxilato 
86	*terc*-butil (1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-il)metilcarbamato 		365	2-fluoro-4,5-dimetoxibenzaldehído  y *terc*-butil (pirrolidin-3-ilmetil)carbamato 
87	(*R*)-*terc*-butil 1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato 		351	2-fluoro-4,5-dimetoxibenzaldehído  y *terc*-butil (3*R*)-pirrolidin-3-ilcarbamato 

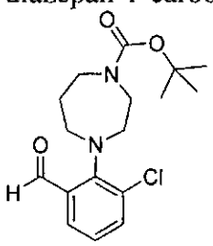
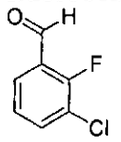
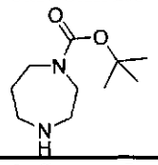
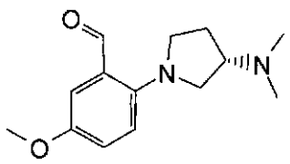
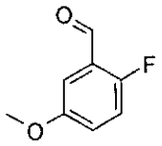
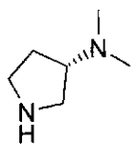
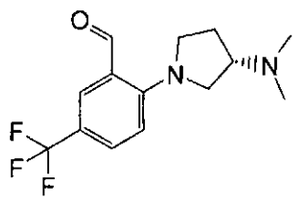
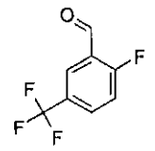
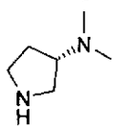
88	(*S*)-*terc*-butil 1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato 		351	2-fluoro-4,5-dimetoxibenzaldehído  y *terc*-butil (3*S*)-pirrolidin-3-ilcarbamato 
89	*terc*-butil 4-(2-formilfenil)-1,4-diazepan-1-carboxilato 		305	2-fluorobenzaldehído  y *terc*-butil 1,4-diazepan-1-carboxilato 
90	*terc*-butil 1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato 		351	2-fluoro-4,5-dimetoxibenzaldehído  y *terc*-butil pirrolidin-3-ilcarbamato 

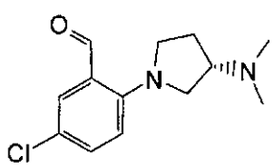
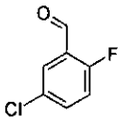
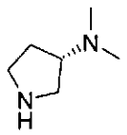
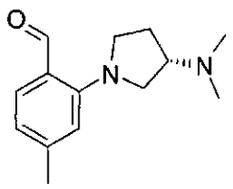
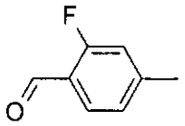
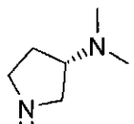
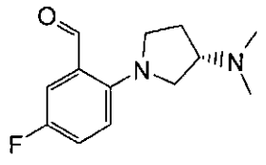
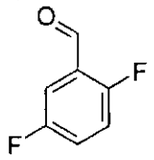
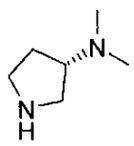
91	(*R*)-*terc*-butil (1-(2-cloro-6-formilfenil)pirrolidin-3-il)metilcarbamato 		339	3-cloro-2-fluorobenzaldehído  y (*S*)-*terc*-butil pirrolidin-3-ilmetilcarbamato 
92	(*S*)-*terc*-butil (1-(2-cloro-6-formilfenil)pirrolidin-3-il)metilcarbamato 		339	3-cloro-2-fluorobenzaldehído  y *(R)*-*terc*-butil pirrolidin-3-ilmetilcarbamato 
93	(*R*)-*terc*-butil 1-(2-cloro-6-formilfenil)piperidin-3-ilcarbamato 		339	3-cloro-2-fluorobenzaldehído  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 

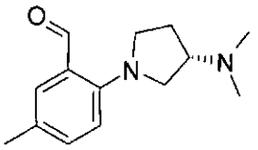
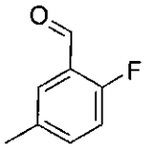
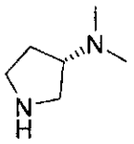
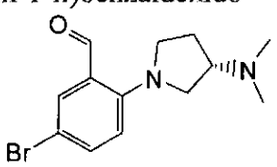
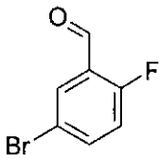
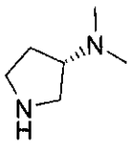
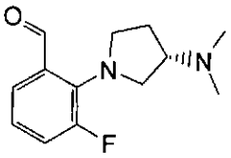
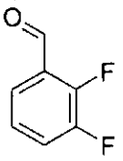
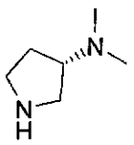
94	(*R*)-*terc*-butil 1-(2-formil-6-metoxifenil)piperidin-3-ilcarbamato 		335	2-fluoro-3-metoxibenzaldehído  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
95	(*R*)-*terc*-butil 1-(2-bromo-6-formilfenil)piperidin-3-ilcarbamato 		385	3-bromo-2-fluorobenzaldehído  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
96	(*R*)-*terc*-butil 1-(2-cloro-6-formilfenil)pirrolidin-3-ilcarbamato 		325	3-cloro-2-fluorobenzaldehído  y (*R*)-*terc*-butil pirrolidin-3-ilcarbamato 

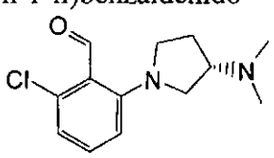
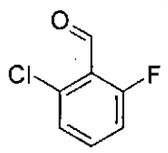
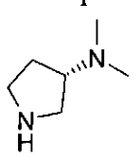
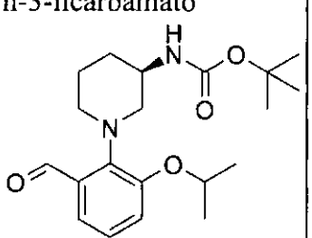
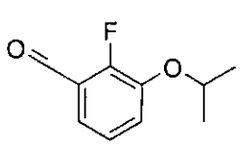
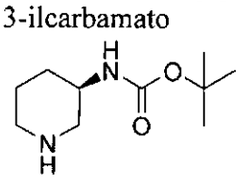
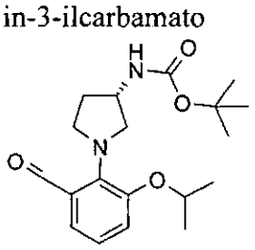
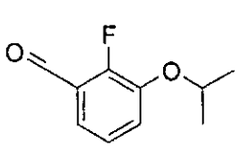
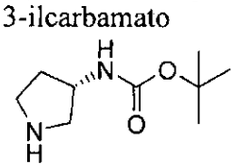
97	(*S*)-*terc*-butil 1-(2-bromo-6-formilfenil)pirrolidin-3-ilcarbamato 		371	3-bromo-2-fluorobenzaldehído  y (*S*)-*terc*-butil pirrolidin-3-ilcarbamato 
98	(*R*)-*terc*-butil 1-(2-etoxi-6-formilfenil)piperidin-3-ilcarbamato 		349	3-etoxi-2-fluorobenzaldehído Método 172  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
99	(*R*)-*terc*-butil 1-(2-formil-6-isobutoxifenil)piperidin-3-ilcarbamato 		377	2-fluoro-3-isobutoxibenzaldehído Método 173  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 

100	(*R*)-*terc*-butil 1-(2-(ciclohexilmetoxi)-6-formilfenil)piperidin-3-ilcarbamato 		417	3-(ciclohexilmetoxi)-2-fluorobenzaldehído Método 174  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
101	(*R*)-*terc*-butil 1-(2-(ciclohexiloxi)-6-formilfenil)piperidin-3-ilcarbamato 		403	3-(ciclohexiloxi)-2-fluorobenzaldehído Método 175  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
102	(±)-*terc*-butil-1-(2-cloro-6-formilfenil)-4-hidroxipiperidin-3-ilcarbamato 		354	3-cloro-2-fluorobenzaldehído  y (±)-*terc*-butil-4-hidroxipiperidin-3-ilcarbamato Método 189 

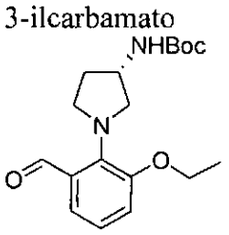
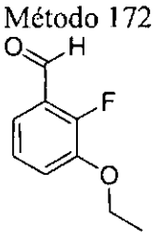
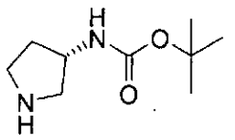
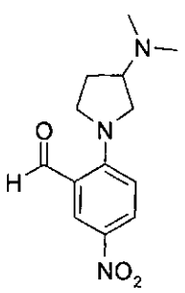
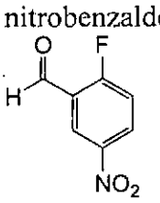
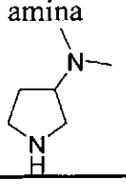
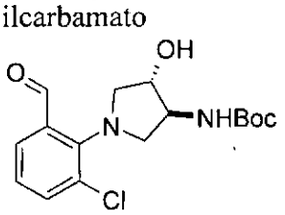
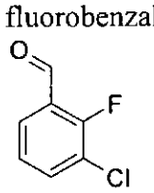
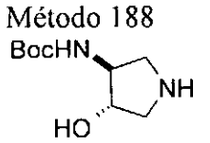
103	*terc*-butil 4-(2-cloro-6-formilfenil)-1,4-diazepan-1-carboxilato 	10,49 (s, 1 H), 7,75 (d, 1 H), 7,63 (d, 1 H), 7,25 (t, 1 H), 3,37 (brs, 4 H), 1,88 (brs, 2 H), 1,53 (s, 9 H)	339	3-cloro-2-fluorobenzaldehído  y *terc*-butil 1,4-diazepan-1-carboxilato 
104	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-5-metoxibenzaldehído 		249	2-fluoro-5-metoxibenzaldehído  y (*S*)-*N*,*N*-dimetilpirrolidin-3-amina 
105	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-5-(trifluorometil)benzaldehído 		287	2-fluoro-5-(trifluorometil)benzaldehído  y (*S*)-*N*,*N*-dimetilpirrolidin-3-amina 

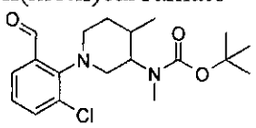
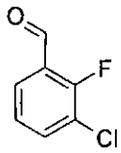
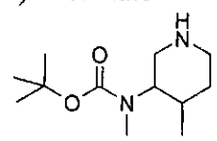
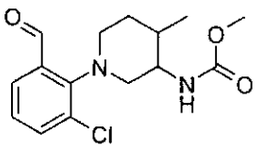
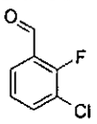
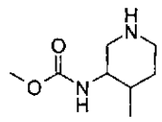
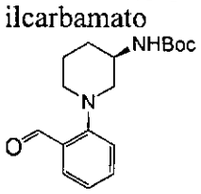
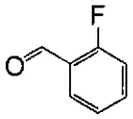
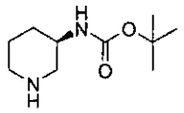
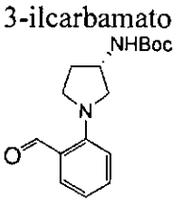
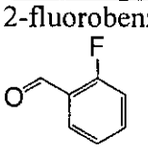
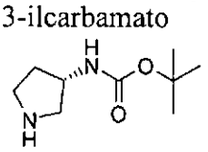
106	(*S*)-5-cloro-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído 		253	5-cloro-2-fluorobenzaldehído  y (*S*)-*N*,*N*-dimetilpirrolidin-3-amina 
107	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-4-metilbenzaldehído 		233	2-fluoro-4-metilbenzaldehído  y (*S*)-*N*,*N*-dimetilpirrolidin-3-amina 
108	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-5-fluorobenzaldehído 		237	2,5-difluorobenzaldehído  y (*S*)-*N*,*N*-dimetilpirrolidin-3-amina 

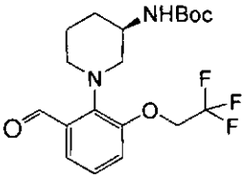
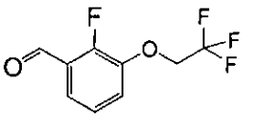
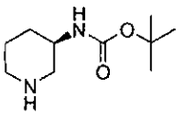
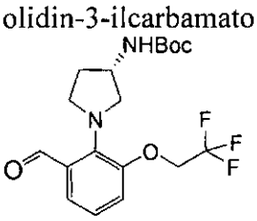
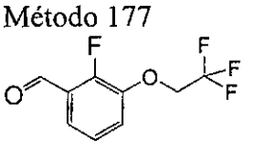
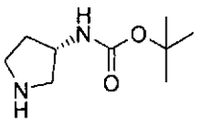
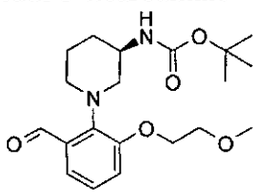
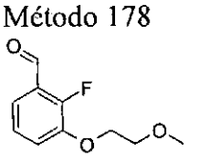
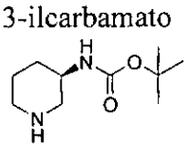
109	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-5-metilbenzaldehído 		233	2-fluoro-5-metilbenzaldehído  y (*S*)-*N,N*-dimetilpirrolidin-3-amina 
110	(*S*)-5-bromo-2-(3-(dimetilamino)pirrolidin-1-il)benzaldehído 		298	5-bromo-2-fluorobenzaldehído  y (*S*)-*N,N*-dimetilpirrolidin-3-amina 
111	(*S*)-2-(3-(dimetilamino)pirrolidin-1-il)-3-fluorobenzaldehído 		237	2,3-difluorobenzaldehído  y (*S*)-*N,N*-dimetilpirrolidin-3-amina 

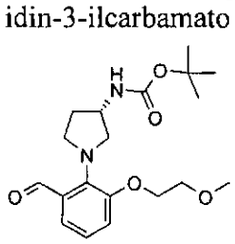
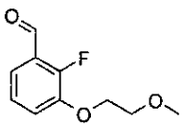
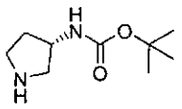
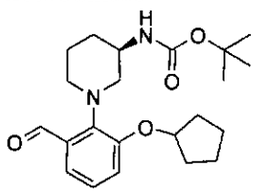
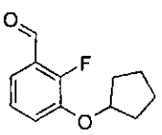
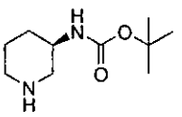
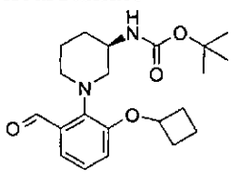
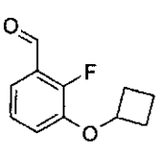
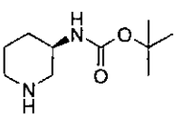
112	(S)-2-cloro-6-(3-(dimetilamino)pirrolidin-1-il)benzaldehído 		253	2-cloro-6-fluorobenzaldehído  y (*S*)-*N*,*N*-dimetilpirrolidin-3-amina 
113	(*R*)-*terc*-butil 1-(2-formil-6-isopropoxifenil)piperidin-3-ilcarbamato 		363	2-fluoro-3-isopropoxibenzaldehído Método 176  (*R*)-*terc*-butil piperidin-3-ilcarbamato 
114	(*S*)-*terc*-butil 1-(2-formil-6-isopropoxifenil)pirrolidin-3-ilcarbamato 		349	2-fluoro-3-isopropoxibenzaldehído Método 176  (*S*)-*terc*-butil pirrolidin-3-ilcarbamato 

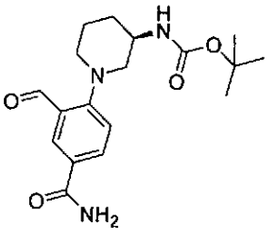
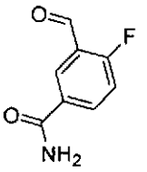
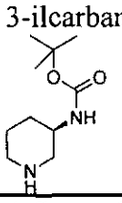
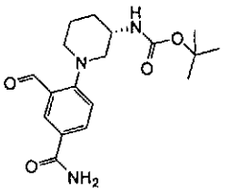
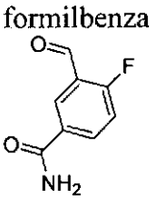
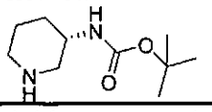
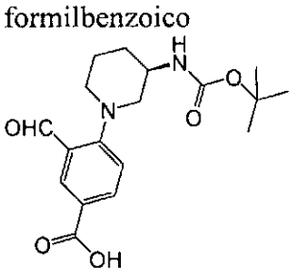
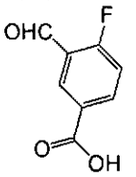
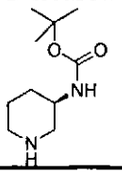
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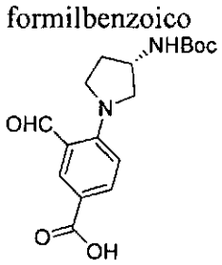
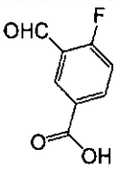
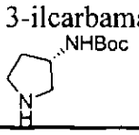
115	(*S*)-*terc*-butil 1-(2-etoxi-6-formilfenil)pirrolidin-3-ilcarbamato 		334	3-etoxi-2-fluorobenzaldehído Método 172  y (*S*)-*terc*-butil pirrolidin-3-ilcarbamato 
116	2-(3-(dimetilamino)pirrolidin-1-il)-5-nitrobenzaldehído 		263	2-fluoro-5-nitrobenzaldehído  y *N,N*-dimetilpirrolidin-3-amina 
117	(±)-*terc*-butil-1-(2-cloro-6-formilfenil)-4-hidroxipirrolidin-3-ilcarbamato 	10,30 (s, 1 H) 7,76 (dd, 1 H) 7,65 (dd, 1 H) 7,29-7,24(m, 1 H) 5,05 (brs, 1 H) 4,41 (brs, 1 H) 4,20 (brs, 1 H) 3,87 (dd, 1 H) 3,78 (dd, 1 H) 3,64-3,47 (m, 1 H) 3,36 (brs, 1 H) 3,21 (dd, 1 H) 1,50 (s, 9 H)	341	3-cloro-2-fluorobenzaldehído  y (±)-*terc*-butil-4-hidroxipirrolidin-3-ilcarbamato Método 188 

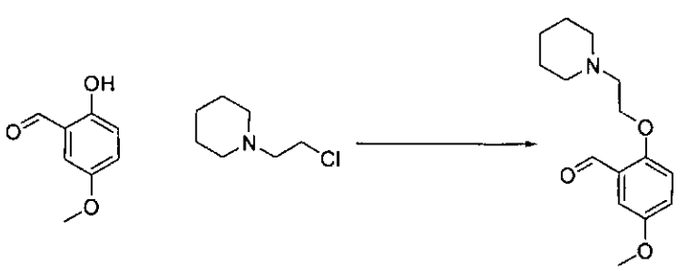
118	*terc*-butil 1-(2-cloro-6-formilfenil)-4-metilpiperidin-3-il(metil)carbamato 		367	3-cloro-2-fluorobenzaldehído  *terc*-butil metil(4-metilpiperidin-3-il)carbamato 
119	metil 1-(2-cloro-6-formilfenil)-4-metilpiperidin-3-ilcarbamato 		310	3-cloro-2-fluorobenzaldehído  metil 4-metilpiperidin-3-ilcarbamato 
120	*(R)-terc*-butil 1-(2-formilfenil)piperidin-3-ilcarbamato 		305	2-fluorobenzaldehído  y *(R)-terc*-butil piperidin-3-ilcarbamato 
121	*(S)-terc*-butil 1-(2-formilfenil)pirrolidin-3-ilcarbamato 		291	2-fluorobenzaldehído  y *(S)-terc*-butil pirrolidin-3-ilcarbamato 

122	(*R*)-*terc*-butil 1-(2-formil-6-(2,2,2-trifluoroetoxi)fenil)piperidin-3-ilcarbamato 		403	2-fluoro-3-(2,2,2-trifluoroetoxi)benzaldehído Método 177  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
123	(*S*)-*terc*-butil 1-(2-formil-6-(2,2,2-trifluoroetoxi)fenil)pirrolidin-3-ilcarbamato 		389	2-fluoro-3-(2,2,2-trifluoroetoxi)benzaldehído Método 177  y (*S*)-*terc*-butil pirrolidin-3-ilcarbamato 
124	(*R*)-*terc*-butil 1-(2-formil-6-(2-metoxietoxi)fenil)piperidin-3-ilcarbamato 		379	2-fluoro-3-(2-metoxietoxi)benzaldehído Método 178  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 

125	(*S*)-*terc*-butil 1-(2-formil-6-(2-metoxietoxi)fenil)pirrolidin-3-ilcarbamato 		365	2-fluoro-3-(2-metoxietoxi)benzaldehído Método 178  y (S)-terc-butil pirrolidin-3-ilcarbamato 
126	(*R*)-*terc*-butil 1-(2-(ciclopentiloxi)-6-formilfenil)piperidin-3-ilcarbamato 		389	3-(ciclopentiloxi)-2-fluorobenzaldehído Método 179  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
127	(*R*)-*terc*-butil 1-(2-ciclobutoxi-6-formilfenil)piperidin-3-ilcarbamato 		375	3-ciclobutoxi-2-fluorobenzaldehído Método 180  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 

