Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SOLICITUD DE

INVENC

No. 13-271927- -00000-0000

Fecha: 2013-11-19 16:32:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

TITULO: COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA

SOLICITANTE: GLAXOSMITHKLINE INTELLECTUAL PROPERTY (No.2) LIMITED

DIRECCIÓN: 980 Great West Road Brentford, Middlesex TW8 9GS United Kingdom. Gran Bretaña

APODERADO: CARLOS R. OLARTE

BOGOTÁ 19 de noviembre de 2013

P2013/000197

OLARTEMOURE

OLARTE MOURE & AS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-271927- -00000-0000

Fecha: 2013-11-19 16:32:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000197**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: GlaxoSmithKline Intellectual Property (No. 2) LIMITED
Nacionalidad o Domicilio: 980 Great West Road Brentford, Middlesex TW8 9GS United Kingdom
Lugar de Constitución: Gran Bretaña
Teléfono: _____ **Fax:** _____
E-mail: _____

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Carrera 5 No. 34-03 Bogotá, Colombia
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

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

INVENTOR (ES) (72)

Nombre: **(1)** Donghui QUIN **(2)** Hemant JOSHI **(3)** Raghuram TANGIRALA
Dirección: **(1)** 1250 South Collegeville Road, Collegeville, PA 19426 **(2)** Navi-Mumbai **(3)** Navi-Mumbai
Nacionalidad o Domicilio: **(1)** Estadounidense **(2)** y **(3)** India

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2012/038520 Fecha Mayo 18, 2012

Publicación Internacional No. WO 2012/162127 A1 Fecha Noviembre 29,2012

(6) **Título (54)** **COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA**

Clasificación Internacional (51) A61K 31/17

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
IN	Mayo 20, 2011	145/DEL2011
US	Junio 09,2011	61/495,049

(9) **Comprobante de pago No.** 13- **Fecha** _____

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la Regla 4.17 (ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(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

3

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 111449

Bogotá D.C., Noviembre 01 de 2013 - 13:42:13

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	558995802	31/10/2013	15.438.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	500.000.00	500.000.00
				$500.000.00

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-271927- -00000-0000

Fecha: 2013-11-19 16:32:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 3

Industria y Comercio SUPERINTENDENCIA	PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA *RELACIÓN DE ANEXOS*	
Dependencia: 2020	Fecha: 13 / 11 / 19 / AAAA MM DD	Recorrido: 3
Tipo de Radicación: Entrada: X Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicador:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	13-271927-	0	7
2			
3			
4			
5			
6			
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8			
9			
10			
11			
12			
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14			
15			
16			
17			

Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	*Soporte Documental*
X	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:

EL CD ANEXO CONTIENE UN TOTAL DE 8 ARCHIVOS. 8 EN FORMATO P.D.F, LOS CUALES FUERON PROCESADOS.

CL.

OLARTEMOURE

OLARTE MOURE & ASOCIADOS LTDA.

Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación.

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2013/000197**

SOLICITUD DE:

1

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

[X] Capítulo I. [ ] Capítulo II.

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SOLICITANTE (71)

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REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
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Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

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Cual _____
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Dirección: **(1)** 1250 South Collegeville Road, Collegeville, PA 19426
(2) Navi-Mumbai **(3)** Navi-Mumbai
Nacionalidad o Domicilio: **(1)** Estadounidense **(2)** y **(3)** India

5

PCT (86)

Solicitud Internacional No. PCT/US2012/038520 Fecha Mayo 18, 2012

Publicación Internacional No. WO 2012/162127 A1 Fecha Noviembre 29,2012

6

Título (54) **COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA**

Clasificación Internacional (51) A61K 31/17

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
IN	Mayo 20, 2011	145/DEL2011
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9

Comprobante de pago No. 13- **Fecha** _____

10 **ANEXOS**

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- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [x] Declaraciones. Declaración bajo la Regla 4.17 (ii) del PCT.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
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- [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

Carlos R. Olarte
Juan G. Moure

Alexander Agudelo
Carlos A. Parra
Juan Felipe Acosta
Andrés Rincón
Mónica Guevara
Andrés Alvarado
Ella Ponce
Liliana Galindo
María Clara Calderón
Mauricio Ávila
Laura Escobar
José Jairo Dangond
Gina Cáceres
Isabella Herrera
Zaava Ravid

Medellín
María Clara Múnera

OLARTEMOURE
OLARTE MOURE & ASOCIADOS LTDA.

The undersigned, Los suscritos,

domiciled in GlaxoSmithKline Intellectual Property (NO.2) Limited domiciliados en

980 Great West Road
Brentford, Middlesex
TW8 9GS
United Kingdom

hereby appoint to **Carlos R. Olarte and/or Juan Guillermo Moure** legal representatives with faculties to receive notifications and to appoint judicial or extrajudicial agents in **Patents for Inventions, Utility Models and Industrial Designs,** in the Republic of Colombia, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

nombramos por el presente a **Carlos R. Olarte y/o Juan Guillermo Moure** nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en **Patentes de Invención, Modelos de Utilidad y Diseños Industriales,** en la República de Colombia, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

Signature/Firma:

Name/Nombre:
Title/Cargo:

Date/Fecha:

City,Country/Ciudad,País:

Signature/Firma: Theodore R. Furman

Name/Nombre: Theodore R. Furman
Title/Cargo:
Authorized Attorney and Official on behalf of GlaxoSmithKline Intellectual Property (NO.2) Limited

Date/Fecha: 06 February 2013

City,Country/Ciudad,País:
King of Prussia, Pennsylvania, USA

NO LEGALIZATION IS REQUIRED

COMMONWEALTH OF PENNSYLVANIA)
) ss
COUNTY OF MONTGOMERY)

Before me, Deborah A. Becker, a Notary Public in and for the Commonwealth and County aforesaid, personally came Theodore R. Furman known to me to be the person whose name is subscribed to the foregoing Power of Attorney and known to me to be an Authorized Attorney and Official for GlaxoSmithKline Intellectual Property (NO.2) Limited and acknowledged to me that he executed said instrument for the purposes and consideration therein expressed and as the act of said Corporation.

Given under my hand and official seal of office this 6th day Of February 2013.

Deborah A. Becker
NOTARY PUBLIC

COMMONWEALTH OF PENNSYLVANIA
NOTARIAL SEAL
DEBORAH A. BECKER, Notary Public
Upper Merion Twp., Montgomery County
My Commission Expires April 6, 2016

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

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61/495,049 9 June 2011 (09.06.2011) US

(71) Applicant *(for all designated States except US)*: **GLAXOSMITHKLINE LLC** [US/US]; One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102 (US).

(71) Applicant *(for US only)*: **CHRISTENSEN, Rowena** (heiress of the deceased inventor) [US/US]; 520 State Street, New Orleans, LA 70118 (US).

(72) Inventor: **CHRISTENSEN, Siegfried, Benjamin, IV** *(deceased)*.

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **QIN, Donghui** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **JOSHI, Hemant** [IN/IN]; Navi-Mumbai (IN). **TANGIRALA, Reghuram** [IN/IN]; Navi-Mumbai (IN).

(74) Agents: **PENG, Tony, W.** et al.; GlaxoSmithKline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, 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, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, 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, RS, 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))*

WO 2012/162127 A1

(54) Title: NOVEL COMPOUNDS AS DIACYLGLYCEROL ACYLTRANSFERASE INHIBITORS

(57) Abstract: This invention relates to novel compounds which are inhibitors of acyl coenzymeA: diacylglycerol acyltransferase 1 (DGAT-1), to pharmaceutical compositions containing them, to processes for their preparation, and to their use in therapy for the prevention or treatment of diseases related to DGAT- 1 dysfunction or where modulation of DGAT- 1 activity may have therapeutic benefit including but not limited to obesity, obesity related disorders, hypertriglyceridemia, hyperlipoproteinemia, chylomicronemia, dyslipidemia, non-alcoholic steatohepatitis, diabetes, insulin resistance, metabolic syndrome, hepatitis C virus infection and acne or other skin disorders.

NOVEL COMPOUNDS AS DIACYLGLYCEROL ACYLTRANSFERASE INHIBITORS

FIELD OF INVENTION

This invention relates to novel compounds which are inhibitors of acyl coenzymeA: diacylglycerol acyltransferase 1 (DGAT-1), to pharmaceutical compositions containing them, to processes for their preparation, and to their use in therapy for the prevention or treatment of diseases related to DGAT-1 dysfunction or where modulation of DGAT-1 activity may have therapeutic benefit including but not limited to obesity, obesity related disorders, hypertriglyceridemia, hyperlipoproteinemia, chylomicronemia, dyslipidemia, non-alcoholic steatohepatitis, diabetes, insulin resistance, metabolic syndrome, hepatitis C virus infection and acne or other skin disorders.

BACKGROUND OF THE INVENTION

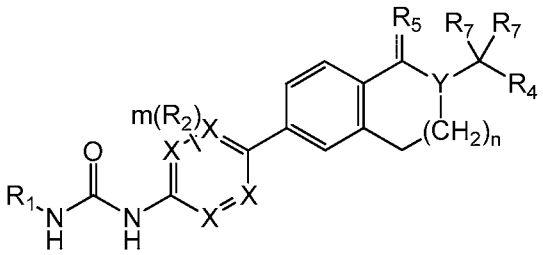
Obesity is a medical condition that is reaching epidemic proportions among humans in a number of countries throughout the world. It is a condition that is also associated with or induces other diseases or conditions that disrupt life activities and lifestyles. Obesity is recognized as a serious risk factor for other diseases and conditions such as diabetes, hypertension, and arteriosclerosis. It is also known that increased body weight due to obesity can place a burden on joints, such as knee joints, causing arthritis, pain, and stiffness.

Because overeating and obesity have become such a problem in the general population, many individuals are now interested in losing weight, reducing weight, and maintaining a healthy body weight and desirable lifestyle. One approach to treating obesity is to reduce food intake and/or hyperlipidemia. It has been suggested that molecules which are developed to prevent the accumulation of triglyceride would not only reduce obesity but also have the additional beneficial effect of reducing insulin resistance, a primary factor contributing to the development of diabetes.

Acyl coenzymeA:diacylglycerol acyltransferase 1 (DGAT-1) is one of two known DGAT enzymes that catalyze the final step in mammalian triglyceride synthesis. DGAT-1 is an enzyme that is implicated in the development of both diabetes and insulin resistance. Studies of DGAT-1 deficient mice show that DGAT-1 deficiency protects against insulin resistance and obesity, see Chen, H.C. et al., J Clin Invest., 109(8), 1049-1055 (2002). Therefore, inhibitors of DGAT-1 should be useful for the treatment of metabolic disorders, e.g. obesity, Type 2 diabetes, and insulin resistance syndrome (or metabolic syndrome) and other associated or related diseases and conditions.

SUMMARY OF THE INVENTION

This invention relates to compounds for Formula (I):



(I)

wherein

R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl and heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

R_5 is hydrogen, hydroxyl, or oxo;

each R_7 is independently H or C_1-C_3alkyl;

each X is independently C or N, provided that at least two X's are C;

Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

n is 0-1, provided that when n is 0, Y is CR_3;

or a pharmaceutically acceptable salt thereof.

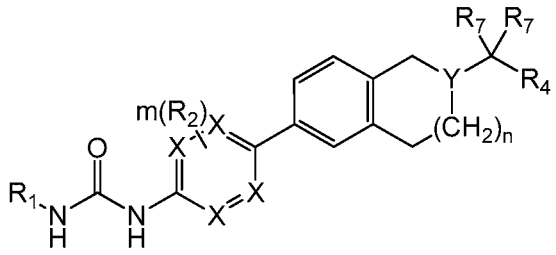
This invention also relates to a pharmaceutical composition comprising a compound of Formula (I) and a pharmaceutically acceptable carrier.

This invention also relates to a method of treating obesity comprising administering to a human in need thereof an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in a pharmaceutical composition.

DETAIL DESCRIPTION OF THE INVENTION

This invention relates to compounds of the Formula (I) as defined above.

This invention also relates to compounds of Formula (I)(A)



(I)(A)

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

each R_7 is independently H or C_1-C_3alkyl;

each X is independently C or N, provided that at least two X's are C;

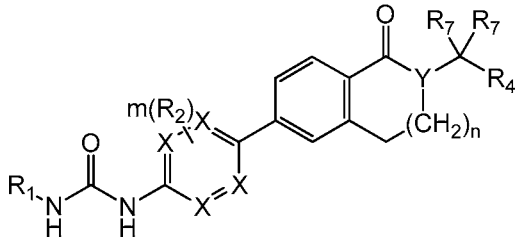
Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

n is 0-1, provided that when n is 0, Y is CR_3;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(B),



(I)(B)

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

each R_7 is independently H or C_1-C_3alkyl;

each X is independently C or N, provided that at least two X's are C;

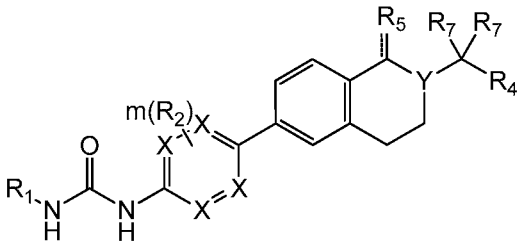
Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

n is 0-1, provided that when n is 0, Y is CR_3;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(C):



(I)(C);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

R_5 is hydrogen, hydroxyl, or oxo;

each R_7 is independently H or C_1-C_3alkyl;

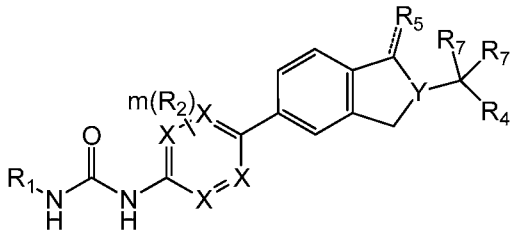
each X is independently C or N, provided that at least two X's are C;

Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(D):



(I)(D);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

R_5 is hydrogen, hydroxyl, or oxo;

each R_7 is independently H or C_1-C_3alkyl;

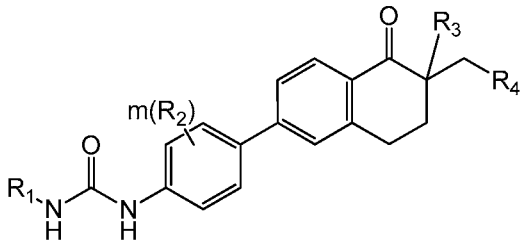
each X is independently C or N, provided that at least two X's are C;

Y is CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(E):



(I)(E);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

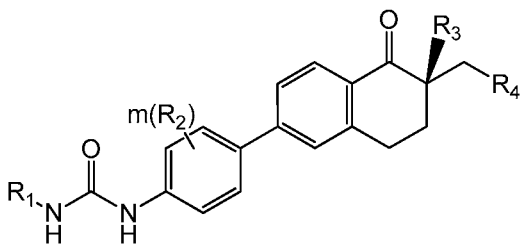
R_4 is CH_2COOH, COOH, ester, or amide;

R_3 is C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(F):



(I)(F);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

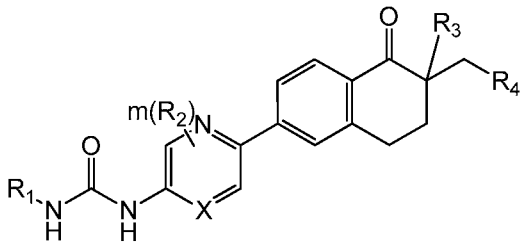
R_4 is CH_2COOH, COOH, ester, or amide;

R_3 is C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(G):



(I)(G);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

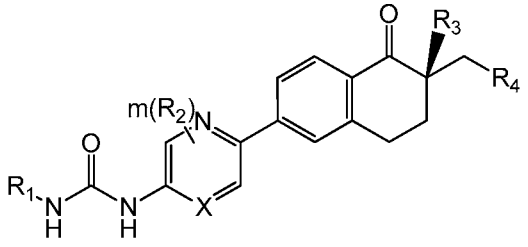
X is independently C or N;

R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-2;

or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I)(H):



(I)(H);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

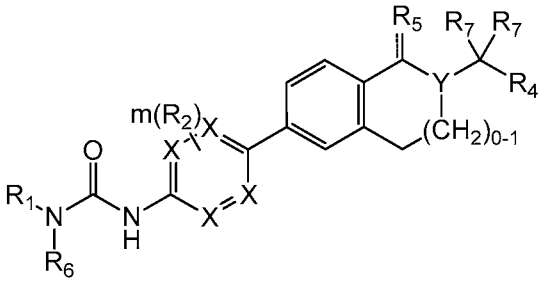
R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

X is independently C or N;

R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;
m is 0-2;
or a pharmaceutically acceptable salt thereof.

This invention relates to compounds for Formula (I)(K):



(I)(K)

wherein R_1 is C_3-C_7cycloalkyl, aryl or heteroaryl, which may be substituted with one to three groups selected from the group consisting of: acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halogen, urea, amide, hydroxyl, SF_5, oxo, and nitro,
and R_6 is H or C_1-C_3alkyl,
or R_1 and R_6 together with the N they are attached to form a mono- or bicyclic ring which may contain 0-3 hetero atoms and may be substituted with one to three halogen, C_1-C_3alkyl, or alkoxy,
R_2 is selected from the group consisting of: H, C_1-C_6alkyl, alkoxy, cyano, halogen, urea, amide, hydroxyl, oxo, and nitro,
R_4 is CH_2COOH, COOH, ester, or amide,
R_5 is hydrogen, hydroxyl, or oxo,
each R_7 is independently H or C_1-C_3alkyl,
each X is independently C or N, provided that at least two X's are C,
Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halogen, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from: halogen, hydroxyl, alkoxy, carboxylic acid, and ester,
m is 0-3;
or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), wherein R_5 is hydroxyl, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(G) or (I)H),wherein X's are C, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C) or (I)(D), wherein X is independently C or N, and two X's are N, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G) or (I)(H), wherein R_1 is phenyl which may be substituted with one to three groups selected from the group consisting of methyl, ethyl, OCF_3, $-OCF_2H$, trifluoromethyl, methoxy, ethoxy, cyano, Cl or F, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G) or (I)(H), wherein R_1 is C_1-C_6alkyl, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G) or (I)(H), wherein R_2 is C_1-C_3alkyl, F, Cl, or CN, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), or (I)(F), (I)(G) or (I)(H), wherein Y is CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C) or (I)(D), wherein Y is CR_3, wherein R_3 is methyl, CH_2CF_3, CH_2OCH_3 or ethyl, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C) or (I)(D), wherein Y is N, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(E), (I)(F), (I)(G) or (I)(H), wherein m is 0.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G) or (I)(H), wherein R_4 is CH_2COOH or COOH, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C) or (I)(D), wherein Y is CR_3, wherein R_3 is H, methyl, ethyl, propyl, isopropyl, hydroxyl, halo, alkoxymethyl, hydroxyl alkyl or alkoxy, or a pharmaceutically acceptable salt thereof.

This invention also relates to compounds that are exemplified in the Experimental section.

Specific compounds of this invention include:

2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetic acid;

2-{1-oxo-6-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetic acid;

2-[6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl]acetic acid;

2-{1-oxo-6-[4-({[4-(trifluoromethoxy)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetic acid;

2-{6-[4-({[3-methyl-5-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl}acetic acid;

3-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}propanoic acid;

3-{1-oxo-6-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}propanoic acid;

3-[6-(4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl]propanoic acid;

2-{[6-(4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl]methyl}pentanedioic acid;

2-(6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{6-[2-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrimidin-5-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(2-{[(3-methylphenyl)carbamoyl]amino}pyrimidin-5-yl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[4-({[3,5-bis(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-fluorophenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(4-fluorophenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-cyanophenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-nitrophenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[4-({[2-(trifluoromethoxy)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[4-({[4-fluoro-3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[4-({[3-(trifluoromethoxy)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[4-({[3-(pentafluoroλ^6-sulfanyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(4-methylphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-methoxyphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[4-({[3-(difluoromethoxy)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

rel-2-[(2R)-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-1);

rel-2-[(2R)-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-2);

2-{6-[3-fluoro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[3-fluoro-4-({[4-fluoro-3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(3-fluoro-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3,5-dimethylphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyridin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrazin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyrazin-2-yl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{2-hydroxy-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{2-hydroxy-6-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{2-ethyl-1-oxo-5-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2,3-dihydro-1H-inden-2-yl}acetic acid;

2-{1-oxo-5-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2,3-dihydro-1H-inden-2-yl}acetic acid;

2-{1-oxo-5-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2,3-dihydro-1H-inden-2-yl}acetic acid;

2-[5-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-2,3-dihydro-1H-inden-2-yl]acetic acid;

2-[5-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-2,3-dihydro-1H-inden-2-yl]acetic acid;

2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{1-oxo-6-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{1-oxo-6-[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(4-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{1-oxo-6-[4-({[2-(trifluoromethoxy)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{6-[3-fluoro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(3-fluoro-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(6-{3-fluoro-4-[(phenylcarbamoyl)amino]phenyl}-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(3-fluoro-4-{[(3-fluorophenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-3-fluorophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(3-fluoro-4-{[(3-methoxyphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3,5-dimethylphenyl)carbamoyl]amino}-3-fluorophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(3-fluoro-4-{[(2-fluoro-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-cyanophenyl)carbamoyl]amino}-3-fluorophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[2-fluoro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(2-fluoro-4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(6-{2-fluoro-4-[(phenylcarbamoyl)amino]phenyl}-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrimidin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{1-hydroxy-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

3-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}propanoic acid;

3-(1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)propanoic acid;

3-[6-(4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]propanoic acid;

3-[6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]propanoic acid;

3-{6-[3-fluoro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}propanoic acid;

3-[6-(3-fluoro-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]propanoic acid;

3-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-3-fluorophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]propanoic acid;

2-methyl-2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}propanoic acid;

2-methyl-2-(1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)propanoic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]-2-methylpropanoic acid;

2-{2-methyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[2-methyl-6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-methyl-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(4-{[(3-methoxyphenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-fluorophenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(2-fluoro-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(2-chloro-4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-2-methyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-1);

rel-2-[(2R)-2-methyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-2);

2-{6-[3-fluoro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-3-fluorophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(6-{3-fluoro-4-[(phenylcarbamoyl)amino]phenyl}-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(3-fluoro-4-{[(3-fluorophenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(3-fluoro-4-{[(3-methoxyphenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[3-chloro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-2,5-difluorophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(6-{2,5-difluoro-4-[(phenylcarbamoyl)amino]phenyl}-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-2-methylphenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-methyl-6-{2-methyl-4-[(phenylcarbamoyl)amino]phenyl}-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[2-methyl-6-(2-methyl-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{2-methyl-6-[2-methyl-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{2-methyl-6-[2-methyl-4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(4-chlorophenyl)carbamoyl]amino}-2-methylphenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[2-fluoro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-2-fluorophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[2-chloro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-(6-{2-chloro-4-[(phenylcarbamoyl)amino]phenyl}-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-(6-{2-cyano-4-[(phenylcarbamoyl)amino]phenyl}-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyridin-2-yl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{2-methyl-1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyridin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-(2-methyl-1-oxo-6-{5-[(phenylcarbamoyl)amino]pyridin-2-yl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{2-methyl-1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrazin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyrazin-2-yl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-methyl-1-oxo-6-{5-[(phenylcarbamoyl)amino]pyrimidin-2-yl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{2-methyl-1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrimidin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{2-ethyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{2-ethyl-1-oxo-6-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{2-ethyl-1-oxo-6-[4-({[2-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-(2-ethyl-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(4-{[(3-methoxyphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(6-{4-[(cyclohexylcarbamoyl)amino]phenyl}-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[2-ethyl-6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(4-{[(4-methoxyphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(4-{[(4-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(4-{[(3-fluorophenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3,5-dimethylphenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[(2S)-2-ethyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[(2R)-2-ethyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-1);

rel-2-[(2R)-6-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-2);

2-[6-(2-chloro-4-{[(3-methoxyphenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(2-chloro-4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[2-chloro-4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(2-chloro-4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(2-chloro-4-{[(3,5-dimethylphenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{6-[2-chloro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(2-chloro-4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(6-{2-chloro-4-[(phenylcarbamoyl)amino]phenyl}-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-(2-ethyl-6-{3-fluoro-4-[(phenylcarbamoyl)amino]phenyl}-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-(6-{4-[(cyclohexylcarbamoyl)amino]-3-fluorophenyl}-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{2-ethyl-6-[3-fluoro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-3-fluorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(3-fluoro-4-{[(3-fluorophenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(4-chlorophenyl)carbamoyl]amino}-3-fluorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3,5-dimethylphenyl)carbamoyl]amino}-3-fluorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(3-fluoro-4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{2-ethyl-1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyridin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyridin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-ethyl-1-oxo-6-{5-[(phenylcarbamoyl)amino]pyridin-2-yl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(5-{[(3,5-dimethylphenyl)carbamoyl]amino}pyridin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(5-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}pyridin-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-ethyl-1-oxo-6-{5-[(phenylcarbamoyl)amino]pyrazin-2-yl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{2-ethyl-1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrazin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyrazin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(5-{[(3,5-dimethylphenyl)carbamoyl]amino}pyrazin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-ethyl-6-(5-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}pyrazin-2-yl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{2-ethyl-1-oxo-6-[6-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyridazin-3-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(6-{[(3-chlorophenyl)carbamoyl]amino}pyridazin-3-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{2-ethyl-1-oxo-6-[6-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyridin-3-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(6-{[(3-chlorophenyl)carbamoyl]amino}pyridin-3-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-ethyl-1-oxo-6-{6-[(phenylcarbamoyl)amino]pyridin-3-yl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[(2S)-6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyridin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[(2R)-6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyridin-2-yl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-2-ethyl-1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrazin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-1);

rel-2-[(2R)-2-ethyl-1-oxo-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrazin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-2);

2-(1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-2-propyl-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{1-oxo-2-propyl-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1-oxo-2-propyl-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{1-oxo-2-propyl-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyridin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyridin-2-yl)-1-oxo-2-propyl-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(1R,2S)-2-ethyl-1-hydroxy-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(1R,2S)-2-ethyl-1-hydroxy-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

(2S)-3-methyl-2-(2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetamido)butanoic acid;

2-(2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetamido)acetic acid;

(2S)-3-methyl-2-(2-{6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetamido)butanoic acid;

(2S)-3-methyl-2-(2-{6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetamido)pentanoic acid;

(2S)-2-{2-[6-(3-fluoro-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetamido}-3-methylbutanoic acid;

(2S)-2-{2-[6-(3-fluoro-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetamido}-3-methylpentanoic acid;

2-{2-[6-(3-fluoro-4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetamido}acetic acid;

2-{2-fluoro-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-fluoro-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{2-hydroxy-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(2-fluorophenyl)carbamoyl]amino}phenyl)-2-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-hydroxy-6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(2-methoxy-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-{2-methoxy-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-2);

rel-2-[(2R)-6-(4-{[(4-chlorophenyl)carbamoyl]amino}phenyl)-2-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid (enantiomer-1);

2-[6-(4-{[(3,5-dimethylphenyl)carbamoyl]amino}phenyl)-2-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-(methoxymethyl)-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-3-fluorophenyl)-2-(hydroxymethyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-(hydroxymethyl)-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[2-(hydroxymethyl)-6-(4-{[(3-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-(1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-(1-hydroxy-6-{4-[(phenylcarbamoyl)amino]phenyl}-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid;

2-[6-(4-{[(3,5-dimethylphenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-methoxyphenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1-hydroxy-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(2-methoxy-5-methylphenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-{2-ethyl-1-hydroxy-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyridin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-{2-ethyl-1-hydroxy-6-[5-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)pyrazin-2-yl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid;

2-[2-(methoxymethyl)-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-(methoxymethyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(2-chloro-4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(2-chloro-4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(5-{[(3,4-difluorophenyl)carbamoyl]amino}pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-{5-[(cyclohexylcarbamoyl)amino]pyrazin-2-yl}-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

2-[(2S)-6-(4-{[(3,4-difluorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-[2-chloro-4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-1-oxo-6-(5-{[(pentan-3-yl)carbamoyl]amino}pyrazin-2-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(5-{[(4-ethylphenyl)carbamoyl]amino}pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-{4-[(butylcarbamoyl)amino]phenyl}-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-1-oxo-2-(2,2,2-trifluoroethyl)-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(5-{[(3-chlorophenyl)carbamoyl]amino}pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(4-{[(3,5-dichlorophenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(4-{[(4-ethylphenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-{4-[(cyclohexylcarbamoyl)amino]phenyl}-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(2-chloro-4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-2-methoxy-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

rel-2-[(2R)-6-{5-[(cyclobutylcarbamoyl)amino]pyrazin-2-yl}-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid;

or a pharmaceutically acceptable salt thereof.

A person of ordinary skills in the art recognizes that compounds of the present invention may have alternative names when different naming software is used.

The following exemplified compounds have alternative chemical names as illustrated in table below.