128	(*R*)-*terc*-butil 1-(4-carbamoil-2-formilfenil)piperidin-3-ilcarbamato 		348	4-fluoro-3-formilbenzamida  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 
129	(*S*)-*terc*-butil 1-(4-carbamoil-2-formilfenil)piperidin-3-ilcarbamato 		348	4-fluoro-3-formilbenzamida  y (*S*)-*terc*-butil piperidin-3-ilcarbamato 
130	ácido (*R*)-4-(3-(*terc*-butoxicarbonilamino)piperidin-1-il)-3-formilbenzoico 		348	ácido 4-fluoro-3-formilbenzoico  y (*R*)-*terc*-butil piperidin-3-ilcarbamato 

131	ácido (*S*)-4-(3-(*terc*-butoxicarbonilamino)pirrolidin-1-il)-3-formilbenzoico 		334	ácido 4-fluoro-3-formilbenzoico  y (*S*)-*terc*-butil pirrolidin-3-ilcarbamato 

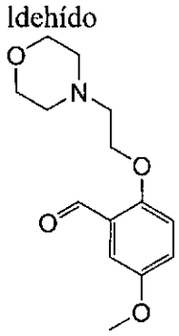
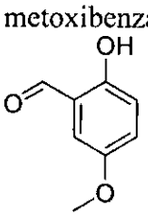
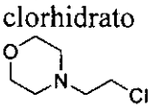
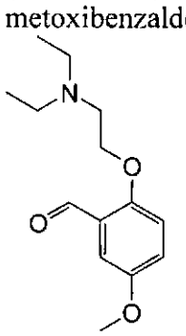
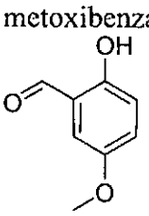
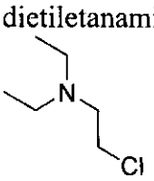
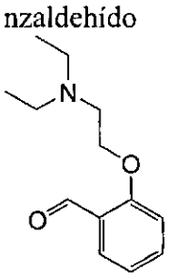
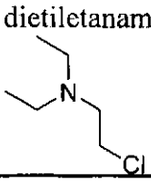


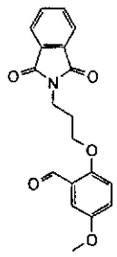
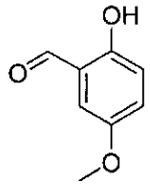
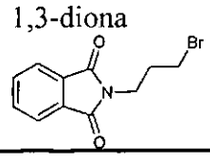
Método 27:

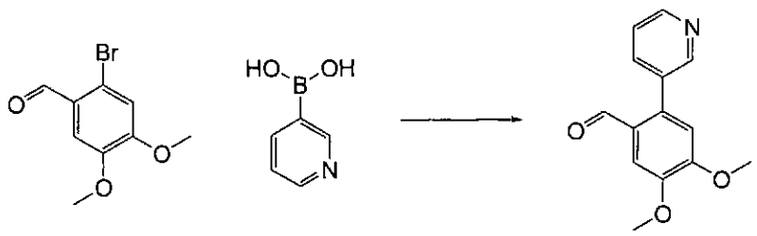
5-metoxi-2-(2-(piperidin-1-il)etoxi)benzaldehído:

Una mezcla de 2-hidroxi-5-metoxibenzaldehído (0,761 g, 5 mmol), 1-(2-cloroetil)piperidina clorhidrato (0,921 g, 5,00 mmol), K_2CO_3 (2;07 g, 14,99 mmol) y yoduro de sodio (0,075 g, 0,50 mmol) en acetonitrilo (40 mL) se agitó a 100°C durante toda la noche. La reacción se dejó enfriar hasta alcanzar la temperatura ambiente y se agregó K_2CO_3 saturado acuoso a la mezcla de reacción. La mezcla se vertió en un embudo de separación y se extrajo con EtOAc. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró a través de un lecho de Celite y se concentró al vacío para proporcionar el producto que se purificó mediante cromatografía en gel de sílice (80 g) utilizando EtOAc/hexanos (4:1) como eluyente para proporcionar el compuesto del título como un aceite marrón (0,551 g, 42 %); *m/z* 264.

Los siguientes intermediarios se prepararon mediante el procedimiento del Método 27, utilizando los materiales de partida apropiados.

Método	Compuesto	^{1}H NMR	m/z	MP
28	5-metoxi-2-(2-morfolinoetoxi)benzaldehído 		266	2-hidroxi-5-metoxibenzaldehído  y 4-(2-cloroetil)morfolina clorhidrato 
29	2-(2-(dietilamino)etoxi)-5-metoxibenzaldehído 		252	2-hidroxi-5-metoxibenzaldehído  y 2-cloro-*N*,*N*-dietiletanamina 
30A	2-(2-(dietilamino)etoxi)benzaldehído 		222	Salicilaldehído  y 2-cloro-*N*,*N*-dietiletanamina 

30B	2-(3-(1,3-dioxoisoindolin-2-il)propoxi)-5-metoxibenzaldehído 	10,18 (s, 1 H) 7,69 (m, 4 H) 7,11 (m, 2 H) 6,97 (d, 1 H) 4,05 (m, 2 H) 3,83 (m, 2 H) 3,67 (s, 3 H) 2,12 (m, 2 H)	340	2-hidroxi-5-metoxibenzaldehído  y 2-(3-bromopropil)isoindolina-1,3-diona 

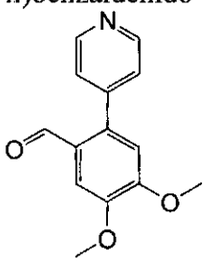
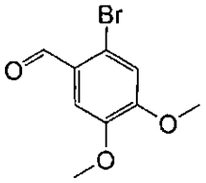
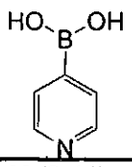
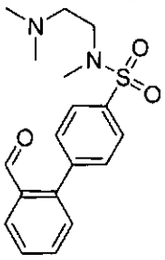
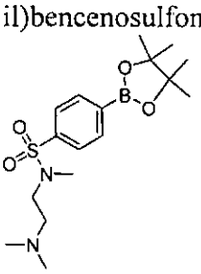
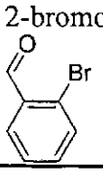


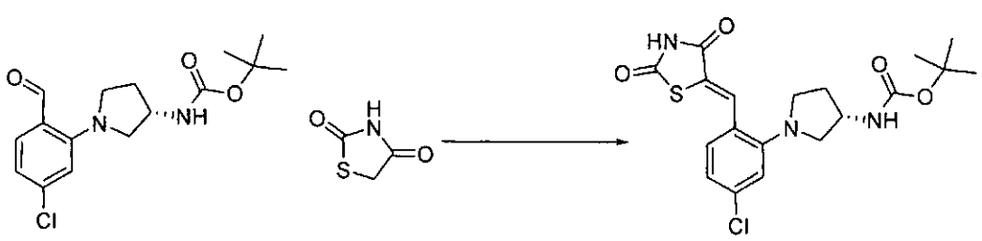
Método 31:

4,5-dimetoxi-2-(piridin-3-il)benzaldehído:

Una mezcla de 2-bromo-4,5-dimetoxibenzaldehído (0,368 g, 1,5 mmol), ácido piridin-3-ilborónico (0,246 g, 2,0 mmol), $Pd(PPh_3)_4$ (0,173 g, 0,150 mmol) y carbonato de cesio (0,977 g, 3 mmol) se suspendieron en dioxano (4 mL) y agua (1 mL). La mezcla se calentó hasta alcanzar 140 °C en un microondas durante 1 h. El recipiente de reacción se dejó enfriar hasta alcanzar la temperatura ambiente, se diluyó con acetato de etilo (~ 25 mL), se filtró a través de un lecho de Celite y se concentró al vacío para proporcionar el aldehído que se purificó mediante cromatografía en SiO_2 (40 g) utilizando acetato de etilo / hexanos (5:1) como eluyente para proporcionar el compuesto del título como un sólido blanco (0,340 g, 93 %); *m/z* 244.

Los siguientes intermediarios se prepararon mediante el procedimiento del Método 31, utilizando los materiales de partida apropiados.

Método	Compuesto	^{1}H NMR	m/z	MP
32A	4,5-dimetoxi-2-(piridin-4-il)benzaldehído 		244	2-bromo-4,5-dimetoxibenzaldehído  y ácido piridin-4-ilborónico 
32B	*N*-(2-(dimetilamino)etil)-2'-formil-*N*-metilbifenil-4-sulfonamida 	9,95 (s, 1 H), 8,05 (d, 1 H), 7,96 (d,2 H), 7,72 – 7,83 (m, 1 H), 7,57 – 7,72 (m, 3 H), 7,53 (d, 1 H), 3,24 (t, 2 H), 2,79 – 2,91 (m, 3 H), 2,65 (t, 2 H), 2,37 (s, 6 H)	346	*N*-(2-(dimetilamino)etil)-N-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)bencenosulfonamida  y 2-bromobenzaldehído 



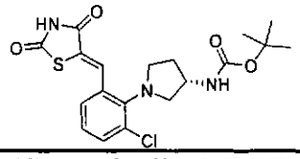
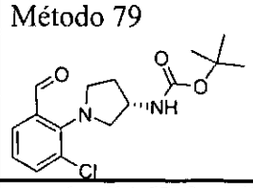
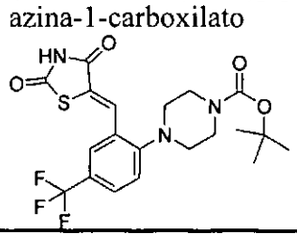
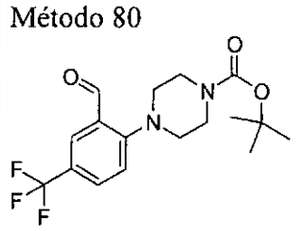
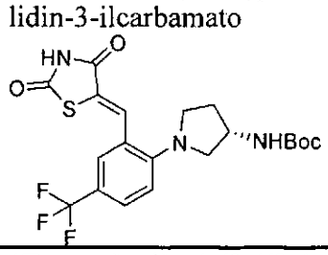
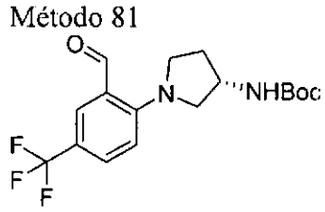
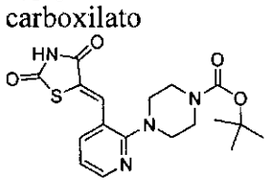
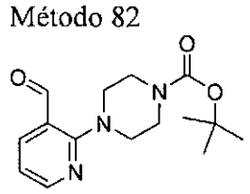
Método 33:

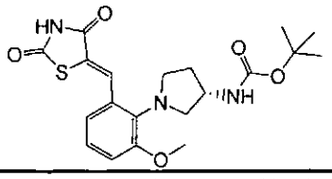
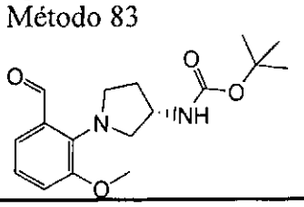
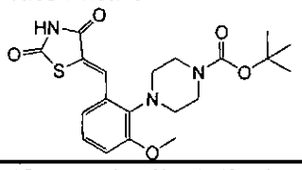
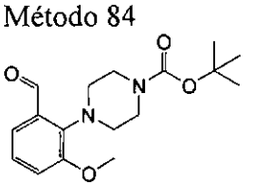
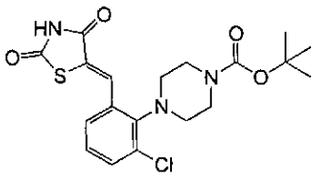
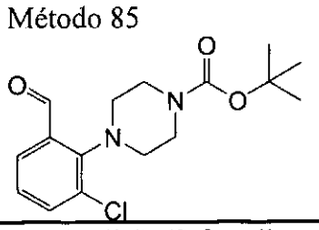
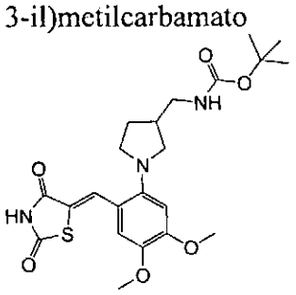
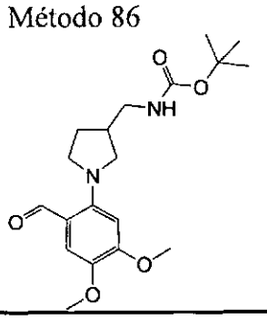
(*S,Z*)-*terc*-butil 1-(5-cloro-2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato:

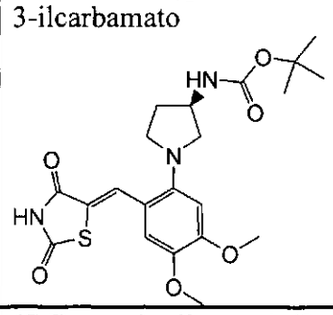
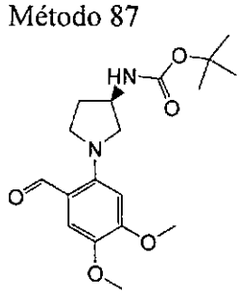
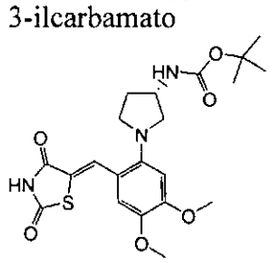
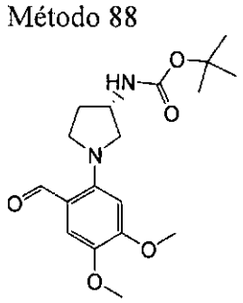
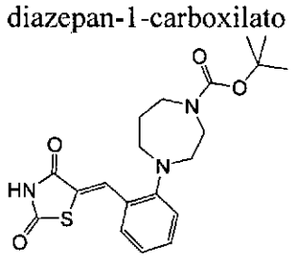
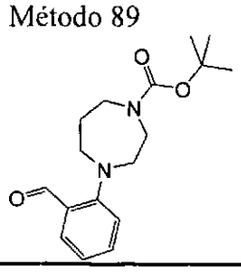
Un matraz de fondo redondo de 100 mL se cargó con una barra de agitación magnética, (*S*)-*terc*-butil 1-(5-cloro-2-formilfenil)pirrolidin-3-ilcarbamato (Método 78) (1,100 g, 3,39 mmol), tiazolidina-2,4-diona (0,397 g, 3,39 mmol) y etanol (11,29 ml). Se agregó piperidina (0,034 mL, 0,34 mmol) y la reacción se calentó hasta alcanzar reflujo durante 2 h. Cuando se estimó que la reacción se había completado mediante LCMS, se dejó enfriar hasta alcanzar la temperatura ambiente y se concentró al vacío para proporcionar el compuesto del título (1,310 g, 91 %) que se utilizó en la siguiente etapa sin purificación adicional.; *m/z* 425.

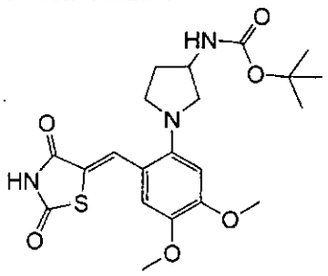
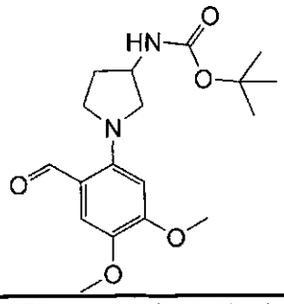
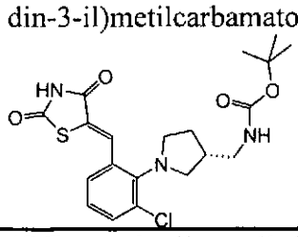
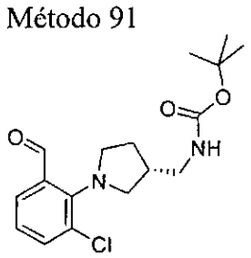
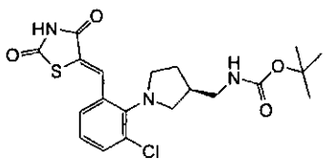
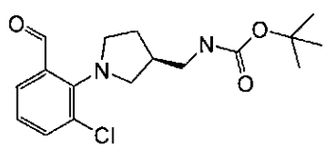
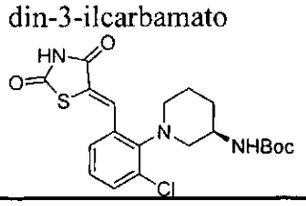
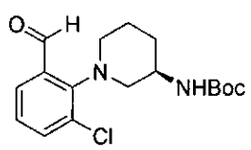
Los siguientes intermediarios se prepararon mediante el procedimiento del Método 33, utilizando los materiales de partida apropiados.

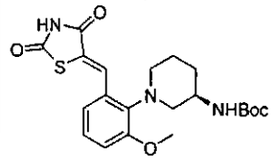
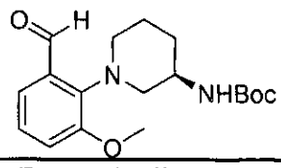
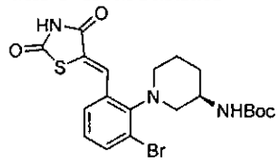
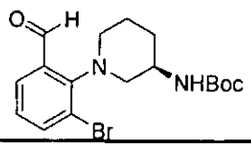
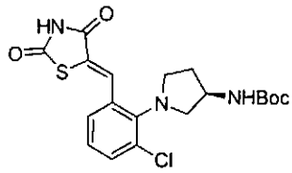
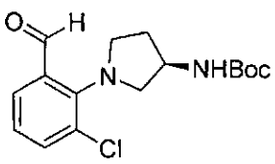
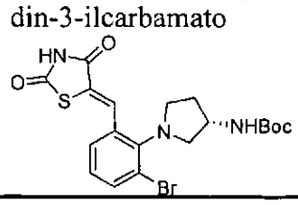
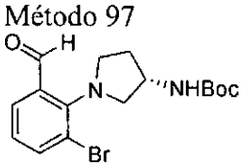
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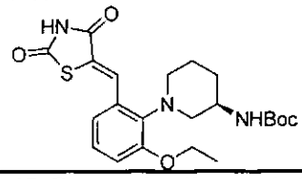
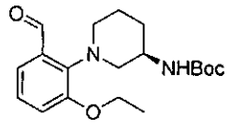
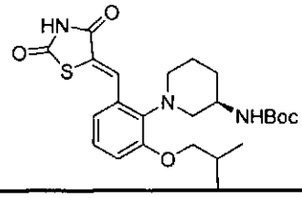
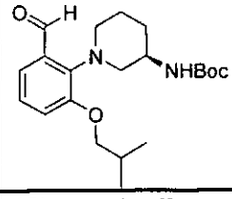
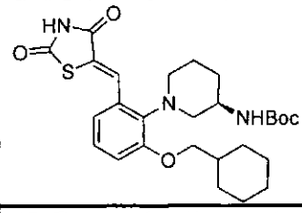
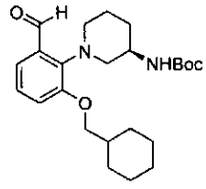
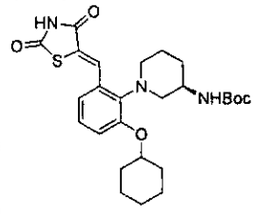
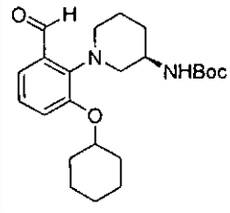
Método	Compuesto	^{1}H NMR	m/z	MP
34	(*S,Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato 		425	*terc*-butil [(3*S*)-1-(2-cloro-6-formilfenil)pirrolidin-3-il]carbamato Método 79 
35	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)piperazina-1-carboxilato 		459	*terc*-butil4-[2-formil-4-(trifluorometil)fenil]piperazina-1-carboxilato Método 80 
36	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)pirrolidin-3-ilcarbamato 		459	*terc*-butil{(3*S*)-1-[2-formil-4-(trifluorometil)fenil]pirrolidin-3-il}carbamato Método 81 
37	(*Z*)-*terc*-butil 4-(3-((2,4-dioxotiazolidin-5-ilideno)metil)piridin-2-il)piperazina-1-carboxilato 		391	*terc*-butil 4-(3-formilpiridin-2-il)piperazina-1-carboxilato Método 82 

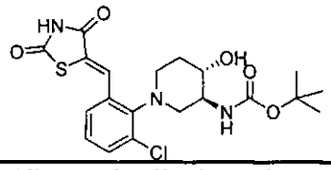
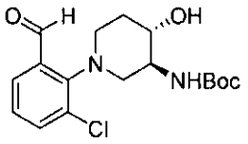
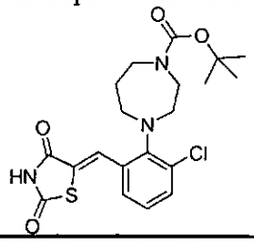
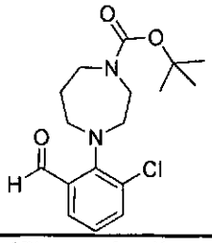
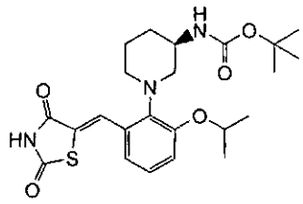
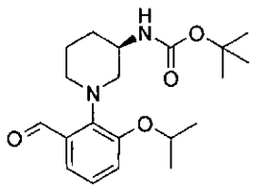
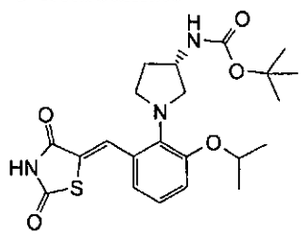
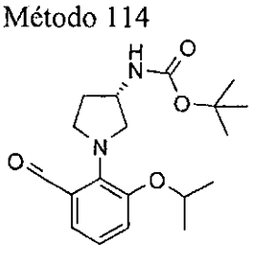
44	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)pirrolidin-3-ilcarbamato 		421	*terc*-butil [(3*S*)-1-(2-formil-6-metoxifenil)pirrolidin-3-il]carbamato Método 83 
45	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)piperazina-1-carboxilato 		421	*terc*-butil 4-(2-formil-6-metoxifenil)piperazina-1-carboxilato Método 84 
46	(*Z*)-*terc*-butil 4-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carboxilato 		425	*terc*-butil 4-(2-cloro-6-formilfenil)piperazina-1-carboxilato Método 85 
47	(*Z*)-*terc*-butil (1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-il)metilcarbamato 		465	*terc*-butil (1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-il)metilcarbamato Método 86 

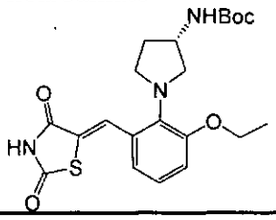
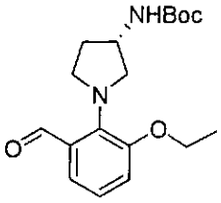
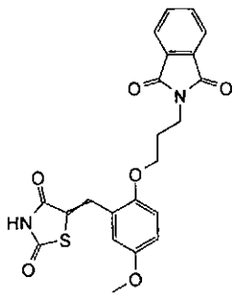
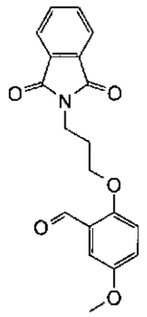
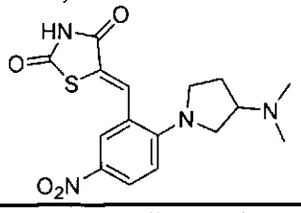
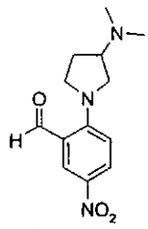
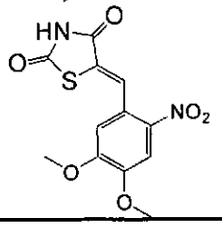
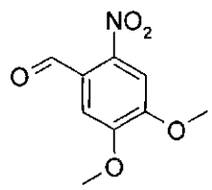
48	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato 		451	(*R*)-*terc*-butil 1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato Método 87 
49	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato 		451	(*S*)-*terc*-butil 1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato Método 88 
54	(*Z*)-*terc*-butil 4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-carboxilato 		404	*terc*-butil 4-(2-formilfenil)-1,4-diazepan-1-carboxilato Método 89 

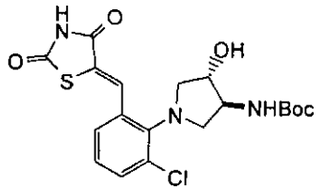
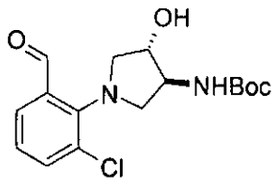
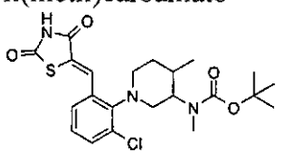
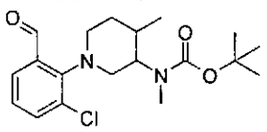
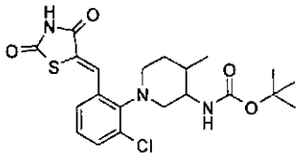
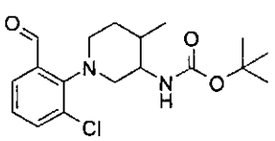
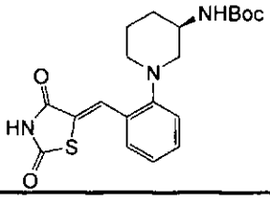
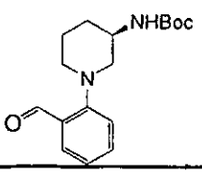
65	*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato 		451	*terc*-butil 1-(2-formil-4,5-dimetoxifenil)pirrolidin-3-ilcarbamato Método 90 
132	(*R*,*Z*)-*terc*-butil (1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)metilcarbamato 		439	(*R*)-*terc*-butil (1-(2-cloro-6-formilfenil)pirrolidin-3-il)metilcarbamato Método 91 
133	(*S*,*Z*)-*terc*-butil (1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-il)metilcarbamato 		439	(*S*)-*terc*-butil (1-(2-cloro-6-formilfenil)pirrolidin-3-il)metilcarbamato Método 92 
134	(*R*,*Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		438	*(R)*-*terc*-butil 1-(2-cloro-6-formilfenil)piperidin-3-ilcarbamato Método 93 

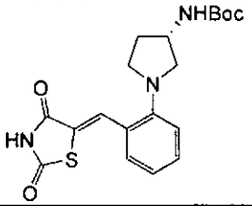
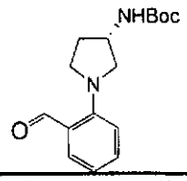
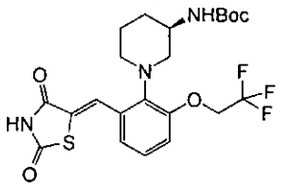
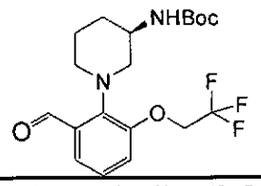
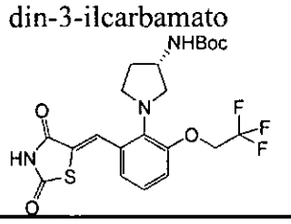
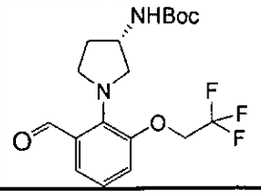
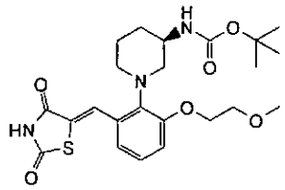
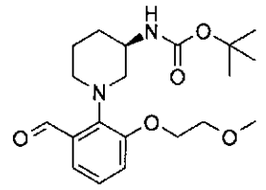
135	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)piperidin-3-ilcarbamato 		434	(*R*)-*terc*-butil 1-(2-formil-6-metoxifenil)piperidin-3-ilcarbamato Método 94 
136	(*R,Z*)-*terc*-butil 1-(2-bromo-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		484	(*R*)-*terc*-butil 1-(2-bromo-6-formilfenil)piperidin-3-ilcarbamato Método 95 
137	(*R,Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato 		424	(*R*)-*terc*-butil 1-(2-cloro-6-formilfenil)pirrolidin-3-ilcarbamato Método 96 
138	(*S,Z*)-*terc*-butil 1-(2-bromo-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato 		470	(*S*)-*terc*-butil 1-(2-bromo-6-formilfenil)pirrolidin-3-ilcarbamato Método 97 

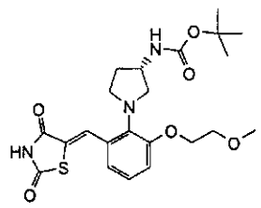
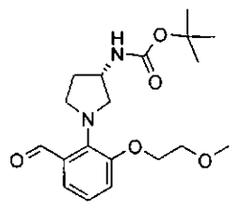
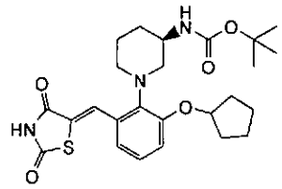
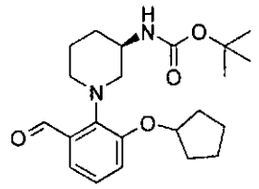
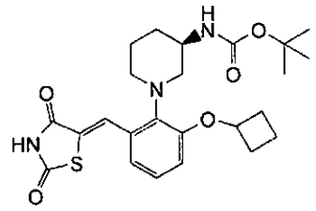
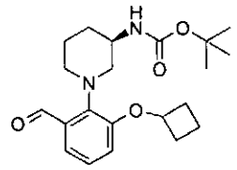
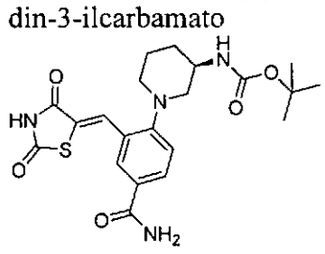
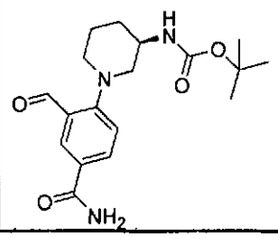
139	(*R*,*Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-etoxifenil)piperidin-3-ilcarbamato 		448	(*R*)-*terc*-butil 1-(2-etoxi-6-formilfenil)piperidin-3-ilcarbamato Método 98 
140	(*R*,*Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-isobutoxifenil)piperidin-3-ilcarbamato 		476	(*R*)-*terc*-butil 1-(2-formil-6-isobutoxifenil)piperidin-3-ilcarbamato Método 99 
141	(*R*,*Z*)-*terc*-butil 1-(2-(ciclohexilmetoxi)-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		516	(*R*)-*terc*-butil 1-(2-(ciclohexilmetoxi)-6-formilfenil)piperidin-3-ilcarbamato Método 100 
142	(*R*,*Z*)-*terc*-butil 1-(2-(ciclohexiloxi)-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		501	(*R*)-*terc*-butil 1-(2-(ciclohexiloxi)-6-formilfenil)piperidin-3-ilcarbamato Método 101 

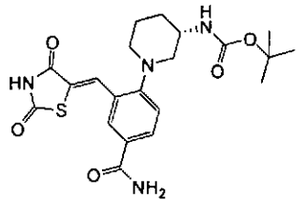
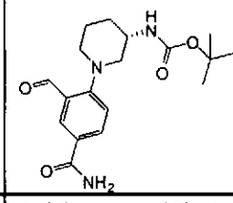
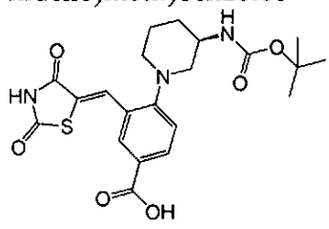
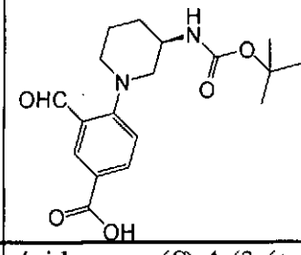
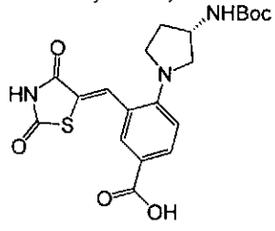
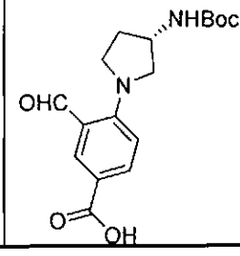
143	(±)-*terc*-butil-1-(2-cloro-6-((*Z*)-(2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-hidroxipiperidin-3-ilcarbamato 		454	(±)-*terc*-butil-1-(2-cloro-6-formilfenil)-4-hidroxipiperidin-3-ilcarbamato Método 102 
144	(*Z*)-*terc*-butil 4-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-carboxilato 	8,66 (brs, 1 H), 8,36 (brs, 1 H), 7,47 (d, 1 H), 7,39 (d, 1 H), 7,22 (t, 1 H), 3,61 (brs, 3 H), 3,52 (brs, 2 H), 3,27 (brs, 3 H), 1,91 (brs, 2 H), 1,52 (s, 9 H)	438	*terc*-butil 4-(2-cloro-6-formilfenil)-1,4-diazepan-1-carboxilato Método 103 
145	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-isopropoxifenil)piperidin-3-ilcarbamato 		462	(*R*)-*terc*-butil 1-(2-formil-6-isopropoxifenil)piperidin-3-ilcarbamato Método 113 
146	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-isopropoxifenil)pirrolidin-3-ilcarbamato 		448	(*S*)-*terc*-butil 1-(2-formil-6-isopropoxifenil)pirrolidin-3-ilcarbamato Método 114 

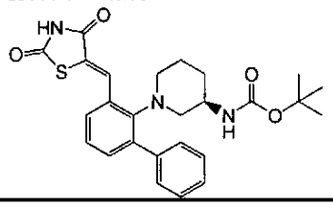
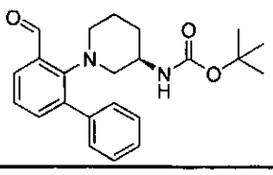
147	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-etoxifenil)pirrolidin-3-ilcarbamato 		334	(*S*)-*terc*-butil 1-(2-etoxi-6-formilfenil)pirrolidin-3-ilcarbamato Método 115 
148	5-(2-(3-(1,3-dioxoisoindolin-2-il)propoxi)-5-metoxibencilideno)tiazolidina-2,4-diona 	12,54 (s, 1 H) 7,83-7,79 (m, 5 H) 7,04 (s, 2 H) 6,86 (s, 1 H) 4,08 (m, 2 H) 3,80-3,75 (m, 5 H) 2,11 (m, 2 H)	438	2-(3-(1,3-dioxoisoindolin-2-il)propoxi)-5-metoxibenzaldehído Método 30B 
149	5-(2-(3-(dimetilamino)pirrolidin-1-il)-5-nitrobencilideno)tiazolidina-2,4-diona 	8,20 (s, 1 H) 8,07 (d, 1 H) 7,82 (s, 1 H) 6,96 (d, 1H) 3,58-3,51 (m, 3H) 3,36 (m, 1 H) 3,04 (m, 1 H) 2,51 (s, 6 H), 2,40 (m, 1 H), 1,86 (m, 1 H)	363	2-(3-(dimetilamino)pirrolidin-1-il)-5-nitrobenzaldehído Método 116 
150	(*Z*)-5-(4,5-dimetoxi-2-nitrobencilideno)tiazolidina-2,4-diona 	8,32 (s, 1 H) 8,25 (brs, 1 H) 7,79 (s, 1 H) 7,02 (s, 1 H) 4,03 (s, 6 H)	309	4,5-dimetoxi-2-nitrobenzaldehído 

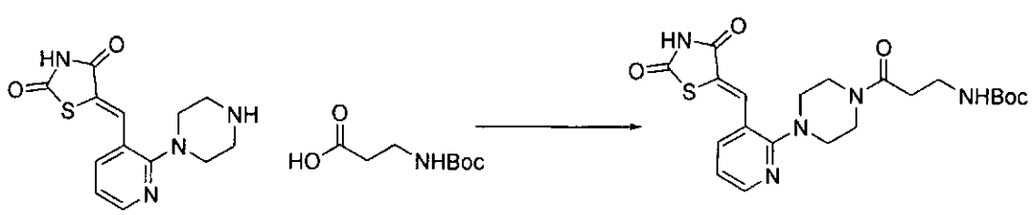
151	*terc*-butil (3*S*,4*S*)-1-(2-cloro-6-((*Z*)-(2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-hidroxipirrolidin-3-ilcarbamato 	8,30 (s, 1 H) 7,49 (d, 1 H) 7,42 (d, 1 H) 7,28-7,20 (m, 1 H) 5,01 (d, 1 H) 4,39 (brs, 1 H) 4,27 (brs, 1 H) 4,05 (s, 1 H) 3,83 (dd, 1 H) 3,69 (dd, 1 H) 3,27 (brs, 1 H) 3,19 (dd, 1 H), 1,50 (s, 9 H)	439	*terc*-butil (3*S*,4*S*)-1-(2-cloro-6-formilfenil)-4-hidroxipirrolidin-3-ilcarbamato Método 117 
152	(*Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-metilpiperidin-3-il(metil)carbamato 		465	*terc*-butil 1-(2-cloro-6-formilfenil)-4-metilpiperidin-3-il(metil)carbamato Método 118 
153	(*Z*)-*terc*-butil 1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-4-metilpiperidin-3-ilcarbamato 		451	*terc*-butil 1-(2-cloro-6-formilfenil)-4-metilpiperidin-3-ilcarbamato Método 119 
154	(*R*,*Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		404	(*R*)-*terc*-butil 1-(2-formilfenil)piperidin-3-ilcarbamato Método 120 

155	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)pirrolidin-3-ilcarbamato 		390	(*S*)-*terc*-butil 1-(2-formilfenil)pirrolidin-3-ilcarbamato Método 121 
156	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2,2,2-trifluoroetoxi)fenil)piperidin-3-ilcarbamato 		502	(*R*)-*terc*-butil 1-(2-formil-6-(2,2,2-trifluoroetoxi)fenil)piperidin-3-ilcarbamato Método 122 
157	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2,2,2-trifluoroetoxi)fenil)pirrolidin-3-ilcarbamato 		488	(*S*)-*terc*-butil 1-(2-formil-6-(2,2,2-trifluoroetoxi)fenil)pirrolidin-3-ilcarbamato Método 123 
158	(*R,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2-metoxietoxi)fenil)piperidin-3-ilcarbamato 		478	(*R*)-*terc*-butil 1-(2-formil-6-(2-metoxietoxi)fenil)piperidin-3-ilcarbamato Método 124 

159	(*S,Z*)-*terc*-butil 1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-(2-metoxietoxi)fenil)pirrolidin-3-ilcarbamato 		464	(*S*)-*terc*-butil 1-(2-formil-6-(2-metoxietoxi)fenil)pirrolidin-3-ilcarbamato Método 125 
160	(*R,Z*)-*terc*-butil 1-(2-(ciclopentiloxi)-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		488	(*R*)-*terc*-butil 1-(2-(ciclopentiloxi)-6-formilfenil)piperidin-3-ilcarbamato Método 126 
161	(*R,Z*)-*terc*-butil 1-(2-ciclobutoxi-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		474	(*R*)-*terc*-butil 1-(2-ciclobutoxi-6-formilfenil)piperidin-3-ilcarbamato Método 127 
162	(*R,Z*)-*terc*-butil 1-(4-carbamoil-2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		447	(*R*)-*terc*-butil 1-(4-carbamoil-2-formilfenil)piperidin-3-ilcarbamato Método 128 

163	(*S,Z*)-*terc*-butil 1-(4-carbamoil-2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilcarbamato 		447	(*S*)-*terc*-butil 1-(4-carbamoil-2-formilfenil)piperidin-3-ilcarbamato Método 129 
164	ácido (*R,Z*)-4-(3-(*terc*-butoxicarbonilamino)piperidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzoico 		447	ácido (*R*)-4-(3-(*terc*-butoxicarbonilamino)piperidin-1-il)-3-formilbenzoico Método 130 
165	ácido (*S,Z*)-4-(3-(*terc*-butoxicarbonilamino)pirrolidin-1-il)-3-((2,4-dioxotiazolidin-5-ilideno)metil)benzoico 		433	ácido (*S*)-4-(3-(*terc*-butoxicarbonilamino)pirrolidin-1-il)-3-formilbenzoico Método 131 

166	(*R*,*Z*)-*terc*-butil 1-(3-((2,4-dioxotiazolidin-5-ilideno)metil)bifenil-2-il)piperidin-3-ilcarbamato 		480	(*R*)-*terc*-butil 1-(3-formilbifenil-2-il)piperidin-3-ilcarbamato Método 201 



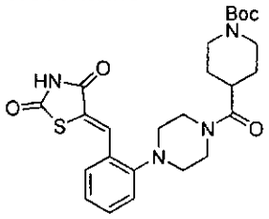
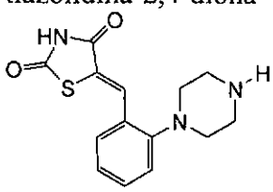
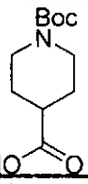
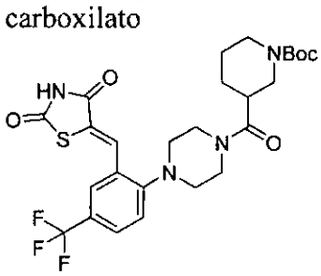
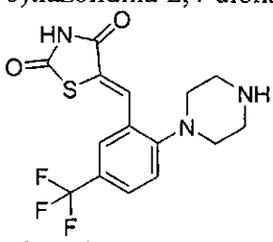
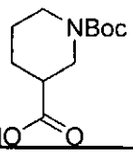
Método 38:

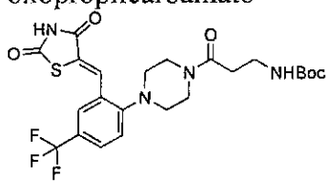
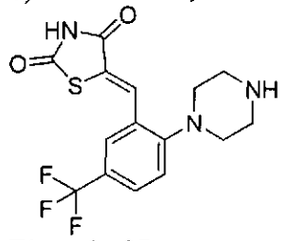
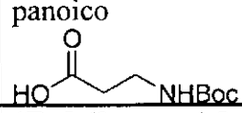
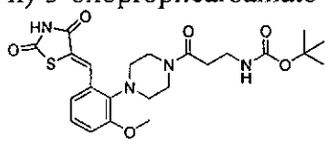
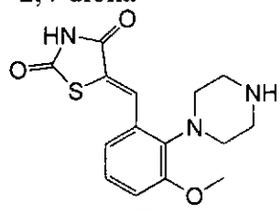
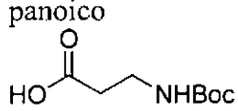
(*Z*)-*terc*-butil 3-(4-(3-((2,4-dioxotiazolidin-5-ilideno)metil)piridin-2-il)piperazin-1-il)-3-oxopropilcarbamato:

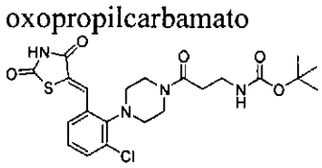
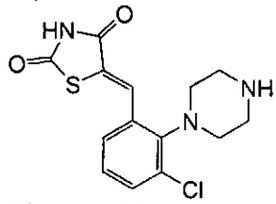
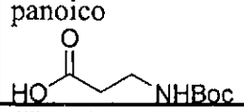
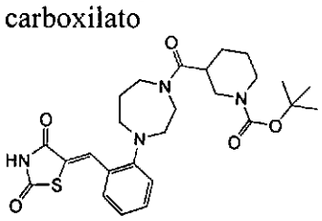
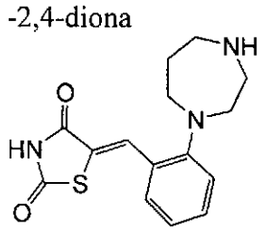
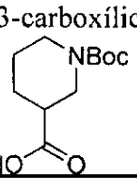
Un vial de 50 mL se cargó con una barra de agitación magnética, (*Z*)-5-((2-(piperazin-1-il)piridin-3-il)metileno)tiazolidina-2,4-diona clorhidrato (Ejemplo 89) (0,125 g, 0,38 mmol), ácido 3-(*terc*-butoxicarbonilamino)propanoico (0,109 g, 0,57 mmol), DMF (1,912 ml) y diisopropiletilamina (0,334 ml, 1,91 mmol). Con agitación, se agregó HATU (0,291 g, 0,76 mmol) y la reacción se entibió hasta alcanzar 50°C durante 3 h. La reacción luego se diluyó con agua y se extrajo con acetato de etilo (3 X 50 mL). El extracto orgánico combinado se secó con $MgSO_4$, se filtró a través de un lecho de Celite y se concentró al vacío para proporcionar el producto que se purificó mediante cromatografía en gel de sílice (80 g) utilizando acetato de etilo/hexanos (1:1) como eluyente para proporcionar el compuesto del título como un sólido blancuzco (0,080 g, 45,3 %); *m/z* 462.