Example #	Chemical Name	Alternative Chemical Names
1	2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydroisoquinolin-2-yl}acetic acid	2-(1-Oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetic acid
10	2-(6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid	2-(6-(4-(3-Phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid

40	2-{2-hydroxy-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	2-(2-Hydroxy-6-(4-(3-(3-(trifluoromethyl) phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
42	2-{2-ethyl-1-oxo-5-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-2,3-dihydro-1H-inden-2-yl}acetic acid	2-(2-ethyl-1-oxo-5-(4-(3-(3-(trifluoromethyl) phenyl) ureido)phenyl)-2,3-dihydro-1H-inden-2-yl) acetic acid
47	2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	2-(1-Oxo-6-(4-(3-(3-(trifluoromethyl) phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
68	2-{1-hydroxy-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	2-(1-hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl) -1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
69	3-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}propanoic acid	3-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl) -1,2,3,4-tetrahydronaphthalen-2-yl)propanoic acid
76	2-methyl-2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}propanoic acid	2-Methyl-2-(1-oxo-6-(4-(3-(3-(trifluoromethyl) phenyl) ureido) phenyl)-1,2,3,4-tetrahydro naphthalen-2-yl) propanoic acid
79	2-{2-methyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	2-(2-Methyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl) -1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
115	2-{2-ethyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	2-(2-Ethyl-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
116	2-{2-ethyl-1-oxo-6-[4-({[4-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	2-(2-Ethyl-1-oxo-6-(4-(3-(4-(trifluoromethyl)phenyl)ureido)phenyl) -1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
129	2-[(2S)-2-ethyl-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	(*S*)-2-(2-Ethyl-1-oxo-6-(4-(3-phenylureido) phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
173	rel-2-[(1R,2S)-2-ethyl-1-hydroxy-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-((2S)-2-Ethyl-1-hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl) -1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
175	(2S)-3-methyl-2-(2-{1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetamido)butanoic acid	(2S)-3-Methyl-2-(2-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl) -1,2,3,4-tetrahydronaphthalen-2-yl)acetamido)butanoic acid
182	2-{2-fluoro-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	2-(2-Fluoro-1-oxo-6-(4-(3-(3-(trifluoromethyl) phenyl) ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
185	2-{2-hydroxy-1-oxo-6-[4-({[3-	2-(2-Hydroxy-1-oxo-6-(4-(3-(3-

	(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl}acetic acid	(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
190	2-(2-methoxy-1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid	2-(2-Methoxy-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
197	2-[2-(methoxymethyl)-1-oxo-6-[4-({[3-(trifluoromethyl)phenyl]carbamoyl}amino)phenyl]-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-(2-(Methoxymethyl)-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
198	2-[6-(4-{[(3-chlorophenyl)carbamoyl]amino}-3-fluorophenyl)-2-(hydroxymethyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-(6-(4-(3-(3-Chlorophenyl) ureido)-3-fluorophenyl)-2-(hydroxymethyl)-1-oxo-1,2,3,4-tetrahydro naphthalen-2-yl)acetic acid
201	2-(1-oxo-6-{4-[(phenylcarbamoyl)amino]phenyl}-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid	2-(1-Oxo-6-(4-(3-phenylureido)phenyl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
212	rel-2-[(2R)-6-(2-chloro-4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-(6-(2-Chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:
213	rel-2-[(2R)-6-(2-chloro-4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-(6-(2-chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
214	rel-2-[(2R)-6-(4-{[(3-chlorophenyl)carbamoyl]amino}phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-(6-(4-(3-(3-Chlorophenyl)ureido)phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
215	rel-2-[(2R)-6-(5-{[(3,4-difluorophenyl)carbamoyl]amino}pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-(6-(5-(3-(3,4-Difluorophenyl)ureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
216	rel-2-[(2R)-6-{5-[(cyclohexylcarbamoyl)amino]pyrazin-2-yl}-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	2-(6-(5-(3-cyclohexylureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid
217	2-[(2S)-6-(4-{[(3,4-difluorophenyl)carbamoyl]amino}phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl]acetic acid	(S)-2-(6-(4-(3-(3,4-Difluorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(E), (I)(F), (I)(G), (I)(H), (I)(K) or any of the exemplified compounds, or their pharmaceutically acceptable salts thereof, for use as a medicament.

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This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G), (I)(H), (I)(K), or any of the exemplified compounds, or their pharmaceutically acceptable salts thereof, for use in the treatment of obesity.

This invention also relates to compounds of Formula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G), (I)(H), (I)(K), or any of the exemplified compounds, or their pharmaceutically acceptable salts thereof, in the manufacture of a medicament for the treatment of obesity.

Typically, but not absolutely, the salts of the present invention are pharmaceutically acceptable salts. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Salts of the disclosed compounds containing a basic amine or other basic functional group may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, trifluoroacetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid or the like. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, phenylacetates, phenylpropionates, phenylbutrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates mandelates, and sulfonates, such as xylenesulfonates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates and naphthalene-2-sulfonates.

Salts of the disclosed compounds containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine,

dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, choline, quinine, quinoline, and basic amino acid such as lysine and arginine.

Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of this invention and these should be considered to form a further aspect of the invention. These salts, such as oxalic or trifluoroacetate, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts.

As used herein, the term "a compound of Formula (I)" or "the compound of Formula (I)" refers to one or more compounds according to Formula (I). The compound of Formula (I) may exist in solid or liquid form. In the solid state, it may exist in crystalline or noncrystalline form, or as a mixture thereof. The skilled artisan will appreciate that pharmaceutically acceptable solvates may be formed for crystalline or non-crystalline compounds. In crystalline solvates, solvent molecules are incorporated into the crystalline lattice during crystallization. Solvates may involve non-aqueous solvents such as, but not limited to, ethanol, isopropanol, DMSO, acetic acid, ethanolamine, or ethyl acetate, or they may involve water as the solvent that is incorporated into the crystalline lattice. Solvates wherein water is the solvent incorporated into the crystalline lattice are typically referred to as "hydrates." Hydrates include stoichiometric hydrates as well as compositions containing variable amounts of water. The invention includes all such solvates.

The skilled artisan will further appreciate that certain compounds of the invention that exist in crystalline form, including the various solvates thereof, may exhibit polymorphism (i.e. the capacity to occur in different crystalline structures). These different crystalline forms are typically known as "polymorphs." The invention includes all such polymorphs. Polymorphs have the same chemical composition but differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. Polymorphs, therefore, may have different physical properties such as shape, density, hardness, deformability, stability, and dissolution properties. Polymorphs typically exhibit different melting points, IR spectra, and X-ray powder diffraction patterns, which may be used for identification. The skilled artisan will appreciate that different polymorphs may be produced, for example, by changing or adjusting the reaction conditions or reagents, used in making the compound. For example, changes in temperature, pressure, or solvent may result in polymorphs. In addition, one polymorph may spontaneously convert to another polymorph under certain conditions.

The compound of Formula (I) or a salt thereof may exist in stereoisomeric forms (e.g., it contains one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that a compound or salt of Formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention. It is to be understood that the present invention includes all combinations and subsets

of the particular groups defined hereinabove. The scope of the present invention includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/diastereomerically enriched mixtures. It is to be understood that the present invention includes all combinations and subsets of the particular groups defined hereinabove.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula (I) and following, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention and pharmaceutically acceptable salts thereof include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulphur, fluorine, iodine, and chlorine, such as 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O, 31P, 32P, 35S, 18F, 36Cl, 123I and 125I.

Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as 3H, 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H, and carbon-14, i.e., 14C, isotopes are particularly preferred for their ease of preparation and detectability. 11C and 18F isotopes are particularly useful in PET (positron emission tomography), and 125I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. Further, substitution with heavier isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

DEFINITIONS

Terms are used within their accepted meanings. The following definitions are meant to clarify, but not limit, the terms defined.

As used herein, unless defined otherwise, the term "alkyl" (or "alkylene") refers to a straight or branched chain alkyl, preferably having from one to twelve carbon atoms, which may be unsubstituted or substituted, saturated or unsaturated with multiple degrees of substitution, preferably one, two or three, included within the present invention. Suitable substituents are selected from the group consisting of halo, amino, substituted amino, cyano, hydroxyl, alkoxy, ester, carboxylic acid and alkylthio. Examples of "alkyl" as used herein include, but are not

limited to, methyl, trifluoromethyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, t-butyl, isopentyl, n-pentyl, and the like, as well as substituted versions thereof.

As used herein, unless defined otherwise, the term "cycloalkyl" refers to an unsubstituted or substituted mono- or polycyclic non-aromatic saturated ring, which optionally includes an alkylene linker through which the cycloalkyl may be attached. Exemplary "cycloalkyl" groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, as well as unsubstituted and substituted versions thereof.

As used herein, unless defined otherwise, the term "alkoxy" refers to the group -OR^a, where R^a is C_1-C_4alkyl or cycloalkyl as defined above.

As used herein, the term "amide" refers to the group –$C(O)NR^cR^d$, wherein R^c and R^d are each independently H, C_1-C_6alkyl, or C_3-C_6cycloalkyl, or R^c is the remaining portion of a natural or un-natural amino acid.

As used herein, the term "heterocycle" or "heterocyclyl" refers to unsubstituted and substituted mono- or polycyclic non-aromatic ring system containing one or more heteroatoms. Preferred heteroatoms include N, O, and S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to eight-membered and is either fully saturated or has one or more degrees of unsaturation. Multiple degrees of substitution are included within the present definition. Examples of "heterocyclic" groups include, but are not limited to tetrahydrofuranyl, pyranyl, 1,4-dioxanyl, 1,3-dioxanyl, piperidinyl, pyrrolidinyl, morpholinyl, azetidinyl, piperazinyl, pyrrolidinonyl, piperazinonyl, pyrazolidinyl, and their various tautomers.

As used herein, the term "aryl", unless otherwise defined, is meant aromatic, hydrocarbon, ring system. The ring system may be monocyclic or fused polycyclic (e.g., bicyclic, tricyclic, etc.), substituted or unsubstituted. In various embodiments, the monocyclic aryl ring is C5-C10, or C5-C7, or C5-C6, where these carbon numbers refer to the number of carbon atoms that form the ring system. A C6 ring system, i.e. a phenyl ring, is a suitable aryl group. In various embodiments, the polycyclic ring is a bicyclic aryl group, where suitable bicyclic aryl groups are C8-C12, or C9-C10. A naphthyl ring, which has 10 carbon atoms, is a suitable polycyclic aryl group. Suitable substituents for aryl are described below in the definition of "optionally substituted".

As used herein, the term "heteroaryl", unless otherwise defined, is meant an aromatic ring system containing carbon(s) and at least one heteroatom. Heteroaryl may be monocyclic or polycyclic, substituted or unsubstituted. A monocyclic heteroaryl group may have 1 to 4 heteroatoms in the ring, while a polycyclic heteroaryl may contain 1 to 10 hetero atoms. A polycyclic heteroaryl ring may contain fused, spiro or bridged ring junctions, for example, bicyclic heteroaryl is a polycyclic heteroaryl. Bicyclic heteroaryl rings may contain from 8 to 12 member atoms. Monocyclic heteroaryl rings may contain from 5 to 8 member atoms (carbons and heteroatoms). Exemplary heteroaryl groups include but are not limited to: benzofuran, benzothiophene, furan, imidazole, indole, isothiazole, oxazole, pyrazine, pyrazole, pyridazine,

pyridine, pyrimidine, pyrrole, quinoline, quinazoline, quinoxaline, thiazole, and thiophene. Suitable substituents for heteroaryl are described below in the definition of "optionally substituted".

As used herein, the term "cyano" refers to the group -CN.

As used herein, the term "acyl" refers to the group $-C(O)R^b$, where R^b is alkyl, cycloalkyl, or heterocyclyl, as each is defined herein.

As used herein, the term "ester" refers to the group $-C(O)OR^e$, where R^e is C_1-C_6alkyl, or C_3-C_6cycloalkyl.

As used herein, the term "urea" refers to the group $-NR^cC(O)NR^d$, wherein R^c and R^d are each independently H, C_1-C_6alkyl, or C_3-C_6cycloalkyl.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) that occur and event(s) that do not occur.

As used herein, unless otherwise defined, the phrase "optionally substituted" or variations thereof denote an optional substitution, including multiple degrees of substitution, with one or more substituent group, preferably one, two or three. The phrase should not be interpreted as duplicative of the substitutions herein described and depicted. Exemplary optional substituent groups include acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, oxo, and nitro.

PHARMACEUTICAL COMPOSITIONS

The invention further provides a pharmaceutical composition (also referred to as pharmaceutical formulation) comprising a compound of Formula I or pharmaceutically acceptable salt, thereof and one or more excipients (also referred to as carriers and/or diluents in the pharmaceutical arts). The excipients are acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof (i.e., the patient).

In accordance with another aspect of the invention there is provided a process for the preparation of a pharmaceutical composition comprising mixing (or admixing) a compound of Formula I or salt thereof with at least one excipient.

Pharmaceutical compositions may be in unit dose form containing a predetermined amount of active ingredient per unit dose. Such a unit may contain a therapeutically effective dose of the compound of Formula I or salt thereof or a fraction of a therapeutically effective dose such that multiple unit dosage forms might be administered at a given time to achieve the desired therapeutically effective dose. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well-known in the pharmacy art.

Pharmaceutical compositions may be adapted for administration by any appropriate route, for example, by oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intramuscular, intravenous, or intradermal) routes. Such compositions may be prepared by any method known in the art of pharmacy, for example, by bringing into association the active ingredient with the excipient(s).

When adapted for oral administration, pharmaceutical compositions may be in discrete units such as tablets or capsules; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; oil-in-water liquid emulsions or water-in-oil liquid emulsions. The compound or salt thereof of the invention or the pharmaceutical composition of the invention may also be incorporated into a candy, a wafer, and/or tongue tape formulation for administration as a "quick-dissolve" medicine.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders or granules are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agents can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin or non-gelatinous sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicine when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars, such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, xanthan gum, and the like.

Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, and aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a

quaternary salt, and/or an absorption agent such as bentonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compound or salt of the present invention can also be combined with a free-flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear opaque protective coating consisting of a sealing coat of shellac, a coating of sugar, or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different dosages.

Oral fluids such as solutions, syrups, and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of active ingredient. Syrups can be prepared by dissolving the compound or salt thereof of the invention in a suitably flavoured aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound or salt of the invention in a non-toxic vehicle. Solubilizers and emulsifiers, such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil, natural sweeteners, saccharin, or other artificial sweeteners, and the like, can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as, for example, by coating or embedding particulate material in polymers, wax, or the like.

In the present invention, tablets and capsules are preferred for delivery of the pharmaceutical composition.

As used herein, the term “treatment” includes prophylaxis and refers to alleviating the specified condition, eliminating or reducing one or more symptoms of the condition, slowing or eliminating the progression of the condition, and preventing or delaying the reoccurrence of the condition in a previously afflicted or diagnosed patient or subject. Prophylaxis (or prevention or delay of disease onset) is typically accomplished by administering a drug in the same or similar manner as one would to a patient with the developed disease or condition.

The present invention provides a method of treatment in a mammal, especially a human, suffering from obesity, diabetes, hypertension, depression, anxiety, drug addiction, substance addiction, or a combination thereof. Such treatment comprises the step of administering a therapeutically effective amount of a compound of Formula I or salt thereof to said mammal, particularly a human. Treatment can also comprise the step of administering a therapeutically effective amount of a pharmaceutical composition containing a compound of Formula I or salt thereof to said mammal, particularly a human.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought, for instance, by a researcher or clinician.

The term “therapeutically effective amount” means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function. For use in therapy, therapeutically effective amounts of a compound of Formula I, as well as salts thereof, may be administered as the raw chemical. Additionally, the active ingredient may be presented as a pharmaceutical composition.

While it is possible that, for use in therapy, a therapeutically effective amount of a compound of Formula I or salt thereof may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or formulation.

The precise therapeutically effective amount of a compound or salt thereof of the invention will depend on a number of factors, including, but not limited to, the age and weight of the subject (patient) being treated, the precise disorder requiring treatment and its severity, the nature of the pharmaceutical formulation/composition, and route of administration, and will ultimately be at the discretion of the attending physician or veterinarian. Typically, a compound of Formula I or salt thereof will be given for the treatment in the range of about 0.1 to 100 mg/kg body weight of recipient (patient, mammal) per day and more usually in the range of 0.1 to 10 mg/kg body weight per day. Acceptable daily dosages may be from about 1 to about 1000 mg/day, and preferably from about 1 to about 100 mg/day. This amount may be given in a single dose per day or in a number (such as two, three, four, five, or more) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt thereof may be determined as a proportion of the effective amount of the compound of Formula I per se. Similar dosages should be appropriate for treatment (including prophylaxis) of the other conditions referred herein for treatment. In general, determination of appropriate dosing can be readily arrived at by one skilled in medicine or the pharmacy art.

Additionally, the present invention comprises a compound of Formula I or salt thereof or a pharmaceutical composition thereof with at least one other anti-obesity drug and/or at least one anti-diabetes drug. Such anti-obesity drugs can include, for example, Metformin (or glucophage), CB1 receptor antagonists, GLP-1 agonists, opioid antagonists, and neurotransmitter reuptake inhibitors. When a compound of the invention is employed in combination with another anti-obesity drug or anti-diabetes drug, it is to be appreciated by those skilled in the art that the dose of each compound or drug of the combination may differ from that when the drug or compound is used alone. Appropriate doses will be readily appreciated and determined by those skilled in the art. The appropriate dose of the compound of Formula I or salt thereof and the other

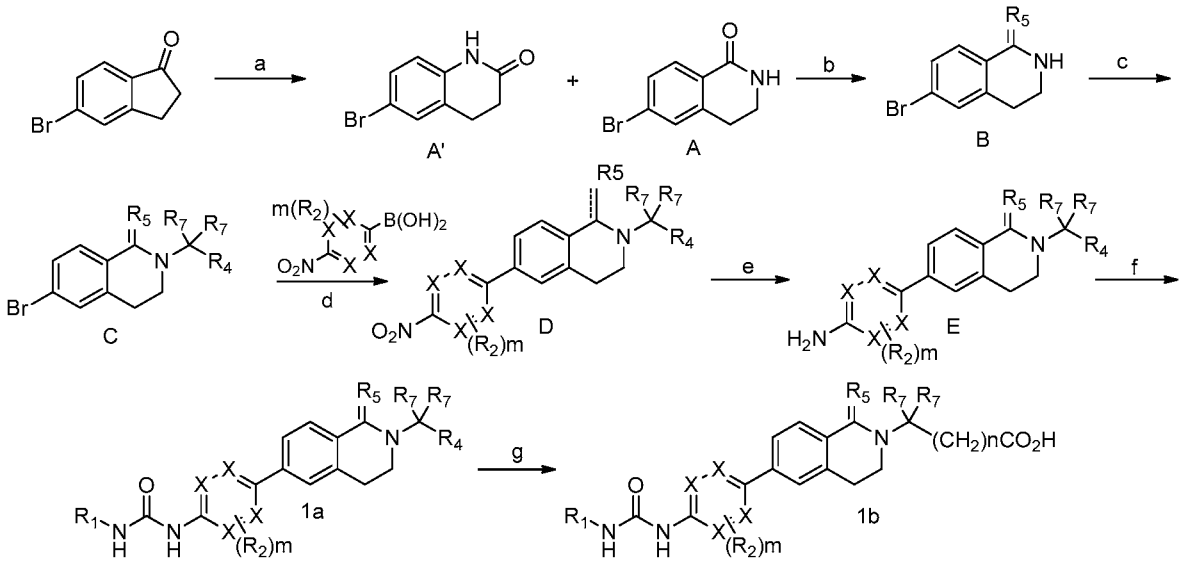
therapeutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect, and are with the expertise and discretion of the attending doctor or clinician.

COMPOUNDS PREPARATION

Generic Synthesis Schemes

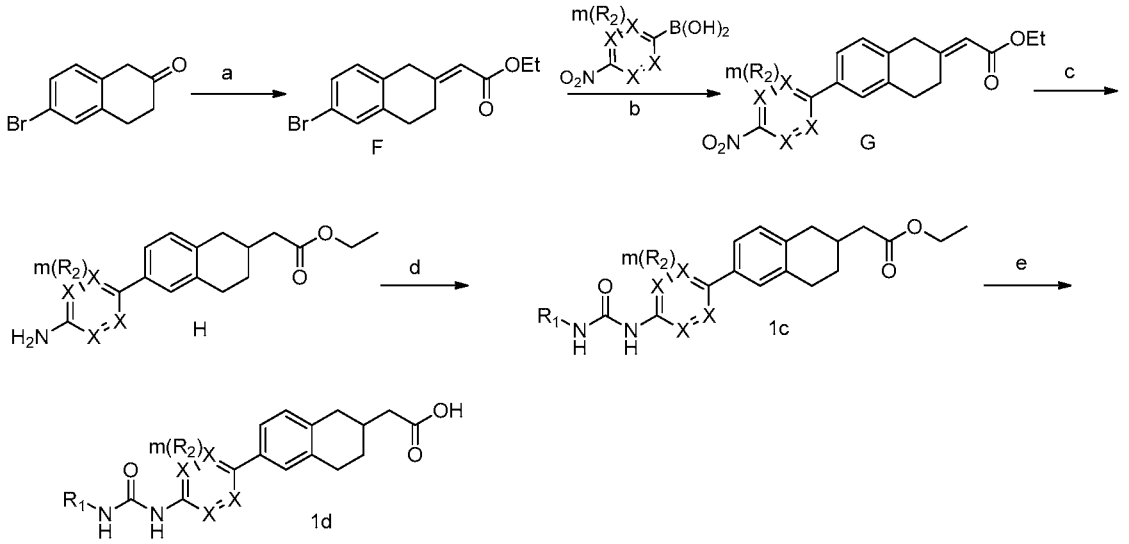
The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working examples. The skilled artisan will appreciate that if a substituent described herein is not compatible with the synthetic methods described herein, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions. The protecting group may be removed at a suitable point in the reaction sequence to provide a desired intermediate or target compound. In all of the schemes described below, protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles of synthetic chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T.W. Green and P.G.M. Wuts, (1991) *Protecting Groups in Organic Synthesis*, John Wiley & Sons, incorporated by reference with regard to protecting groups). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection of processes as well as the reaction conditions and order of their execution shall be consistent with the preparation of compounds of the present invention.

The synthesis of the compounds of the general Formula (I) and pharmaceutically acceptable derivatives and salts thereof may be accomplished as outlined below in Schemes 1 – 15 by those skilled in the art. In the following description, the groups are as defined above for compounds of Formula (I) unless otherwise indicated. Starting materials are commercially available or are made from commercially available starting materials using methods known to those skilled in the art.



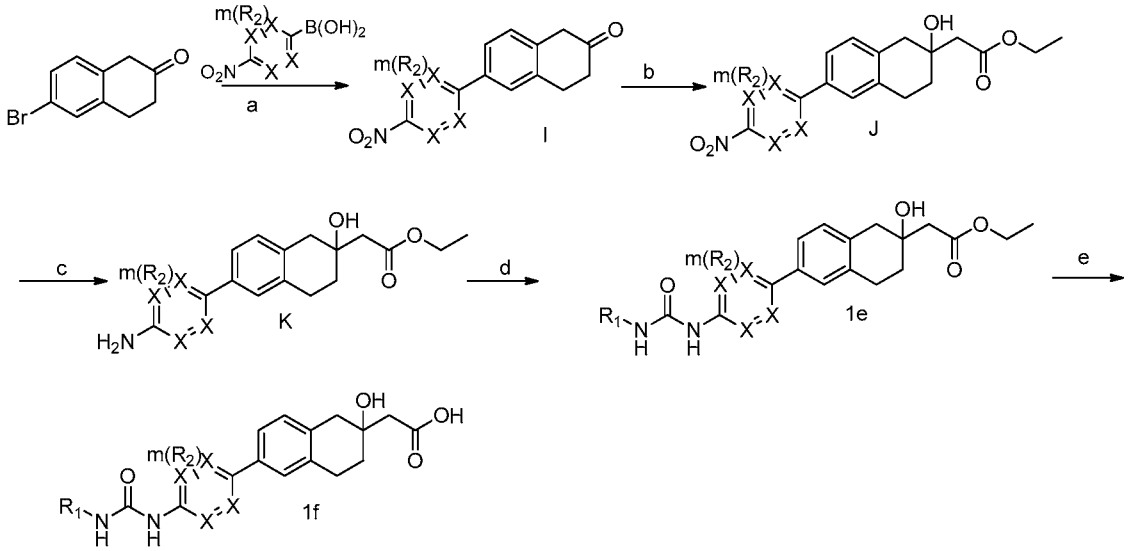
Scheme 1. Reagents and conditions: a) NaN_3, $MeSO_3H$, CH_2Cl_2, RT; b) BH_3:SMe_2, THF, 60 °C; c) X-C(R_7)(R_7)R_4, Et_3N, CH_2Cl_2, RT; d) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; e) 10% Pd/C, EtOH, H_2, RT; f) R_1NCO, Et_3N, THF, RT; g) LiOH, THF-H_2O, RT.

Compounds of Formula (I) may be prepared as illustrated in Scheme 1. Intermediate **A** can be obtained by rearrangement reaction of 5-bromo-1-indanone with NaN_3 in $MeSO_3H$ in solvents such as CH_2Cl_2. Reduction of intermediate **A** with reducing agent such as BH_3:SMe_2 in solvents such as THF affords intermediate **B** (R_5=H) which can be alkylated using appropriately substituted alkyl halide (X-C(R_7)(R_7)R_4) and base such as Et_3N under standard conditions known to those skills in the art to form **C**. Intermediate **A** can also be alkylated directly with appropriately substituted alkyl halide under similar conditions to form intermediate **C** where R_5 is oxo. Palladium-catalyzed Suzuki coupling of intermediate **C** with appropriately substituted boronic acid or ester in the presence of base such as Cs_2CO_3 under standard conditions affords intermediate **D**. Reduction of nitro functional group in **D** under standard hydrogenation reduction condition provides aniline intermediate **E**. Coupling of **E** with appropriately substituted isocyanate affords urea compounds of Formula (I) (**1a** where R_5 is H). In compound **1a** where R_4 is $–CH_2C(O)OR^e$ or $-C(O)OR^e$, hydrolysis of the ester group with base such as LiOH provides another compound of Formula (I)(**1b**) where R_4 is $–CH_2C(O)OH$ or $–C(O)OH$ respectively.



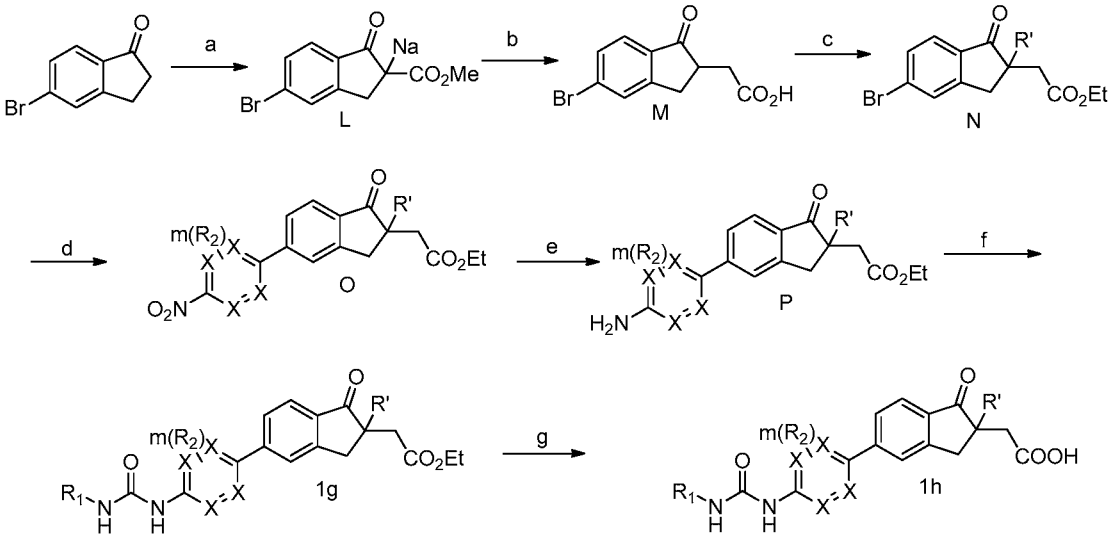
Scheme 2. Reagents and conditions: a) $Ph_3P=CHCO_2Et$, NaH, DMF, RT; b) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; c) Pd/C, MeOH, H_2, RT; d) R_1NCO, Et_3N, THF, RT; e) LiOH, THF-H_2O, RT.

Compounds of Formula (I) may be prepared as illustrated in Scheme 2. Intermediate **F** can be prepared from 6-bromo-2-tetralone using standard Wittig reaction conditions such as $Ph_3P=CHCO_2Et$ with base such as NaH in solvent such as DMF. Palladium catalyzed Suzuki coupling of **F** with appropriately substituted boronic acid/ester in the presence of base such as Cs_2CO_3 affords nitro intermediate **G**. Standard hydrogenation reduction reaction converts **G** to aniline **H** which can be coupled with appropriately substituted isocyanate (R_1NCO) to form compound of Formula (I) (**1c**). The ester in **1c** can be further hydrolyzed under basic conditions such as LiOH in THF-H_2O to another compound of Formula (I) (**1d**).



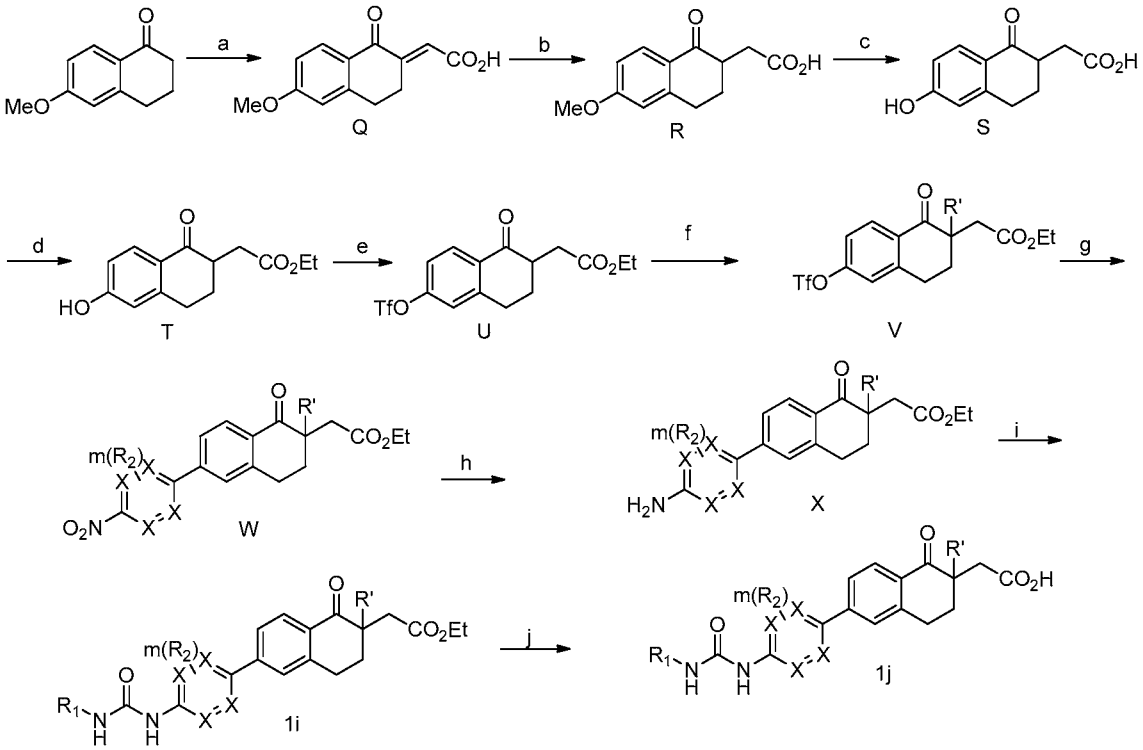
Scheme 3. Reagents and conditions: a) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; b) EtOAc, LiHMDS, THF, -78 °C to RT; c) Pd/C, MeOH, H_2, RT; d) R_1NCO, Et_3N, THF, RT; e) NaOH, MeOH-THF-H_2O, RT.

Compounds of Formula (I) may be prepared as illustrated in Scheme 3. Palladium-catalyzed Suzuki coupling of 6-bromo-2-tetralone with appropriately substituted boronic acid/ester affords intermediate **I** which can be converted to intermediate **J** in the presence of ethyl acetate in Li-HMDS in solvent such as THF. Reduction of the nitro group in **J** using standard hydrogenation conditions provides aniline **K** which can be coupled with appropriately susbstituted isocyanate (R_1NCO) to provide compound of Formula (I) (**1e**). Further hydrolysis of the ester group in **1e** with base such as NaOH in solvent such as MeOH-THF-H_2O affords another compound of Formula (I) (**1f**).



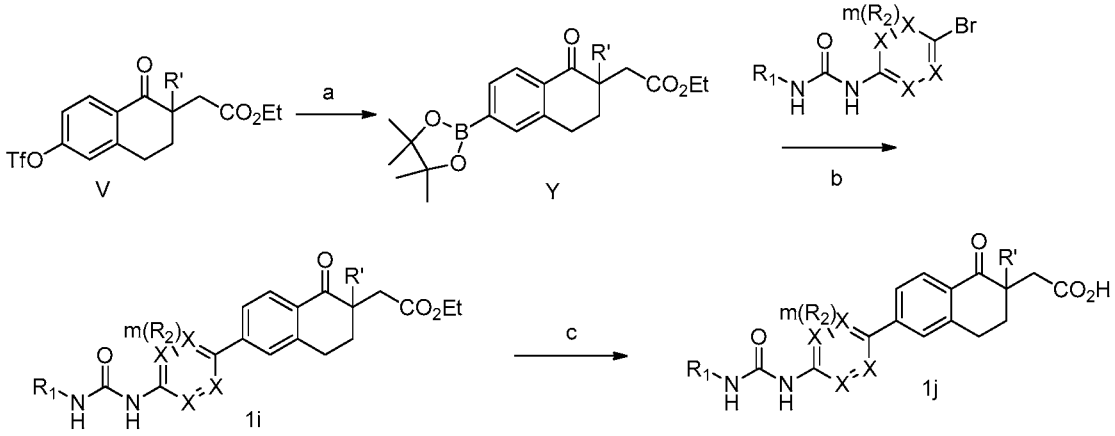
Scheme 4. Reagents and conditions: a) $CO(OMe)_2$, NaH, THF, 75 °C; b) $BrCH_2COOEt$, THF, 75 °C; c) NaH, R'-X, DMF, RT; d) substituted boronic acid/ester, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; e) Fe/NH_4Cl, EtOH-H_2O, 85 °C; f) R_1NCO, Et_3N, THF, RT; g) LiOH, Dioxane-H_2O, RT.

Compounds of Formula (I) may be prepared as illustrated in Scheme 4. 5-Bromo indanone can be converted to intermediate **L** in the presence of NaH and dimethyl carbonate. Intermediate **L** can be converted to intermediate **M** with ethyl bromo acetate followed by decarboxylation conditions. Alkylation of **M** with appropriately substituted alkylating agent such as alkyl halide (eg R'-X wherein R' can be substituted C_1-C_3alkyl, and X can be halo such as iodo) provides intermediate **N** which can be converted to compounds of Formula (I) (**1g**, **1h**) using Suzuki coupling, nitro reduction, urea formation, and/or subsequent hydrolysis conditions as described in Scheme 1-2. Intermediate **M** can also undergo similar chemical transformation (Suzuki coupling, nitro reduction, urea formation, and/or subsequent hydrolysis condition) to form compounds of Formula (I) (**1g**, **1h**) where R' is H.



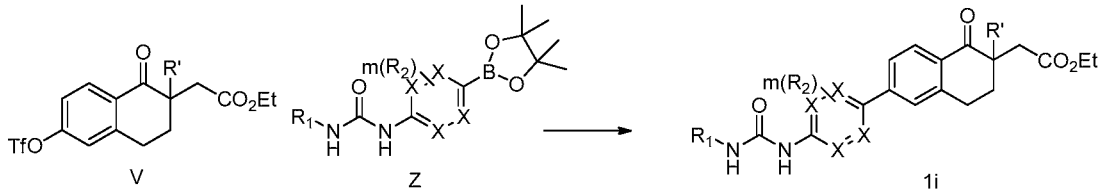
Scheme 5. Reagents and conditions: a) Glyoxalic acid, H_2SO_4, diglyme, 85 °C; b) Zn, AcOH, 80 °C; c) Aq. HBr, 100 °C; d) $MeSO_3H$, EtOH, RT; e) Tf_2O, CH_2Cl_2, Et_3N, RT; f) R'-X, NaH, DMF, RT; g) Substituted boronic acid/ester, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; h) Pd/C, H_2, EtOH, RT; i) R_1NCO, Et_3N, THF, RT; j) LiOH, EtOH-H_2O, RT.

Compounds of Formula (I) may be prepared as illustrated in Scheme 5. 6-Methoxytetralone can be converted to intermediate **Q** using glyoxalic acid followed by sulphuric acid in diglyme under heating condition. Reduction of the olefin in the presence of reducing condition such as Zn in AcOH affords intermediate **R** which can be demethylated using aqueous HBr to provide phenol compound **S**. Esterification of **S** under standard conditions provides ester **T** where phenol functional group can be protected as triflate **U** using triflate anhydride under basic conditions. Alkylation of **U** with appropriately substituted alkyl halide (R'-X) such as methyl iodide, ethyl iodide, propyl iodide or trifluoroethyl iodide provides intermediate **V** which can be converted to compounds of Formula (I) (**1i**, **1j**) using Suzuki coupling, nitro reduction, urea formation, and/or subsequent hydrolysis conditions as described in Scheme 1-2. Intermediate **U** can also undergo similar chemical transformation (Suzuki coupling, nitro reduction, urea formation, and/or subsequent hydrolysis condition) to form compounds of Formula (I) (**1i**, **1j**) where R' is H.



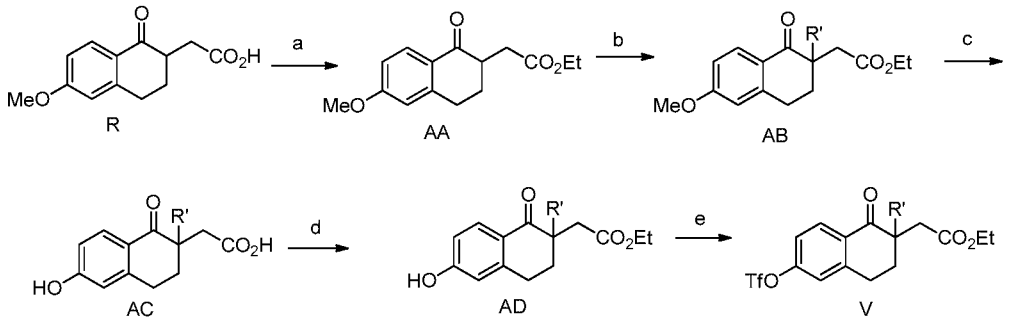
Scheme 6. Reagents and conditions: a) 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane, $PdCl_2(dppf)$, KOAc, Dioxane, 100 °C; b) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; c) LiOH, EtOH-H_2O, RT.

Alternatively compounds of Formula (I) may be prepared as illustrated in Scheme 6. Intermediate **V** can be converted to boronic ester which can then undergo Palladium catalyzed Suzuki reaction with the appropriately substituted aryl or heteroaryl halide to form compounds of Formula (I) (**1i**). Appropriately substituted aryl or heteroaryl halides can be prepared using reaction conditions known to those skilled in the art, eg, by coupling of appropriately substituted amines with appropriately substituted isocyanates. **1i** can be subsequently converted to another compounds of Formula (I) (**1j**) by standard hydrolysis conditions.



Scheme 7.

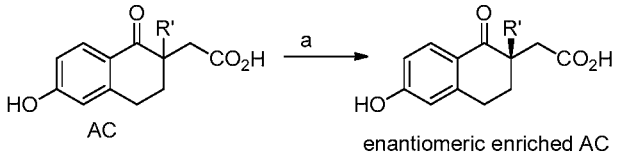
Alternatively compounds of Formula (I) may be prepared as illustrated in Scheme 7 by reversing the coupling partners as in Scheme 6. Intermediate **V** can be coupled with appropriately substituted boronic ester **Z** to form compounds of Formula (I) (**1i**) using palladium-catalyzed Suzuki coupling conditions. Appropriately substituted boronic ester **Z** can be prepared using reaction conditions known to those skilled in the art, eg, by converting the appropriately substituted aryl or heteroaryl halides to boronic esters using bis-pinacolato diborance in the presence of KOAc and catalytic amount of $PdCl_2(dppf)$ in solvent such as DMF under heated conditions.



Scheme 8. Reagents and conditions: a) $MeSO_3H$, EtOH, RT; b) R'-X, NaH, DMF, RT; c) Aq. HBr, 100 °C; d) $MeSO_3H$, EtOH, RT; e) Tf_2O, CH_2Cl_2, Et_3N, RT.

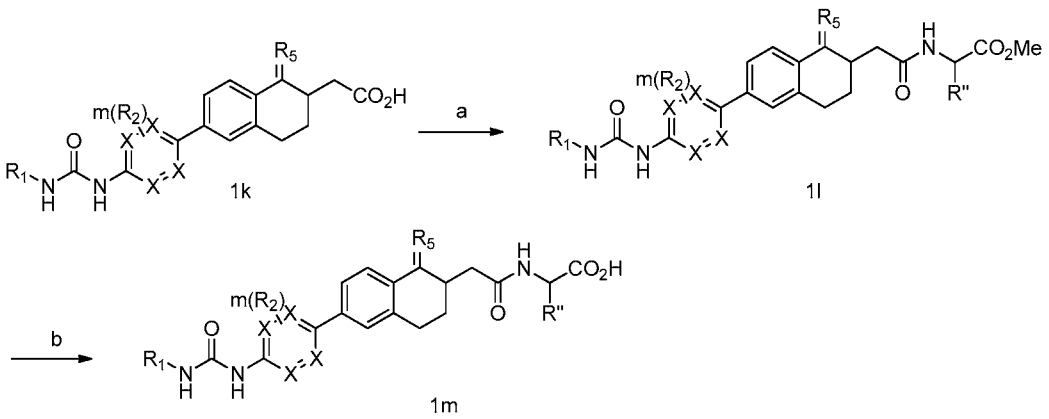
Intermediate **V** may also be prepared as illustrated in Scheme 8. Esterification of **R** provides ester **AA** which can be alkylated with appropriately substituted alkyl halide (R'-X) such as MeI, EtI and trifluoroethyl iodide to give intermediate **AB**. Demethylation of **AB** provides phenol **AC** which can be esterified to afford **AD**. Phenol group can then be protected as triflate to form intermediate **V**. Intermediate **V** can be converted to compounds of Formula (I) using Schemes 5-7 described above.

Enantiomeric enriched compounds may be obtained by chiral separation of appropriate intermediates or compounds of Formula (I). For example, for the racemic mixture of compounds **1i**, pure enantiomers may be separated on the chiral column using chiral columns such as CHIRAL PAKIA (4.6x250 mm) 5 μ and appropriate mobile phases to give enantiomeric enriched compounds of **1i**. The enantiomeric enriched compounds of **1i** can then undergo additional chemical transformation such as ester hydrolysis to provide enantiomeric enriched compounds of **1j**.



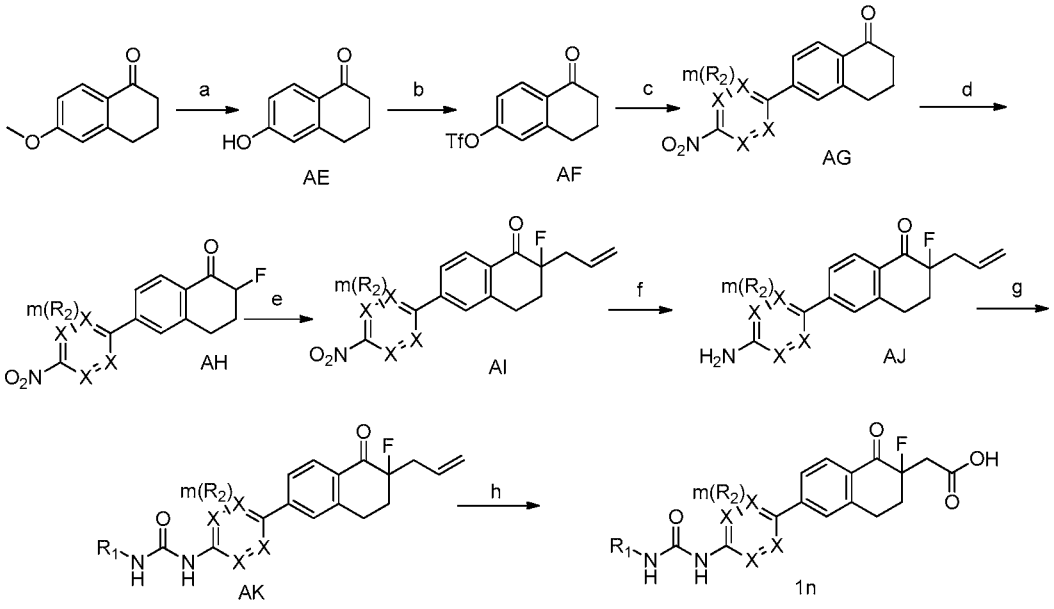
Scheme 9. Reagents and conditions: a) Cinchonidine, IPA-H_2O, 80 °C – RT, 24h then 6N HCl.

Alternatively, enantiomeric enriched compounds may be obtained by chemical resolution of racemic mixture of compounds. For example, as shown in Scheme 9, racemic intermediate **AC** can be resolved to enantiomeric pure **AC** using cinchonidine in the presence of solvents such as IPA-H_2O. The enantiomeric enriched intermediate AC can then converted to enantiomeric enriched compounds of Formula (I) (**1i**, **1j**) using reactions similarly to those described in Schemes 5-8.



Scheme 10. Reagents and conditions: a) HATU, THF, amino acid methyl ester (NH_2-CH(R")CO_2Me), RT; b) LiOH, THF-H_2O, RT.

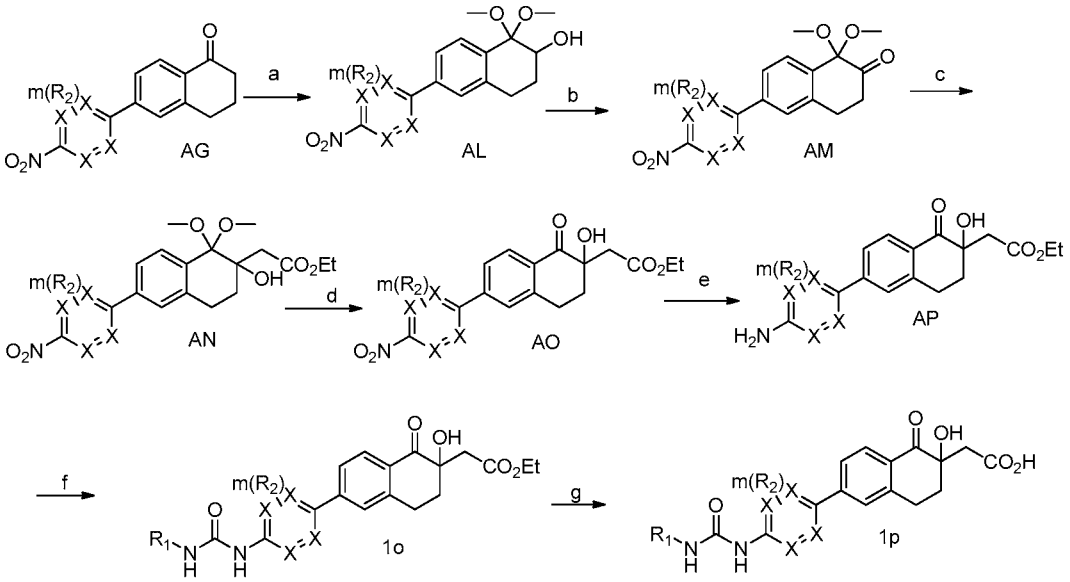
Compound of Formula (I) may be converted to another compound of Formula (I) using chemical transformation known to those skilled in the art. For example, as shown in Scheme 10, compound of Formula (I) (**1k**) can be coupled with methyl ester of amino acid (NH_2-CH(R")CO_2Me) under coupling conditions known to those skilled in the art to another compound of formula I (**1l**) which can then be hydrolyzed to form compound of Formula (I) (**1m**).



Scheme 11. Reagents and conditions: a) Aq HBr Reflux; b) Tf_2O, DMAP, Py, RT; c) Substituted aryl/heteroaryl boronic acid or ester, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; d) select Fluor, MeOH, 80 °C; e) Allyl bromide, TBAI, KOH, RT; f) Fe/NH_4Cl, EtOH, H_2O, Reflux; g) R_1NCO, Et_3N, THF, RT; h) $KMnO_4$, $NaIO_4$, acetone-H_2O, RT.

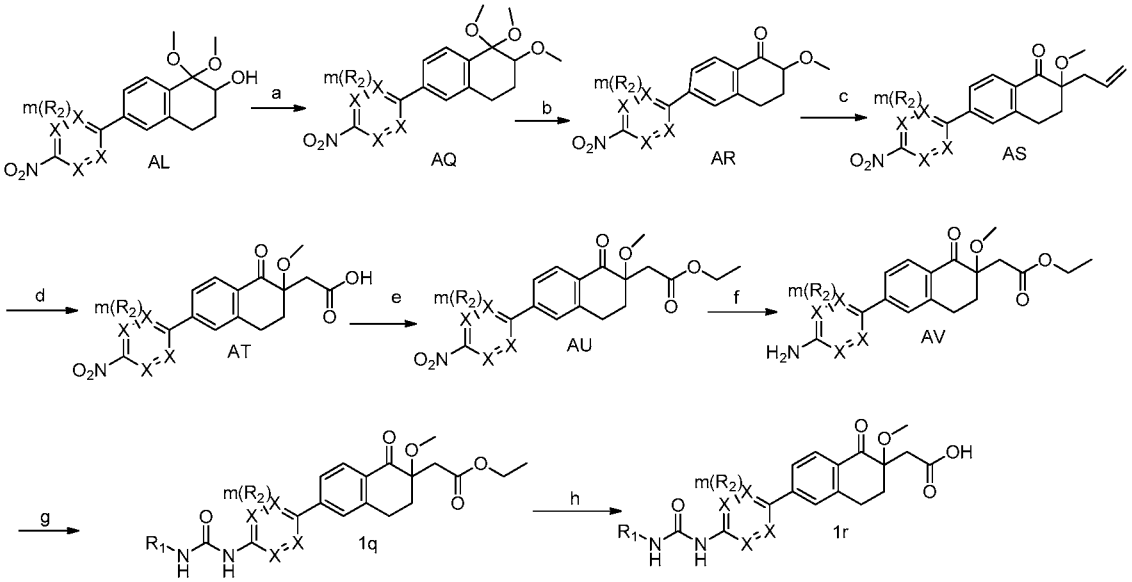
Compounds of Formula (I) may be prepared as illustrated in Scheme 11. 6-Methoxy-1-tetralone can be demethylated to give phenol **AE** which is then protected as triflate **AF**. Palladium catalyzed Suzuki coupling of **AF** with appropriately substituted aryl/heteroaryl boronic acid or ester affords **AG** which can be fluorinated to give **AH**. Alkylation with allyl bromide provides **AI** which can be reduced by hydrogenation conditions to provide **AJ**. Coupling of **AJ** with

appropriately substituted isocyanate affords **AK**. Oxidation of **AK** with oxidizing agents such as $KMnO_4$ and $NaIO_4$ in solvents such as acetone-water provides compound of Formula (I) (**1n**).



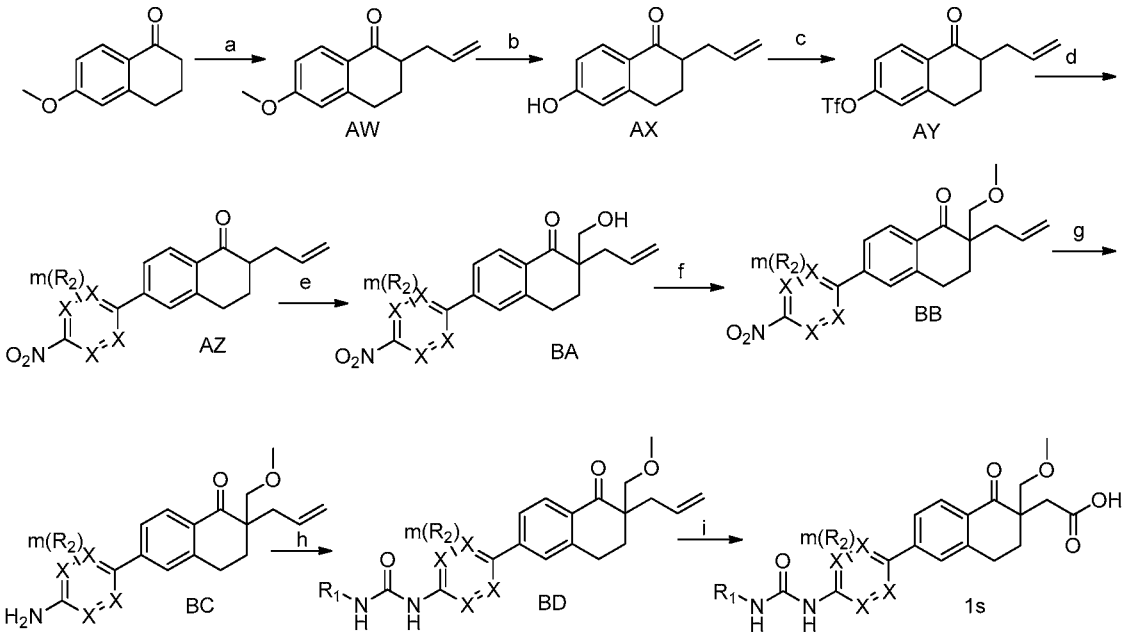
Scheme 12. Reagents and conditions: a) $PhI(OAc)_2$, KOH, MeOH, RT; b) Pyridinum dichromate, AcOH, CH_2Cl_2, RT; c) LiHMDS, EtOAc, THF, 0 °C to RT; d) 3N HCl, MeOH, RT; e) Pd/C, H_2, EtOH, RT; f) R_1NCO, Et_3N, THF, RT; g) LiOH, MeOH-THF-H_2O, RT.

Compounds of Formula (I) may be prepared as illustrated in Scheme 12. Hydroxylation of **AG** provides **AL** which can be oxidized to ketone **AM**. Addition of EtOAc in LiHMDS to ketone **AM** affords **AN** which then reacts with 3N HCl to provides **AO**. Hydrogenation of the nitro group in **AO** gives aniline **AP** which can react with appropriately substituted isocyanate to provide urea compound of Formula (I) (**1o**). Hydrolysis of **1o** provides another compound of Formula (I) (**1p**).



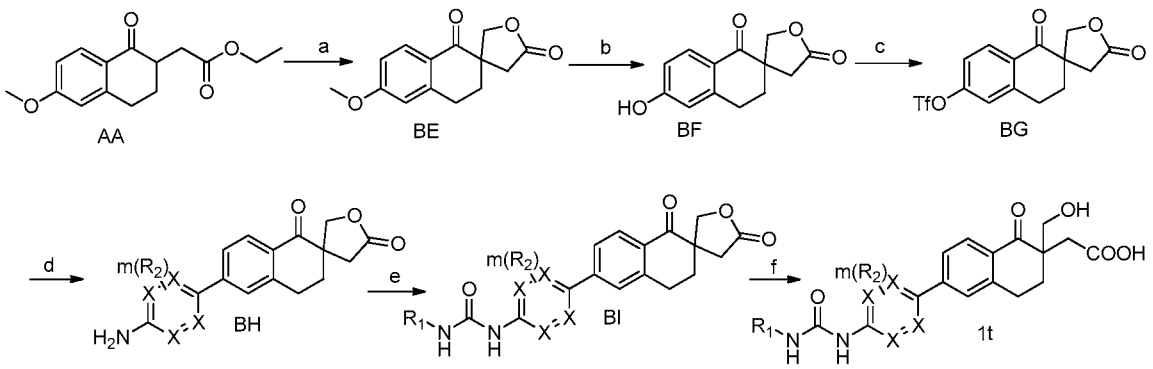
Scheme 13. Reagents and conditions: a) NaH, MeI, THF, RT; b) 3N HCl, EtOH, RT; c) Allyl bromide, TBAI, KOH, toluene, RT; d) $KMnO_4$, $NaIO_4$, RT; e) $MeSO_3H$, EtOH, RT; f) Fe-NH_4Cl, EtOH-H_2O, 90 °C; g) R_1NCO, Et_3N, THF, RT; h) LiOH, THF-H_2O, RT, 12h.

Compounds of Formula (I) may be prepared as illustrated in Scheme 13. Alkylation of intermediate **AL** with alkylating agent such as MeI under basic condition provides **AQ** which then reacts with HCl to provide ketone **AR**. Alkylation of **AR** with allyl bromide affords **AS** which can be oxidized to acid **AT**. Esterification of **AT** provides **AU** which then undergoes reduction and urea formation to form compound of Formula (I) (**1q**). Subsequent hydrolysis of **1q** provides another compound of Formula (I) (**1r**).



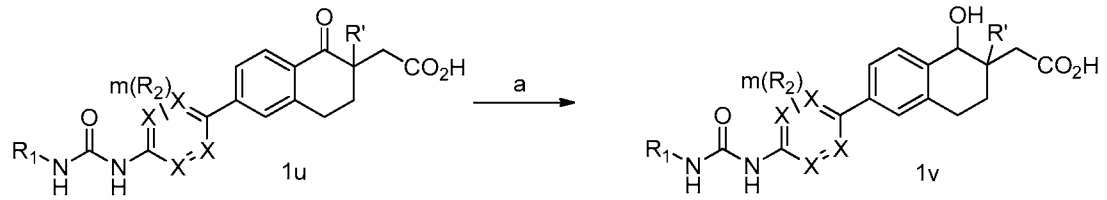
Scheme 14. Reagents and conditions: a) Allyl bromide, KOtBu, THF, RT; b) BBr_3, CH_2Cl_2, RT; c) Tf_2O, Py, CH_2Cl_2, RT; d) Substituted aryl/heteroaryl boronic acid/ester, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; e) HCHO, 2N NaOH, THF, RT; f) NaH, MeI, THF, RT; g) Fe-NH_4Cl, EtOH-H_2O, 90 °C; h) R_1NCO, Et_3N, THF, RT; i) $KMnO_4$, $NaIO_4$, Acetone-H_2O, RT.

Compounds of Formula (I) may be prepared as illustrated in Scheme 14. Alkylation of 6-methoxy-1-tetralone with allyl bromide under basic condition affords **AW**. Demethylation of **AW** gives phenol **AX** which forms triflate **AY** using standard conditions known to those skilled in the art. Suzuki coupling of **AY** with appropriately substituted boronic acid or ester provides nitro intermediate **AZ** which then reacts with formaldehyde to form alcohol **BA**. Alkylation of alcohol with alkylating agent such as methyl iodide provides **BB**. Hydrogenation of the nitro group in **BB** affords aniline **BC** which can then react with appropriately substituted isocyanate to form urea compound **BD**. Oxidation of the olefin in **BC** provides compound of Formula (I) (**1s**).



Scheme 15. Reagents and conditions: a) HCHO, 2N NaOH, THF, RT; b) Aq HBr, 100 °C; c) Tf_2O, Py, CH_2Cl_2, RT; d) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; e) R_1NCO, Et_3N, THF, RT; f) LiOH, THF-H_2O, RT;

Compounds of Formula (I) may be prepared as illustrated in Scheme 15. Cyclic ester **BE** can be formed from intermediate **AA** using formaldehyde in NaOH and THF as solvent. Demethylation of **BE** with aqueous HBr affords phenol **BF** which can be converted to triflate **BG** using triflate anhydride and pyridine. Suzuki coupling of **BG** with appropriately substituted boronic acid or ester affords aniline **BH**. Coupling of **BH** with appropriately substituted isocyanate provides urea **BI** which can be hydrolyzed to form compound of Formula I (**1t**).



Scheme 16. Reagents and conditions: a) $NaBH_4$, MeOH, RT.

Compound of Formula (I) may be converted to another compound of Formula (I). For example, as illustrated in Scheme 16, compound of Formula I (**1u**) can be reduced under standard reduction conditions known to those skilled in the art to alcohol as in compound **1v**.

EXPERIMENTALS

The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention. Unless otherwise noted, reagents are commercially available or are prepared according to procedures in the literature. The symbols and conventions used in the descriptions of processes,

schemes, and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry.

In the Examples:

Chemical shifts are expressed in parts per million (ppm) units. Coupling constants (J) are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), dt (double triplet), m (multiplet), br (broad).

Flash column chromatography was performed on silica gel.