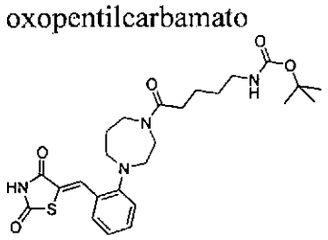
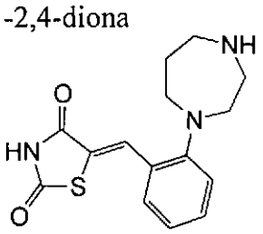
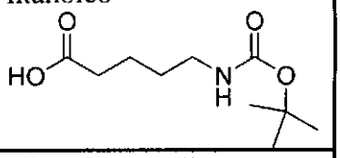
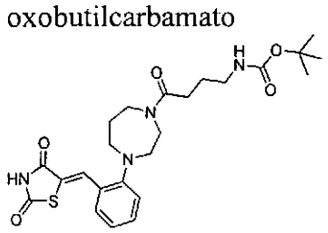
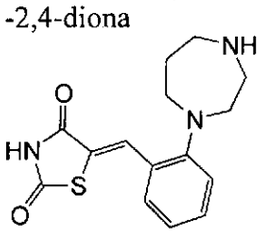
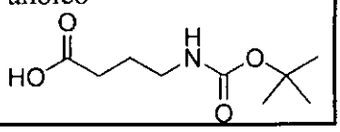
Los siguientes intermediarios se prepararon mediante el procedimiento del Método 38,

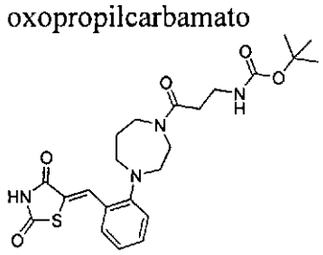
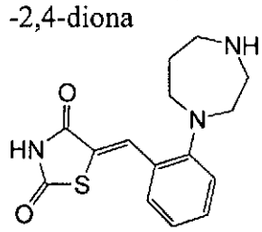
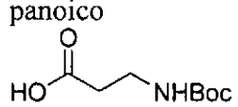
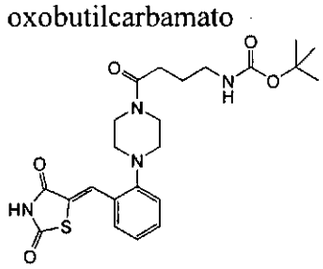
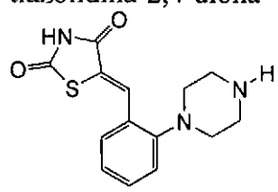
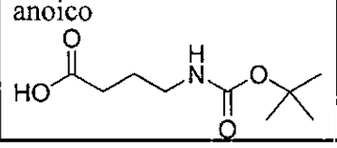
utilizando los materiales de partida apropiados.

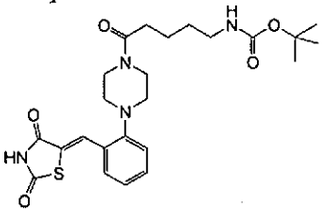
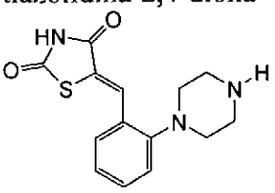
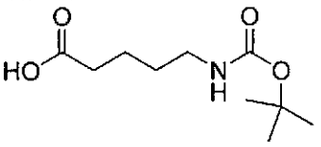
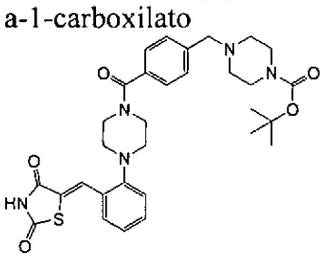
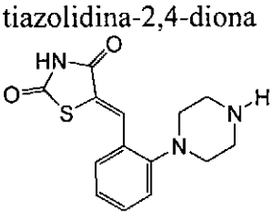
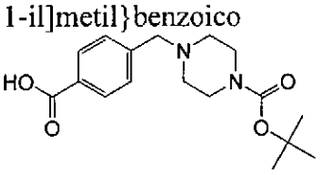
Método	Compuesto	^{1}H NMR	m/z	MP
39	(*Z*)-*terc*-butil 4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)piperidina-1-carboxilato 		502	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 1-(*terc*-butoxicarbonil)piperidina-4-carboxílico 
40	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)piperazina-1-carbonil)piperidina-1-carboxilato 		560	(*Z*)-5-(2-(piperazin-1-il)-5-(trifluorometil)benciliden o)tiazolidina-2,4-diona  Ejemplo 87 y ácido 1-(*terc*-butoxicarbonil)piperidina-3-carboxílico 

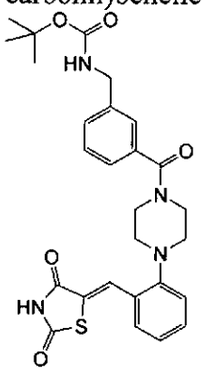
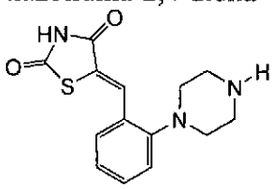
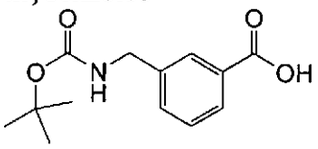
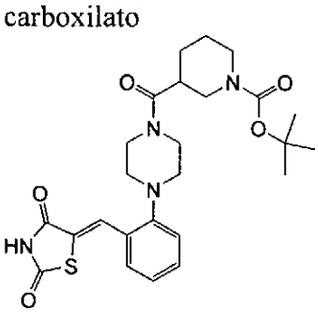
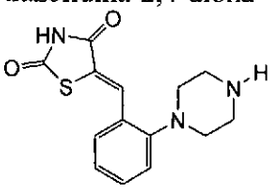
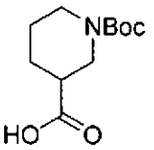
41	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4-(trifluorometil)fenil)piperazin-1-il)-3-oxopropilcarbamato 		530	(*Z*)-5-(2-(piperazin-1-il)-5-(trifluorometil)benciliden o)tiazolidina-2,4-diona  Ejemplo 87 y ácido 3-[(*terc*-butoxicarbonil)amino]pro panoico 
42	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-6-metoxifenil)piperazin-1-il)-3-oxopropilcarbamato 		492	(*Z*)-5-(3-metoxi-2-(piperazin-1-il)bencilideno)tiazolidina-2,4-diona  Ejemplo 97 y ácido 3-[(*terc*-butoxicarbonil)amino]pro panoico 

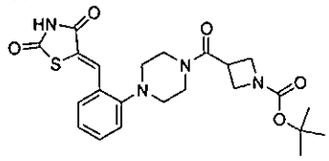
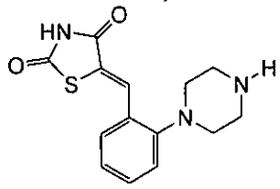
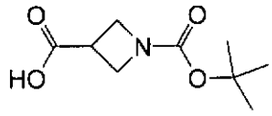
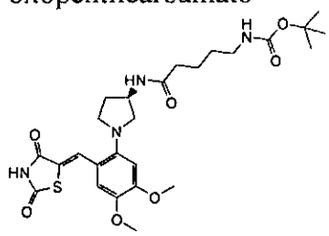
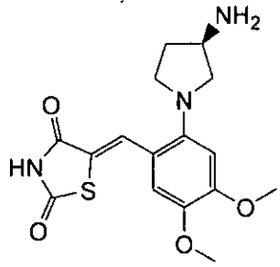
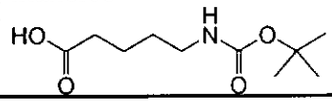
43	(*Z*)-*terc*-butil 3-(4-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)-3-oxopropilcarbamato 		496	(*Z*)-5-(3-cloro-2-(piperazin-1-il)bencilideno)tiazolidina-2,4-diona  Ejemplo 98 y ácido 3-[(*terc*-butoxicarbonil)amino]propanoico 
50	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-carbonil)piperidina-1-carboxilato 		516	(*Z*)-5-(2-(1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona  Ejemplo 106 y ácido 1-(*terc*-butoxicarbonil)piperidina-3-carboxílico 

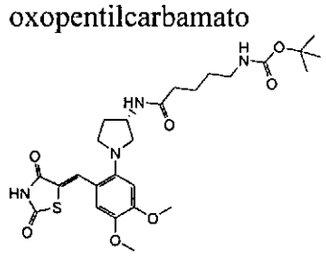
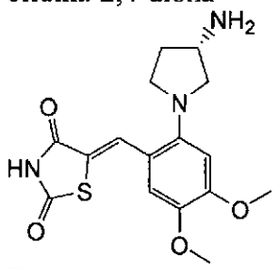
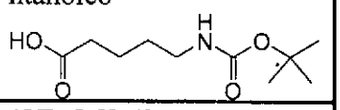
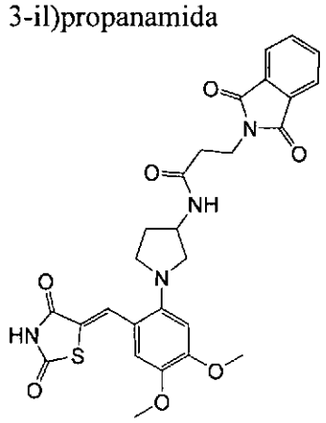
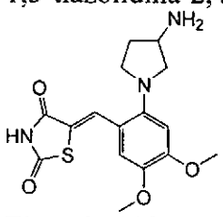
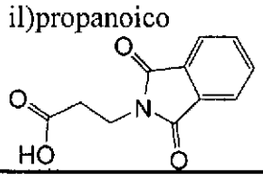
51	(*Z*)-*terc*-butil 5-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-il)-5-oxopentilcarbamato 		504	(*Z*)-5-(2-(1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona  Ejemplo 106 y ácido 5-[(*terc*-butoxicarbonil)amino]pentanoico 
52	(*Z*)-*terc*-butil 4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-il)-4-oxobutilcarbamato 		490	(*Z*)-5-(2-(1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona  Ejemplo 106 y ácido 4-[(*terc*-butoxicarbonil)amino]butanoico 

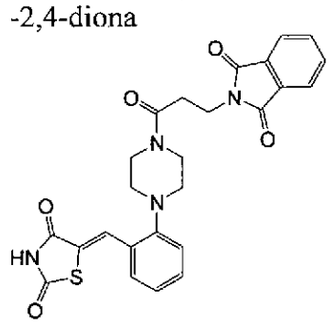
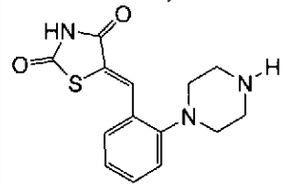
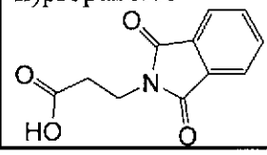
53	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)-1,4-diazepan-1-il)-3-oxopropilcarbamato 		475	(*Z*)-5-(2-(1,4-diazepan-1-il)bencilideno)tiazolidina-2,4-diona  Ejemplo 106 y ácido 3-[(*terc*-butoxicarbonil)amino]propanoico 
55	(*Z*)-*terc*-butil 4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)-4-oxobutilcarbamato 		476	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 4-[(*terc*-butoxicarbonil)amino]butanoico 

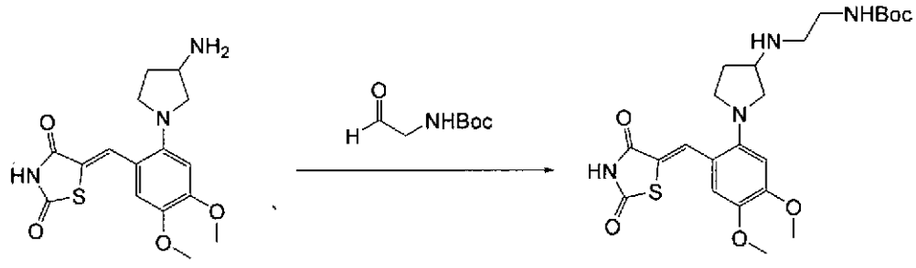
56	(*Z*)-*terc*-butil 5-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)-5-oxopentilcarbamato 		490	(5Z)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 5-[(*terc*-butoxicarbonil)amino]pentanoico 
57	(*Z*)-*terc*-butil 4-(4-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)bencil)piperazina-1-carboxilato 		593	(5Z)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 4-{[4-(*terc*-butoxicarbonil)piperazin-1-il]metil}benzoico 

58	(*Z*)-*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)bencilcarbamato 		524	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 3-{[(*terc*-butoxicarbonil)amino]metil}benzoico 
63	*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)piperidina-1-carboxilato 		501	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 1-(*terc*-butoxicarbonil)piperidina-3-carboxílico 

64	*terc*-butil 3-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazina-1-carbonil)azetidina-1-carboxilato 		473	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 1-(*terc*-butoxicarbonil)azetidina-3-carboxílico 
66	(*R*,*Z*)-*terc*-butil 5-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)-5-oxopentilcarbamato 		550	(*R*,*Z*)-5-(2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona  Ejemplo 100 y ácido 5-[(*terc*-butoxicarbonil)amino]pentanoico 

67	(*S,Z*)-*terc*-butil 5-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)-5-oxopentilcarbamato 		550	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona  Ejemplo 101 y ácido 5-[(*terc*-butoxicarbonil)amino]pentanoico 
75	(*Z*)-3-(1,3-dioxoisoindolin-2-il)-N-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-il)propanamida 		552	(5*Z*)-5-[2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno]-1,3-tiazolidina-2,4-diona  Ejemplo 118 y ácido 3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)propanoico 

76	5Z)-(2-(4-(3-(1,3-dioxoisoindolin-2-il)propanoil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona 			(5Z)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y ácido 3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)propanoico 



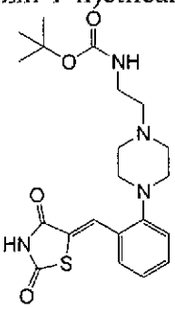
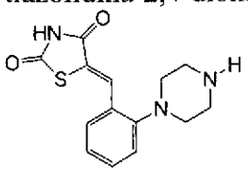
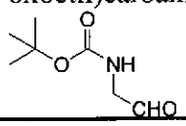
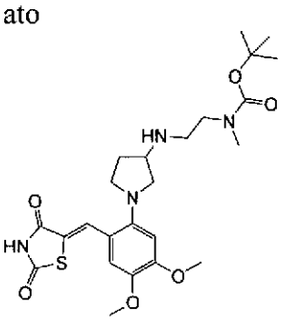
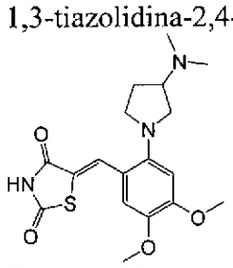
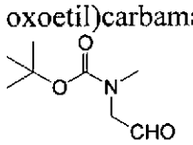
Método 59:

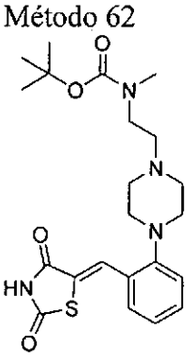
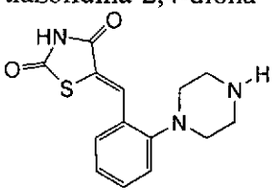
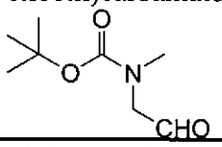
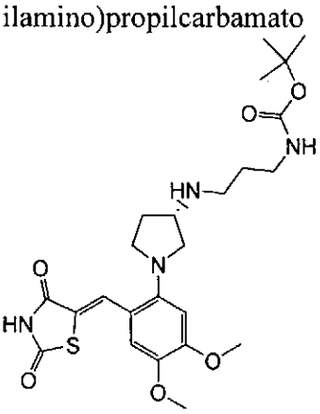
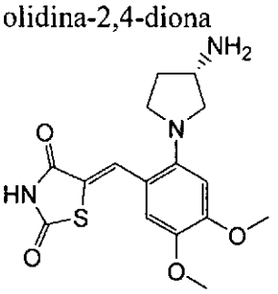
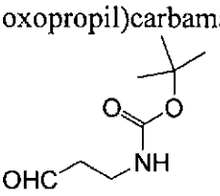
(*Z*)-*terc*-butil 2-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)etilcarbamato:

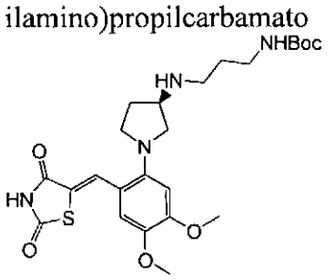
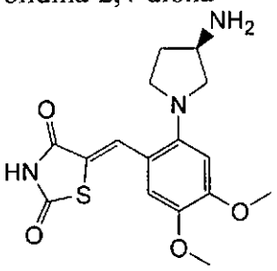
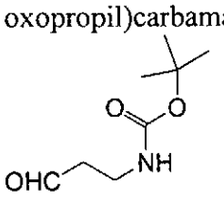
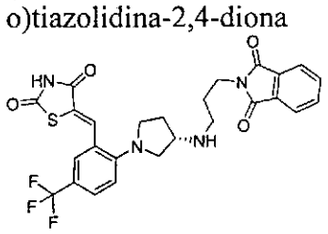
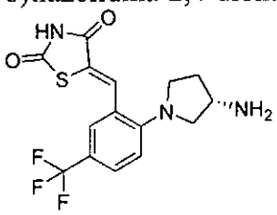
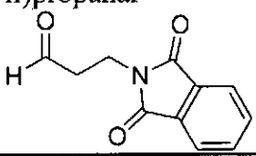
Una mezcla de (5Z)-5-{2-[3-(dimetilamino)pirrolidin-1-il]-4,5-dimetoxibencilideno}-1,3-tiazolidina-2,4-diona (Ejemplo 52)(120 mg, 0,31 mmol) y terc-butil 2-oxoetilcarbamato (198 mg, 1,24 mmol) en CH_2Cl_2 (20 mL) se calentó hasta alcanzar reflujo durante 15 min y luego se agregó triacetoxihidroborato de sodio (65,9 mg, 0,31 mmol). La mezcla de reacción se sometió a reflujo durante toda la noche antes de dejarse enfriar hasta alcanzar la temperatura ambiente. Se agregó agua (~ 0,5 mL) y la mezcla se dejó agitar durante 15 min antes de cargarse en una columna de gel de sílice que se eluyó con acetato de etilo/hexano (10:1) para proporcionar el compuesto del título como un sólido naranja (60,0 mg, 39,2 %); *m/z* 493.