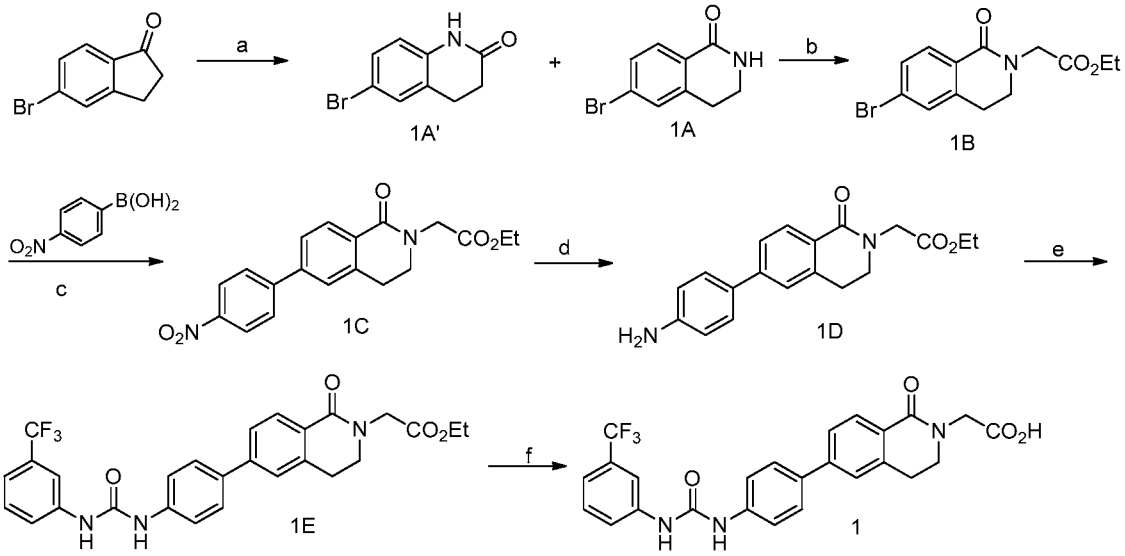
The naming programs used are ACDLABs 11.0 Namebatch, ACD IUPAC or Chem Draw.

Abbreviations

BH_3:SMe_2	borane:dimethyl sulfide
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
Cs_2CO_3	cesium carbonate
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
Fe	iron
h	hour(s)
H_2	hydrogen gas
H_2O	water
HATU	O-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
HBr	hydrobromic acid
HCl	hydrochloric acid
KOH	potassium hydroxide
KMnO4	potassium permanganate
LiHMDS	lithium hexamethyldisilazide
LiOH	lithium hydroxide
NaH	sodium hydride
$NaIO_4$	sodium periodate
NaN_3	sodium azide
NH_4Cl	ammonium chloride

MeI	methyl iodide
MeOH	methanol
$MeSO_3H$	methane sulfonic acid
Pd/C	palladium on carbon
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
Py	pyridine
rt	room temperature
TBAI	tetrabutyl ammonium iodide
THF	tetrahydrofuran
Tf_2O	triflate anhydride

Example-1



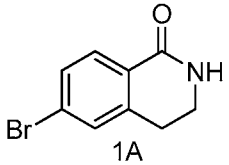
Reagents and conditions: a) NaN_3, $MeSO_3H$, CH_2Cl_2, RT, 8h; b) $BrCH_2CO_2Et$, NaH, THF, RT, 3h; c) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; d) 10% Pd/C, EtOH, H_2, RT, 4h; e) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; f) LiOH, THF-H_2O, RT, 14h.

.

Procedures:

2-(1-Oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetic acid:

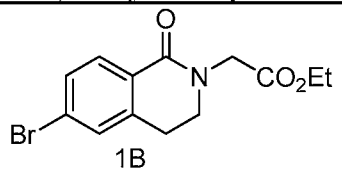
6-Bromo-3,4-dihydroisoquinolin-1(2H)-one (1A):



NaN_3 (6.2 g, 94.78 mmol) was added to a solution of 5-bromo-1-indanone (10 g, 47.39 mmol) in 40 mL of mixture of methane sulphonic acid and dichloromethane (1:1) in portion wise at 0 °C-5 °C. The resulting mixture was stirred for 8 h at room temperature. The reaction mixture was cooled to 0 °C in ice bath, neutralized with 5% aq. NaOH, and aqueous layer was extracted with ethyl acetate (2x100 mL). The combined organic layer was washed with water and brine solution, dried

over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum and purified by silica gel flash column chromatography using 30 % ethyl acetate in hexane to afford title compound (6.4 g, 60%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.4 Hz, 1H), 7.5 (d, J = 8.4 Hz, 1H), 7.4 (s, 1H), 6.1 (bs, 1H), 3.6 (t, J = 6.8 Hz, 2H), 3 (t, J = 6.4 Hz, 2H).

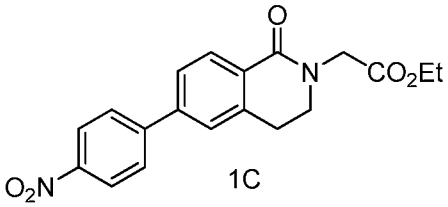
Ethyl 2-(6-bromo-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1B):



1B

NaH (0.42 g, 17.7 mmol) was added to an ice-cold solution of product of Example 1A (2 g, 8.8 mmol) in THF (40 ml) portion wise, and the mixture was stirred for 15 min. Ethyl bromo acetate (2.2 g, 13.2 mmol) was then added to the solution, and the mixture was stirred at room temperature for 3 h. Reaction mixture was quenched with ice-cold water and diluted with ethyl acetate. Organic layer was separated, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to afford title compound (3.3 g, 80%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.36 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.65 (t, J = 7.2 Hz, 2H), 3.04 (t, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H).

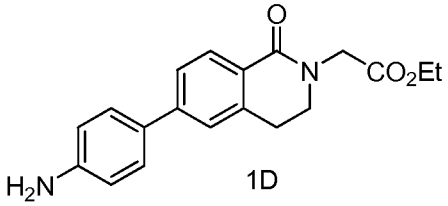
Ethyl 2-(6-(4-nitrophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1C):



1C

$Pd(PPh_3)_4$ (0.133 g, 0.115 mmol) was added to a solution of product of Example 1B (3 g, 9.6 mmol) in 35 mL of 1,4 dioxane-H_2O (5:1) mixture under argon atmosphere, followed by cesium carbonate (9.38 g, 28.7 mmol) and 4-nitrophenyl boronic acid (1.6 g, 9.6 mmol). The reaction mixture was degassed for 10 min. The reaction mixture was then refluxed for 5 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography using 30% ethyl acetate in hexane to afford title compound (2 g, 64%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33-8.3 (m, 2H), 8.2 (d, J = 7.5 Hz, 1H), 7.79-7.75 (m, 2H), 7.61 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 7.45 (s, 1H), 4.39 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.72 (t, J = 6.9 Hz, 2H), 3.16 (t, J = 6.9 Hz, 2H), 1.3 (t, J = 6.9 Hz, 3H).

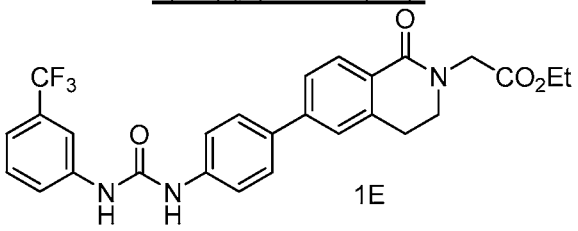
Ethyl 2-(6-(4-aminophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1D):



1D

Excess 10% Pd/C (0.5 g) was added to a solution of product of Example 1C (1.1 g, 3.09 mmol) in 20 mL of ethanol, and the mixture was stirred under H_2 atmosphere at room temperature for 4 h. The reaction mixture was filtered over celite bed, and filtrate was removed under reduced pressure and triturated with diethyl ether and pentane to afford title compound (0.97 g, 97%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 1H), 7.43 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.39 (m, 2H), 7.27 (s, 1H), 6.7 (m, 2H), 4.28 (s, 2H), 4.15 (q, J = 6.8 Hz, 2H), 3.69 (bs, 2H), 3.61 (t, J = 6.4 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H).

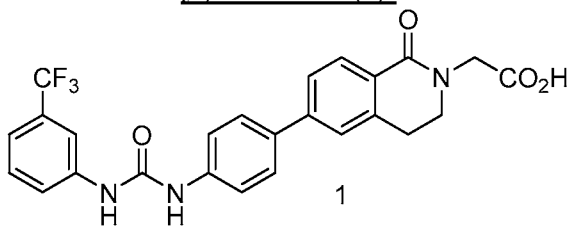
Ethyl 2-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetate (1E):



1E

3-(Trifluoromethyl)phenyl isocyanate (0.14 g, 0.769 mmol) was added to a solution of product of Example 1D (0.25 g, 0.76 mmol) and triethylamine (0.23 g, 2.3 mmol) in THF (10 mL), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was triturated with diethyl ether and pentane to afford title compound (0.26 g, 66%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.1 (bs, 1H), 8.97 (bs, 1H), 8.03 (s, 1H), 7.9 (d, J = 7.5 Hz, 1H), 7.71-7.5 (m, 8H), 7.34 (d, J = 7.5 Hz, 1H), 4.31 (s, 2H), 4.17 (q, J = 7.5 Hz, 2H), 3.67 (t, J = 6.3 Hz, 2H), 3.07 (t, J = 6.3 Hz, 2H), 1.22 (t, J = 6.9 Hz, 3H).

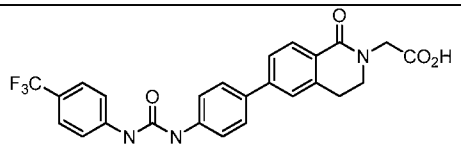
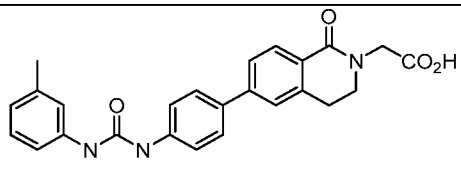
2-(1-Oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-3,4-dihydroisoquinolin-2(1H)-yl)acetic acid (1):

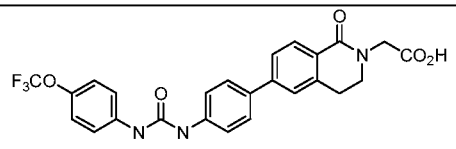
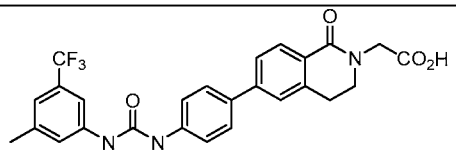
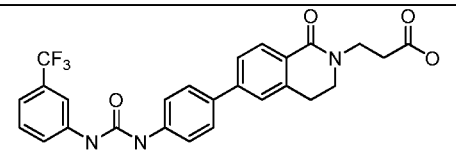
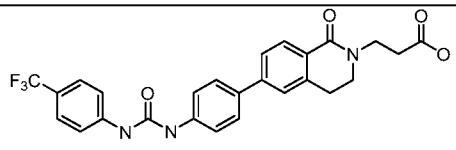
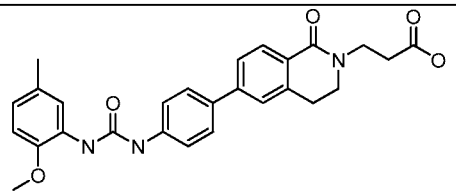
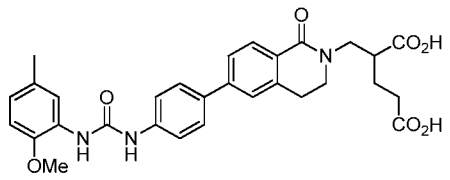


1

Lithium hydroxide (0.054 g, 1.17 mmol) was added to a solution of product of Example 1E (0.2 g, 0.39 mmol) in 10 mL of THF-water (4:1) mixture, and the mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 ^{0}C, and solids were collected by filtration and dried under vacuum to afford title compound (0.15 g, 79%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.2 (bs, 1H), 9.0 (bs, 1H), 8.05 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.68 (m, 3H), 7.64-7.58 (m, 4H), 7.52 (m, 1H), 7.0 (m, 1H), 4.2 (s, 2H), 3.65 (m, 2H), 3.05 (m, 2H); ESI-MS m/z = 482 $(M-H)^-$; HPLC purity: 96%.

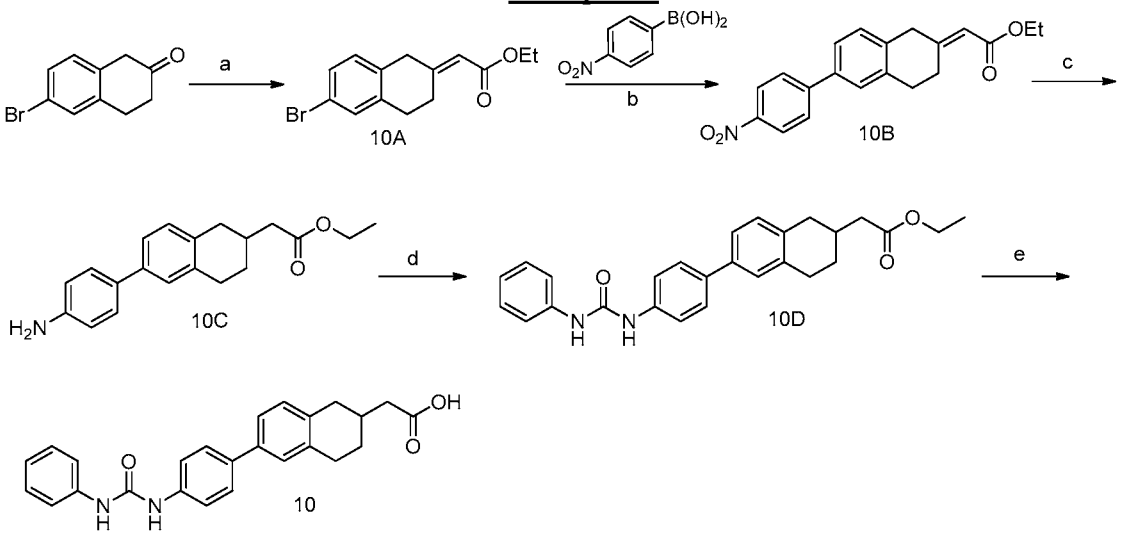
Examples 2 - 9 were prepared using procedures analogous to those described in Example 1 with appropriate starting materials.

Ex	Structure	^{1}H NMR data	Mass/Purity
2		^{1}H NMR (300 MHz, DMSO-d_6): δ 10.6 (bs, 1H), 7.9-7.78 (m, 4H), 7.6-7.3 (m, 7H), 4.0 (s, 2H), 3.7 (m, 2H), 3.0 (m, 2H).	ESI-MS m/z = 482 $(M-H)^-$; HPLC purity: 98.5%.
3		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.8 (bs, 1H), 9.2 (bs, 1H), 8.9 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.72-7.56 (m, 6H), 7.36-7.12 (m, 2H), 7.06 (t, 1H), 6.8 (d, J = 7.4 Hz, 1H), 4.2 (s, 2H), 3.65 (t, J = 6.8 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H), 2.26 (s, 3H).	ESI-MS m/z = 428 $(M-H)^-$; HPLC purity: 99%.

4		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.7 (bs, 1H), 9.1 (bs, 1H), 9.06 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.76-7.56 (m, 8H), 7.3 (m, 2H), 4.2 (s, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 3.05 (t, *J* = 6.6 Hz, 2H).	ESI-LCMS *m/z*: 500 $(M+H)^+$; (purity 97 %).
5		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.8 (bs, 1H), 9.7 (bs, 1H), 9.6 (bs, 1H), 7.9 (d, *J* = 8.1, 1H), 7.85 (s, 1H), 7.7-7.6 (m, 6H), 7.5 (s, 1H), 7.1 (s, 1H), 4.1 (s, 2H), 3.7 (m, 2H), 3.1 (m, 2H), 2.3 (s, 3H).	ESI-LCMS *m/z*: 497 (purity 96 %); HPLC purity 99 %.
6		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.47 (bs, 1H), 9.32 (bs, 1H), 8.05 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.67-7.56 (m, 7H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 6.8 Hz, 2H), 3.0 (t, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H).	ESI-LCMS *m/z*: 498 (purity 95 %).HPLC purity 93 %.
7		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.59 (bs, 1H), 9.39 (bs, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71-7.57 (m, 10H), 3.69 (m, 2H), 3.62 (m, 2H), 3.0 (m, 2H), 2.54 (m, 2H).	ESI-LCMS *m/z*: 498 (purity 95 %); HPLC purity 96.6 %.
8		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.50 (s, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.68-7.55 (m, 6H), 6.90 (d, *J* = 8 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.68 (t, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 6.8 Hz, 2H), 3.0 (t, *J* = 6.0 Hz, 2H), 2.54 (m, 2H), 2.24 (s, 3H).	ESI-LCMS *m/z*: 474 (purity 98.5 %); HPLC purity 98 %.
9		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.40 (s, 1H), 8.21 (s, 1H), 7.99 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.57-7.55 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.75 (m, 1H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.51 (m, 1H), 3.0 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 1H), 2.4-2.25 (m, 2H), 2.23 (s, 3H), 1.7 (q, *J* = 7.6 Hz,	ESI-LCMS *m/z*: 546 $(M+H)^+$; HPLC purity: 96%.

		2H).	

Example-10

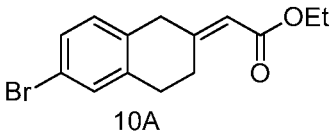


Reagents and conditions: a) $Ph_3P=CHCO_2Et$, NaH, DMF, RT, 18h; b) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 ^{0}C, 6h; c) Pd/C, MeOH, H_2, RT, 18h; d) PhNCO, Et_3N, THF, RT, 12h; e) LiOH, THF-H_2O, RT, 12h.

Procedure:

2-(6-(4-(3-(3,5-bis(Trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronapthalen-2-yl)acetic acid:

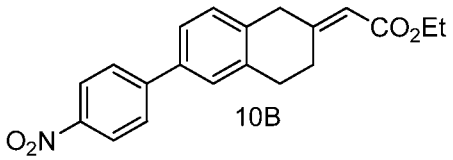
Ethyl 2-(6-bromo-3,4-dihydronapthalen-2(1*H*)-ylidene)acetate (10A):



10A

$Ph_3P=CHCO_2Et$ (5 g, 22.22 mmol) was added to an ice cold solution of 6-Bromo-2-tetralone (5.0 g, 22.22 mmol) and NaH (0.69 g, 28.88 mmol) in DMF (40 mL). The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with diethyl ether (2X100 mL). The organic layer wasdried over sodium sulphate, filtered and removed under reduced pressure to give crude product whicg was purified by flash chromatography using 2% ethyl acetate in hexanes to afford title compound (4.0 g, 61%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 2H), 6.96 (d, J = 7.8 Hz, 1H), 6.33 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.22 (s, 2H), 2.74 (t, J = 7.2 Hz, 2H), 2.21 (t, J = 7.8 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 297 $(M+H)^+$.

Ethyl 2-(6-(4-nitrophenyl)-3,4-dihydronapthalen-2(1*H*)-ylidene)acetate (10B):

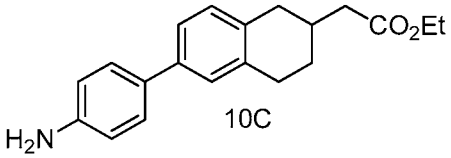


10B

$Pd(PPh_3)_4$ (0.18 g, 0.16 mmol) was added to a solution of product of Example 10A (4.0 g, 13.55 mmol) in 80 mL of 1,4 dioxane-H_2O (3:1) mixture under Argon atmosphere, followed by cesium carbonate (8.8 g, 27.11 mmol) and 4-nitrophenyl boronic acid (2.25 g, 13.55 mmol). The reaction

mixture was degassed for 5 min. The reaction mixture was refluxed for 6 h and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 12% ethyl acetate in hexanes to afford title compound (4.0 g, 87%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 9.3 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.40 (m, 2H), 7.12 (d, J = 7.8 Hz, 1H), 6.41 (s, 1H), 4.19 (q, J = 7.8 Hz, 2H), 3.25 (s, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.41 (t, J = 7.8 Hz, 2H), 1.28 (t, J = 6.9 Hz, 3H).

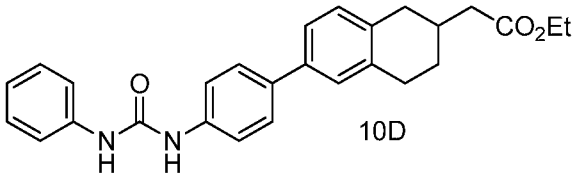
Ethyl 2-(6-(4-aminoophenyl)-1,2,3,4-tetrahydronapthalen-2-yl)acetate (10C):



10C

Excess 10% Pd/C (1.0 g) was added to a solution of product of Example 10B (4.0 g, 11.86 mmol) in 30 mL of ethanol. The mixture was stirred under H_2 atmosphere at room temperature for 18 h. The reaction mixture was filtered over celite bed, filtrate was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed in vacuum. The crude product was washed with diethyl ether and pentane to afford title compound (3.2 g, 87%) as solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 7.40 (d, J = 8.4 Hz, 2H), 7.26 (m, 2H), 7.05 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 8.8 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 2.86-2.78 (m, 3H), 2.50-2.35 (m, 3H), 2.12 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H), 1.20 (t, J = 6.8 Hz, 3H). ESI-MS m/z = 310 $(M+H)^+$.

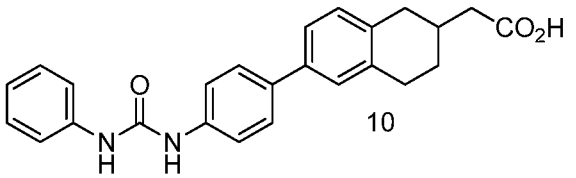
Ethyl 2-(6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (10D):



10D

Phenyl isocyanate (0.084 g, 0.71 mmol) was added to a solution of product of Example 10C (0.2 g, 0.64 mmol) and triethylamine (0.098 g, 0.96 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and product purified by flash chromatography using 1% methanol in chloroform to afford title compound (0.14 g, 50%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.75 (bs, 1H), 8.65 (bs, 1H), 7.60-7.40 (m, 6H), 7.3-7.21 (m, 4H), 7.10 (d, J = 8.4 Hz, 1H), 6.95 (m, 1H), 4.12 (q, J = 6.9 Hz, 2H), 2.9 (m, 3H), 2.45 (m, 3H), 2.15 (m, 1H), 1.90 (m, 1H), 1.45 (m, 1H), 1.2 (t, J = 7.2 Hz, 3H); ESI-MS m/z = 429 $(M+H)^+$.

2-(6-(4-(3-Phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (10):

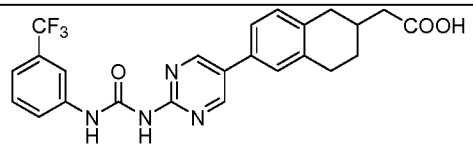
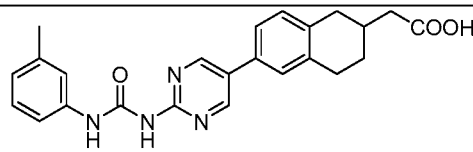
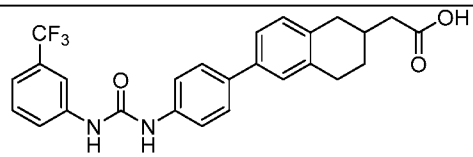
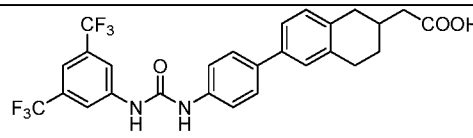
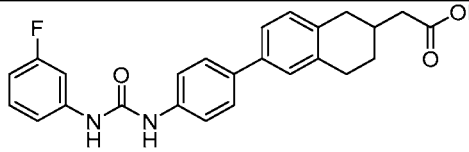


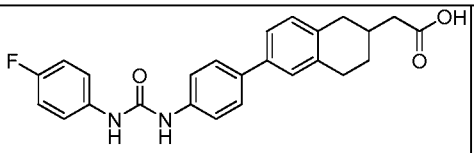
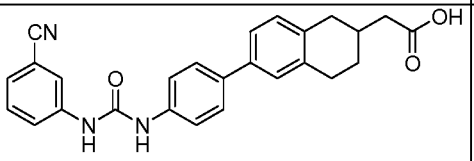
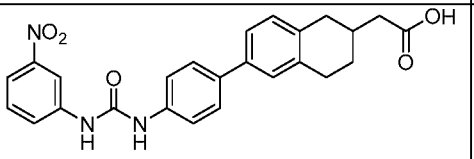
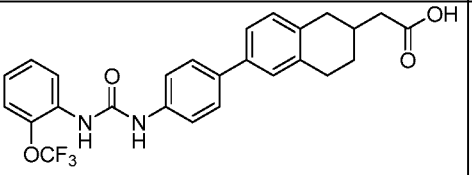
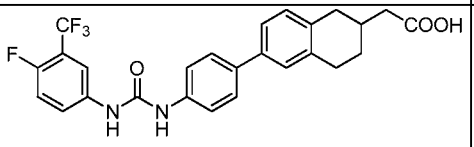
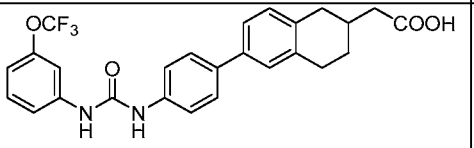
10

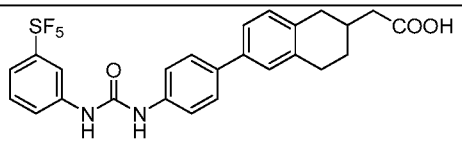
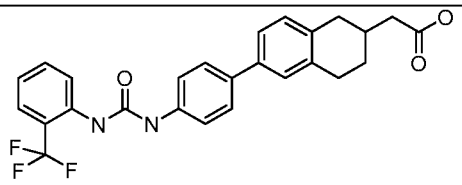
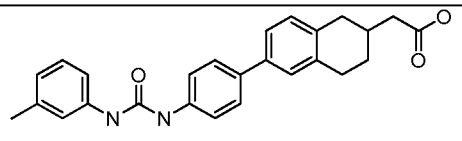
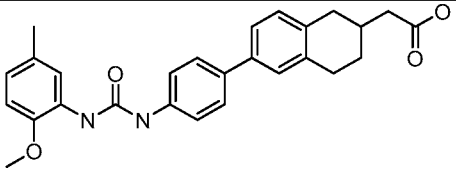
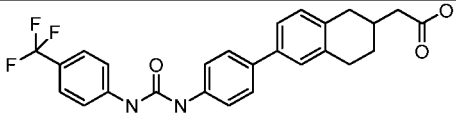
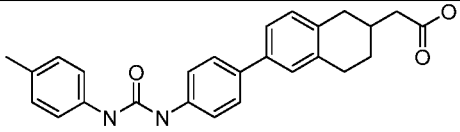
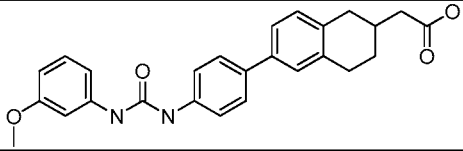
Lithium hydroxide (0.068 g, 1.62 mmol) was added to a solution of product of Example 10D (0.14 g, 0.327 mmol) in 10 mL of THF-water (3:1). Reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuum, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were

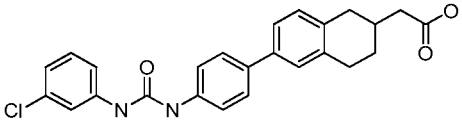
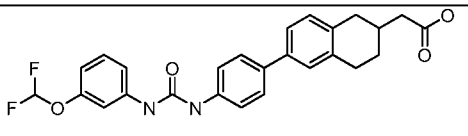
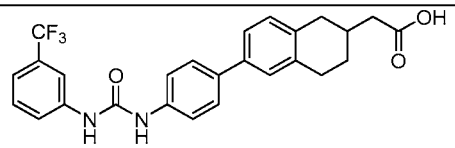
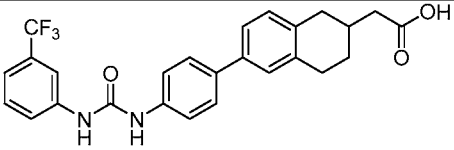
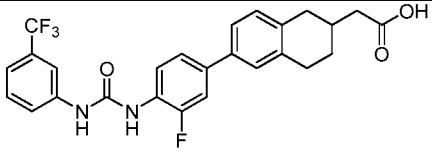
collected by filtration and dried under vacuum to afford title compound (0.1 g, 76%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.13 (bs, 1H), 7.56-7.42 (m, 6H), 7.40-7.24 (m, 4H), 7.10 (d, J = 8.4 Hz, 1H), 7.0-6.94 (m, 1H), 2.90-2.71 (m, 3H), 2.45 (m, 1H), 2.29 (d, J = 6.9 Hz, 2H), 2.10 (m, 1H), 1.91 (m, 1H), 1.42 (m, 1H); ESI-MS m/z = 401 $(M+H)^+$; HPLC purity: 90%.

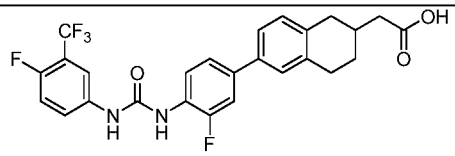
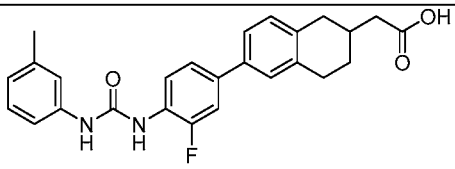
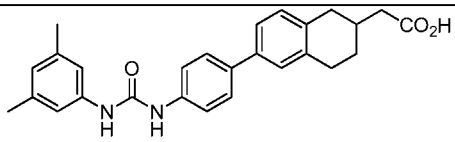
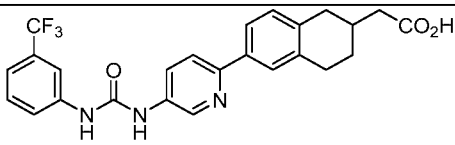
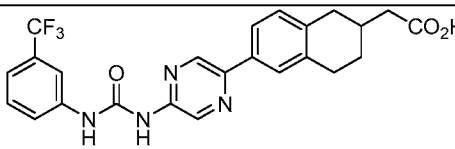
Examples 11 - 39 were prepared by analogous procedures as described for Example 10 using appropriate starting materials. Chiral compounds were separated using procedures analogous to those described in Example 129.

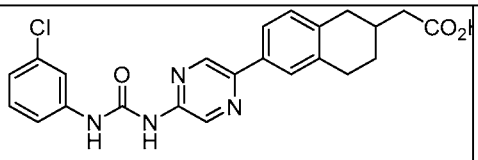
Ex	Structure	^{1}H NMR Data	Mass/purity
11		^{1}H NMR (400 MHz, DMSO-d_6): δ 11.8 (s, 1H), 10.46 (s, 1H), 9.02 (s, 2H), 8.09 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.5-7.45 (m, 3H), 7.2 (d, J = 8.0 Hz, 1H), 2.95-2.8 (m, 4H), 2.28 (d, J = 7.2 Hz, 2H), 2.12 (m, 1H), 1.94 (m, 1H), 1.45 (m, 1H).	ESI-MS m/z = 471 $(M+H)^+$; HPLC purity: 92%.
12		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H),11.5 (s, 1H), 10.23 (s, 1H), 9.0 (s, 2H), 7.5-7.4 (m, 4H), 7.3-7.1 (m, 2H), 6.88 (d, J = 7.2 Hz, 1H), 2.95-2.8 (m, 4H), 2.3 (m, 5H), 2.12 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS m/z = 417 $(M+H)^+$; HPLC purity: 92%.
13		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.46 (bs, 1H), 9.20 (bs, 1H), 8.04 (s, 1H), 7.63-7.47 (m, 6H), 7.36-7.27 (m, 3H), 7.10 (d, J = 8.4 Hz, 1H), 2.90-2.72 (m, 3H), 2.45 (m, 1H), 2.28 (d, J = 7.2 Hz, 2H), 2.13 (m, 1H), 1.92 (m, 1H), 1.43 (m, 1H).	ESI-MS m/z = 469 $(M+H)^+$. HPLC purity: 95.96%.
14		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.11 (s, 1H), 9.61 (s, 1H), 9.19 (s, 1H), 8.14 (s, 2H), 7.64 (s, 1H), 7.65-7.52 (m, 4H), 7.35 (m, 2H), 7.11 (d, J = 8.4 Hz, 1H), 2.9-2.80 (m, 3H), 2.45 (m, 1H), 2.30 (d, J = 6.8 Hz, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.45 (m, 1H).	ESI-MS m/z = 537 $(M+H)^+$; HPLC purity: 98.4%.
15		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.19 (s, 1H), 9.07 (s, 1H), 7.58-7.45 (m, 5H), 7.35-7.25 (m, 3H), 7.18-7.05 (m, 2H), 6.77 (t, J = 7.2 Hz, 1H), 2.9-2.8 (m, 3H), 2.42 (m, 1H), 2.28 (d, J = 6.8 Hz, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.50-1.40 (m, 1H).	ESI-MS m/z = 419 $(M+H)^+$. HPLC purity: 94.4%.

16		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 8.9 (m, 2H), 7.58-7.45 (m, 6H), 7.35-7.31 (m, 2H), 7.1 (m, 3H), 2.91-2.70 (m, 3H), 2.42 (m, 1H), 2.29 (d, *J* = 7.2 Hz, 2H), 2.1 (m, 1H), 1.9 (m, 1H), 1.50 (m, 1H).	ESI-MS *m/z* = 419 $(M+H)^+$. HPLC purity: 96.14%.
17		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.28 (bs, 1H), 9.10 (bs, 1H), 7.99 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60-7.45 (m, 5H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.34 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 2.9-2.8 (m, 3H), 2.45 (m, 1H), 2.30 (d, *J* = 6.8 Hz, 2H), 2.11 (m, 1H), 1.91 (m, 1H), 1.41 (m, 1H).	ESI-MS *m/z* = 426 $(M+H)^+$. HPLC purity: 93.67%
18		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.67 (bs, 1H), 9.28 (bs, 1H), 8.55 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.54 (m, 5H), 7.33 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 2.90-2.80 (m, 3H), 2.45 (m, 1H), 2.28 (d, *J* = 6.9 Hz, 2H), 2.10 (m, 1H), 1.88 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 446 $(M+H)^+$. HPLC purity: 93.25%.
19		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.89 (bs, 1H), 9.00 (bs, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.55 (m, 4H), 7.38-7.30 (m, 4H), 7.12-7.05 (m, 2H), 2.91-2.72 (m, 3H), 2.45 (m, 1H), 2.19 (m, 2H), 2.11 (m, 1H), 1.91 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 484 $(M+H)^+$. HPLC purity: 94.0%.
20		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.19 (s, 1H), 9.0 (s, 1H), 8.02 (s, 1H), 7.64 (m, 1H), 7.6-7.5 (m, 4H), 7.44 (m, 1H), 7.33 (m, 2H), 7.1 (d, *J* = 8.4 Hz, 1H), 2.95-2.75 (m, 3H), 2.5-2.35 (m, 1H), 2.35 (d, *J* = 6.8 Hz, 2H), 2.2 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 487 $(M+H)^+$; HPLC purity: 90%.
21		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1bs, 1H), 9.05 (s, 1H8.87 (s, 1H), 7.7 (s, 1H), 7.54 (m, 4H), 7.45-7.25 (m, 4H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 2.95-2.75 (m, 3H), 2.5-2.35 (m, 1H), 2.3 (d, *J* = 7.2 Hz, 2H), 2.15 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 485 $(M+H)^+$. LCMS purity: 96%.

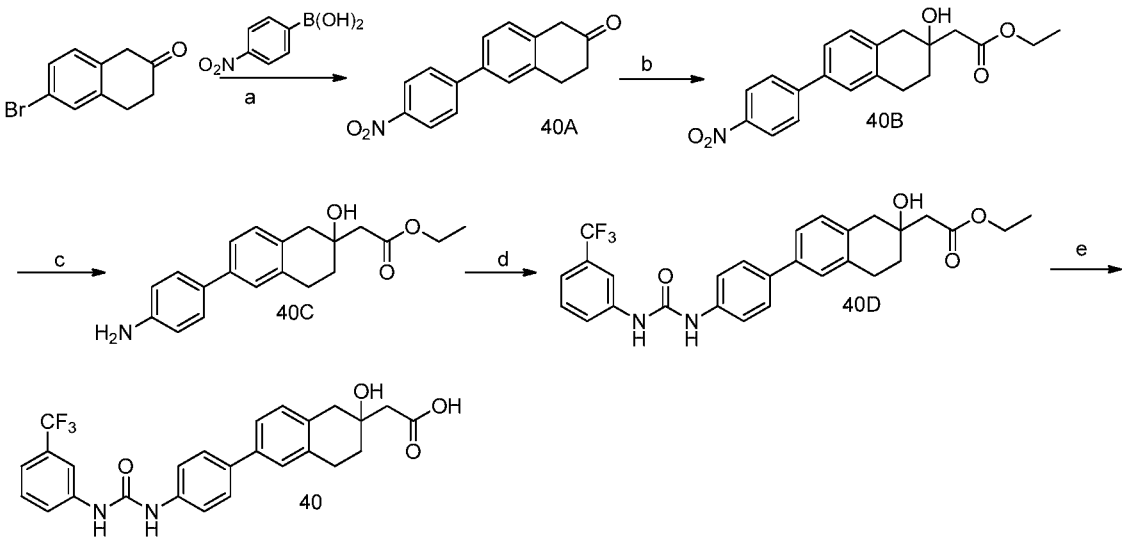
22		^{1}H NMR (300MHz, DMSO-d_6): δ 12.2 (bs, 1H), 10.12 (bs, 1H) 9.78 (bs, 1H), 8.3 (s, 1H), 7.65-7.45 (m, 9H), 7.1 (m, 1H), 2.95-2.75 (m, 3H), 2.45-2.25 (m, 3H), 2.0 (m, 2H), 1.43 (m, 1H).	ESI-MS *m/z* = 527 $(M+H)^+$; HPLC purity: 96%.
23		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 9.44 (bs, 1H), 8.08 (bs, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.69-7.62 (m, 2H), 7.54 (m, 4H), 7.35-7.26 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.90-2.80 (m, 3H), 2.45 (m, 1H), 2.32 (d, *J* = 6.8 Hz, 2H), 2.10 (m, 1H), 1.92 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 469 $(M+H)^+$; HPLC purity: 92%.
24		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 8.71 (bs, 4H), 8.58 (bs, 1H), 7.56- 7.49 (q, *J* = 8.7 Hz, 4H), 7.32 (m, 3H), 7.24-7.08 (m, 3H), 6.78 (d, *J* = 7.5 Hz, 1H), 2.88 (m, 3 H), 2.82 (m, 1H), 2.49 (m, 1H), 2.39 (m, 5H), 1.98 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 415 $(M+H)^+$; HPLC purity: 92%.
25		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.6 (bs, 1H), 8.3 (bs, 1H), 8.0 (s, 1H), 7.5 (m, 4H), 7.3 (m, 2H), 7.1 (d, *J* = 8.8 Hz, 1H), 6.9 (d, *J* = 8.4 Hz, 1H), 6.7 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 3.85 (s, 3H), 2.8 (m, 2H), 2.4 (m, 1H), 2.35 (s, 3H), 2.2 (d, *J* = 8.8 Hz, 2H), 2.1 (s, 1H), 1.9 (m, 1H), 1.8 (s, 1H), 1.4 (m, 1H).	ESI-MS *m/z* = 445 $(M+H)^+$; HPLC purity: 89%.
26		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.6 (bs, 1H), 12.2 (bs, 1H), 7.8 (d, *J* = 9.2 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.3 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 2.80 (m, 3H), 2.15 (m, 2H), 2.0 (m, 3H), 1.45 (m, 1H).	ESI-MS *m/z* = 469 $(M+H)^+$; HPLC purity: 90%.
27		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.68 (bs, 1H), 8.55 (bs, 1H), 7.55-7.49 (q, *J* = 8.8 Hz, 4H), 7.32 (m, 4H), 7.07 (m, 3H), 2.88-2.73 (m, 3H), 2.45 (m, 1H), 2.29 (d, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 2.11 (m, 1H) 1.92 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 415 $(M+H)^+$; HPLC purity: 92%.
28		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.0 (bs, 2H), 7.55 (m, 4H), 7.35 (m, 2H), 7.2 (m, 2H), 7.1 (d, *J* = 7.6 Hz, 1H),	ESI-MS *m/z* = 431 $(M+H)^+$; HPLC purity: 92%.

		6.95 (d, J = 8.0 Hz, 1H), 6.55 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 3.75 (s, 3H), 3.15 (d, J = 8.8 Hz, 1H), 2.85 (m, 3H), 2.30 (d, J = 7.2 Hz, 2H), 2.15 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	
29		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.9 (bs, 1H), 10.8 (bs, 1H), 7.86 (s, 1H), 7.56 (d, J = 7.6 Hz, 2H), 7.47-7.41 (m, 3H), 7.29-7.24 (m, 3H), 7.03 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 2.90-2.83 (m, 3H), 2.45 (m, 1H), 2.20 (d, J = 6.0 Hz, 2H), 2.14 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H).	ESI-MS m/z = 435 $(M+H)^+$; HPLC purity: 89%.
30		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.99 (bs, 1H), 8.88 (bs, 1H), 7.57-7.48 (m, 5H), 7.40-7.02 (m, 6H), 6.77 (d, J = 7.2 Hz, 1H), 2.89-2.80 (m, 3H), 2.45 (m, 1H), 2.29 (m, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.42 (m, 1H).	ESI-MS m/z = 467 $(M+H)^+$; HPLC purity: 91%.
31	 Chiral: enantiomer-1	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.07 (bs, 1H), 8.88 (bs, 1H), 8.04 (s, 1H), 7.60-7.47 (m, 6H), 7.36-7.27 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 2.88-2.80 (m, 3H), 2.41 (m, 1H), 2.30 (d, J = 6.8 Hz, 2H), 2.16 (m, 1H), 1.92 (m, 1H), 1.43 (m, 1H).	ESI-MS m/z = 469 $(M+H)^+$. HPLC purity: 97%.
32	 Chiral: enantiomer-2	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.07 (bs, 1H), 8.88 (bs, 1H), 8.02 (s, 1H), 7.60-7.47 (m, 6H), 7.36-7.27 (m, 3H), 7.10 (d, J = 8.0 Hz, 1H), 2.88-2.80 (m, 3H), 2.41 (m, 1H), 2.30 (d, J = 6.8 Hz, 2H), 2.16 (m, 1H), 1.92 (m, 1H), 1.43 (m, 1H).	ESI-MS m/z = 469 $(M+H)^+$. HPLC purity: 94%.
33		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 9.41 (s, 1H), 8.69 (s, 1H), 8.18 (t, J = 8.8 Hz, 1H), 8.04 (s, 1H), 7.58- 7.51 (m, 3H), 7.45 (d, J = 8.8 Hz, 1H), 7.39 (m, 2H), 7.34 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 2.90-2.76 (m, 3H), 2.42 (m, 1H), 2.31 (d, J = 6.8 Hz, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.45 (m, 1H).	ESI-MS m/z = 485 $(M-H)^-$. HPLC purity: 91%.

34		^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.0 (bs, 1H), 9.55 (bs, 1H), 8.80 (bs, 1H), 8.15 (m, 1H), 8.02 (dd, J_1 = 2.1 Hz, J_2 = 6.3 Hz, 1H), 7.75-7.30 (m, 6H), 7.15 (d, J = 8.4 Hz, 1H), 2.95-2.80 (m, 3H), 2.45 (m, 1H), 2.30 (d, J = 7.2 Hz, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS m/z = 503(M-H)$^-$. HPLC purity: 97%.
35		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.03 (bs, 1H), 8.60 (s, 1H), 8.20 (t, J = 8.8 Hz, 1H), 7.52 (d, J = 12.0 Hz, 1H), 7.43 (m, 3H), 7.31 (s, 1H), 7.24-7.10 (m, 3H), 6.68 (d, J = 8.0 Hz, 1H), 2.89-2.80 (m, 3H), 2.45 (m, 1H), 2.30 (m, 5H), 2.11 (m, 1H), 1.92 (m, 1H), 1.43 (m, 1H).	ESI-MS m/z = 433 (M+H)$^+$. HPLC purity: 97%.
36		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 9.05 (bs, 1H), 8.86 (bs, 1H), 7.52 (m, 4H), 7.31 (m, 2H), 7.08 (m, 3H), 6.60 (m, 1H), 2.87 (m, 3H), 2.45 (m, 1H), 2.26 (m, 2H), 2.23 (s, 6H), 2.11 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H).	ESI-MS m/z = 429 (M+1); HPLC purity: 96%.
37		^{1}H NMR (300 MHz, DMSO-d$_6$): δ 12.0 (bs, 1H) 9.25 (bs, 1H), 9.1 (s, 1H), 8.7 (s, 1H), 8.0 (m, 2H), 7.85 (m, 1H), 7.75 (m, 2H), 7.65 (m, 1H), 7.5 (m, 1H), 7.35 (m, 1H), 7.15 (m, 1H), 2.8 (m, 3H), 2.5 (m, 1H), 2.3 (m, 2H), 2.1 (m, 1H), 2.0 (m, 1H), 1.5 (m, 1H).	ESI-LCMS m/z: 469 Purity: 97%.
38		^{1}H NMR (300 MHz, DMSO-d$_6$): δ 10.67 (bs, 2H), 9.0 (s, 2H), 8.29 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 3.11-3.07 (m, 3H), 2.92-2.86 (m, 1H), 2.68-2.54 (m, 2H), 2.20-2.07 (m, 2H), 1.4 (m, 1H).	ESI-LCMS m/z: 470 Purity: 94%; HPLC Purity: 94 %

39		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.8 (s, 1H), 9.7 (s, 1H), 9.1 (s, 1H), 8.9 (d, *J* = 8.0 Hz, 1H), 7.8 (m, 3H), 7.4-7.3 (m, 2H), 7.2 (d, *J* = 8.0 Hz, 1H), 7.1 (m, 1H), 3-2.8 (m, 3H), 2.5-2.4 (m, 1H), 2.3 (d, *J* = 6.8 Hz, 2H), 2.1 (m, 1H), 2-1.9 (m, 1H), 1.5-1.4 (m, 1H).	ESI-LCMS *m/z*: 437 purity: 96% HPLC purity: 96 %

Example-40

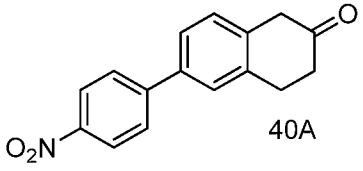


Reagents and conditions: a) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 4h; b) EtOAc, LiHMDS, THF, -78 °C to RT, 4h; c) Pd/C, MeOH, H_2, RT, 3h; d) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; e) NaOH, MeOH-THF-H_2O, RT, 12h.

Procedure:

2-(2-Hydroxy-6-(4-(3-(3-(trifluoromethyl) phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

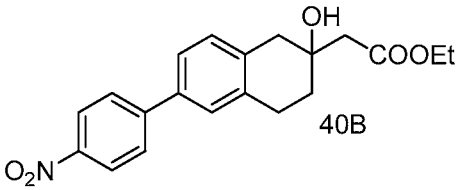
6-(4-nitrophenyl)-3,4-dihydronaphthalen-2(1H)-one (40A):



$Pd(PPh_3)_4$ (0.0736 g, 0.06 mmol) was added to a solution of 6-bromo-2-tetralone (1.5 g, 6.66 mmol) in 50 mL of 1,4 dioxane-H_2O (3:1) mixture under argon atmosphere, followed by cesium carbonate (6.49 g, 19.99 mmol) and 4-nitrophenyl boronic acid (1.32 g, 7.99 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 4 h and solvent removed under reduced pressure. The residue partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 18% ethyl acetate in hexane to afford title compound (0.9 g, 50%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.74 (d,

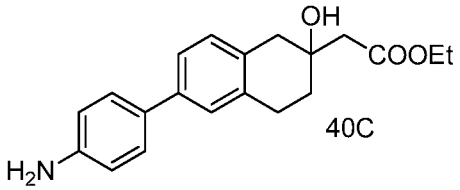
J = 8.4 Hz, 2H), 7.5 (m, 2H), 7.27 (s, 1H), 3.66 (s, 2H), 3.16 (t, J = 6.9 Hz, 2H), 2.61 (t, J = 6.9 Hz, 2H).

Ethyl 2-(2-hydroxy-6-(4-nitrophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (40B):



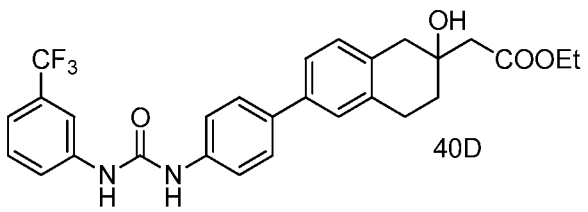
Ethyl acetate (0.44 g, 5.05 mmol) was added to a solution of Li-HMDS (0.83 g, 5.05 mmol) in 20 mL of THF at -78 °C. The mixture was stirred for 15 min, followed by addition of product of Example 40A (0.4 g, 3.37 mmol). The reaction mixture was then brought to room temperature and stirred for 4 h. The reaction mixture was quenched with 1N HCl. The reaction mixture was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 30% ethyl acetate in hexane to afford title compound (0.35 g, 66%) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.38 (m, 2H), 7.18 (d, J = 8.4 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 3.8 (bs, 1H), 3.16 (m, 1H), 3.0 (d, J = 16.8 Hz, 1H), 2.92-2.83 (m, 2H), 2.62 (s, 2H), 2.04 (m, 1H), 1.86 (m, 1H), 1.31 (t, J = 8.0 Hz, 3H). ESI-MS m/z = 356 $(M+H)^+$.

Ethyl 2-(6-(4-aminophenyl)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (40C):



Excess 10% Pd/C (0.15 g) was added to a solution of product of Example 40B (0.35 g, 0.98 mmol) in 10 mL of ethanol. The reaction mixture was stirred under H_2 atmosphere at room temperature for 3 h. The reaction mixture was filtered over celite bed, filtrate was removed under reduced pressure and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed in vacuum. The crude product was washed with diethyl ether and pentane to afford title compound (0.26 g, 81%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.2 Hz, 2H), 7.28 (m, 2H), 7.08 (d, J = 8.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 2H), 4.24 (q, J = 6.8 Hz, 2H), 3.80 (bs, 2H), 3.10 (m, 1H), 2.99-2.79 (m, 3H), 2.62 (s, 2H), 2.01 (m, 1H), 1.83 (m, 1H), 1.29 (t, J = 6.4 Hz, 3H). ESI-MS m/z = 326 $(M+H)^+$.

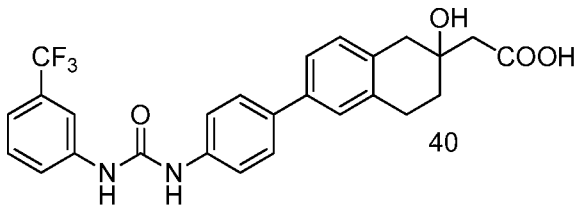
Ethyl 2-(2-hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)-acetate (40D):



3-(Trifluoromethyl)phenyl isocyanate (0.082 g, 0.44 mmol) was added to a solution of product of Example 40C (0.13 g, 0.40 mmol) and triethylamine (0.12 g, 1.20 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (0.1 g, 50%) as pale yellow solid. ^{1}H NMR (300 MHz, DMSO-

d_6): δ 9.05 (s, 1H), 8.86 (s, 1H), 8.02 (s, 1H), 7.62-7.50 (m, 6H), 7.35-7.25 (m, 3H), 7.08 (m, 1H), 4.7 (s, 1H), 4.07 (q, J = 6.9 Hz, 2H), 2.90 (m, 2H), 2.75 (m, 2H), 2.5 (s, 2H), 1.86 (m, 2H), 1.20 (t, J = 7.8 Hz, 3H). ESI-MS m/z = 513 $(M+H)^+$.

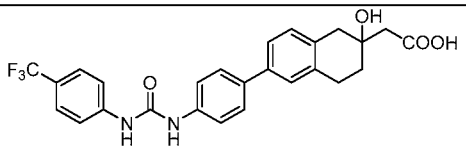
2-(2-Hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (40):



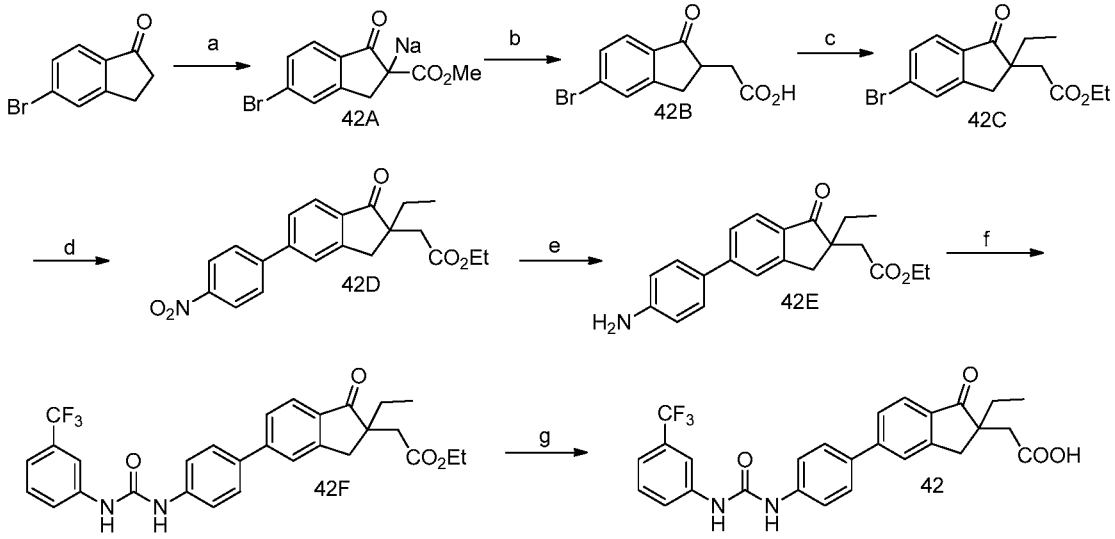
40

Sodium hydroxide (0.023 g, 0.58 mmol) was added to a solution of product of Example 40D (0.1 g, 0.19 mmol) in 15 mL THF-methanol-water (2:1:1) mixture. The reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuum, the residue was dissolved in water andwashed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.06 g, 63%) as brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.1 (s, 1H), 8.9 (s, 1H), 8.03 (s, 1H), 7.65-7.45 (m, 6H), 7.4-7.35 (m, 3H), 7.08 (d, J = 8.4 Hz, 1H), 4.8 (bs, 1H), 3.05-2.95 (m, 2H), 2.8 (m, 2H), 2.5 (s, 2H), 1.85 (m, 2H); ESI-MS m/z = 485 $(M+H)^+$.

Examples 41 was prepared by the procedures analogous to those described in Example 40 using appropriate starting materials.

Ex	Structure	^{1}H NMR Data	Mass/purity
41		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H),9.24 (s, 1H), 9.0 (s, 1H), 7.64 (m, 4H), 7.55 (m, 4H), 7.3 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 4.7 (bs, 1H), 3.05-2.95 (m, 2H), 2.85-2.75 (m, 2H), 2.5 (s, 2H), 1.85 (m, 2H).	ESI-MS m/z = 485 $(M+H)^+$; LCMS purity: 96%.

Example 42

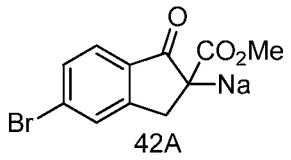


Reagents and conditions: a) $CO(OMe)_2$, NaH, THF, 75 °C, 16h; b) $BrCH_2COOEt$, THF, 75 °C, 5h; c) NaH, EtI, DMF, RT, 4h; d)$Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; e) Fe/NH_4Cl, EtOH-H_2O, 85 °C, 3h; f) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; g) LiOH, Dioxane-H_2O, RT, 12h.

Procedure:

2-(2-ethyl-1-oxo-5-(4-(3-(3-(trifluoromethyl) phenyl) ureido)phenyl)-2,3-dihydro-1H-inden-2-yl) acetic acid:

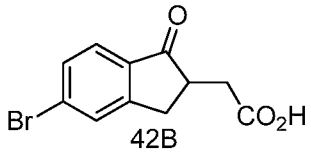
(5-Bromo-2-(methoxycarbonyl)-1-oxo-2,3-dihydro-1H-inden-2-yl) sodium (42A):



42A

5-Bromo indanone (8 g, 37.9 mmol) was added to an ice cold solution of sodium hydride (2.72 g, 113.3 mmol) in THF (100 mL) and stirred at room temperature for 30 min. Dimethyl carbonate (17.25 g, 189.56 mmol) was then added and mixture was refluxed for 16 h. Reaction mixture was cooled to room temperature and poured into ice water. pH of solution was made basic using saturated aqueous solution of NaOH solution and extracted with twice with ethyl acetate and concentrated under vacuum. Residue obtained was dissolved in diethyl ether and cooled to 0^0C. A solution of saturated aqueous solution of NaOH was added (10 mL) while stirring. Resulting sodium salt was collected by filtration and dried under vacuum to afford crude title compound (7 g) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.52 (s, 1H), 7.40 (m, 1H), 7.34 (m, 1H), 3.52 (s, 3H), 3.3 (s, 2H).

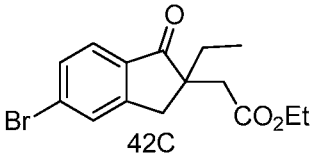
2-(5-Bromo-1-oxo-2,3-dihydro-1H-inden-2-yl)acetic acid (42B):



42B

Ethyl bromo acetate (10.08 g, 60 mmol) was added to a solution of product of Example 42A (7 g, 24 mmol) in THF (50 mL). The reaction mixture was refluxed for 5 h. Reaction mixture was cooled and partitioned between ethyl acetate and water. Separated organic layer was washed with brine, dried over sodium sulphate, filtered and concentrated under vacuum. 1:1 HCl –acetic acid mixture (40 mL) was added to residue and refluxed for 16 h. Reaction mixture was cooled to 0 °C, and solids were collected by filtration, washed with water and dried under vacuum to afford title compound (6 g, 60%) as solid. ^{1}H NMR(400 MHz, DMSO-d_6): δ 7.84 (s, 1H), 7.62-7.56 (m, 2H), 3.4-3.3 (m, 1H), 3.0-2.84 (m, 2H), 2.8-2.6 (m, 2H).

Ethyl 2-(5-bromo-2-ethyl-1-oxo-2,3-dihydro-1H-inden-2-yl) acetate (42C):

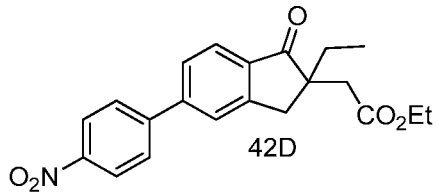


42C

A solution of product of Example 42B (4.5 g, 16.8 mmol) in DMF (30 mL) was added over a period of 30 min to an ice cold solution of NaH (2 g, 50 mmol) in DMF (50 mL). The reaction mixture was stirred for 10 min. Ethyl iodide (13.1 g, 84.2 mmol) was then added and the mixture was stirred for 4 h at room temperature. The reaction was then brought to 0 °C, excess NaH was quenched with ice water and extracted aqueous layer with ethyl acetate (2x100 mL). The combined organic layers were dried over sodium sulphate, filtered and removed under vacuum to

give crude title compound (1 g, 18%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.6 (m, 2H), 7.5 (m, 1H), 4.0 (m, 2H), 3.18 (d, *J* = 17.2 Hz, 1H), 3.01 (d, *J* = 17.2 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H), 2.66 (d, *J* = 16.8 Hz, 1H), 1.6 (m, 2H), 1.1 (t, *J* = 7.3 Hz, 3H), 0.75 (t, *J* = 7.6 Hz, 3H).