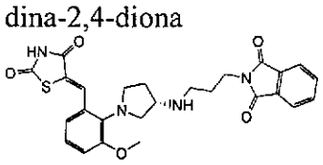
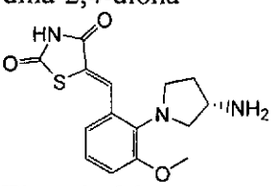
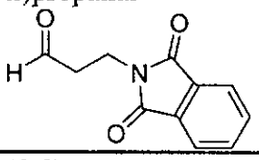
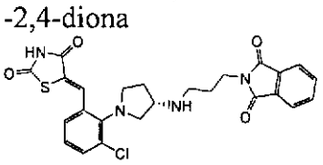
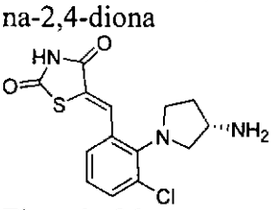
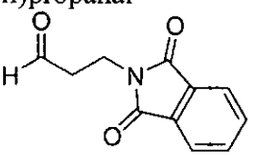
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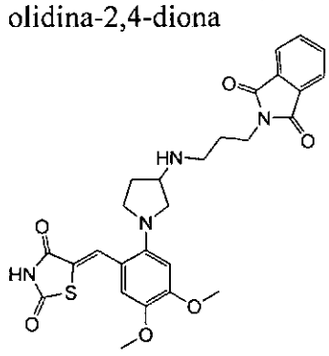
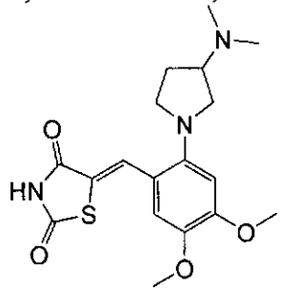
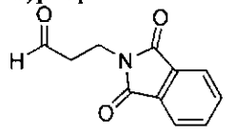
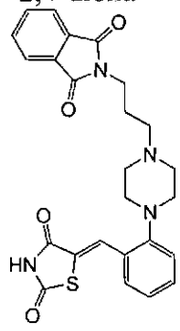
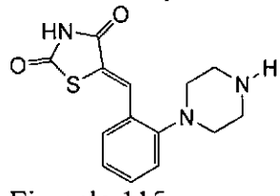
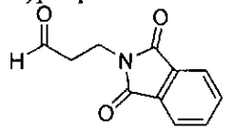
Los siguientes intermediarios se prepararon mediante el procedimiento del Método 59, utilizando los materiales de partida apropiados.

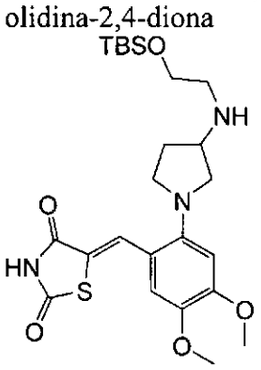
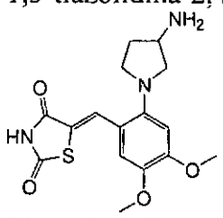
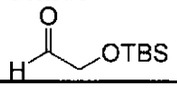
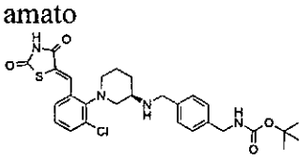
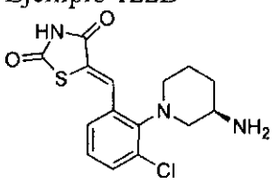
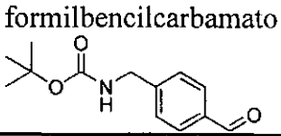
Método	Compuesto	^{1}H NMR	m/z	MP
60	(*Z*)-*terc*-butil 2-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)etilcarbamato 		433	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y *terc*-butil (2-oxoetil)carbamato 
61	(*Z*)-*terc*-butil 2-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)etil(metil)carbamato 		507	(5*Z*)-5-{2-[3-(dimetilamino)pirrolidin-1-il]-4,5-dimetoxibencilideno}-1,3-tiazolidina-2,4-diona  Ejemplo 52 y *terc*-butil metil(2-oxoetil)carbamato 

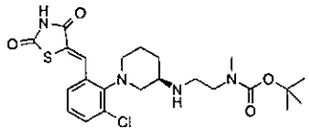
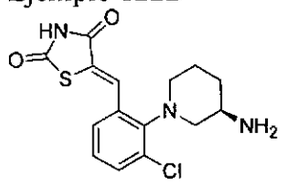
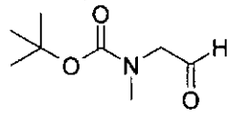
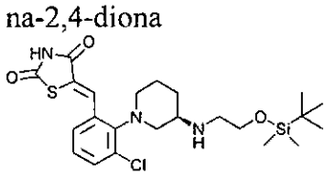
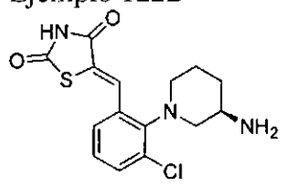
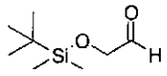
62	(*Z*)-*terc*-butil 2-(4-(2-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperazin-1-il)etil(metil)carbamato Método 62 		448	(5*Z*)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y *terc*-butil metil(2-oxoetil)carbamato 
68	(*S,Z*)-*terc*-butil 3-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)propilcarbamato 		507	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona  Ejemplo 101 y *terc*-butil (3-oxopropil)carbamato 

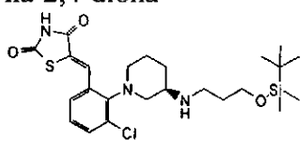
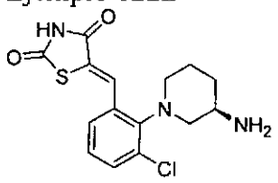
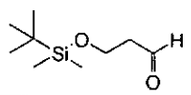
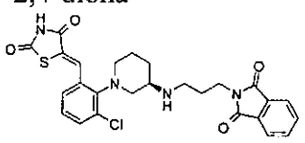
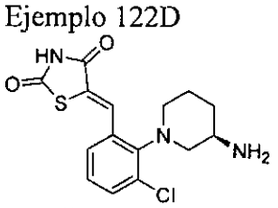
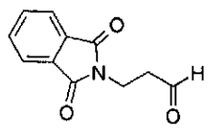
69	(*R*,*Z*)-*terc*-butil 3-(1-(2-((2,4-dioxotiazolidin-5-ilideno)metil)-4,5-dimetoxifenil)pirrolidin-3-ilamino)propilcarbamato 		507	(*R*,*Z*)-5-(2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona  Ejemplo 100 y *terc*-butil (3-oxopropil)carbamato 
70	(*S*,*Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)-5-(trifluorometil)benciliden o)tiazolidina-2,4-diona 		545	(*S*,*Z*)-5-(2-(3-aminopirrolidin-1-il)-5-(trifluorometil)benciliden o)tiazolidina-2,4-diona  Ejemplo 88 y 3-(1,3-dioxoisoindolin-2-il)propanal 

71	(*S,Z*)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona 		508	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-metoxibencilideno)tiazolidina-2,4-diona  Ejemplo 96 y 3-(1,3-dioxoisoindolin-2-il)propanal 
72	(*S,Z*)-5-(3-cloro-2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)bencilideno)tiazolidina-2,4-diona 		512	(*S,Z*)-5-(2-(3-aminopirrolidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona  Ejemplo 86 y 3-(1,3-dioxoisoindolin-2-il)propanal 

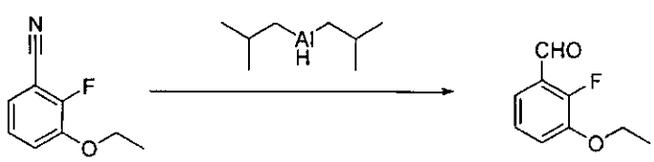
73	(Z)-5-(2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona 		507	(5Z)-5-{2-[3-(dimetilamino)pirrolidin-1-il]-4,5-dimetoxibencilideno}-1,3-tiazolidina-2,4-diona  Ejemplo 52 y 3-(1,3-dioxoisoindolin-2-il)propanal 
74	(Z)-5-(2-(4-(3-(1,3-dioxoisoindolin-2-il)propil)piperazin-1-il)bencilideno)tiazolidina-2,4-diona 		477	(5Z)-5-(2-piperazin-1-ilbencilideno)-1,3-tiazolidina-2,4-diona  Ejemplo 115 y 3-(1,3-dioxoisoindolin-2-il)propanal 

77	(*Z*)-5-(2-(3-(2-(*terc*-butildimetilsililoxi)etilamino)pirrolidin-1-il)-4,5-dimetoxibencilideno)tiazolidina-2,4-diona 		509	(5*Z*)-5-[2-(3-aminopirrolidin-1-il)-4,5-dimetoxibencilideno]-1,3-tiazolidina-2,4-diona  Ejemplo 118 y 2-(*terc*-butildimetilsililoxi)acetaldehído 
167	(*R,Z*)-*terc*-butil 4-((1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilamino)metil)bencilcarbamato 		557	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato Ejemplo 122D  y *terc*-butil 4-formilbencilcarbamato 

168	(*R,Z*)-*terc*-butil 2-(1-(2-cloro-6-((2,4-dioxotiazolidin-5-ilideno)metil)fenil)piperidin-3-ilamino)etil(metil)carbamato 		496	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato Ejemplo 122D  y *terc*-butil metil (2-oxoetil)carbamato 
169	(*R,Z*)-5-(2-(3-(2-*(terc*-butildimetilsililoxi)etilamino)piperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona 		496	(*R,Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato Ejemplo 122D  y 2-(*terc*-butildimetilsililoxi)acetaldehído 

170	(*R*,*Z*)-5-(2-(3-(3-(*terc*-butildimetilsililoxi)propil amino)piperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona 		510	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato Ejemplo 122D  y 3-(*terc*-butildimetilsililoxi)propanal 
171	(*R*,*Z*)-5-(3-cloro-2-(3-(3-(1,3-dioxoisoindolin-2-il)propilamino)piperidin-1-il)bencilideno)tiazolidina-2,4-diona 		525	(*R*,*Z*)-5-(2-(3-aminopiperidin-1-il)-3-clorobencilideno)tiazolidina-2,4-diona clorhidrato Ejemplo 122D  3-(1,3-dioxoisoindolin-2-il)propanal 

Método 172

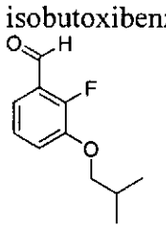
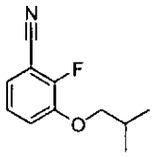
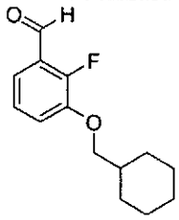
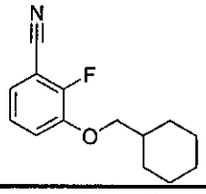
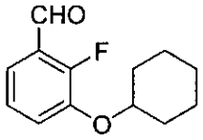
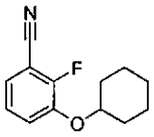
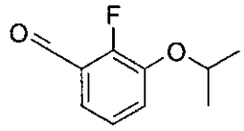
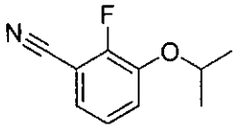
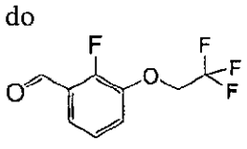
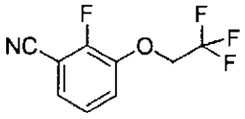


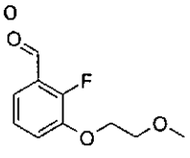
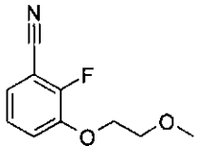
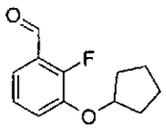
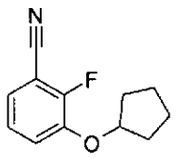
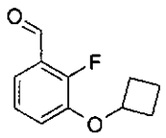
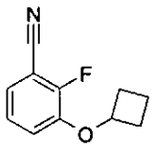
3-etoxi-2-fluorobenzaldehído:

Un matraz de fondo redondo de 200 mL se cargó con una barra de agitación magnética, 3-etoxi-2-fluorobenzonitrilo (1,000 g, 6,05 mmol) y tolueno anhidro (12,92 ml). La solución se colocó bajo argón y se enfrió hasta alcanzar 0°C con un baño de hielo. Luego se agregó por goteo DIBAL-H (7,27 ml, 7,27 mmol) (1M en PhMe) mediante una

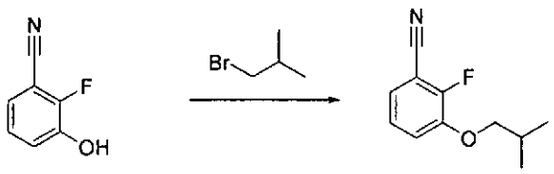
jeringa y la reacción se dejó agitar hasta alcanzar la TA durante toda la noche. A esta mezcla se agregó 10 % de HCl hasta que la solución alcanzó un pH de ~ 2. La mezcla resultante luego se dejó agitar durante 0,5 h. y luego se vertió en un embudo de separación y se extrajo con acetato de etilo (2 x 200 mL). El extracto orgánico combinado se secó con $MgSO_4$, se filtró y se concentró al vacío para proporcionar el producto bruto que se purificó mediante cromatografía en gel de sílice (80 g) utilizando acetato de etilo/hexanos (1:4) como eluyente para proporcionar 3-etoxi-2-fluorobenzaldehído puro (0,810 g, 80 %). *m/z* 196.

Los siguientes intermediarios se prepararon mediante el procedimiento del Método 172, utilizando los materiales de partida apropiados.

173	2-fluoro-3-isobutoxibenzaldehído 		197	2-fluoro-3-isobutoxibenzonitrilo Método 181 
174	3-(ciclohexilmetoxi)-2-fluorobenzaldehído 		237	3-(ciclohexilmetoxi)-2-fluorobenzonitrilo Método 182 
175	3-(ciclohexiloxi)-2-fluorobenzaldehído 		223	3-(ciclohexiloxi)-2-fluorobenzonitrilo Método 183 
176	2-fluoro-3-isopropoxibenzaldehído 		183	2-fluoro-3-isopropoxibenzonitrilo Método 184 
177	2-fluoro-3-(2,2,2-trifluoroetoxi)benzaldehído 		223	2-fluoro-3-(2,2,2-trifluoroetoxi)benzonitrilo Método 200 

178	2-fluoro-3-(2-metoxietoxi)benzaldehído 	10,32 (s, 1 H) 7,56-7,35 (m, 2 H) 7,13-6,96 (m, 1 H) 4,33-4,22 (m, 2 H) 3,84-3,77 (m, 2 H) 3,42 (s, 3 H)	199	2-fluoro-3-(2-metoxietoxi)benzonitrilo Método 185 
179	3-(ciclopentiloxi)-2-fluorobenzaldehído 		195	3-(ciclopentiloxi)-2-fluorobenzonitrilo Método 187 
180	3-ciclobutoxi-2-fluorobenzaldehído 	10,31 (s, 1 H) 7,41-7,36 (m, 2 H) 7,05-7,03 (m, 1 H) 4,94-4,85 (m, 1 H) 2,01-1,83 (m, 8 H)	209	3-ciclobutoxi-2-fluorobenzonitrilo Método 186 

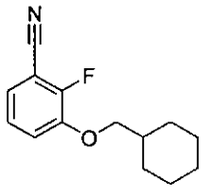
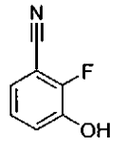
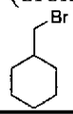
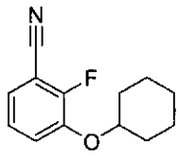
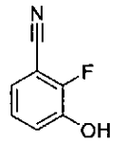
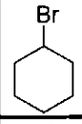
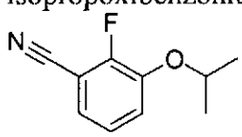
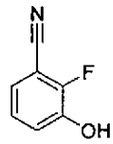
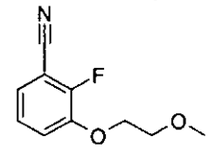
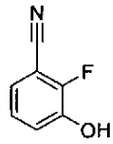
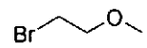
Método 181



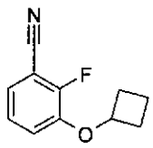
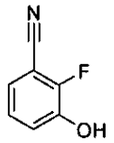
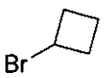
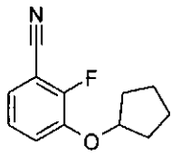
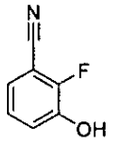
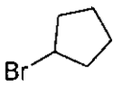
Un matraz de fondo redondo de 100 mL se cargó con una barra de agitación magnética, 2-fluoro-3-hidroxibenzonitrilo (0,500 g, 3,65 mmol), MeCN (13,89 ml), 1-bromo-2-metilpropano (0,699 ml, 7,29 mmol) y K_2CO_3 (1,008 g, 7,29 mmol). La mezcla luego se colocó en un baño de aceite y se calentó hasta alcanzar 60°C con agitación durante toda la noche. Esta mezcla luego se enfrió hasta alcanzar la TA, se filtró a través de un lecho de Celite y se concentró al vacío. El material bruto se purificó mediante cromatografía en gel de sílice (40 g) utilizando acetato de etilo/hexanos (1:4) como eluyente para proporcionar 2-fluoro-3-isobutoxibenzonitrilo puro (0,610 g, 87 %) como un aceite incoloro. *M/z* 194.

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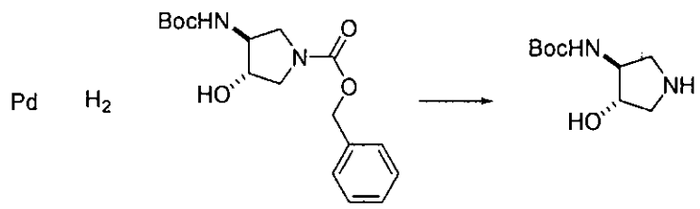
Los siguientes intermediarios se prepararon mediante el procedimiento del Método 181, utilizando los materiales de partida apropiados.

182	3-(ciclohexilmetoxi)-2-fluorobenzonitrilo 		234	2-fluoro-3-hidroxibenzonitrilo  y (bromometil)ciclohexano 
183	3-(ciclohexiloxi)-2-fluorobenzonitrilo 		220	2-fluoro-3-hidroxibenzonitrilo  y Bromociclohexano 
184	2-fluoro-3-isopropoxibenzonitrilo 		179	2-fluoro-3-hidroxibenzonitrilo  y 2-yodopropano 
185	2-fluoro-3-(2-metoxietoxi)benzonitrilo 		196	2-fluoro-3-hidroxibenzonitrilo  y 1-bromo-2-metoxietano 

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186	3-ciclobutoxi-2-fluorobenzonitrilo 		192	2-fluoro-3-hidroxibenzonitrilo  y bromociclobutano 
187	3-(ciclopentiloxi)-2-fluorobenzonitrilo 			2-fluoro-3-hidroxibenzonitrilo  y bromociclopentano 

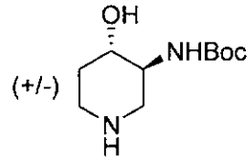
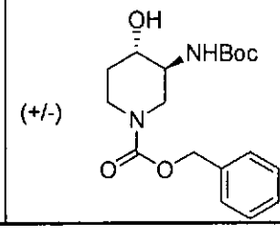
Método 188



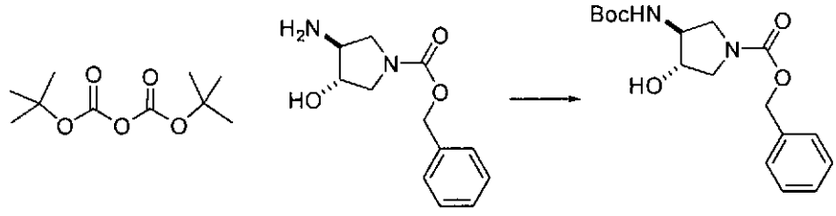
(±)-*terc*-butil-4-hidroxipirrolidin-3-ilcarbamato

Una mezcla racémica de *trans*-bencil 3-(*terc*-butoxicarbonilamino)-4-hidroxipirrolidina-1-carboxilato (3,36 g, 9,99 mmol) (Método 190) en MeOH (40 mL) se desgasificó, luego se agregó 10 % p de Pd/C (3,19 g, 3,00 mmol). La mezcla desgasificada, se cargó con H_2 y se agitó durante toda la noche. La mezcla se filtró a través de un lecho de Celite, se lavó con metanol, el filtrado se secó sobre Na_2SO_4 anhidro, se filtró y se concentró al vacío para proporcionar un sólido blanco como terc-butil-4-hidroxipirrolidin-3-ilcarbamato racémico (2,020 g, 100 %). ^{1}H NMR (400 MHz, MeOD) δ ppm 4,13 (dt, 1 H), 3,89-3,75 (m, 1 H), 3,35 (brs, 1 H), 3,14 (dd, 1 H), 2,93-2,73 (m, 2 H), 1,46 (s, 10 H); *m/z* 203.

Los siguientes intermediarios se prepararon mediante el procedimiento del Método 188, utilizando los materiales de partida apropiados.