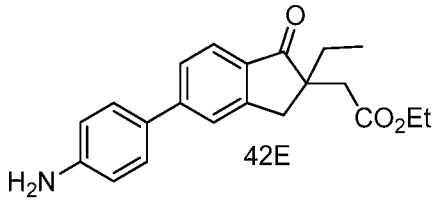
Ethyl 2-(2-ethyl-5-(4-nitrophenyl)-1-oxo-2,3-dihydro-1H-inden-2-yl) acetate (42D):



42D

$Pd(PPh_3)_4$ (0.037 g, 0.032 mmol) was added to a solution of product of Example 42C (0.87 g, 2.7 mmol) in 20 mL 1,4 dioxane-H_2O (3:1) mixture under Argon atmosphere, followed by cesium carbonate (2.6 g, 8.1 mmol) and 4-nitrophenyl boronic acid (0.497 g, 2.9 mmol). The reaction mixture was degassed for 10 min. The reaction mixture was refluxed for 5 h and solvent removed under reduced pressure. The residue partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography eluting with 20% ethyl acetate in hexane to afford title compound (0.8 g, 90%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.4-8.3 (m, 2H), 7.86 (m, 1H), 7.76 (m, 2H), 7.7-7.6 (m, 2H), 4.0 (q, *J* = 6.3 Hz, 2H), 3.28 (d, *J* = 17.7 Hz, 1H), 3.11 (d, *J* = 17.4 Hz, 1H), 2.92 (d, *J* = 16.2 Hz, 1H), 2.7 (d, *J* = 16.8 Hz, 1H), 1.8-1.6 (m, 2H), 1.1 (t, *J* = 7.2 Hz, 3H), 0.8 (t, *J* = 6.9 Hz, 3H).

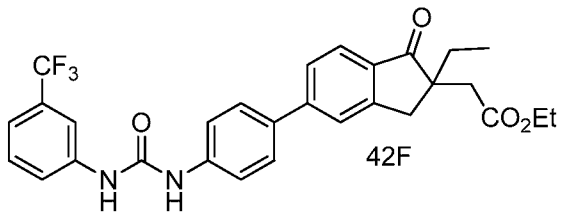
Ethyl 2-(5-(4-aminophenyl)-2-ethyl-1-oxo-2,3-dihydro-1H-inden-2-yl) acetate (42E):



42E

Iron powder (0.36 g, 6.5 mmol) was added to a solution of product of Example 42D (0.8 g, 2.17 mmol) in 15 mL ethanol-water mixture (2:1) followed by NH_4Cl (0.058 g, 1.08 mmol). The reaction mixture was refluxed for 3 h. The solvent was removed under reduced pressure and residue partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed in vacuo to give title compound (0.65 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.58-7.52 (m, 2H), 7.5-7.44 (m, 2H), 6.8-6.76 (m, 2H), 4.0 (m, 2H), 3.2 (d, *J* = 17.4 Hz, 1H), 3.05 (d, *J* = 16.8 Hz, 1H), 2.84 (d, *J* = 15.6 Hz, 1H), 2.66 (d, *J* = 16.8 Hz, 1H), 1.8-1.6 (m, 2H), 1.05(m, 3H), 0.8 (m, 3H).

Ethyl 2-(2-ethyl-1-oxo-5-(4-(3-(3-(trifluoromethyl)phenyl)ureido) phenyl)-2,3-dihydro-1H-inden-2-yl) acetate (42F):

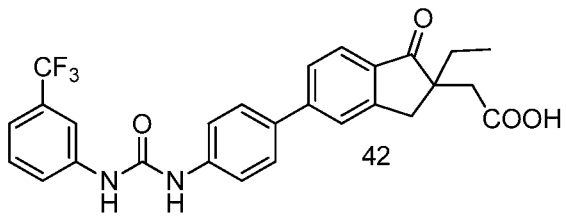


42F

3-(Trifluoromethyl) phenyl isocyanate (0.12 g, 0.65 mmol) was added to a solution of product of Example 42E (0.22 g, 0.65 mmol) and triethylamine (0.2 g, 1.95 mmol) in THF (10 mL) and stirred at room temperature overnight. The solvent was removed under reduced pressure and product triturated with diethyl ether and pentane to afford title compound (0.21 g, 54%) as solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.7 (m, 2H), 7.68-7.62 (m, 1H), 7.54 (m, 1H), 7.44-7.36 (m, 4H), 7.34 (m, 1H), 7.28 (m, 2H), 4.0 (q, *J* = 6.9 Hz, 2H), 3.2 (d, *J* = 17.4 Hz, 1H), 3.1 (d, *J* = 17.4 Hz, 1H), 3.0 (d, *J* = 16.5 Hz, 1H), 2.7 (d, *J* = 16.8 Hz, 1H), 1.7 (m, 2H), 1.1 (t, *J* = 6.9 Hz, 3H), 0.8 (t, *J* = 7.8 Hz, 3H).

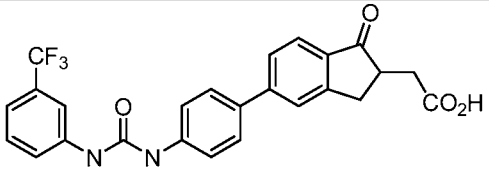
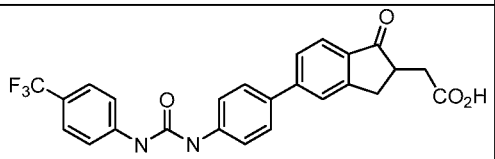
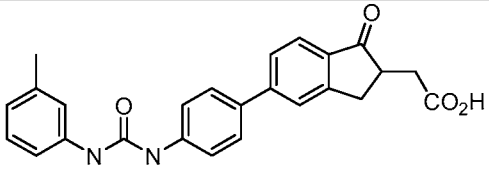
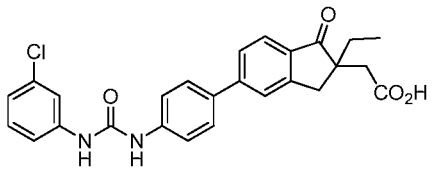
2-(2-Ethyl-1-oxo-5-(4-(3-(3-(trifluoromethyl) phenyl)ureido)phenyl)-2,3-dihydro-1H-inden-2-yl) acetic acid (42):



42

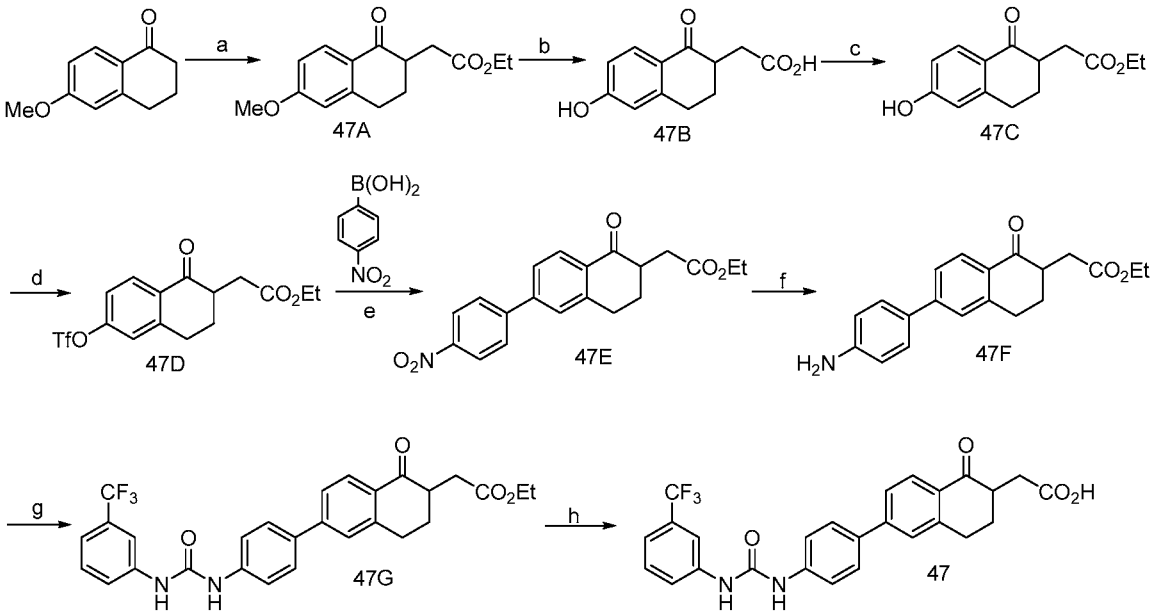
Lithium hydroxide (0.048 g, 1.1 mmol) was added to a solution of product of Example 42F (0.2 g, 0.38 mmol) in 4 mL of 1,4-dioxane-water (3:1) mixture. The reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.15 g, 79%) as solid. ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.1 (s, 1H), 7.8-7.6 (m, 4H), 7.46-7.4 (m, 3H), 7.3-7.2 (m, 3H), 3.2 (d, *J* = 17.2 Hz, 1H), 3.0 (d, *J* = 17.2 Hz, 1H), 2.7 (d, *J* = 16.4 Hz, 1H), 2.5 (d, *J* = 16.4 Hz, 1H), 1.5 (m, 2H), 0.7 (t, *J* = 7.2 Hz, 3H); ESI-MS m/z: 497 (M+H); HPLC purity: 95.6%.

Examples 43 - 46 were prepared by the procedures analogous to those described in Example 42 using appropriate starting materials except that for Examples 43-45, alkylation step with ethyl iodide in the presence of NaH as in Example 42 was not performed.

Ex	Structure	^{1}H NMR Data	Mass/Purity
43		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.15 (s, 1H), 9.05 (bs, 1H), 8.05 (bs, 1H), 7.85 (s, 1H), 7.75-7.66 (m, 4H), 7.65-7.5 (m, 5H), 3.4 (m, 1H), 3.0-2.9 (m, 2H), 2.8-2.6 (m, 2H).	ESI-MS *m/z* = 469 $(M+H)^+$; HPLC purity: 91.8%.
44		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.3 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 7.86 (s, 1H), 7.8-7.9 (m, 10H), 3.4 (m, 1H), 3.0-2.6 (m, 4H).	ESI-MS *m/z* = 469 $(M+H)^+$; HPLC purity: 93.7%.
45		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.3 (bs, 1H), 9.0 (bs, 1H), 8.8 (bs, 1H), 7.8 (s, 1H), 7.7 (m, 4H), 7.56 (m, 2H), 7.3 (s, 1H), 7.28-7.0 (m, 2H), 6.8 (m, 1H), 3.4 (m, 1H), 3.0-2.86 (m, 2H), 2.8-2.6 (m, 2H), 2.26 (s, 3H).	ESI-MS *m/z* = 415 $(M+H)^+$; LCMS purity: 91%.
46		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.25 (bs, 1H), 7.8-7.5 (m, 8H), 7.3 (bs, 2H), 7.0 (s, 1H), 3.2 (d, *J* = 17.2 Hz, 1H), 3.05 (d, *J* = 17.2 Hz, 1H), 2.7 (d, *J* = 16.4 Hz, 1H), 2.5 (d, *J* = 16.4 Hz, 1H),	ESI-MS m/z: 463 (M+H); HPLC purity: 95%.

		1.5 (m, 2H), 0.8 (t, J = 6.8 Hz, 3H).	

Example 47

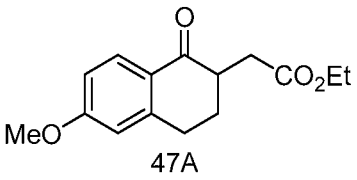


Reagents and conditions: a) n-BuLi, i-Pr_2NH_2,-60 °C, 16 h; b) Aq. HBr, 100 °C, 16 h; c) $MeSO_3H$, EtOH, RT, 5h; d) Tf_2O, CH_2Cl_2, Et_3N, RT, 2h; e) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 2h; f) Pd/C, H_2, EtOH, RT, 3h; g) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; h) LiOH, EtOH-H_2O, RT, 12h.

Procedures:

2-(1-Oxo-6-(4-(3-(3-(trifluoromethyl) phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

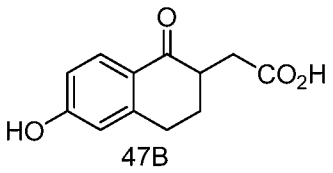
2-(6-Methoxy-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl)acetic acid (47A):



n-Butyl lithium (3.27 g, 51.04 mmol) was added to a solution of di-isopropyl amine (6.88 g, 68.11 mmol) in THF (50 mL) at -60 °C, and the mixture was stirred for 0.5 h. 6-methoxy-1-tetralone (6 g, 34.09 mmol) in THF (10 mL) was slowly added to the reaction mixture, the mixture was stirred for 45 min and ethyl bromoacetate (11.9 g, 71.25 mmol) was added. The reaction mixture was then stirred at room temperature for 16 h and quenched with saturated NH_4Cl solution. The reaction mixture was extracted with EtOAc (X2), combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentration to give 5.3 g of the title compound.

Alternatively Example 47A can be obtained using similar procedures as described for Example 79C.

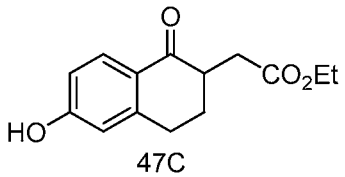
2-(6-Hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (47B):



47B

Aqueous HBr (75 mL) was added to product of Example 47A (5 g, 19.08 mmol), and the reaction mixture was refluxed for 16 h. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The crude product was purified by flash chromatography using 25% ethyl acetate in pet ether to afford title compound (3 g, 71%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 10.3 (bs, 1H), 7.73 (d, J = 8.4 Hz, 1H), 6.7 (m, 1H), 6.6 (m, 1H), 3.3-2.93 (m, 2H), 2.84-2.77 (m, 1H), 2.68 (m, 1H), 2.35 (m, 1H), 2.1 (m, 1H), 1.85 (m, 1H).

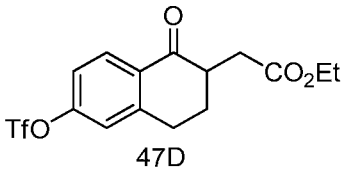
Ethyl 2-(6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (47C):



47C

Methanesulphonic acid (5 mL) was added to a solution of Example 47B (2 g, 9.09 mmol) in ethanol (30 mL), and the mixture was stirred at room temperature for 6 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and washed with brine solution. The organic layer was dried over sodium sulphate, filtered and removed under vacuum to afford title compound (2.15 g, 97%) as solid.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 2H), 6.26 (bs, 1H), 4.2 (q, J = 6.8 Hz, 2H), 3.1-2.85 (m, 4H), 2.4 (m, 1H), 2.2 (m, 1H), 1.95 (m, 1H), 0.8 (t, J = 6.8 Hz, 3H).

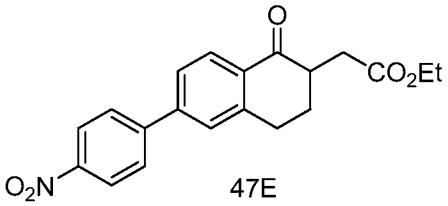
Ethyl 2-(1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (47D):



47D

Triflic anhydride (3.41 g, 12.09 mmol) was added to an ice cold solution of product of Example 47C (3 g, 12.09 mmol) and pyridine (1.05 g, 13.29 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous solution of NaCl (50 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 5% ethyl acetate in pet ether to give title compound (2.8 g, 62%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.8 Hz, 1H), 7.24-7.12 (m, 2H), 4.2 (q, J = 6.8 Hz, 2H), 3.2 (m, 1H), 3.1-2.9 (m, 3H), 2.5 (m, 1H), 2.3 (m, 1H), 2.0 (m, 1H), 1.2 (t, J = 6.8 Hz, 3H).

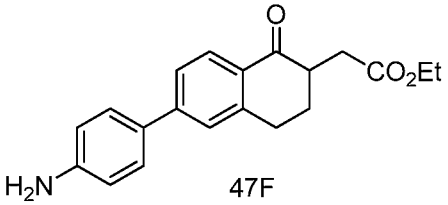
Ethyl 2-(6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (47E):



47E

$Pd(PPh_3)_4$ (0.174 g, 0.15 mmol) was added to a solution of product of Example 47D (4.8 g, 12.6 mmol) in 26 mL of 1,4 dioxane-H_2O (4:1) mixture under argon atmosphere, followed by cesium carbonate (11.73 g, 36 mmol) and 4-nitrophenyl boronic acid (2.3 g, 13.8 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 2 h and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to give crude product which was purified by flash chromatography to afford title compound (2.2 g, 59%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.4 (d, J = 7.6 Hz, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.5 (s, 1H), 4.2 (q, J = 6.8 Hz, 2H), 3.3-3.0 (m, 4H), 2.5 (m, 1H), 2.3 (m, 1H), 2.05 (m, 1H), 1.3 (t, J = 6.8 Hz, 3H).

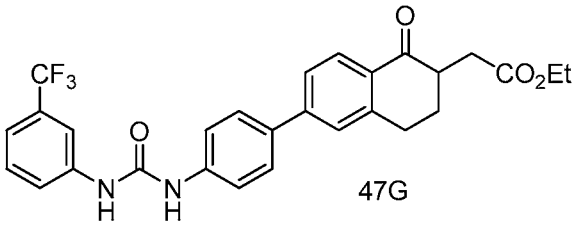
Ethyl 2-(6-(4-aminophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (47F):



47F

Excess 10% Pd/C (0.2 g) was added to a solution of product of Example 47E (1.1 g, 3.11 mmol) in 30 mL of ethanol, and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered over celite bed, filtrate was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and concentrated in vacuo. The crude product was washed with diethylether and pentane to afford title compound (0.8 g, 80%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 1H), 7.46-7.39 (m, 4H), 6.75 (m, 2H), 4.19 (m, 2H), 3.8 (bs, 2H), 3.14-3.04 (m, 4H), 2.42 (m, 1H), 2.26 (m ,1H), 2.0 (m, 1H), 1.29 (m, 3H).

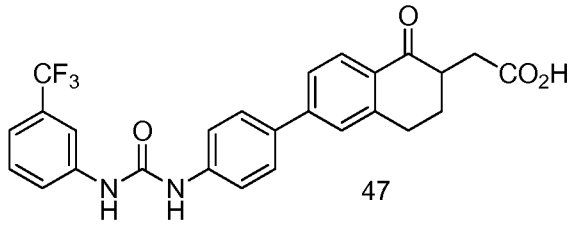
Ethyl 2-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (47G):



47G

3-(Trifluoromethyl) phenyl isocyanate (0.234 g, 0.18 mmol) was added to a solution of product of Example 47F (0.26 g, 0.18 mmol) and triethylamine (0.656 g, 0.55 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and product purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (0.1 g, 31%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.3 (bs, 1H), 9.0 (bs, 1H), 8.04 (s, 1H), 7.9 (m, 1H), 7.79-7.46 (m, 8H), 7.34 (m, 1H), 4.1 (q, J = 6.8 Hz, 2H), 3.2-2.9 (m, 3H), 2.75 (m, 2H), 2.2 (m, 1H), 1.2 (t, J = 6.8 Hz, 3H).

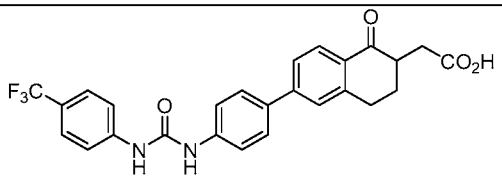
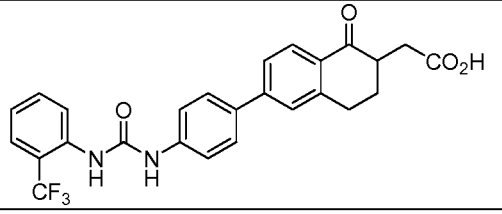
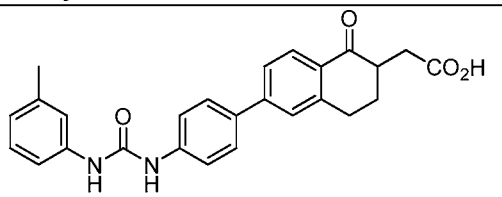
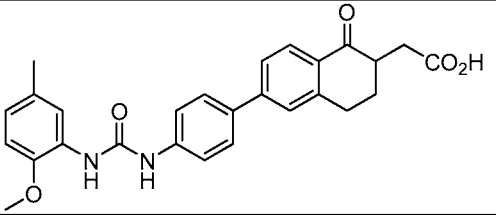
2-(1-Oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (47):

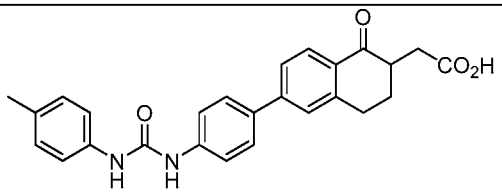
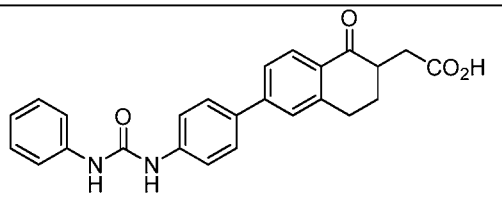
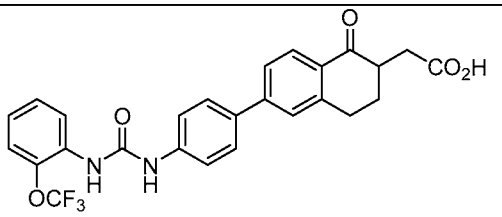
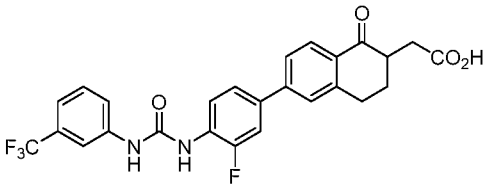
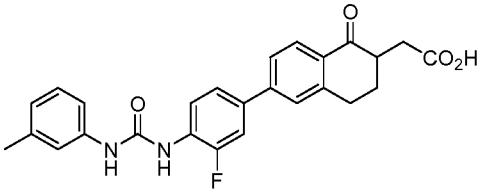
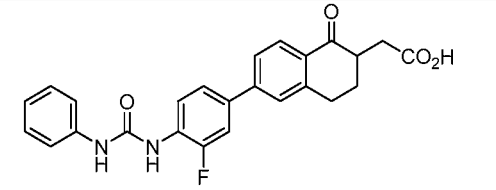


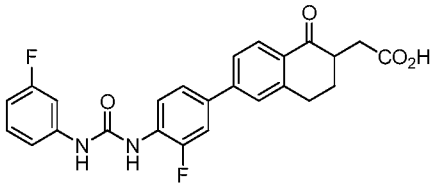
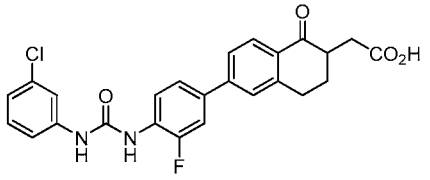
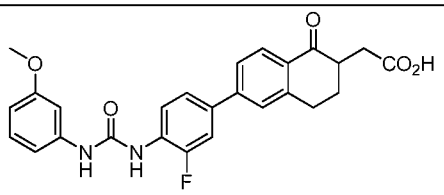
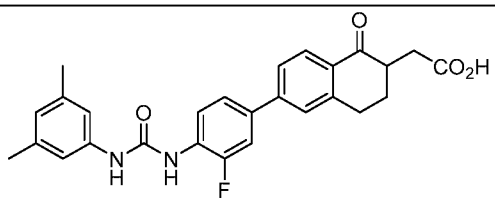
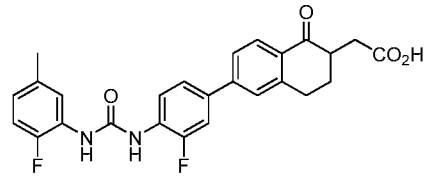
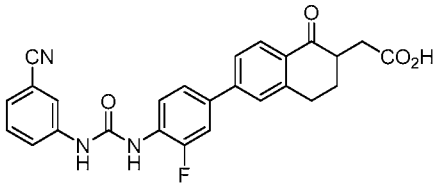
47

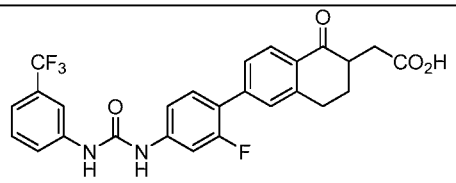
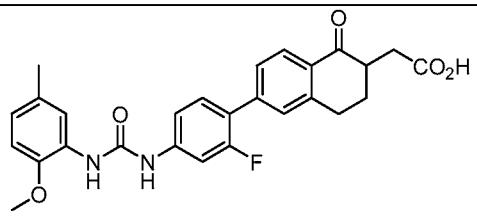
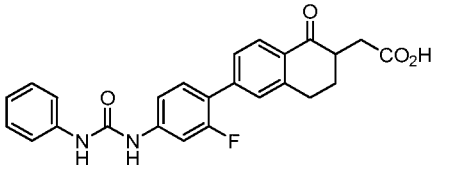
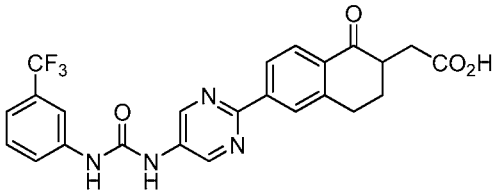
Lithium hydroxide (0.015 g, 0.35 mmol) was added to a solution of product of Example 47H (0.06 g, 0.11 mmol) in 4 mL of ethanol-water (3:1) mixture. The reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 ^{0}C, and solids were collected by filtration and dried under vacuum to afford title compound (0.042 g, 75%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 -9.0 (bs, 2H), 8.0 (m, 1H), 7.9 (m, 1H), 7.7 -7.54 (m, 7H), 7.46 (m, 1H), 7.3 (m, 1H), 3.2 -3.0 (m, 2H), 2.8 (m, 1H), 2.5 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H); ESI-MS *m/z* = 483 $(M+H)^+$; HPLC purity: 92.5%.

Examples 48 - 67 were prepared by the analogous procedures as described above for Example 47 using appropriate starting materials. The requisite boronic acids (and appropriately functional-group-protected versions thereof) utilized herein were purchased if available commercially, were synthesized as described in the literature or by routine modifications thereof known by those skilled in the art, or were synthesized by alternative procedures known by those skilled in the art.

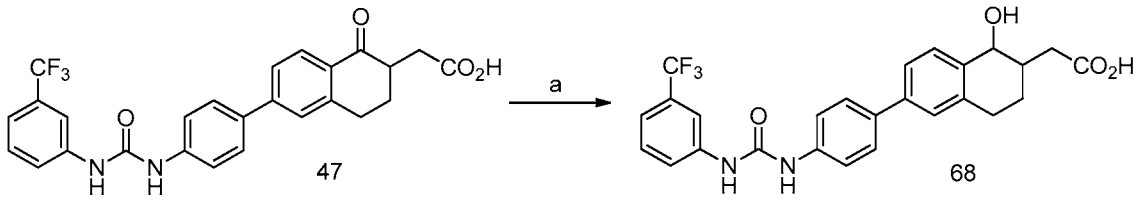
Ex	Structure	^{1}H NMR Data	Mass/Purity
48		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.25 (bs, 1H), 9.05 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.75 -7.55 (m, 10H), 3.2-2.8 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 483 $(M+H)^+$; HPLC purity: 90%.
49		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.6 (bs, 1H), 8.2 (bs, 1H), 8.0-7.9 (m, 2H), 7.8-7.5 (m, 8H), 7.3 (t, *J* = 8.0 Hz, 1H), 3.2-2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 483 $(M+H)^+$; HPLC purity: 95%.
50		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.85 (bs, 1H), 8.65 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.74-7.54 (m, 6H), 7.3 (s, 1H), 7.24 (m, 1H), 7.16 (m, 1H), 6.8 (d, *J* = 6.8 Hz, 1H), 3.2-2.9 (m , 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.26 (s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 429 $(M+H)^+$; LCMS purity: 95%.
51		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.5 (bs, 1H), 8.2 (bs, 1H), 8.0 (s, 1H), 7.9 (m, 1H), 7.7 - 7. 5 (m, 6H), 6.9 (m, 1H), 6.8 (m, 1H), 3.8 (s, 3H), 3.2 -2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.26 (s,	ESI-MS *m/z* = 459 $(M+H)^+$; LCMS purity: 96.7%.

		3H), 2.2 (m, 1H), 2.0 (m, 1H).	
52		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.6 (bs, 1H), 9.3 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7-7.5 (m, 6H), 7.4 (m, 2H), 7.06 (m, 2H), 3.2-2.8 (m, 3H), 2.7-2.6 (m, 2H), 2.26 (s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	HPLC purity: 91%.
53		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 7.9 (d, J = 8.1 Hz, 1H), 7.7-7.45 (m, 8H), 7.25 (t, J = 7.5 Hz, 2H), 6.95 (t, J = 7.8 Hz, 1H), 3.2-2.85 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	HPLC purity: 92%.
54		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.5 (bs, 1H), 8.6 (bs, 1H), 8.36 (m, 1H), 7.9 (m, 1H), 7.76 -7.56 (m, 6H), 7.38 (m, 2H),7.3 (m, 1H), 3.2-2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	HPLC purity: 94.7%.
55		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 9.7 (bs, 1H), 8.9 (bs, 1H), 8.27 (t, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.9 (d, J = 8.7 Hz, 1H), 7.7 (m, 3H), 7.65-7.5 (m, 3H), 7.35 (d, J = 6.6 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	HPLC purity: 96.75%.
56		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.15 (bs, 1H), 8.75 (bs, 1H), 8.3 (t, J = 8.8 Hz, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7 (m, 3H), 7.6 (d, J = 8.8 Hz, 1H), 7.32 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.8 (d, J = 7.2 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.3(s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 447 $(M+H)^+$. HPLC purity: 94.65%.
57		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (s, 1H), 8.7 (s, 1H), 8.3 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 9.0 Hz, 1H), 7.7 (m, 3H), 7.6 (d, J = 8.1 Hz, 1H), 7.5 (d, J = 8.4 Hz, 2H), 7.3 (t, J = 7.5 Hz, 2H), 7.0 (t, J = 7.8 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 433 $(M+H)^+$. HPLC purity: 95.40%.

58		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.35 (s, 1H), 8.75 (s, 1H), 8.3 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 8.0 Hz, 1H) 7.7 (m, 3H), 7.6 (d, J = 8.8 Hz, 1H), 7.5 (d, J = 11.6 Hz, 1H), 7.3 (m, 1H), 7.1(d, J = 8.0 Hz, 1H), 6.82 (m, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 449 $(M-H)^-$. LCMS purity: 90.46%.
59		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.3 (s, 1H), 8.8 (s, 1H), 8.3 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 8.4 Hz, 1H) 7.7 (m, 4H), 7.6 (d, J = 8.4 Hz, 1H), 7.35-7.2 (m, 2H), 7.05 (d, J = 7.6 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 467 $(M+H)^+$. HPLC purity: 96.38%.
60		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.25 (s, 1H), 8.8 (s, 1H), 8.3 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 9.0 Hz, 1H) 7.7 (m, 3H), 7.6 (d, J = 9.0 Hz, 1H), 7.2 (m, 2H), 6.95 (d, J = 8.4 Hz, 1H), 6.6 (d, J = 6.3 Hz, 1H), 3.75 (s, 3H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 463 $(M+H)^+$. HPLC purity: 97.89%.
61		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.0 (s, 1H), 8.7 (s, 1H), 8.3 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 8.4 Hz, 1H) 7.7 (m, 3H), 7.6 (d, J = 8.4 Hz, 1H), 7.1 (s, 2H), 6.65 (s, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.25(s, 6H), 2.18 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 461 $(M+H)^+$. HPLC purity: 93.13%.
62		1H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (s, 1H), 9.05 (s, 1H), 8.35 (t, J = 8.4 Hz, 1H), 8.0 (d, J = 6.9 Hz, 1H) 7.9 (d, J = 8.4 Hz, 1H), 7.75-7.65 (m, 3H), 7.6 (d, J = 8.1 Hz, 1H), 7.1 (m, 1H), 6.83 (m, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.3(s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 465 $(M+H)^+$. HPLC purity: 90.7%.
63		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.45 (s, 1H), 8.85 (s, 1H), 8.25 (t, J = 8.8 Hz, 1H), 8.0 (s, 1H), 7.9 (d, J = 8.0 Hz, 1H) 7.75-7.65 (m, 4H), 7.6 (d, J = 8.8 Hz, 1H), 7.55-7.45 (m, 2H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.18 (m, 1H), 2.0 (m, 1H).	ESI-MS m/z = 458 $(M+H)^+$. HPLC purity: 94.94%.

64		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.4 (bs, 1H), 9.0 (bs, 1H), 8.0 (s, 1H), 7.9 (m ,1H), 7.7-7.45 (m, 6H), 7.3 (m, 2H), 3.2-2.9 (m, 4H), 2.7 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 499 $(M-H)^-$; LCMS purity: 90%.
65		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.7 (bs, 1H), 8.28 (bs, 1H), 7.98 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.66 (m, 1H), 7.56-7.46 (m, 3H), 7.2 (m, 1H), 6.9 (m, 1H), 6.76 (m, 1H), 3.8 (s, 3H), 3.2-2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m ,2H), 2.26 (s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 477 $(M+H)^+$; LCMS purity: 93%.
66		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.05 (bs, 1H), 8.9 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.6 (m, 1H), 7.56-7.44 (m, 5H), 7.3 (m, 3H), 7.0 (m, 1H), 3.2-2.9 (m ,2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	HPLC purity: 91%.
67		^{1}H NMR (300 MHz, DMSO-d_6): δ 10.7 (bs, 1H), 9.0 (2s, 2H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.25 (s, 1H), 8.1 (m, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.7 (d, *J* = 8.4 Hz, 1H), 7.5 (t, *J* = 7.5 Hz, 1H), 7.3 (d, *J* = 7.5 Hz, 1H), 3.1 (m, 2H), 2.8 (m, 1H), 2.6 (m, 2H), 2.4 (m, 2H).	ESI-LCMS *m/z*: 486 (purity 89 %); HPLC purity 96 %.

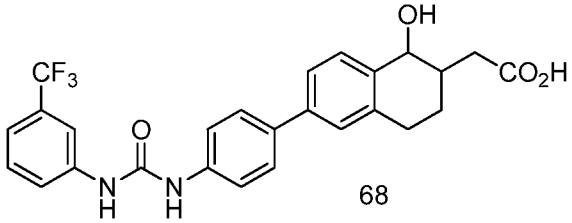
Example-68



Reagents and conditions: a) $NaBH_4$, MeOH, RT, 16h.

Procedures:

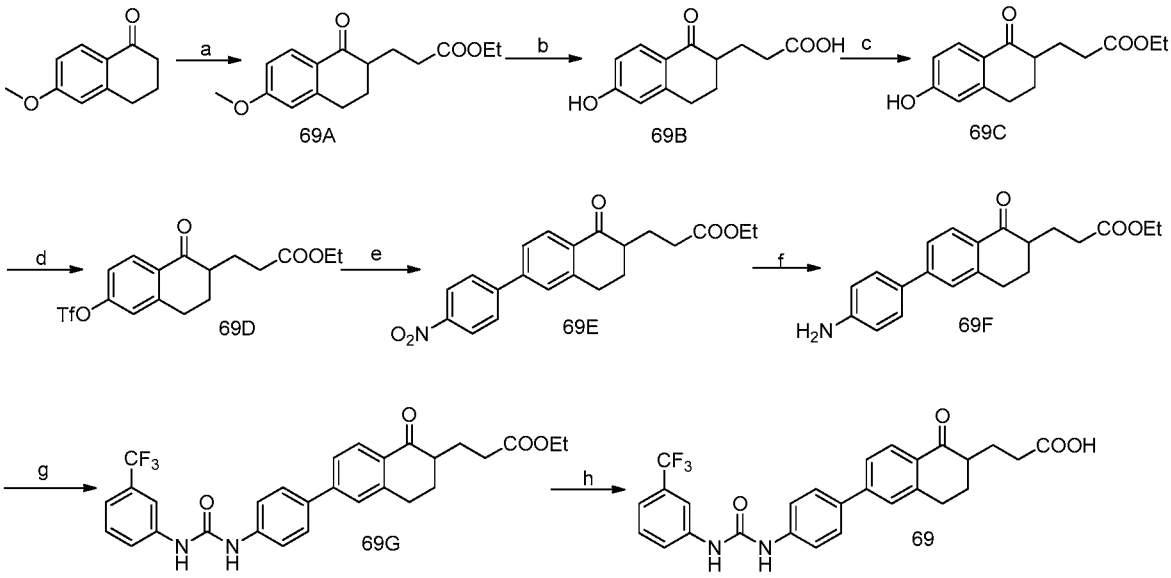
2-(1-hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (68):



Sodium borohydride (0.025 g, 0.66 mmol) was added portion wise to an ice cold solution of product of Example 47 (0.08 g, 0.16 mmol) in methanol (5 mL), and the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and diluted with water. The resulting solids were filtered and triturated with diethyl ether and n-pentane to afford title compound (0.068 g, 85%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0

(bs, 1H), 9.4 (bs, 1H), 9.0 (bs, 1H), 8.1 (s, 1H), 7.7 (m, 1H), 7.6-7.44 (m, 6H), 7.4-7.2 (m, 4H), 4.6 (m, 1H), 4.3 (m, 1H), 2.8 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H), 1.7 (m, 1H), 1.2 (m, 1H).

Example-69

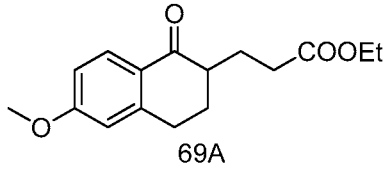


Reagents & conditions: a) LDA, Ethyl bromo propionate, THF, -78 °C-RT, 10 h ; b) Aq. HBr, 100 °C, 12 h; c) $MeSO_3H$, EtOH, RT, 18 h; d) Tf_2O, CH_2Cl_2, Py, RT, 2 h; e) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 3 h; f) Pd/C, H_2, EtOH, RT, 1 h; g) 3-CF_3PhNCO, Et_3N, THF, RT, 12 h; h) LiOH, THF-H_2O, RT, 12 h.

Procedures:

3-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)propanoic acid:

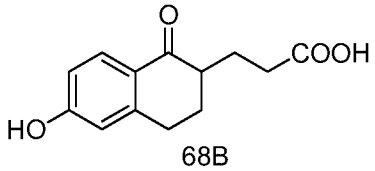
Ethyl-3-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (69A):



69A

Freshly prepared 1.8M LDA (24.4 mL, 44.0 mmol) was added to pre-cooled solution of 6-methoxy-1-tetralone (4 g, 22.0 mmol) in THF (30 mL) over a period of 15 min at -78 °C. The reaction mixture was stirred for 1 h at -78 °C. Ethyl bromo propionate (4.4 mL, 39.37 mmol) was added over a period of 10 min at -78 °C, and the mixture was stirred at room temperature for 10 h. The reaction mixture was then poured in saturated NH_4Cl (100 mL) solution and extracted with ethyl acetate (2x100 mL). The combined organic layers were washed with water followed by brine solution, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford crude title product (4.5 g, 69 %) as liquid.

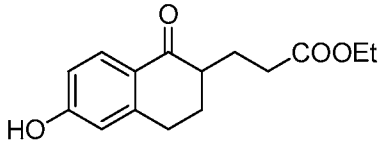
3-(6-Hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoic acid (69B):



68B

Aqueous HBr (50 mL) was added to product of Example 69A (4.5 g, 16.0 mmol), and the reaction mixture was refluxed for overnight. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The organic layer was dried over Na_2SO_4 and removed under reduced pressure. The product was purified by flash chromatography using 40% ethyl acetate in hexanes to afford title compound (0.85 g, 24%) as solid. 1H NMR (300MHz, DMSO-d_6): δ 12.01 (bs, 1H), 10.27 (s, 1H), 7.74 (d, J = 9.0 Hz, 1H), 6.70 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 6.62 (s, 1H), 2.86 (m, 2H), 2.43 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H), 2.12-1.98 (m, 2H), 1.78-1.69 (m, 1H), 1.65-1.53 (m, 1H).

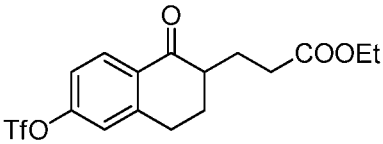
Ethyl 3-(6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (69C):



69C

Methane sulphonic acid (0.3 mL) was added to a solution of product of Example 69B (0.85 g, 3.63 mmol) in ethanol (20 mL), and the mixture was stirred at room temperature for 18 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and washed with brine solution. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography using 20% ethyl acetate in hexanes to afford the title compound (0.9 g, 24%) as solid. 1H NMR (300MHz, DMSO-d_6): δ 10.27 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 6.70 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 6.62 (s, 1H), 4.05 (q, J = 6.9 Hz, 2H), 2.86 (m, 2H), 2.43 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H) 2.13-1.98 (m, 2H), 1.77-1.57 (m, 2H), 1.17 (t, J = 6.9 Hz, 3H).

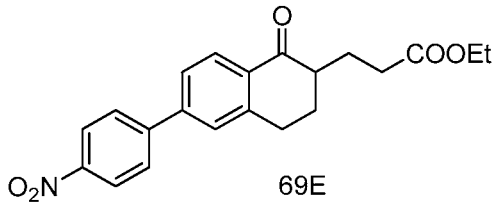
Ethyl 3-(1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (69D):



69D

Triflic anhydride (1.16 g, 4.12 mmol) was added to an ice cold solution of product of Example 69C (0.9 g, 3.43 mmol) and pyridine (0.325 g, 4.12 mmol) in dichloromethane (30 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane (50 mL) and washed with saturated aqueous solution of NaCl (50 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography using 5% ethyl acetate in hexanes to afford title compound (0.95 g, 70%) as solid. 1H NMR (400MHz, DMSO-d_6): δ 8.02 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.45 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 4.05 (q, J = 6.9 Hz, 2H), 3.04 (m, 2H), 2.68-2.61 (m, 1H), 2.42 (t, J = 7.6 Hz, 2H), 2.20-2.06 (m, 2H), 1.89-1.80 (m, 1H), 1.78-1.63 (m, 1H), 1.18 (t, J = 6.8 Hz, 3H).

Ethyl 3-(6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)propanoate (69E):

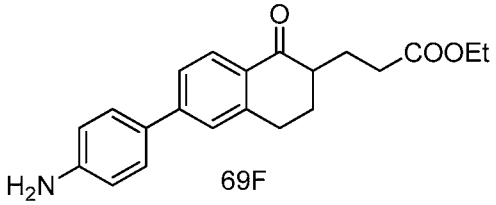


69E

$Pd(PPh_3)_4$ (0.034 g, 0.028 mmol) was added to a solution of product of Example 69D (0.95 g, 2.41 mmol) in 30 mL of 1,4 dioxane-H_2O (4:1) mixture under argon atmosphere, followed by cesium carbonate (1.95 g, 6.02 mmol) and 4-nitro phenyl boronic acid (0.48 g, 2.89 mmol). The

reaction mixture was degassed for 15 min. The reaction mixture was then refluxed for 3 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by flash chromatography using 10% % ethyl acetate in hexanes to give title compound (0.7 g, 79%) as solid. 1H NMR (400MHz, DMSO-d_6): δ 8.33 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.78-7.74 (m, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.08 (m, 2H), 2.66-2.59 (m, 1H), 2.43 (t, J = 8.0 Hz, 2H), 2.23-2.11 (m, 2H), 2.11-1.81 (m, 1H), 1.72-1.67 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H).

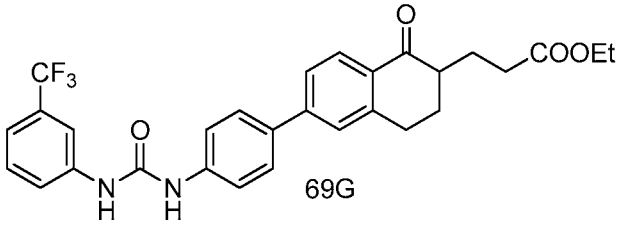
Ethyl 2-(6-(4-aminophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) propanoate (69F):



69F

Excess 10% Pd/C (0.2 g) was added to a solution of product of Example 69E (0.7 g, 1.90 mmol) in 20 mL of ethanol, and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered over celite bed, filtrate was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over Na_2SO_4, filtered and removed in vacuo. The crude product was washed with Et_2O and pentane to afford title compound (0.61 g, 95%) as yellow solid. 1H NMR (300MHz, DMSO-d_6): δ 7.83 (d, J = 8.4 Hz, 1H), 7.53-7.44 (m, 4H), 6.64 (d, J = 7.5 Hz, 2H), 5.41 (bs, 2H), 4.06 (q, J = 6.9 Hz, 2H), 3.0 (m, 2H), 2.44 (m, 3H), 2.15-2.10 (m, 2H), 1.90-1.66 (m, 2H), 1.18 (t, J = 6.9 Hz, 3H).

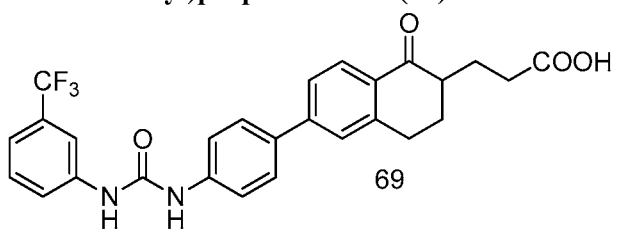
Ethyl 3-(1-oxo-6-(4-(3-(3-(trifluoromethyl) phenyl) ureido) phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl) propanoate (69G):



69G

3-(Trifluoromethyl) phenyl isocyanate (0.1 g, 0.534 mmol) was added to a solution of product of Example 69F (0.18 g, 0.534 mmol) and triethylamine (0.065 g, 0.64 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (0.1 g, 35%) as solid. 1H NMR (300MHz, DMSO-d_6): δ 9.10 (s, 1H), 8.98 (s, 1H), 8.03 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.72-7.69 (m, 2H), 7.62-7.49 (m, 6H), 7.31 (d, J = 7.2 Hz, 1H), 4.06 (q, J = 6.9 Hz, 2H), 3.05 (m, 2H), 2.43 (m, 3H), 2.19-2.11 (m, 2H), 1.82-1.65 (m, 2H), 1.18 (t, J = 7.8 Hz, 3H).

3-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)propanoic acid (69):

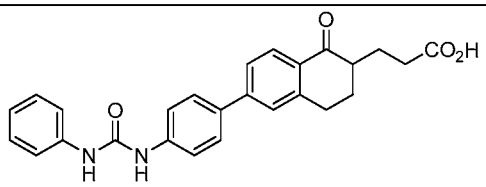
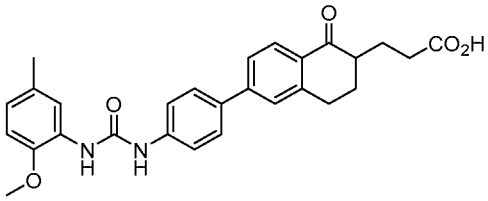
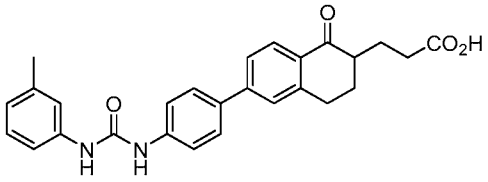
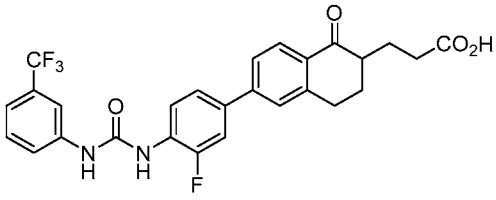


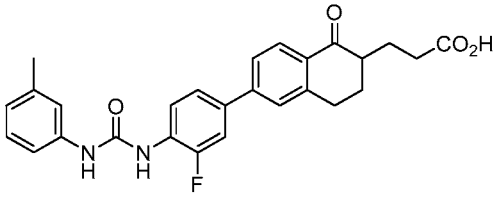
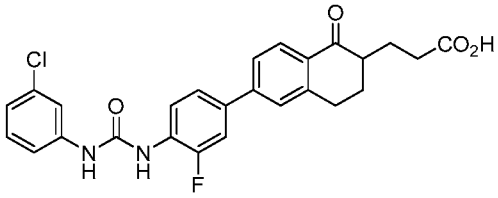
69

Lithium hydroxide (0.024 g, 0.572 mmol) was added to a solution of product of Example 69G (0.1 g, 0.19 mmol) in 20 mL of THF-water (2:1) mixture, and the mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water

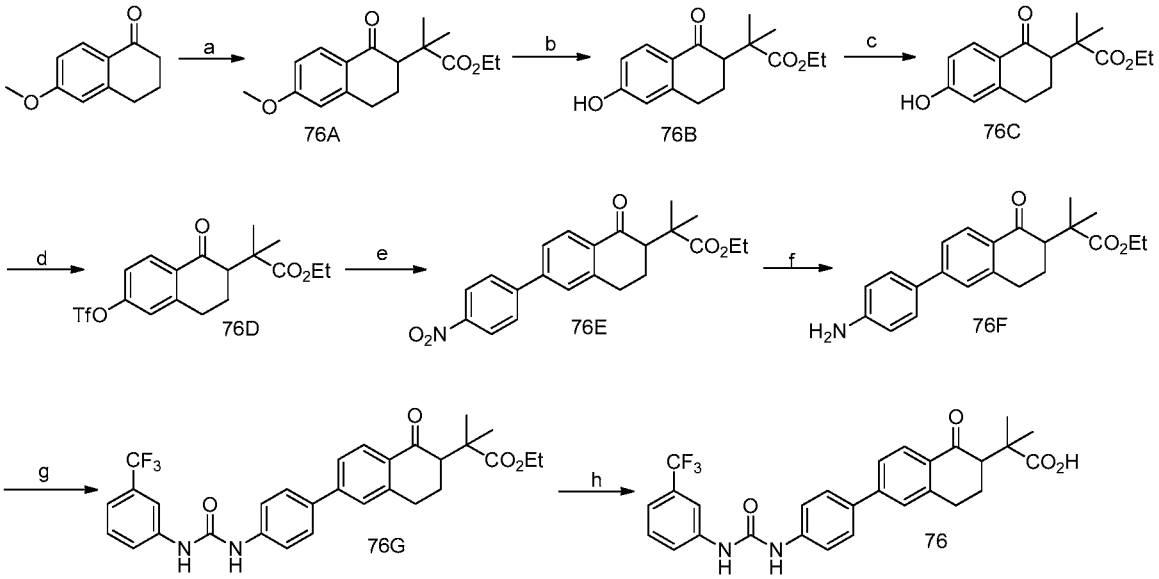
and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.060 g, 63%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.20 (bs, 1H), 9.12 (bs, 1H), 8.02 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H) 7.72-7.68 (m, 2H),7.65-7.49 (m, 6H), 7.32 (d, J = 7.5 Hz, 1H), 3.06-3.02 (m, 2H), 2.56-2.50 (m, 1H), 2.35 (t, J = 7.5 Hz, 2H) 2.27-2.08 (m, 2H), 1.82-1.63 (m, 2H). ESI-MS m/z = 496 $(M+H)^+$; HPLC purity: 99.22 %.

Examples 70 - 75 were prepared by the procedures analogous to those described for Example 69 using appropriate starting materials. The requisite boronic acids (and appropriately functional-group-protected versions thereof) utilized herein were purchased if available commercially, were synthesized as described in the literature or by routine modifications thereof known by those skilled in the art, or were synthesized by alternative procedures known by those skilled in the art.

Ex	Structure	^{1}H NMR Data	Mass/Purity
70		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 8.86 (s, 1H), 8.73 (s, 1H), 7.91 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 9.2 Hz, 2H) 7.64-7.56 (m, 4H), 7.46 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H) 6.98 (t, J = 6.8 Hz, 1H), 3.05 (m, 2H), 2.68-2.53 (m, 1H), 2.35 (t, J = 7.6 Hz, 2H) 2.22-2.09 (m, 2H), 1.82 (m, 1H), 1.66 (m, 1H).	ESI-MS m/z = 429 $(M+H)^+$. LCMS Purity: 95.03 %.
71		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.51 (s, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H) 7.64-7.56 (m, 4H), 6.90 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.05 (m, 2H), 2.59-2.54 (m, 1H) 2.35 (t, J = 8.0 Hz, 2H), 2.24 (s, 3H), 2.22-2.07 (m, 2H), 1.83 (m, 1H), 1.65 (m, 1H).	ESI-MS m/z = 473 $(M+H)^+$. HPLC purity: 94.49 %.
72		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.03 (bs, 1H), 8.83 (bs, 1H), 7.93-7.88 (m, 1H), 7.68-7.60 (m, 6H), 7.33-7.14 (m, 3H) 6.80 (m, 1H), 3.05 (m, 2H), 2.56 (m, 1H), 2.40-2.05 (m, 7H), 1.83-1.65 (m, 2H).	HPLC purity: 94.84 %.
73		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.51 (bs, 1H), 8.82 (bs, 1H), 8.27 (t, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H) 7.79-7.65 (m, 3H),7.62-7.50 (m,	HPLC purity: 90.44 %.

		3H), 7.35 (m, 1H), 3.06 (m, 2H), 2.59-2.55 (m, 1H), 2.35 (t, J = 7.8 Hz, 2H) 2.28-2.04 (m, 2H), 1.85 (m, 1H), 1.66 (m, 1H).	
74		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.06 (s, 1H), 8.70 (s, 1H), 8.30 (t, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H) 7.72-7.56 (m, 4H),7.32-7.14 (m, 3H), 6.82 (d, J = 7.5 Hz, 1H), 3.05 (m, 2H), 2.55 (m, 1H), 2.39-2.21 (m, 5H), 2.19-2.06 (m, 2H), 1.82 (m, 1H), 1.64 (m, 1H).	ESI-MS m/z = 459 $(M-H)^-$. HPLC purity: 96.45 %.
75		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.30 (s, 1H), 8.77 (s, 1H), 8.26 (t, J = 8.4 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H) 7.76-7.66 (m, 4H),7.60 (d, J = 8.8 Hz, 1H), 7.33 (m, 1H), 7.25 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H) 3.05 (m, 2H), 2.59-2.56 (m, 1H), 2.35 (t, J = 7.6 Hz, 2H), 2.23-2.07 (m, 2H), 1.82 (m, 1H), 1.66 (m, 1H).	ESI-MS m/z = 480 $(M-H)^-$. LCMS purity: 98.96 %.

Example-76

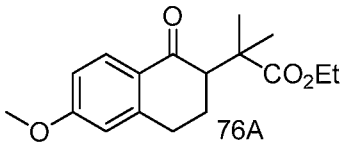


Reagents and conditions: a) Ethyl α-bromo isobutyrate, NaH, THF, RT; b) Aq. HBr, 100 °C; c) $MeSO_3H$, EtOH, RT; d) Tf_2O, CH_2Cl_2, Et_3N, RT; e) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C; f) Pd/C, H_2, EtOH, RT; g) 3-CF_3PhNCO, Et_3N, THF, RT; h) LiOH, THF-H_2O, RT.

Procedures:

2-Methyl-2-(1-oxo-6-(4-(3-(3-(trifluoromethyl) phenyl) ureido) phenyl)-1,2,3,4-tetrahydro naphthalen-2-yl) propanoic acid (76):

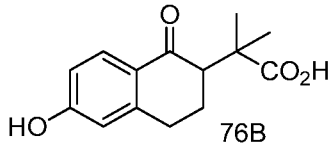
Ethyl 2-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methylpropanoate (76A):



76A

Sodium hydride (2.18 g, 90.9 mmol) was added to an ice cold solution of 6-methoxy-1-tetralone (8 g, 136 mmol) in THF (90 mL), and the mixture was stirred for 10 min. Ethyl α-bromo isobutyrate (17.7 g, 90.9 mmol) was added, and the mixture was stirred for 3 h. Reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to afford the title compound (13 g) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 9.2 Hz, 1H), 6.8 (m, 1H), 6.68 (m, 1H), 4.2 (m, 2H), 3.8 (s, 3H), 3.15-3.0 (m, 3H), 2.2 (m, 1H), 1.9 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

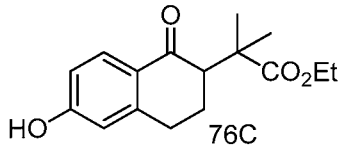
2-(6-Hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methylpropanoic acid (76B):



76B

Aqueous HBr (190 mL) was added to product of Example 76A (13 g, 44.8 mmol), and the reaction mixture was refluxed for overnight. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford title compound (11 g) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.2 (bs, 1H), 7.7 (m, 1H), 6.7 (m, 1H), 6.6 (s, 1H), 3.1-2.8 (m, 3H), 2.15 (m, 1H), 1.7 (m, 1H), 1.15 (s, 3H), 1.0 (s, 3H).

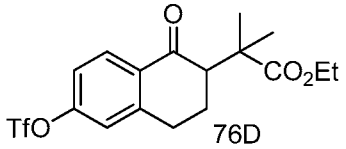
Ethyl 2-(6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methyl propanoate (76C):



76C

Methane sulphonic acid (20 mL) was added to a solution of product of Example 76B (11 g, 44.3 mmol) in ethanol (150 mL), and the mixture was stirred at room temperature for 5 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and water. The organic layer was separated, dried over Na_2SO_4 and filtered. The filtrate was concentrated under vacuum to afford title compound (6.4 g, 51%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (m, 1H), 6.74 (m, 1H), 6.66 (bs, 1H), 4.2 (m, 2H), 3.1-2.8 (m, 3H), 2.1 (m, 1H), 1.95 (m, 1H), 1.3 (m, 6H), 1.15 (s, 3H).