Método	Compuesto	^{1}H NMR	m/z	MP
189	(±)-*terc*-butil-4-hidroxipiperidin-3-ilcarbamato 		216	(±)-bencil 3-(*terc*-butoxicarbonilamino)-4-hidroxipiperidina-1-carboxilato Método 191 

Método 190

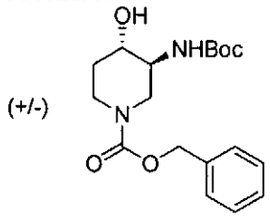
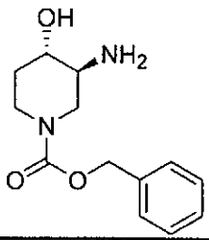
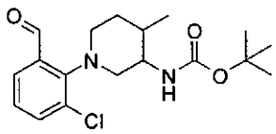
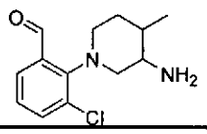


(±)-bencil 3-(*terc*-butoxicarbonilamino)-4-hidroxipirrolidina-1-carboxilato

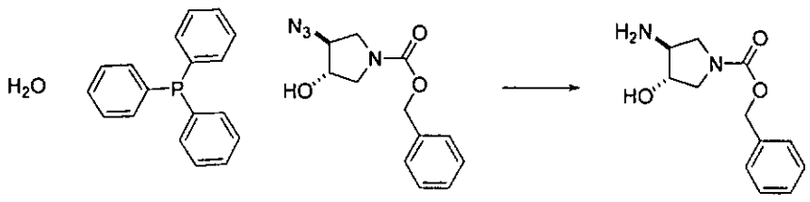
A una mezcla de *trans*-bencil 3-amino-4-hidroxipirrolidina-1-carboxilato racémico (2,67 g, 11,30 mmol) (Método 193) y di-*terc*-butil dicarbonato (3,70 g, 16,95 mmol) en CH_2Cl_2 (50 mL) se agregó Et_3N (4,73 mL, 33,90 mmol) a 0°C. La mezcla luego se agitó a TA durante 48 h. La mezcla de reacción luego se concentró al vacío para proporcionar un residuo que se purificó mediante cromatografía en gel de sílice (40% a 90% de acetato de etilo/hexano) para proporcionar un sólido blanco como (±)-bencil 3-(*terc*-butoxicarbonilamino)-4-hidroxipirrolidina-1-carboxilato (3,36 g, 88 %). ^{1}H NMR (400 MHz, Diclorometano-d2) δ ppm 7,48-7,32 (m, 5 H), 5,21-5,00 (m, 2 H), 4,78 (brs, 1 H), 4,29-4,18 (m, 1 H), 3,84 (dd, 1 H), 3,74 (d, 1 H), 3,41-3,12 (m, 2 H), 1,49-1,33 (m, 9 H); *m/z* 337

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Los siguientes materiales de partida se prepararon mediante el procedimiento del Método 190 utilizando los materiales de partida apropiados.

Método	Compuesto	^{1}H NMR	m/z	MP
191	(±)-bencil 3-(*terc*-butoxicarbonilamino)-4-hidroxipiperidina-1-carboxilato 		350	(±)-bencil 3-amino-4-hidroxipiperidina-1-carboxilato Método 194 
192	*terc*-butil 1-(2-cloro-6-formilfenil)-4-metilpiperidin-3-ilcarbamato 		352	2-(3-amino-4-metilpiperidin-1-il)-3-clorobenzaldehído Método 199 

Método 193

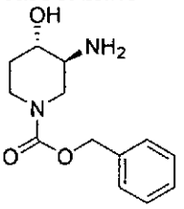
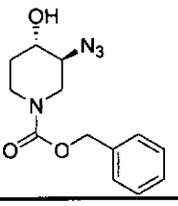


(±)-bencil 3-amino-4-hidroxipirrolidina-1-carboxilato:

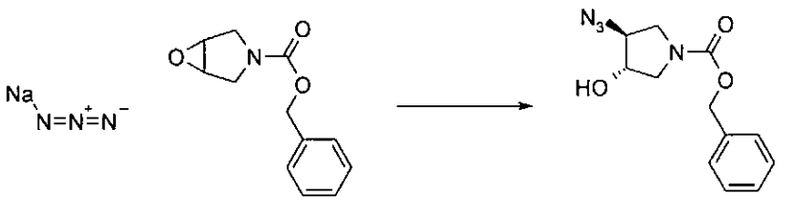
Una mezcla de *trans*-bencil 3-azido-4-hidroxipirrolidina-1-carboxilato racémico (2,96 g, 11,29 mmol) (Método 195) y trifenilfosfina (3,11 g, 11,85 mmol) en THF (25 mL) se agitó a TA durante 7 h. Luego se agregó agua (2 mL, 111 mmol) y la mezcla luego se agitó a 50°C durante toda la noche. La mezcla luego se concentró a presión reducida y el residuo se purificó mediante cromatografía en gel de sílice (100% DCM a 37:3:60/metanol:Et_3N:DCM) para proporcionar el compuesto del título (2,96 g, 11,29

mmol) como un aceite. ^{1}H NMR (400 MHz, diclorometano-d2) δ ppm 7,38-7,19 (m, 5 H), 5,02 (s, 2 H), 3,89 (brs, 1 H), 3,62 (dd, 2 H), 3,29-3,15 (m, 2 H), 3,12-3,01 (m, 1 H); *m/z* 236.

Los siguientes materiales de partida se prepararon mediante el procedimiento del Método 193 utilizando los materiales de partida apropiados.

Método	Compuesto	^{1}H NMR	m/z	MP
194	(±)-bencil 3-amino-4-hidroxipiperidina-1-carboxilato 		250	(±)-bencil 3-azido-4-hidroxipiperidina-1-carboxilato Método 196 

Método 195



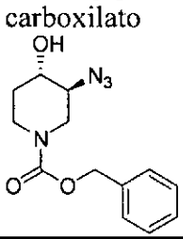
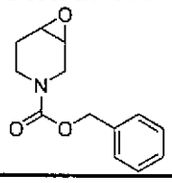
(±)-bencil 3-azido-4-hidroxipirrolidina-1-carboxilato

A una mezcla agitada de bencil 6-oxa-3-azabiciclo[3,1,0]hexano-3-carboxilato (5,2 g, 23,72 mmol) (Método 197) en DMF (30 mL) se agregó azida de sodio (2,313 g, 35,58 mmol) en una mezcla de acetona (20,00 mL) y agua (10,00 mL). La mezcla resultante se agitó a 80°C durante 24 h. La mezcla luego se diluyó con agua y éter, se separó y la capa orgánica se lavó con salmuera, se secó y se concentró al vacío. El material resultante se purificó mediante cromatografía en gel de sílice (eluyó con 15% a 35% de acetato de etilo/hexano), proporcionando el compuesto del título como un sólido amarillo (4,10 g, 65,9 %). ^{1}H NMR (400 MHz, diclorometano-d2) δ ppm 7,50-7,25 (m, 5 H), 5,43-5,25

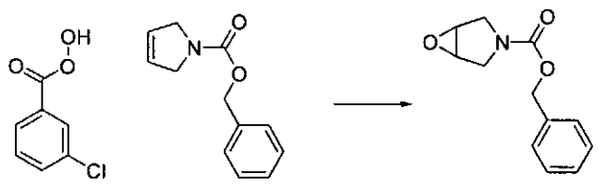
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(m, 2 H), 4,31 (brs, 1 H), 4,00 (brs, 1 H), 3,77 (dd, 1 H), 3,69 (dd, 1 H), 3,53 (d, 1 H), 3,44 (dd, 1 H), 2,17 (brs, 1 H); *m/z* 263.

Los siguientes materiales de partida se prepararon mediante el procedimiento del Método 195 utilizando los materiales de partida apropiados.

Método	Compuesto	^{1}H NMR	m/z	MP
196	(±)-bencil 3-azido-4-hidroxipiperidina-1-carboxilato 		276	bencil 7-oxa-3-azabiciclo[4,1,0]heptano-3-carboxilato Método 198 

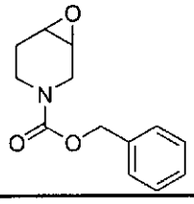
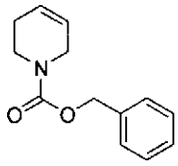
Método 197



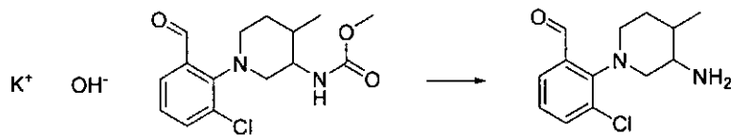
Bencil 6-oxa-3-azabiciclo[3,1,0]hexano-3-carboxilato

A una mezcla agitada de bencil 2,5-dihidro-1H-pirrol-1-carboxilato (5 g, 24,60 mmol) en DCM (80 mL) se agregó ácido 3-clorobenzoperoxoico (6,89 g, 30,75 mmol) a 0°C. La mezcla luego se agitó a TA durante toda la noche. La mezcla de reacción luego se filtró a través de un lecho de Celite y el filtrado se lavó con Na_2CO_3 saturado acuoso y salmuera. Luego lo orgánico se separó y se secó sobre Na_2SO_4 anhidro, se filtró y se concentró al vacío para proporcionar el compuesto del título que se utilizó para la siguiente etapa sin purificación adicional.

Los siguientes materiales de partida se prepararon mediante el procedimiento del Método 197 utilizando los materiales de partida apropiados.

Método	Compuesto	^{1}H NMR	m/z	MP
198	bencil 7-oxa-3-azabiciclo[4,1,0]heptano-3-carboxilato 		217	Bencil 5,6-dihidropiridina-1(2H)-carboxilato 

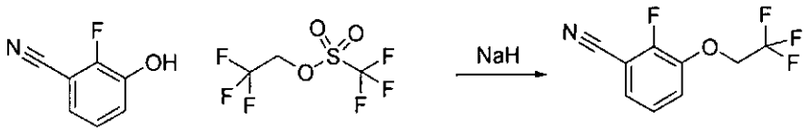
Método 199:



2-(3-amino-4-metilpiperidin-1-il)-3-clorobenzaldehído

A una solución agitada de metil 1-(2-cloro-6-formilfenil)-4-metilpiperidin-3-ilcarbamato (220 mg, 0,71 mmol) (Método 119) en MeOH (3 ml) se agregó 40 % de solución acuosa de KOH (10ml) por goteo y la mezcla resultante se calentó a reflujo durante 16 h. La mezcla se dejó enfriar hasta alcanzar la TA, se diluyó con agua y se extrajo con DCM. El extracto orgánico combinado se secó sobre Na_2SO_4 anhidro, se filtró y se concentró al vacío. El residuo resultante se purificó mediante cromatografía en gel de sílice (100 % de acetato de etilo a 10 % metanol en acetato de etilo) para proporcionar el compuesto del título como una goma amarilla clara (0,057 g, 31,9 %). ^{1}H NMR (400 MHz, CLOROFORMO-d) δ ppm 8,44 (s, 1 H), 7,40 (t, 2 H), 7,07 (t, 1 H), 4,29 (d, 1 H), 3,58 (ddd, 1 H), 3,38 (dd, 1 H), 3,11 (td, 1 H), 2,81 (d, 1 H), 2,20-1,91 (m, 1 H), 1,31-1,14 (m, 1 H), 1,08 (d, 3 H), 0,63-0,37 (m,1 H).

Método 200



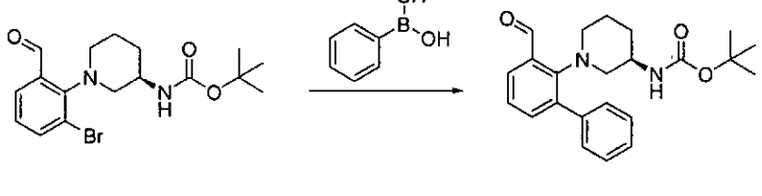
2-fluoro-3-(2,2,2-trifluoroetoxi)benzonitrilo:

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Una solución agitada de 2-fluoro-3-hidroxibenzonitrilo (800 mg, 5,83 mmol) en DMF (10 mL) a 0°C se trató en porciones con NaH (280 mg, 7,00 mmol) (dispersión al 60% en aceite). La mezcla de reacción luego se agitó durante 0,5 h y se agregó 2,2,2-trifluoroetil trifluorometanosulfonato (1490 mg, 6,42 mmol). La reacción se dejó entibiar hasta alcanzar la TA durante toda la noche con agitación. La mezcla de reacción luego se trató con agua (40 mL) y salmuera (5 mL) y se extrajo con acetato de etilo (~ 50 mL). El extracto orgánico se lavó con agua, se secó sobre Na_2SO_4 anhidro, se filtró y se concentró al vacío para proporcionar un residuo que se purificó mediante cromatografía en gel de sílice (10 % a 30 % de acetato de etilo/hexanos) para proporcionar el compuesto del título como un sólido blanco (1040 mg, 81 %). ^{1}H NMR (400 MHz, MeOD) δ ppm 7,56 (td, 1 H), 7,47-7,38 (m, 1 H), 7,38-7,24 (m, 1 H), 4,73 (q, 2 H); *m/z* 220.

Método 201:

(*R*)-*terc*-butil 1-(3-formilbifenil-2-il)piperidin-3-ilcarbamato:



Una mezcla de (*R*)-*terc*-butil 1-(2-bromo-6-formilfenil)piperidin-3-il carbamato (Método 95) (300 mg, 0,78 mmol), ácido fenilborónico (143 mg, 1,17 mmol), complejo de 1,1'-bis(di-*terc*-butilfosfino)ferrocenodicloro paladio (II) (40,8 mg, 0,06 mmol) y Na_2CO_3 (124 mg, 1,17 mmol) se suspendió en dioxano (5 mL) y agua (1,50 mL) y se agitó a 110°C durante toda la noche bajo una atmósfera de nitrógeno. La reacción se enfrió hasta alcanzar la TA y se agregó agua (~ 50 mL) y acetato de etilo (~ 50 mL) a la mezcla. La fase orgánica se separó, se secó sobre $MgSO_4$ anhidro, se filtró y se concentró al vacío para proporcionar un residuo purificado mediante cromatografía en gel de sílice (40 g) utilizando un gradiente de 5% a 30% de acetato de etilo/hexanos para proporcionar el compuesto del título como un sólido de bajo punto de fusión (168 mg, 56,4 %); *m/z* 381.

Pueden purificarse los ejemplos proporcionados anteriormente mediante HPLC de

fase inversa en un disolvente que contenga distintas concentraciones de ácido trifluoroacético o ácido clorhídrico. De este modo, los ejemplos precedentes pueden aislarse como la base libre, sal clorhidrato o sal trifluoroacetato.

Descripción de ensayos de enzima PIM 1 y 2:

Ensayo de cambio de movilidad de PIM1 in vitro

Puede determinarse la actividad de la enzima His-PIM1 [2-313] humana purificada in vitro utilizando un ensayo de cambio de movilidad en un lector Caliper LC3000 (Caliper, MA), que mide la fluorescencia de un FL-Ahx-Bad (FITC-(AHX)RSRHSSYPAGT-COOH, Primm 200606-00289, Primm Biotech, MA) fosforilado y no fosforilado y calcula un valor radiométrico para determinar el recambio porcentual. Puede expresarse PIM1 (Universidad de Dundee, Escocia) en un sistema de baculovirus con un rendimiento típico de >85% de pureza.

Se determina la fosforilación del FL-Ahx-Bad en presencia o ausencia del compuesto de interés. Se preincuban 5ul de mezcla de enzima/sustrato/adenosina trifosfato (ATP) que consiste en PIM1 2,4nM, FL-Ahx-Bad 3,6uM y ATP 240uM en 1,2x solución amortiguadora con 2ul de compuesto durante 20 minutos a 25°C. Se inician las reacciones con 5ul de mezcla metálica que consiste en $MgCl_2$ 24mM en solución amortiguadora 1,2x y se incuba a 25°C durante 90 minutos y las reacciones se detienen mediante la adición de mezcla de detención que consiste en HEPES 100mM, ácido etilendiaminotetraacético 121mM, 0,8% de reactivo Coatin Reagent 3 (Caliper, MA) y 0,01% de Tween. Se detecta el sustrato fosforilado y no fosforilado con un lector Caliper LC3000 (Caliper, MA) en presencia de solución amortiguadora de separación que consiste en HEPES 100mM, ácido etilendiaminotetraacético 16mM, 0,1% de reactivo Coatin Reagent 3 (Caliper, MA), 0,015% de Brij-35, 5% de DMSO y $MgCl_2$ 5,6mM. Pueden utilizarse las siguientes condiciones de separación para un Caliper LC3000: -1,0 PSI, -2000 V voltaje corriente arriba, -400 V voltaje corriente abajo, 0,2 segundos de absorción de muestra, 45 segundos post absorción, 10% de fuerza láser.

Ensayo de cambio de movilidad de PIM2 in vitro

Puede determinarse la actividad de la enzima His-PIM2 [23-299] humana purificada in vitro utilizando un ensayo de cambio de movilidad en un lector Caliper LC3000 (Caliper, MA), que mide la fluorescencia de un FL-Ahx-Bad (FITC-(AHX)RSRHSSYPAGT-COOH, Primm 200606-00289, Primm Biotech, MA) fosforilado y no fosforilado y calcula un valor radiométrico para determinar el recambio porcentual. Puede expresarse PIM2 (producida en AstraZeneca, R&D Boston) en células de *E. coli* con un rendimiento típico de >90% de pureza.

Se determina la fosforilación del FL-Ahx-Bad en presencia o ausencia del compuesto de interés. Se preincuban 5uL de mezcla de enzima/sustrato/adenosina trifosfato (ATP) que consiste en PIM1 2,4nM, FL-Ahx-Bad 3,6uM y ATP 12uM en solución amortiguadora 1,2x con 2ul de compuesto durante 20 minutos a 25°C. Se inician las reacciones con 5uL de mezcla metálica que consiste en $MgCl_2$ 24mM en solución amortiguadora 1,2x y se incuba a 25°C durante 90 minutos. Se detienen las reacciones mediante la adición de 5uL de mezcla de detección que consiste en HEPES 100mM, ácido etilendiaminotetraacético 121mM, 0,8% de reactivo Coatin Reagent 3 (Caliper, MA) y 0,01% de Tween. Se detecta el sustrato fosforilado y no fosforilado con un lector Caliper LC3000 (Caliper, MA) en presencia de solución amortiguadora de separación que consiste en HEPES 100mM, ácido etilendiaminotetraacético 16mM, 0,1% de reactivo Coatin Reagent 3 (Caliper, MA), 0,015% de Brij-35, 5% de DMSO y $MgCl_2$ 5,6mM. Pueden utilizarse las siguientes condiciones de separación para un Caliper LC3000: -1,0 PSI, -2000 V voltaje corriente arriba, -400 V voltaje corriente abajo, 0,2 segundos de absorción de muestra, 45 segundos post absorción, 10% de fuerza láser.

Utilizando los ensayos descritos anteriormente, o modificaciones adecuadas de los mismos, los compuestos preferidos descritos en la presente generalmente tienen un valor de CI_{50} para PIM1 menor que 5 micromolar (uM) y, aun más preferido, menor que 1 micromolar. La tabla 1 que figura a continuación proporciona la inhibición porcentual de PIM1 a 0,3 micromolar para los ejemplos proporcionados en la presente. Varios ejemplos se evaluaron más de una vez. Las variaciones en los resultados experimentales, los valores negativos o los valores con más de 100% de inhibición se deben presumiblemente a errores experimentales inherentes al ensayo.

Tabla 1.

Número de Ejemplo	%I PIM1 a 0,3 uM	%I PIM2 a 0,3 uM
1	>95	77,7
2	>95	>95
3	>95	58,0
4	>95	79,6
5A	>95	79,9
5B	>95	>95
6	79,4	9,5
7	5,4	<5
8	16,3	<5
9	6,9	<5
10	>95	50,1
11	89,4	17,9
12	80,2	<5
13	<5	<5
14	>95	69,9
15	12,9	<5
16	13,9	<5
17	29,8	<5
18	<5	<5
19	>95	38,3

20	86,5	19,1
21	82,9	15,8
22	81,9	8,5
23	87,6	19,7
24	>95	44,3
25	>95	68,4
26	>95	49,6
27	90,8	25,1
28	90,0	27,4
29	92,8	
30	90,8	15,6
31	92,8	23,3
32	94,0	31,9
33	>95	>95
34	>95	39,3
35	<5	<5
36	>95	>95
37	89,7	69,4
38	>95	92,9
39	89,4	57,3
40	>95	89,8
41	74,0	25,1

42	58,8	23,3
43	55,4	14,7
44	83,8	46,7
45	40,1	14,3
46	13,4	15,7
47	50,0	26,3
48	84,4	41,3
49	>95	86,3
50	93,7	45,4
51	85,5	80,6
52	>95	93,5
53	92,3	82,1
54	88,1	73,1
55	11,0	<5
56	90,7	33,5
57	53,3	42,6
58	16,0	7,1
59	<5	6,6
60	35,4	11,3
61	81,8	28,1
62	62,1	17,5
63	79,2	21,5

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64	86,5	25,7
65	45,3	18,9
66	50,3	20,9
67		<5
68	41,9	9,0
69	<5	16,3
70	<5	<5
71	<5	<5
72	<5	<5
73	<5	<5
74		
75	>95	69,5
76	59,6	27,6
77	51,2	22,7
78	71,4	30,0
79	90,0	60,7
80	<5	
81	<5	
82	87,4	58,2
83	34,0	
84A	92,9	54,3
84B		

84C	47,8	29,6
84D	27,8	<5
84E	11,7	6,1
84F	87,4	52,4
84G	92,0	63,0
84H	>95	67,0
84I	>95	82,7
84J	93,3	40,4
84K	>95	90,8
84L	>95	55,2
84M	>95	80,9
84N	92,8	81,4
84O	<5	<5
85	>95	82,4
86	>95	>95
87	>95	84,2
88	>95	88,4
89	48,4	21,5
90	78,2	86,3
91	6,6	16,4
92	>95	81,5
93	>95	66,3

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94	>95	>95
95	>95	>95
96	>95	>95
97	>95	86,4
98	>95	81,4
99	>95	>95
100	93,0	93,9
101	>95	>95
102	93,3	91,9
103	>95	88,7
104	>95	92,4
105	>95	92,4
106	>95	92,8
107	>95	>95
108	>95	>95
109	64,2	65,8
110	90,9	90,7
111	>95	>95
112	>95	>95
113	>95	>95
114	>95	>95
115	93,3	76,1

116	>95	>95
117	>95	>95
118	>95	>95
119	56,2	20,1
120	58,9	22,2
121	>95	87,4
122A	88,2	55,0
122B	>95	92,3
122C	>95	>95
122D	>95	>95
122E	>95	>95
122F	>95	>95
122G	>95	92,1
122H	>95	>95
122I	>95	>95
122J	>95	>95
122K	>95	>95
122L	>95	>95
122M	>95	>95
122N	>95	>95
1220	>95	>95
122P	>95	>95

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122Q	>95	>95
122R	>95	89,6
122S	>95	>95
122T	>95	>95
122U	>95	>95
122V	>95	>95
122W	>95	>95
122X	>95	67,1
122Y	>95	>95
122Z	>95	>95
122AA	>95	>95
122AB	>95	>95
122AC	>95	>95
122AD	>95	>95
122AE	>95	>95
122AF	83,9	87,9
122AG	68,9	86,7
122AH	19,0	14,0
122AI	>95	>95
123	>95	>95
124	>95	>95
125	>95	>95

126	>95	>95
127	>95	>95
128	81,2	49,0
129A	>95	>95
129B	>95	>95
129C	85,0	52,1
130	66,2	45,5
131A	27,1	<5
131B	<5	<5
132	93,0	88,1
133	>95	93,4
134	>95	85,2
135	42,5	10,8
136	82,8	44,6
137	55,1	18,6
138	87,9	63,2
139	58,1	15,1
140	73,3	52,0
141	34,9	<5
142	86,1	75,2
143	85,9	49,8
144	63,2	21,2

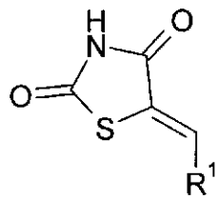
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145	>95	80,1
146	88,9	48,5
147	74,3	36,4
148	91,5	60,8
149	>95	75,4
150	79,8	31,7
151	31,5	13,5
152	10,8	16,7

REIVINDICACIONES

1. Un método para tratar o prevenir cáncer que comprende

a) proporcionar una composición farmacéutica que comprende un compuesto de fórmula I,



fórmula I,

o sales del mismo, que funciona para inhibir una quinasa PIM, en donde

R^1 se selecciona de un carbociclilo, arilo y heterociclilo, en donde R^1 opcionalmente se sustituye por uno o más R^2, iguales o diferentes;

R^2 se selecciona de halógeno, alquiloC_{1-6}, alquiloC_{1-6} halogenado, amino, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino y heterociclilo, en donde R^2 opcionalmente se sustituye por uno o más R^3, iguales o diferentes;

R^3 se selecciona de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, carbociclilo, arilo y heterociclilo, en donde R^3 opcionalmente se sustituye por uno o más R^4, iguales o diferentes;

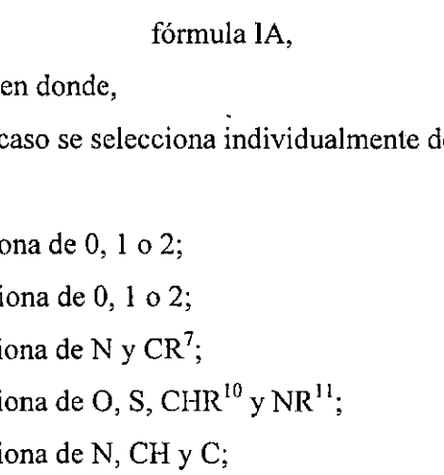
R^4 se selecciona de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, carbociclilo, arilo y heterociclilo, en donde R^4 opcionalmente se sustituye por uno o más R^5, iguales o diferentes; y

R^5 se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-

metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo; y

b) administrar dicha composición farmacéutica a un sujeto al que se le ha diagnosticado, que exhibe síntomas o que corre el riesgo de padecer cáncer.

2. Un compuesto de fórmula IA,



fórmula IA,

o sales del mismo, en donde,

--- en cada caso se selecciona individualmente de un enlace simple y doble;

n se selecciona de 0, 1 o 2;

m se selecciona de 0, 1 o 2;

A se selecciona de N y CR^7;

X se selecciona de O, S, CHR^{10} y NR^{11};

Y se selecciona de N, CH y C;

R^5, R^6 y R^7 se seleccionan cada uno individualmente e independientemente de hidrógeno, alquiloC_{1-6}, halógeno, ciano, nitro, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, carbociclilo, arilo y heterociclilo, en donde R^5, R^6 y R^7 opcionalmente se sustituyen cada uno por uno o más R^{12} iguales o diferentes;

R^8 y R^9 se seleccionan cada uno individualmente e independientemente de hidrógeno, amino, hidroxilo, mercapto, alquiloC_{1-6}, alquilC_{1-6}amino, carbociclilo, arilo y heterociclilo en donde R^8 y R^9 opcionalmente se sustituyen cada uno por uno o más R^{15}, iguales o diferentes;

R^{10} se selecciona de hidrógeno, alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{10} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{11} se selecciona de hidrógeno, formilo, alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, alcoxiC_{1-6}carbonilo, carbociclilo, arilo y heterociclilo, en donde R^{11} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{12} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{12} opcionalmente se sustituye por uno o más R^{16}, iguales o diferentes;

R^{15} se selecciona de alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo y alcoxiC_{1-6}carbonilo en donde R^{15} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

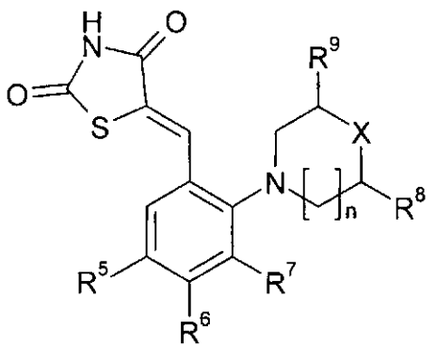
R^{16} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, aminometilo, aminoetilo, aminopropilo, aminobutilo, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-

dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo y *N*-metil-*N*-etilsulfamoilo; y

siempre que R^5, R^6 y R^7 no sean todos hidrógeno y

siempre que el compuesto no sea 5-((5-nitro-2-(1-piperidinil)fenil)metileno)-2,4-tiazolidinadiona o 5-((2-(4-morfolinil)-5-nitrofenil)metileno)-2,4-tiazolidinadiona.

3. Un compuesto de fórmula IB,



fórmula IB,

o sales del mismo, en donde,

n se selecciona de 0, 1 o 2;

X se selecciona de O, CHR^{10} y NR^{11};

R^5, R^6 y R^7 se seleccionan cada uno individualmente e independientemente de hidrógeno, halógeno, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo y *N*-metil-*N*-etilsulfamoilo;

R^8 y R^9 se seleccionan cada uno individualmente e independientemente de hidrógeno, amino, alquiloC_{1-6}, alquilC_{1-6}amino, en donde R^8 y R^9 opcionalmente se sustituyen cada uno por uno o más R^{15}, iguales o diferentes;

R^{10} se selecciona de hidrógeno, alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{10} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{11} se selecciona de hidrógeno, alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo, alcoxiC_{1-6}carbonilo, carbociclilo, arilo y heterociclilo, en donde R^{11} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{12} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{12} opcionalmente se sustituye por uno o más R^{16}, iguales o diferentes;

R^{15} se selecciona de alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo y alcoxiC_{1-6}carbonilo en donde R^{15} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{16} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo,

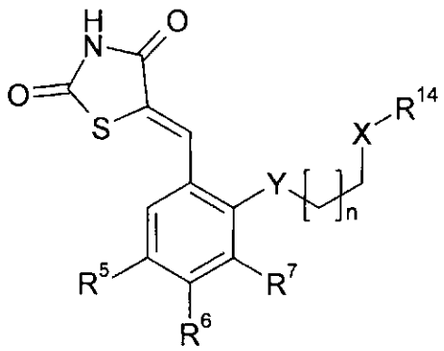
metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo y *N*-metil-*N*-etilsulfamoilo; y

siempre que dicho compuesto no sea,

5-[[2-(4-metil-1-piperazinil)fenil]metileno]-2,4-tiazolidinadiona o

5-[[2-[(2,6-dicloro-3-metilfenil)amino]fenil]metileno]-2,4-tiazolidinadiona.

4. Un compuesto de fórmula IC,



fórmula IC,

o sales del mismo, en donde,

n se selecciona de 0, 1, 2, 3, 4, 5, 6, 7 o 8;

X se selecciona de O, S, CHR^{10} y NR^{11};

Y se selecciona de O, S y NR^{13};

R^5, R^6 y R^7 se seleccionan cada uno individualmente e independientemente de alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, dialquilC_{1-6}amino, carbociclilo, arilo y heterociclilo, en donde R^5, R^6 y R^7 opcionalmente se sustituyen cada uno por uno o más R^{12} iguales o diferentes;

R^{10} se selecciona de hidrógeno, alquiloC_{1-6}, halógeno, nitro, ciano, hidroxi, amino, mercapto, formilo, carboxi, carbamoilo, alcoxiC_{1-6}, alquilC_{1-6}tio, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, alquilC_{1-6}sulfamoilo, arilsulfamoilo, carbociclilo, arilo y heterociclilo, en donde R^{10} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

R^{11}, R^{13} y R^{14} se seleccionan cada uno individualmente e independientemente de hidrógeno, alquiloC_{1-6}, alcanoiloC_{1-6}, alquilC_{1-6}sulfinilo, alquilC_{1-6}sulfonilo, arilsulfonilo y alcoxiC_{1-6}carbonilo en donde R^{11} opcionalmente se sustituye por uno o más R^{12} iguales o diferentes;

o R^{11} y R^{14}, tomados junto con los átomos a los que están unidos forman un anillo heterocíclico de cinco, seis o siete miembros opcionalmente sustituido por uno o más R^{12} iguales o diferentes;

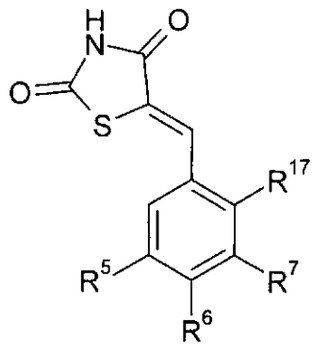
R^{12} se selecciona de halógeno, nitro, ciano, hidroxi, trifluorometoxi, trifluorometilo, amino, formilo, carboxi, carbamoilo, mercapto, sulfamoilo, metilo, etilo, metoxi, etoxi, acetilo, acetoxi, metilamino, etilamino, dimetilamino, dietilamino, *N*-metil-*N*-etilamino, acetilamino, *N*-metilcarbamoilo, *N*-etilcarbamoilo, *N,N*-dimetilcarbamoilo, *N,N*-dietilcarbamoilo, *N*-metil-*N*-etilcarbamoilo, metiltio, etiltio, metilsulfinilo, etilsulfinilo, mesilo, etilsulfonilo, metoxicarbonilo, etoxicarbonilo, *N*-metilsulfamoilo, *N*-etilsulfamoilo, *N,N*-dimetilsulfamoilo, *N,N*-dietilsulfamoilo, *N*-metil-*N*-etilsulfamoilo, carbociclilo, arilo y heterociclilo.

5. Un compuesto de fórmula IC tal como se define en la Reivindicación 4, o sales del mismo, en donde Y es NR^{13}.

6. Un compuesto de fórmula IA, IB o IC, tal como se define en las Reivindicaciones 2-4, o sales del mismo, en donde R^5 es un alquiloC_{1-6} halogenado.

7. Un compuesto de fórmula IA, IB o IC, tal como se define en las Reivindicaciones 2-4, o sales del mismo, en donde R^7 es un halógeno.

8. Un compuesto de fórmula IX,



fórmula IX,

o sales del mismo, en donde

R^5 se selecciona de hidrógeno, alcoxiC_{1-6}, carbamoilo y alquiloC_{1-6} halogenado;

R^6 se selecciona de hidrógeno, halógeno, alcoxiC_{1-6} y 2-(1-piperidil)etoxi;

R^7 se selecciona de hidrógeno, halógeno y alcoxiC_{1-6};

R^{17} es un heterocarbociclilo, en donde R^{17} opcionalmente se sustituye por uno o más R^{18}, iguales o diferentes;

R^{18} se selecciona de halógeno, formilo, amino, alquiloC_{1-6}, alquilC_{1-6}amino, (alquilC_{1-6})$_2$amino, carbociclilo, arilo, heterociclilo, en donde R^{18} opcionalmente se sustituye por uno o más R^{19}, iguales o diferentes;

R^{19} se selecciona de amino, alquiloC_{1-6}, hidroxi, carbociclilo y heterociclilo en donde R^{19} opcionalmente se sustituye por uno o más R^{20}, iguales o diferentes; y

R^{20} se selecciona de amino, alquiloC_{1-6} y halógeno.

9. El compuesto de la Reivindicación 8, o sales del mismo, en donde, R^{17} se selecciona de (3R)-3-aminopirrolidin-1-ilo, (3R)-3-dimetilaminopirrolidin-1-ilo, (3S)-3-(3-aminopropilamino)pirrolidin-1-ilo, (3S)-3-(5-aminopentanoilamino)pirrolidin-1-ilo, (3S)-3-amino-1-piperidilo, (3S)-3-aminopirrolidin-1-ilo, (3S)-3-dimetilaminopirrolidin-1-ilo, (3S,5R)-3,5-dimetilpiperazin-1-ilo, 1,4-diazepan-1-ilo, 2-(1-piperidil)etoxi, 2-dietilaminoetoxi, 2-dimetilaminoetil-metil-amino, 2-hidroxietoxi, 2-morfolinoetoxi, 3-(2-aminoetilamino)pirrolidin-1-ilo, 3-(2-hidroxietilamino)pirrolidin-1-ilo, 3-(2-metilaminoetilamino)pirrolidin-1-ilo, 3-(3-aminopropanoilamino)pirrolidin-1-ilo, 3-(3-aminopropilamino)pirrolidin-1-ilo, 3-(3-metil-1,2,4-oxadiazol-5-il)-1-piperidilo, 3-(aminometil)-1-piperidilo, 3-(aminometil)pirrolidin-1-ilo, 3-acetamidopirrolidin-1-ilo, 3-

aminopirrolidin-1-ilo, 3-dimetilaminopropoxi, 3-dimetilaminopropil-metil-amino, 3-dimetilaminopirrolidin-1-ilo, 3-hidroxipirrolidin-1-ilo, 3-piridilo, 4-(1-metil-4-piperidil)piperazin-1-ilo, 4-(1-piperidil)-1-piperidilo, 4-(2-aminoetil)piperazin-1-ilo, 4-(2-hidroxietil)-1,4-diazepan-1-ilo, 4-(2-hidroxietil)-1-piperidilo, 4-(2-hidroxietil)piperazin-1-ilo, 4-(2-metilaminoetil)piperazin-1-ilo, 4-(2-morfolinoetil)piperazin-1-ilo, 4-(3-aminopropanoil)-1,4-diazepan-1-ilo, 4-(3-aminopropanoil)piperazin-1-ilo, 4-(3-aminopropil)piperazin-1-ilo, 4-(3-hidroxipropil)piperazin-1-ilo, 4-(3-metil-1,2,4-oxadiazol-5-il)-1-piperidilo, 4-(4-aminobutanoil)-1,4-diazepan-1-ilo, 4-(4-aminobutanoil)piperazin-1-ilo, 4-(4-cloro-2-fluoro-fenil)piperazin-1-ilo, 4-(4-fluorofenil)piperazin-1-ilo, 4-(4-piridilmetil)piperazin-1-ilo, 4-(5-aminopentanoil)-1,4-diazepan-1-ilo, 4-(5-aminopentanoil)piperazin-1-ilo, 4-(azetidina-3-carbonil)piperazin-1-ilo, 4-(benzo[1,3]dioxol-5-ilmetil)piperazin-1-ilo, 4-(ciclopropilmetil)piperazin-1-ilo, 4-(hidroximetil)-1-piperidilo, 4-(piperidina-3-carbonil)-1,4-diazepan-1-ilo, 4-(piperidina-3-carbonil)piperazin-1-ilo, 4-(piperidina-4-carbonil)piperazin-1-ilo, 4-[(2-clorofenil)metil]piperazin-1-ilo, 4-[3-(aminometil)benzoil]piperazin-1-ilo, 4-[4-(piperazin-1-ilmetil)benzoil]piperazin-1-ilo, 4-acetilpiperazin-1-ilo, 4-amino-1-piperidilo, 4-butil-1,4-diazepan-1-ilo, 4-ciclopentilpiperazin-1-ilo, 4-dimetilamino-1-piperidilo, 4-hidroxi-1-piperidilo, 4-isobutilpiperazin-1-ilo, 4-isopropilpiperazin-1-ilo, 4-metilpiperazin-1-ilo, 4-morfolino-1-piperidilo, 4-piridilo, 4-pirrolidin-1-il-1-piperidilo, 4-terc-butoxicarbonilpiperazin-1-ilo, 4-terc-butilpiperazin-1-ilo, morfolino, piperazin-1-ilo y pirrolidin-1-ilo.

10. Un compuesto que se selecciona de:

5-({2-[(3S)-3-aminopiperidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3R)-3-aminopiperidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[2-(4-aminopiperidin-1-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({2-[3-(aminometil)piperidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(1,4-diazepan-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-ciclopentilpiperazin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(4-fluorofenil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[4-(1,3-benzodioxol-5-ilmetil)piperazin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(3-metil-1,2,4-oxadiazol-5-il)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-pirrolidin-1-ilpiperidin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(1-metiletil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-metilpropil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-hidroxietil)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(4-cloro-2-fluorofenil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[3-(3-metil-1,2,4-oxadiazol-5-il)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(piridin-4-ilmetil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-clorobencil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(1-metilpiperidin-4-il)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

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5-({3-cloro-2-[4-(2-morfolin-4-iletil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(ciclopropilmetil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-morfolin-4-ilpiperidin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(3-hidroxipropil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(dimetilamino)piperidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-{[3-(dimetilamino)propil](metil)amino}-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-hidroxietil)-1,4-diazepan-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[2-(4-butil-1,4-diazepan-1-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-cloro-2-[4-(2-hidroxietil)piperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-morfolin-4-il-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[2-(4-terc-butilpiperazin-1-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[2-(1,4'-bipiperidin-1'-il)-3-cloro-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-{[3-cloro-2-(4-metilpiperazin-1-il)-5-(trifluorometil)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

5-({3-bromo-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3R,5S)-3,5-dimetilpiperazin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-cloro-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({3-[3-(4-metilpiperazin-1-il)propoxi]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

2-{3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenoxi}acetamida;

(5Z)-5-{[3-(3-piperidin-1-ilpropoxi)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

(5Z)-5-({3-[(4-metilpiperazin-1-il)metil]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

N-[2-(dimetilamino)etil]-2'-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]-N-metilbifenil-4-sulfonamida;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-metoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-(trifluorometil)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({5-cloro-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-4-metilfenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-fluorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-5-metilfenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({5-bromo-2-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-[(3S)-3-(dimetilamino)pirrolidin-1-il]-3-fluorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

5-({2-cloro-6-[(3S)-3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-(aminometil)pirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-(aminometil)pirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-metoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-bromofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-bromofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-etoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(2-metilpropoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclohexilmetoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclohexiloxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R,4R)-3-amino-4-hidroxipiperidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-{[3-cloro-2-(1,4-diazepan-1-il)fenil]metilideno}-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(1-metiletoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-(1-metiletoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-etoxifenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-{[4-(aminometil)bencil]amino}piperidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({3-cloro-2-[(3R)-3-{[2-(metilamino)etil]amino}piperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S,4S)-3-amino-4-hidroxipirrolidin-1-il]-3-clorofenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({3-cloro-2-[4-metil-3-(metilamino)piperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-{[2-(3-amino-4-metilpiperidin-1-il)-3-clorofenil]metilideno}-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(2,2,2-trifluoroetoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-(2,2,2-trifluoroetoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(2-metoxietoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3S)-3-aminopirrolidin-1-il]-3-(2-metoxietoxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclopentiloxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]-3-(ciclobutiloxi)fenil}metilideno)-1,3-tiazolidina-2,4-diona;

4-[(3R)-3-aminopiperidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzamida;

4-[(3S)-3-aminopiperidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzamida;

ácido 4-[(3R)-3-aminopiperidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzoico;

ácido 4-[(3S)-3-aminopirrolidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]benzoico;

(5Z)-5-({2-[(3R)-3-aminopiperidin-1-il]bifenil-3-il}metilideno)-1,3-tiazolidina-2,4-diona;

5-{[2-(3-aminopropoxi)-5-metoxifenil]metilideno}-1,3-tiazolidina-2,4-diona;

N-{4-[3-(dimetilamino)pirrolidin-1-il]-3-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}acetamida;

(5Z)-5-[(3-cloro-2-{(3R)-3-[(2-hidroxietil)amino]piperidin-1-il}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

(5Z)-5-[(3-cloro-2-{(3R)-3-[(3-hidroxipropil)amino]piperidin-1-il}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-1-metil-1H-imidazol-2-carboxamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-metoxiacetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-1-metil-1H-pirazol-3-carboxamida;

N^2-carbamoil-N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]glicinamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-piridin-3-ilacetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-piridin-4-ilacetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-1-metil-1H-pirazol-4-carboxamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-(1-oxidotiomorfolin-4-il)acetamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-4-sulfamoilbutanamida;

N'-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-N,N-dimetilbutanodiamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-N~2~,N~2~-dimetilglicinamida;

N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]-2-cianoacetamida;

N^2-acetil-N-[(3S)-1-{2-cloro-6-[(Z)-(2,4-dioxo-1,3-tiazolidin-5-ilideno)metil]fenil}pirrolidin-3-il]glicinamida;

(5Z)-5-({3-cloro-2-[(3R)-3-(dipropilamino)piperidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona;

(5Z)-5-[(3-cloro-2-{(3R)-3-[(3,3,3-trifluoropropil)amino]piperidin-1-il}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

5-[(5-metoxi-2-{3-[(1-metiletil)amino]propoxi}fenil)metilideno]-1,3-tiazolidina-2,4-diona;

(5Z)-5-({5-amino-2-[3-(dimetilamino)pirrolidin-1-il]fenil}metilideno)-1,3-tiazolidina-2,4-diona; y

5-[(2-amino-4,5-dimetoxifenil)metilideno]-1,3-tiazolidina-2,4-diona,

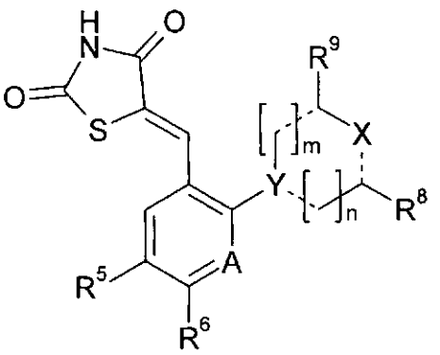
o sales del mismo.

11. Una composición farmacéutica que comprende un compuesto de fórmula I, IA, IB, IC o IX, tal como se define en las Reivindicaciones 1-10, o una sal farmacéuticamente aceptable del mismo.

12. Un método para inhibir una quinasa PIM que comprende proporcionar un compuesto de fórmula I, IA, IB, IC o IX, tal como se define en las Reivindicaciones 1-10, que comprende mezclar una quinasa PIM y dicho compuesto bajo condiciones tales que se inhibe la fosforilación de la quinasa PIM.

13. El uso de un compuesto de la fórmula I, IA, IB, IC o IX, o una sal farmacéuticamente aceptable del mismo, como se reivindica en cualquiera de las reivindicaciones 1-10, para la fabricación de un medicamento para la producción de un efecto anti-cáncer en un sujeto.

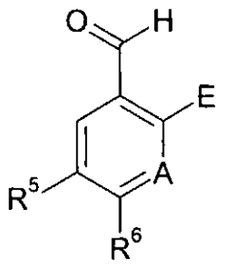
14. Un método para preparar un compuesto de fórmula IA tal como se define en la Reivindicación 2,



fórmula IA,

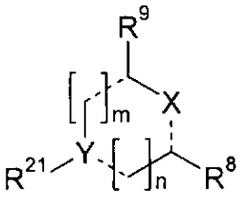
o sal del mismo, que comprende

a) mezclar un compuesto de fórmula XI,



fórmula XI,

o sal del mismo, en donde E es un halógeno y R^5, R^6 y A se definen en la Reivindicación 2, con un compuesto de fórmula XII,



fórmula XII,

o sal del mismo, en donde

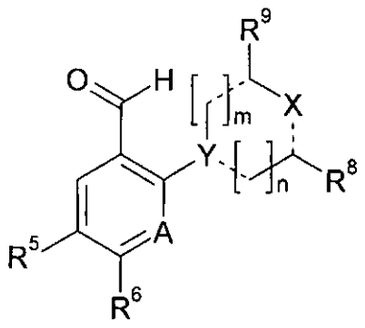
---, R^8, R^9, n, m, Y y X se definen en la Reivindicación 2,

si Y es N, entonces R^{21} es hidrógeno,

si Y es C, entonces R^{21} se selecciona de ácido borónico y un éster borónico y

si Y es CH, entonces R^{21} se selecciona de un haluro de metal,

bajo condiciones tales que se forma una composición que comprende un compuesto de fórmula XIII,

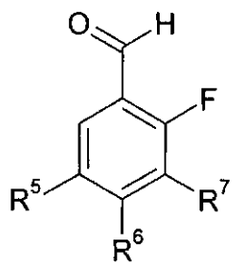


fórmula XIII,

o sal del mismo; y

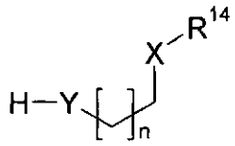
b) mezclar el compuesto de fórmula XIII y tiazolidina-2,4-diona bajo condiciones tales que se forma un compuesto de fórmula IA.

15. Un método para preparar un compuesto de fórmula IC, o sal del mismo, que comprende a) mezclar un compuesto de fórmula V,



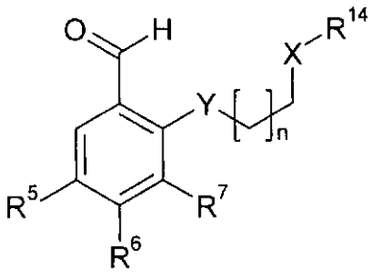
fórmula V,

o sal del mismo, en donde R^5, R^6 y R^7 se definen en la Reivindicación 4, con un compuesto de fórmula VI,



fórmula VII,

o sal del mismo, en donde R^{14}, n, X e Y se definen en la Reivindicación 4, bajo condiciones tales que se forma una composición que comprende un compuesto de fórmula VIII,



fórmula VIII

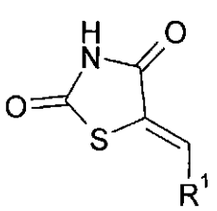
o sal del mismo; y

b) mezclar el compuesto de fórmula VIII y tiazolidina-2,4-diona bajo condiciones tales que se forma un compuesto de fórmula IC.

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RESUMEN

La invención se refiere a compuestos químicos de fórmula I,



fórmula I

y sales de los mismos. En algunas realizaciones, la invención se refiere a inhibidores o moduladores de la actividad o función enzimática de la proteína quinasa PIM-1 y/o PIM-2 y/o PIM-3. En otras realizaciones adicionales, la invención se refiere a composiciones farmacéuticas que comprenden compuestos descritos en la presente y su uso en la prevención y tratamiento de afecciones y enfermedades relacionadas con la quinasa PIM, preferiblemente cáncer.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 103251-1P WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/GB2009/050773	International filing date *(day/month/year)* 02 July 2009 (02.07.2009)	Priority date *(day/month/year)* 02 July 2008 (02.07.2008)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ASTRAZENECA AB		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 05 January 2011 (05.01.2011)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Dorothée Mülhausen e-mail: pt01.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2009/050773	02.07.2009	02.07.2008

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/426 A61K31/427 A61P35/00 C07D277/34

Applicant
ASTRAZENECA AB

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Nyeki, Agnes Telephone No. +49 89 2399-2518

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2009/050773

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1, 12(completely); 2, 6, 7, 11, 13, 14(partially)

because:

☒ the said international application, or the said claims Nos. 1, 12 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 2, 6, 7, 11-14(all partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2009/050773

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☒ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1, 3-5, 8-10, 15(completely); 2, 6, 7, 11-14(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5, 8-10, 15(completely); 2, 6, 7, 14(partially)
	No:	Claims	1, 11-13(all partially)
Inventive step (IS)	Yes:	Claims	3-5, 8-10, 15(completely); 2, 6, 7, 14(partially)
	No:	Claims	1, 11-13(all partially)
Industrial applicability (IA)	Yes:	Claims	3-5, 8-10, 15(completely); 1, 2, 6, 7, 11-14(partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2009/050773

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Prior art documents

1 Reference is made to the following documents:

D1 WO 2004/093809 A2 (INCYTE CORP [US]; TACHDJIAN CATHERINE [US]; GUO JIANHUA [US]; BOUDJELA) 4 November 2004 (2004-11-04)

D2 US 2002/120144 A1 (AKAMA TSUTOMU [US] ET AL) 29 August 2002 (2002-08-29)

D3 OTTANA R ET AL: "In vitro antiproliferative activity against human colon cancer cell lines of representative 4-thiazolidinones. Part I" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB LNKD- DOI:10.1016/J.BMCL.2005.05.093, vol. 15, no. 17, 1 September 2005 (2005-09-01) , pages 3930-3933, XP025314117 ISSN: 0960-894X [retrieved on 2005-09-01]

D4 XIA ZUPING ET AL: "Synthesis and evaluation of novel inhibitors of Pim-1 and Pim-2 protein kinases." JOURNAL OF MEDICINAL CHEMISTRY 8 JAN 2009 LNKD- PUBMED:19072652, vol. 52, no. 1, 8 January 2009 (2009-01-08) , pages 74-86, XP002584626 ISSN: 1520-4804

D5 WO 2009/064486 A2 (MUSC FOUND FOR RES DEV [US]; SMITH CHARLES D [US]; KRAFT ANDREWS S [US) 22 May 2009 (2009-05-22)

D6 WO 2006/069186 A (OHIO STATE RES FOUNDATION [US]; CHEN CHING-SHIH [US]; SHIAU CHUNG-WAI) 29 June 2006 (2006-06-29)

D7 WO 01/34133 A (LILLY CO ELI [US]; SAWYER JASON SCOTT [US]; TEICHER BEVERLY ANN [US]) 17 May 2001 (2001-05-17)

D8 EP 0 976 748 A (SHIONOGI & CO [JP]) 2 February 2000 (2000-02-02)

D9 JP 09 003067 A (HISAMITSU PHARMACEUTICAL CO) 7 January 1997 (1997-01-07)

Re Item III

2 Claims 1 and 12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

Re Item IV

Lack of unity of invention

3 The present international application lacks unity as the claimed 3 inventions are not so linked to form a single general inventive concept as required by Rule 13.1 PCT. The technical problem to be solved in the present application is to provide novel compounds for treating or preventing cancer.

Since the use of 2,4 - thiazolidinedione compounds of formula I for the treatment of cancer, wherein R1 is a phenyl group, is known from documents D6 and D7, there is no unifying novel and inventive concept linking Inventions 1 - 3.

The underlying mechanism of biological activity of 2,4 - thiazolidinedione which makes them useful for the treatment of cancer, namely the PIM kinase inhibitory activity, although not explicitly disclosed in D6 and D7, was necessarily present as a functional characteristic that is inherent to the disclosed 2,4 - thiazolidinedione compounds falling within the scope of formula I of Claim 1.

Although the discovery of such a mechanism may be an important piece of scientific knowledge, it is , however, not in the form of a defined, real treatment of the pathological condition and therefore does not constitute a technical contribution to the art.

The claimed 2,4 - thiazolidinedione compounds for treating or preventing cancer therefore do not form a single general inventive concept.

For the same reasons there is no common special technical feature linking Inventions 1 - 3 in the sense of Rule 13.2 PCT. Each of the Inventions 1 - 3 is a distinct invention characterised by its own special technical feature defining the contribution over the prior art. These own special technical features are the defined group of compounds with the different R1 substituents.

4 Thus the inventions defined by the present claims are considered to be the following:

Invention 1: Claims 1 and 11-13 (partially) defining compounds of formula I for treating or preventing cancer, wherein R1 is a carbocyclyl or a heterocarbocyclyl group.

Invention 2: Claims 1, 2, 6, 7, 11-14 (partially) and Claims 3-5, 8-10 and 15 (entirely) defining compounds of formula I for treating or preventing cancer, wherein R1 is an aryl group, in particular a phenyl group.

Invention 3: Claims 1, 2, 6, 7, 11-14 (partially) defining compounds of formula I for treating or preventing cancer, wherein R1 is a heteroaryl group, in particular a pyridine group.

The terms "carbocyclyl", "heterocarbocyclyl", "aryl" and "heteroaryl" are used according to the definitions given in the description of the present application (see p. 29 and 30).

5 According to the PCT International Search and Preliminary Examination Guidelines Part III, Chapter 10, Point 10.06 the unity of invention is assessed based upon the independent claims.

Article 17(3)(a) PCT stipulates that in case of non - unity the International Search Report should be based upon the "main invention" first mentioned in the claims.

6 The final search report has been drawn up for Inventions 1 and 2 and therefore, this opinion will be restricted to these inventions.

Re Item V

7 Claims 1 and 12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does

not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Opinion on Invention 1

Novelty and Inventive step (Article 33(1) EPC in the sense of Article 33(2) and 33 (3) PCT)

8 D8 discloses a 2,4-thiazolidinedione compound of formula I, wherein R1 is a piperidinyl group, for the treatment of inflammatory diseases.

D9 discloses 2,4-thiazolidinedione compounds of formula I, wherein R1 is a piperidinyl group, for the treatment or prevention of allergic diseases.

9 Since the prior art fails to disclose compounds of formula I, wherein R1 is a carbocyclyl or a heterocarbocyclyl group, for the treatment or prevention of cancer, the subject-matter of Claims 1 and 11-13 can be considered new.

10 The present application provides only 2 compounds falling within the scope of Invention 1, namely (Z)-5-((6-oxo-1,6-dihydropyridin-3-yl)methylene) thiazolidine-2,4-dione (Compound 69) and (Z)-5-((2-oxo-1,2-dihydropyridin-3-yl)methylene)thiazolidine-2,4-dione (Compound 70). However, Compound 70 fails to inhibit both PIM 1 and 2 enzymes and Compound 69 shows only a weak PIM 2 inhibitory activity.

In view of these results, the technical problem is not disclosed to be solved and an inventive step cannot be acknowledged.

Opinion on Invention 2

Novelty and Inventive step (Article 33(1) EPC in the sense of Article 33(2) and 33 (3) PCT)

11 D1 discloses substituted isochroman compounds for the treatment of cancer. The compound 5-[4-dimethylamino-3-(1,1,4,4,7-pentamethyl-isochroman-6-yl)-benzylidene]-thiazolidine-2,4-dione is explicitly disclosed.

D2 discloses thiazolidinedione compounds falling within the scope of present Claim 1 for the treatment of cancer.

Although the claimed mechanism of action, namely the inhibition of a PIM kinase, is neither disclosed in D1 nor in D2, it is considered to be a characteristic inherent to the disclosed compounds.

Consequently, in view of D1 and D2, the subject-matter of Claims 1 and 11-13 cannot be considered novel.

12 However, the prior art fails to disclose the compounds of Claims 2-10. Therefore, the subject-matter of Claims 2-10, 14 and 15 is considered new and meets the requirements of Article 33(2) PCT.

13 D3 is regarded as the closest prior art in respect of the subject-matter of Claims 2-10.

D3 discloses the antiproliferative activity of 5-(3-trifluoromethyl-benzylidene)-2,4-thiazolidinedione against human colon cancer cell lines in vitro.

Compared to D3, the distinguishing feature in present Claims 2-10 is that other thiazolidinedione compounds are defined. Since the PIM kinase inhibitory activity of these compounds are not suggested in the prior art, the subject-matter of Claims 2-10 appears to involve an inventive step. As a consequence, the method of preparation of a compound of Formula IA and Formula IC defined in Claims 14 and 15, respectively, also appears inventive.

Re Item VI

14 The Applicant is warned that the disclosure of documents D4 and D5 may become relevant in respect of novelty and/or inventive step according to national/regional patent law. This matter will be considered further by the relevant national/regional examining authorities, if and when the present application enters the national/regional phase(s).

D4 discloses 5-(3-trifluoromethylbenzylidene)thiazolidine-2,4-dione and their derivatives to inhibit PIM protein kinases and suggests their use in the treatment of various cancer types.

D5 discloses thiazolidinedione compounds having a PIM-1 and/or PIM-2 protein kinase inhibitory activity and being useful in the treatment of cancer.

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

(19) World Intellectual Property Organization
International Bureau

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7 January 2010 (07.01.2010)

PCT

(10) International Publication Number
WO 2010/001169 A3

(51) International Patent Classification:
A61K 31/426 (2006.01) *A61P 35/00* (2006.01)
A61K 31/427 (2006.01) *C07D 277/34* (2006.01)

(21) International Application Number:
PCT/GB2009/050773

(22) International Filing Date:
2 July 2009 (02.07.2009)

(25) Filing Language: English

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(30) Priority Data:

61/077,639	2 July 2008 (02.07.2008)	US
61/183,278	2 June 2009 (02.06.2009)	US

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

(72) Inventors; and

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

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

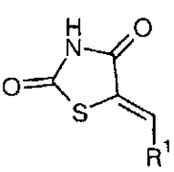
Published:

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

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

(88) Date of publication of the international search report:
5 August 2010

(54) Title: CHEMICAL COMPOUNDS 251



(I)

(57) Abstract: The invention relates to chemical compounds of formula (I), and salts thereof. In some embodiments, the invention relates to inhibitors or modulators of PIM-1 and/or PIM-2, and/or PIM-3 protein kinase activity or enzyme function. In still further embodiments, the invention relates to pharmaceutical compositions comprising compounds disclosed herein, and their use in the prevention and treatment of PIM kinase related conditions and diseases, preferably cancer.

WO 2010/001169 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/050773

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/426 A61K31/427 A61P35/00 C07D277/34
ADD.

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)
A61K A61P C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/093809 A2 (INCYTE CORP [US]; TACHDJIAN CATHERINE [US]; GUO JIANHUA [US]; BOUDJELA) 4 November 2004 (2004-11-04) page 3, line 19 - page 4, line 10 pages 52-53; example 14 claims 1,11-16	1,11-13
X	US 2002/120144 A1 (AKAMA TSUTOMU [US] ET AL) 29 August 2002 (2002-08-29) the whole document	1,11-13

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 May 2010	14/06/2010

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

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/050773

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OTTANA R ET AL: "In vitro antiproliferative activity against human colon cancer cell lines of representative 4-thiazolidinones. Part I" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB LNKD-DOI:10.1016/J.BMCL.2005.05.093, vol. 15, no. 17, 1 September 2005 (2005-09-01), pages 3930-3933, XP025314117 ISSN: 0960-894X [retrieved on 2005-09-01] the whole document page 3931; figure 1; compound 4	1,11-13
X,P	XIA ZUPING ET AL: "Synthesis and evaluation of novel inhibitors of Pim-1 and Pim-2 protein kinases." JOURNAL OF MEDICINAL CHEMISTRY 8 JAN 2009 LNKD- PUBMED:19072652, vol. 52, no. 1, 8 January 2009 (2009-01-08), pages 74-86, XP002584626 ISSN: 1520-4804 the whole document page 78; table 3; compounds 6a, 7a	1,4, 11-13
X,P	WO 2009/064486 A2 (MUSC FOUND FOR RES DEV [US]; SMITH CHARLES D [US]; KRAFT ANDREWS S [US) 22 May 2009 (2009-05-22) claims 2-7	1,11-13
A	WO 2006/069186 A (OHIO STATE RES FOUNDATION [US]; CHEN CHING-SHIH [US]; SHIAU CHUNG-WAI) 29 June 2006 (2006-06-29) page 2, paragraph 5 - page 3 page 8; compounds TG-88 page 33, paragraph 55 - page 34, paragraph 56 page 39, paragraph 71 claim 1	1-15
A	WO 01/34133 A (LILLY CO ELI [US]; SAWYER JASON SCOTT [US]; TEICHER BEVERLY ANN [US]) 17 May 2001 (2001-05-17) claims 5,6	1-15
A	EP 0 976 748 A (SHIONOGI & CO [JP]) 2 February 2000 (2000-02-02) page 39, paragraph 210 page 70, paragraph 251; compounds B-9 page 127, paragraph 377	1,11-13

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/050773

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 09 003067 A (HISAMITSU PHARMACEUTICAL CO) 7 January 1997 (1997-01-07) abstract page 11; compounds 29,31 page 13; compound 41	1,11-13

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2009/050773

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

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

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

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

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

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable 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 report covers only those claims for which fees were paid, specifically claims Nos.:

1, 3-5, 8-10, 15(completely); 2, 6, 7, 11-14(partially)

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1, 11-13(all partially)

   Compounds of formula I for treating or preventing cancer, wherein R1 is a carbocyclyl or a heterocarbocyclyl group.

   ---

2. claims: 3-5, 8-10, 15(completely); 1, 2, 6, 7, 11-14(partially)

   Compounds of formula I for treating or preventing cancer, wherein R1 is an aryl group, in particular a phenyl group.

   ---

3. claims: 2, 6, 7, 11-14(all partially)

   Compounds of formula I for treating or preventing cancer, wherein R1 is a heteroaryl group, in particular a pyridine group.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/050773

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004093809 A2	04-11-2004	AU 2004232326 A1	04-11-2004
		BR PI0409501 A	18-04-2006
		CA 2522759 A1	04-11-2004
		CN 1774246 A	17-05-2006
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		JP 2006523724 T	19-10-2006
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US 2002120144 A1	29-08-2002	WO 02051409 A1	04-07-2002
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WO 0134133 A	17-05-2001	AU 1595001 A	06-06-2001
EP 0976748 A	02-02-2000	AT 255579 T	15-12-2003
		AU 719210 B2	04-05-2000
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		DE 69820248 D1	15-01-2004
		DE 69820248 T2	23-09-2004
		DK 976748 T3	22-03-2004
		ES 2210710 T3	01-07-2004
		HU 0000965 A2	28-04-2001
		WO 9833797 A1	06-08-1998
		JP 3850450 B2	29-11-2006
		NO 993706 A	30-09-1999
		PL 334915 A1	27-03-2000
		PT 976748 E	31-03-2004
		RU 2198174 C2	10-02-2003
		TR 9901847 T2	21-06-2000
		TW 577875 B	01-03-2004
		US 6147100 A	14-11-2000
JP 9003067 A	07-01-1997	JP 3668291 B2	06-07-2005

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-011427- -00000-0000 S

Fecha: 2011-02-01 18:19:42 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 247 0

PATENTE DE INVENCIÓN ☐ **MOD**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
AZTRAZENECA AB

REFERENCIA	Radicación No.	11 011427
	Solicitud internacional	PCT/GB2009/050773
	Fecha inicio fase nacional	02/02/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	005478

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 25 MAR. 2011.
adpa11

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Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
AZTRAZENECA AB

REFERENCIA	Radicación No.	11 011427
	Solicitud internacional	PCT/GB2009/050773
	Fecha inicio fase nacional	02/02/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	0 05479

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

23 MAR. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11