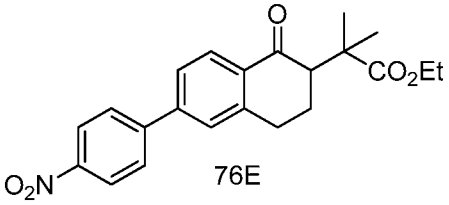
Ethyl 2-methyl-2-(1-oxo-6-(trifluoromethyl sulfonyloxy)-1,2,3,4-tetrahydro naphthalen-2-yl) propanoate (76D):



76D

Triflic anhydride (6.53 g, 23.15 mmol) was added to an ice cold solution of product of Example 76C (6.4 g, 23.1 mmol) and pyridine (2.01 g, 25.44 mmol) in dichloromethane (75 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous solution of NaCl (75 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography using 5% ethyl acetate in hexanes to afford title compound (3.8 g, 40%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (m, 1H), 7.18 (m, 2H), 4.2 (m, 2H), 3.2-3.0 (m, 3H), 2.3 (m, 1H), 2.0 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

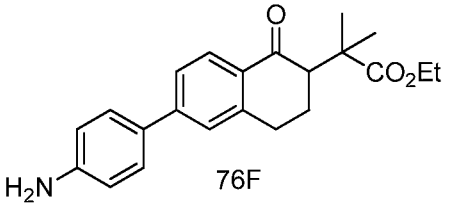
Ethyl 2-methyl-2-(6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) propanoate (76E):



76E

$Pd(PPh_3)_4$ (0.129 g, 0.11 mmol) was added to a solution of product of Example 76D (3.8 g, 9.3 mmol) in 35 mL of 1,4 dioxane-H_2O (3:1) mixture under Argon atmosphere, followed by cesium carbonate (9.1 g, 27.9 mmol) and 4-nitrophenyl boronic acid (1.71 g, 10.23 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was then refluxed for 5 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography to afford title compound (2.5 g, 71%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.0 (m, 1H), 7.5-7.3 (m, 4H), 6.75 (m, 2H), 4.2 (m, 2H), 3.2-3.0 (m, 3H), 2.2 (m, 1H), 2.0 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

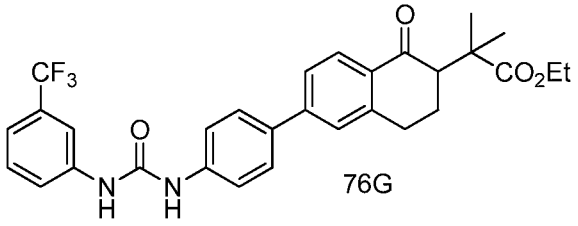
Ethyl 2-(6-(4-aminophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-methylpropanoate (76F):



76F

Iron powder (0.66 g, 11.81 mmol) was added to a solution of product of Example 76E (1.5 g, 3.93 mmol) in 15 mL of ethanol-water mixture (2:1) followed by NH_4Cl (0.106 g, 1.96 mmol). The mixture was refluxed for 3 h. The solvent was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over Na_2SO4, filtered and removed in vacuo to afford title compound (1.3 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.6 (m, 2H), 8.2 (m, 1H), 7.55 (m, 2H), 7.51 (m, 1H), 7.5 (s, 1H), 4.2 (m, 2H), 3.2-3.0 (m, 3H), 2.3 (m, 1H), 2.0 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

Ethyl 2-methyl-2-(1-oxo-6-(4-(3-(3-(trifluoromethyl) phenyl) ureido) phenyl)-1,2,3,4-tetrahydro naphthalen-2-yl) propanoate (76G):

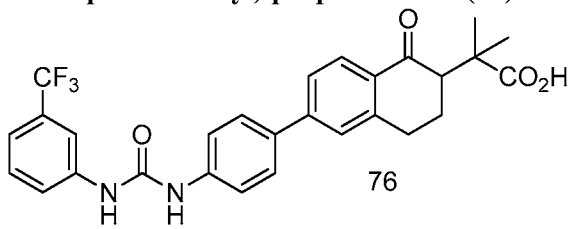


76G

3-(Frifluoromethyl) phenyl isocyanate (0.18 g, 0.997 mmol) was added to a solution of product of Example 76F (0.25 g, 0.71 mmol) and triethylamine (0.28 g, 2.85 mmol) in THF (10 mL), and the

mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was triturated with diethyl ether and pentane to afford title compound (0.2 g, 59%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (m, 1H), 7.74-7.6 (m, 4H), 7.44-7.28 (m, 8H), 4.2 (m, 2H), 3.15-3.0 (m, 3H), 2.26 (m, 1H), 1.9 (m, 1H), 1.3 (m, 6H), 1.2 (s, 3H).

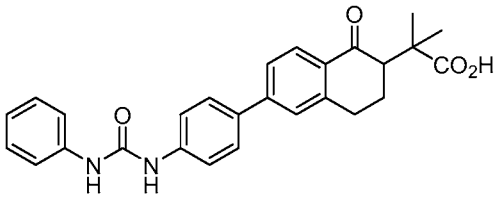
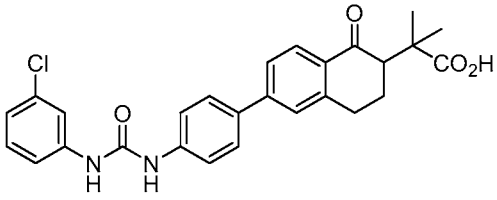
2-Methyl-2-(1-oxo-6-(4-(3-(3-(trifluoromethyl) phenyl) ureido) phenyl)-1,2,3,4-tetrahydro naphthalen-2-yl) propanoic acid (76):



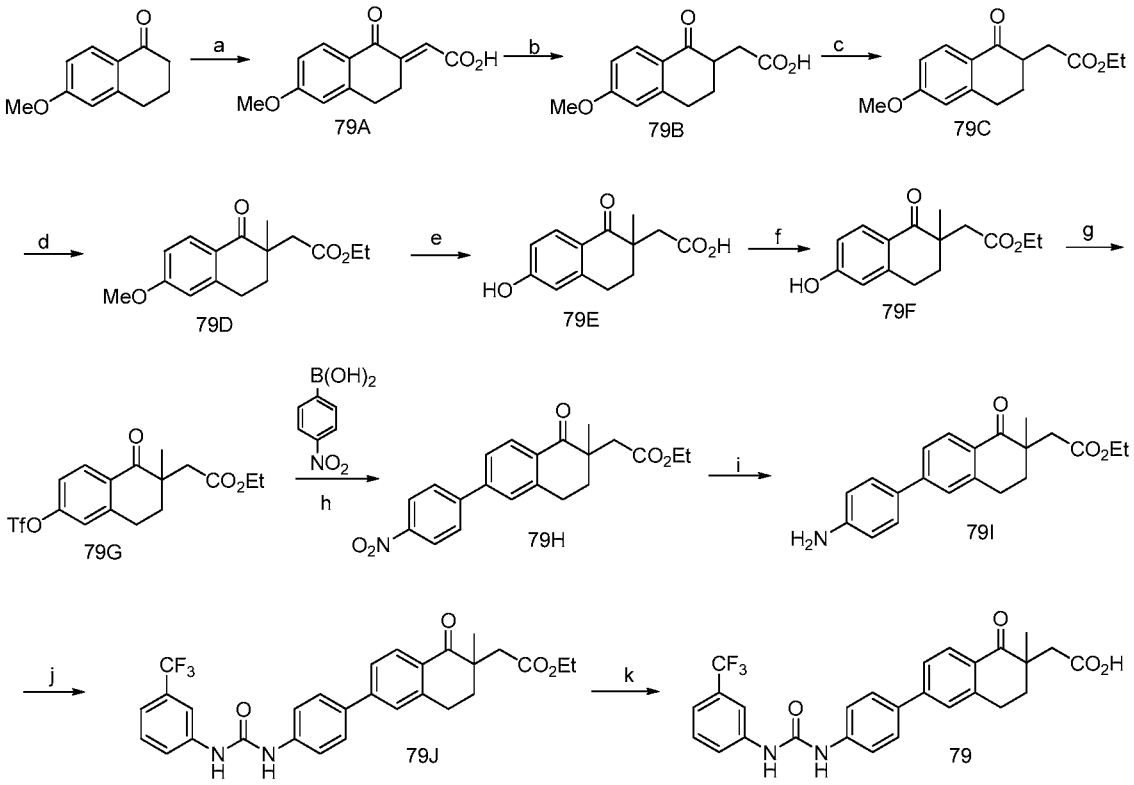
76

Lithium hydroxide (0.062 g, 1.48 mmol) was added to a solution of product of Example 76G (0.2 g, 0.37 mmol) in 4 mL of dioxane-water (3:1) mixture, and the reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 ^{0}C, and solids were collected by filtration, and dried under vacuum to afford title compound (0.075 g, 40%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.1 (bs, 1H), 9.0 (bs, 1H), 8.04 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.7 (d, J = 8.8 Hz, 2H), 7.68-7.58 (m, 5H), 7.52 (t, J = 8 Hz, 1H), 7.3 (d, J = 7.6 Hz, 1H), 3.2-3.0 (m, 3H), 2.25 (m, 1H), 1.8 (m, 1H), 1.2 (s, 3H), 1.05 (s, 3H). ESI-MS m/z = 511 $(M+H)^+$; HPLC purity: 90%.

Examples 77-78 were prepared by the analogous procedures as described above for Example 76 using appropriate starting materials.

Ex	Structure	^{1}H NMR Data	Mass/Purity
77		^{1}H NMR (400 MHz, DMSO-d_6): δ11.9 (bs, 1H), 8.85 (bs, 1H), 8.72 (bs, 1H), 7.87 (d, J = 8 Hz, 1H), 7.7 (d, J = 8.8, 1H), 7.64-7.56 (m, 5H), 7.46 (d, J = 8 Hz, 2H), 7.3 (t, J = 7.6 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.2-3.02 (m, 3H), 2.28-2.2 (m, 1H), 1.9-1.8 (m, 1H), 1.2 (s, 3H), 1.06 (s, 3H).	ESI-MS m/z = 443 $(M+H)^+$; HPLC purity: 97%.
78		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.0 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.75-7.65 (m, 3H), 7.64-7.55 (m, 4H), 7.3 (m, 2H), 7.0 (m, 1H), 3.1 (m, 3H), 2.3 (m, 1H), 1.8 (m, 1H), 1.2 (s, 3H), 1.06 (s, 3H).	ESI-MS m/z = 477 $(M+H)^+$; HPLC purity: 95%.

Example-79

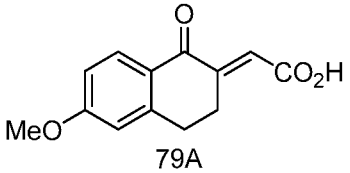


Reagents and conditions: a) Glyoxalic acid, H_2SO_4, diglyme, 85 °C, 12h; b) Zn, AcOH, 80 °C, 2h; c) $MeSO_3H$, EtOH, RT, 5h; d) MeI, NaH, DMF, RT, 4h; e) Aq. HBr, 100 °C, 12h; f) $MeSO_3H$, EtOH, RT, 5h; g) Tf_2O, CH_2Cl_2, Et_3N, RT, 1h; h) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; i) Fe-NH_4Cl, EtOH-H_2O, 85 °C, 3h; j) 3-CF_3PhNCO, Et_3N, THF, RT,12h; k) LiOH, EtOH-H_2O, RT, 12h.

Procedure:

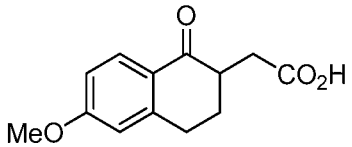
2-(2-Methyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

2-(6-Methoxy-1-oxo-3,4-dihydronaphthalen-2(1H)-ylidene)acetic acid (79A):



Glyoxalic acid (30 mL, 303 mmol) and water (14 mL) were added to a stirred solution of 6-methoxy tetralone (25 g, 141 mmol) in diglyme (50 mL) followed by sulphuric acid (6.5 mL, 35 mmol). The reaction mixture was heated to 85 °C overnight. The reaction mixture was cooled to 0 °C, and resulting solids were filtered off and washed with water (3x25 mL), dried under reduced pressure to afford title compound (28 g, 85%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.9 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.0 (m, 2H), 6.6 (s, 1H), 3.8 (s, 3H), 3.3 (m, 2H), 3.0 (m, 2H). ESI-MS m/z: 233 $(M+H)^+$.

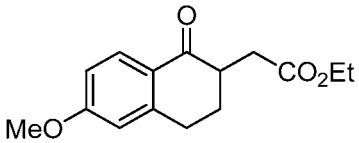
2-(6-Methoxy-1-oxo-1, 2, 3, 4-tetrahydronaphthalen-2-yl)acetic acid (79B):



79B

Zinc (19.6 g, 300 mmol) was added to a solution of product of Example 79A (28 g, 120 mmol) in acetic acid –water mixture (224 mL+84 mL), and the mixture was stirred at 80 °C for 2 h. The reaction mixture was then filtered over celite bed, and the organic layer was removed under reduced pressure. Water (50 mL) was added to the residue. The resulting solids were collected by filtration and dried under vacuum to afford title compound (27 g, 95%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 7.8 (d, J = 8.4 Hz, 1H), 6.9 (m, 2H), 3.8 (s, 3H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.7 (m, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 1.9 (m, 1H).

Ethyl 2-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (79C):



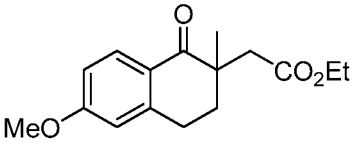
79C

Methane sulphonic acid (20 mL) was added to a solution of product of Example 79B (20 g, 47 mmol) in ethanol (150 mL), and the mixture was stirred at room temperature for 5 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and extracted with brine solution. The organic layer was dried over sodium sulphate, filtered and removed under vacuum to afford title compound (10 g, 71%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.8 Hz, 1H), 6.82 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.67 (s, 1H), 4.2 (m, 2H), 3.8 (s, 3H), 3.12-2.89 (m, 4H), 2.4 (m, 1H), 2.26 (m, 1H), 1.98 (m, 1H), 1.28 (t, J = 7.6 Hz, 3H).

Alternative route:

To a solution of LDA (4.5g, 42.6 mmol) in THF (45 mL) at -60 °C, 6-methoxy-1-tetralone (5g, 28.4 mmol) was slowly added. The rection mixture was stirred for 40 min. Ethyl bromoacetate (5.69 g, 34.09 mmol) was then added, and the reaction mixture was stirred at rt for 5 h. Reaction mixture was then quenched with saturated NH_4Cl solution and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentration to give 7g of the title compound.

Ethyl 2-(6-methoxy-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (79D):

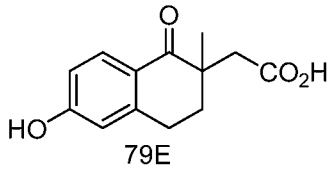


79D

A solution of product of Example 79C (10 g, 38 mmol) in DMF (50 mL) was added over a period of 30 min to an ice cold solution of NaH (4.58 g, 114 mmol) in DMF (100 mL). The reaction mixture was stirred for 10 min. Methyl iodide (27.08 g, 191 mmol) was then added and mixture was stirred for 4 h at room temperature. The reaction was then brought to 0 °C, excess NaH was quenched with ice water and aqueous layer was extracted with ethyl acetate (2X100 mL). The

combined organic layers were dried over sodium sulphate, filtered and removed under vacuum to give crude title compound (12 g) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, J = 8.4 Hz, 2H), 6.7 (dd, J_1= 1.6 Hz, J_2 = 8.4 Hz, 1H), 6.62 (m, 1H), 4.0 (m, 2H), 3.0-2.7 (m, 3H), 2.4 (d, J = 16.0 Hz, 1H), 2.25 (m, 1H), 1.8 (m, 1H), 1.15 (m, 3H), 1.1 (s, 3H).

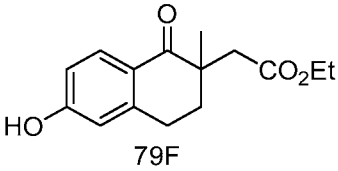
2-(6-Hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (79E):



79E

Aqueous HBr (180 mL) was added to the product of Example 79D (12 g, 43.47 mmol) and the reaction mixture was refluxed for overnight. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure to give crude product which was purified using flash chromatography with 40% ethyl acetate in hexanes to afford title compound (8.2 g, 80.6%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.08 (bs, 1H), 10.29 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 6.7 (m, 1H), 6.62 (m, 1H), 3.0-2.71 (m, 3H), 2.49-2.33 (m, 2H), 1.8 (m, 1H), 1.1 (s, 3H).

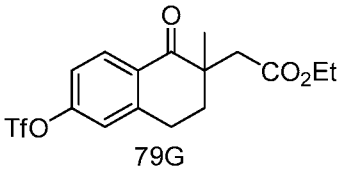
Ethyl 2-(6-hydroxy-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (79F):



79F

Methane sulphonic acid (15 mL) was added to a solution of product of Example 79E (8.2 g, 35 mmol) in ethanol (100 mL), and the mixture was stirred at room temperature for 5 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and extracted with brine solution. The organic layer was dried over sodium sulphate, filtered and removed under vacuum to afford title compound (7.1 g, 77%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J = 9.0 Hz, 1H), 6.72 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 6.63 (s, 1H), 4.1 (q, J = 6.9 Hz, 2H), 3.06-2.8 (m, 3H), 2.5-2.33 (m, 2H), 1.9 (m, 1H), 1.3-1.18 (m, 6H).

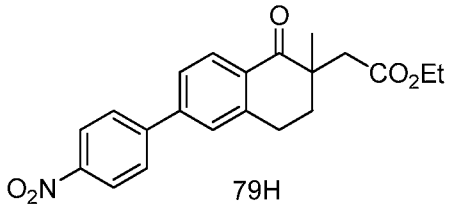
Ethyl 2-(2-methyl-1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (79G):



79G

Triflic anhydride (5.38 g, 19.08 mmol) was added to an ice cold solution of product of Example 79F (5 g, 19.08 mmol) and pyridine (1.65 g, 20.88 mmol) in dichloromethane (40 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous solution of NaCl (75 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 5% ethyl acetate in hexanes to give title compound (4 g, 53%) as syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 8.4 Hz, 1H), 7.2 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 7.16 (s, 1H), 4.1 (q, J = 7.8 Hz, 2H), 3.2 -2.9 (m, 3H), 2.52-2.4 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, J = 7.2 Hz, 3H).

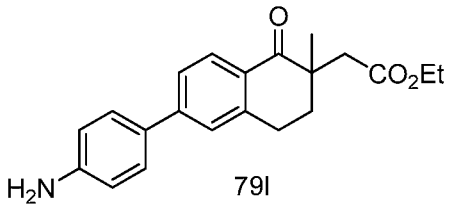
Ethyl 2-(2-methyl-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (79H):



79H

$Pd(PPh_3)_4$ (0.09 g, 0.077 mmol) was added to a solution of product of Example 79G (2.6 g, 6.59 mmol) in 20 mL of 1,4 dioxane-H_2O (3:1) mixture under Argon atmosphere, followed by cesium carbonate (6.45 g, 19.78 mmol) and 4-nitro phenyl boronic acid (1.21 g, 7.24 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 5 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography to afford title compound (1.6 g, 69%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.76 (m, 2H), 7.58 (m, 1H), 7.46 (s, 1H), 4.1 (m, 2H), 3.2-2.95 (m, 3H), 2.5 (m, 2H), 2.0 (m, 1H), 1.3 (s, 3H), 1.25 (m, 3H).

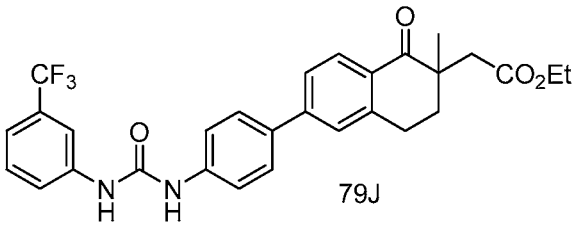
Ethyl 2-(6-(4-aminophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (79I):



79I

Iron powder (0.73 g, 13 mmol) was added to a solution of product of Example 79H (1.6 g, 4.35 mmol) in 45 mL of ethanol-water mixture (2:1) followed by NH_4Cl (0.117 g, 2.16 mmol). The mixture was refluxed for 3 h. The solvent was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed in vacuo to give title compound (1.3 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.49-7.46 (m, 3H), 7.37 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.11 (m, 2H), 3.8 (bs, 2H), 3.11-2.9 (m, 3H), 2.5-2.39 (m, 2H), 1.96 (m, 1H), 1.29 (s, 3H), 1.2 (m, 3H).

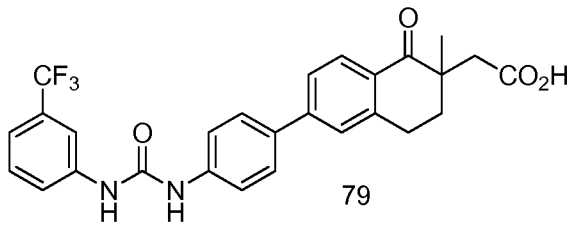
Ethyl 2-(2-methyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphth-alen-2-yl) acetate (79J):



79J

3-(Trifluoromethyl) phenyl isocyanate (0.45 g, 2.44 mmol) was added to a solution of product of Example 79I (0.55 g, 1.63 mmol) and triethylamine (0.49 g, 4.89 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (0.45 g, 53%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.7 (s, 1H), 7.62 (m, 1H), 7.5-7.42 (m, 2H), 7.4-7.3 (m, 6H), 7.1 (m, 1H), 4.1 (q, *J* = 7.2 Hz, 2H), 3.2-2.9 (m, 3H), 2.56-2.44 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, *J* = 7.2 Hz, 3H).

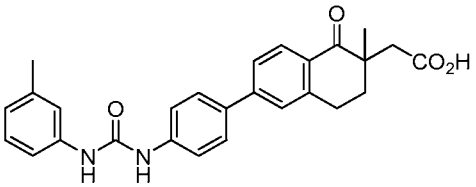
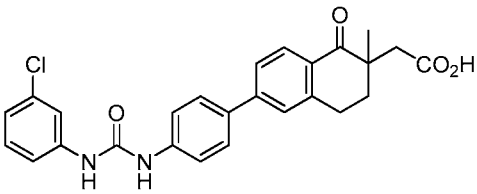
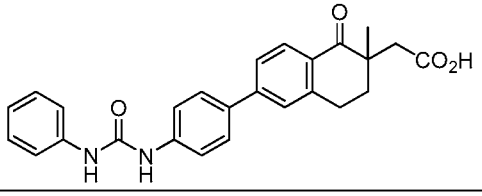
2-(2-Methyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (79):

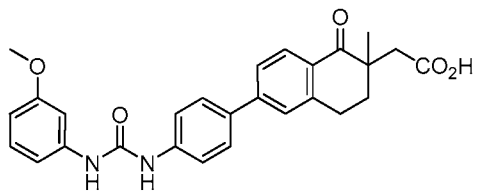
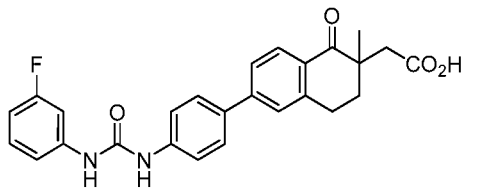
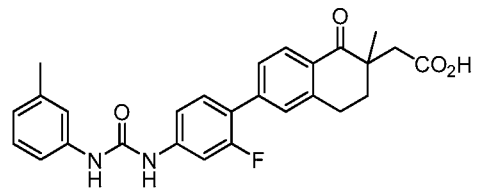
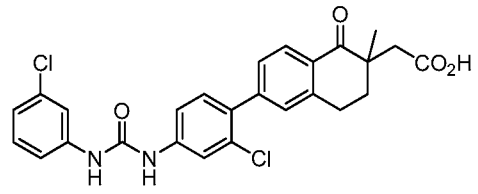
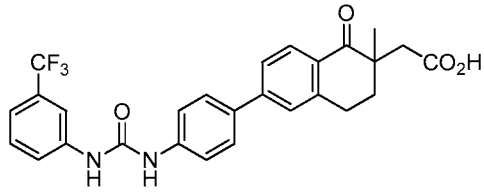


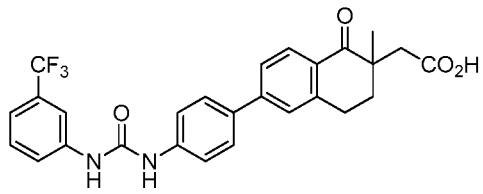
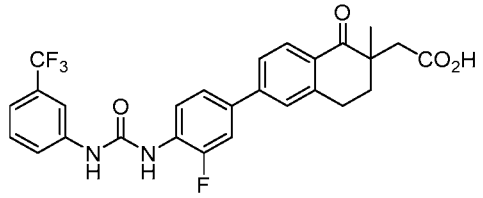
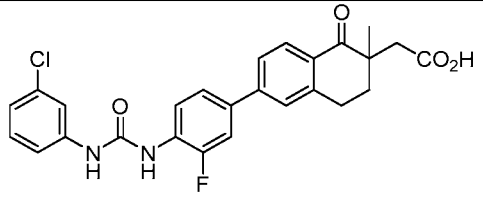
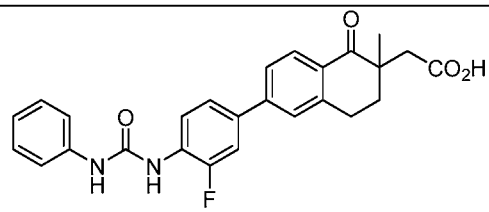
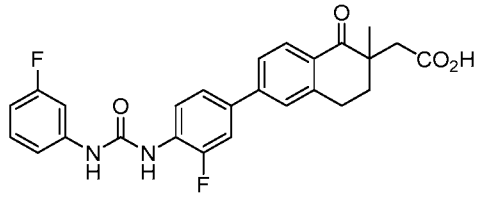
79

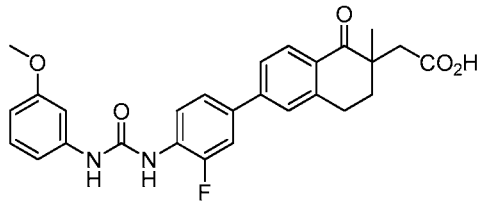
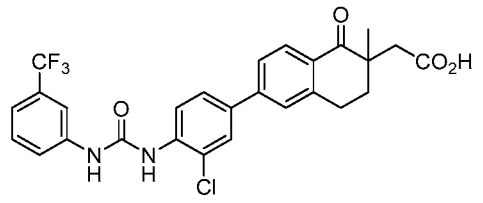
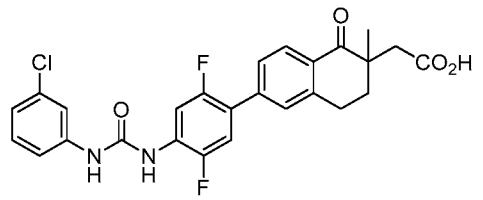
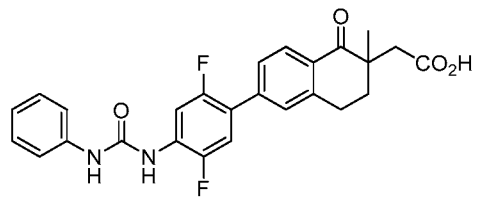
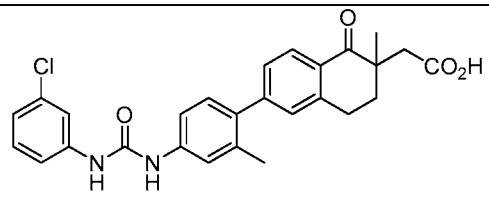
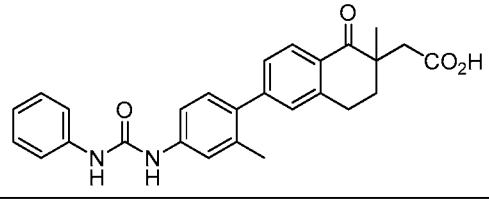
Lithium hydroxide (0.026 g, 0.66 mmol) was added to a solution of product of Example 79J (0.12 g, 0.22 mmol) in 10 mL of ethanol-water (4:1) mixture. The mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.06 g, 54%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.16 (bs, 1H), 9.04 (bs, 1H), 8.04 (m, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.7 (d, J = 8Hz, 2H), 7.66-7.56 (m, 5H), 7.52 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 3.2-2.9 (m, 2H), 2.6 (d, J = 15.6 Hz, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H); ESI-MS m/z = 497 $(M+H)^+$; LCMS Purity: 98%.

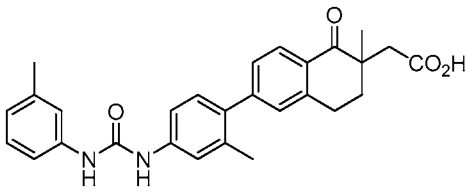
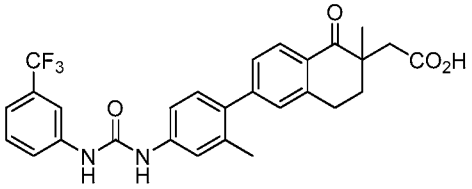
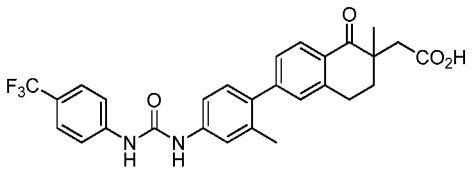
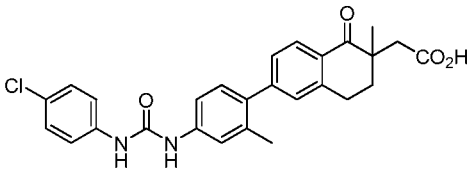
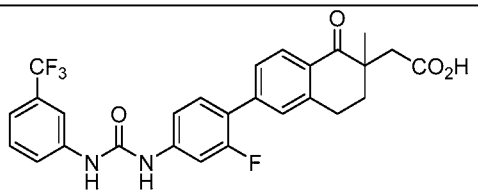
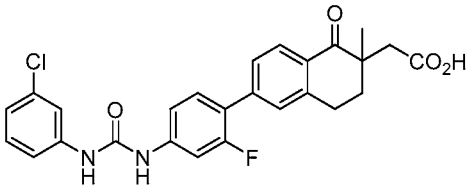
Examples 80 - 114 were prepared by the procedures analogous to those described in Example 79 using appropriate starting materials. The requisite boronic acids (and appropriately functional-group-protected versions thereof) utilized herein were purchased if available commercially, were synthesized as described in the literature or by routine modifications thereof known by those skilled in the art, or were synthesized by alternative procedures known by those skilled in the art. Chiral compounds were obtained using similar procedures as described in Example 129.

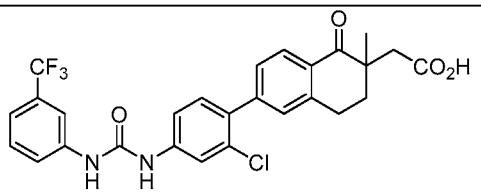
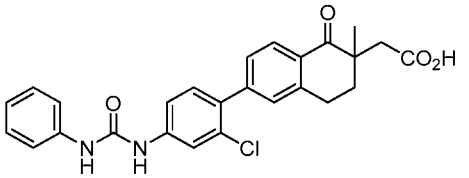
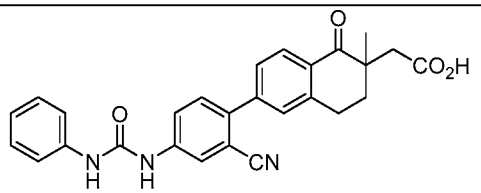
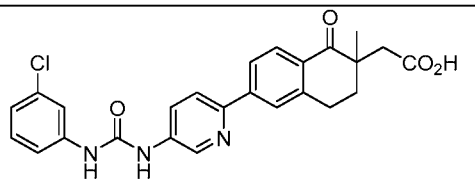
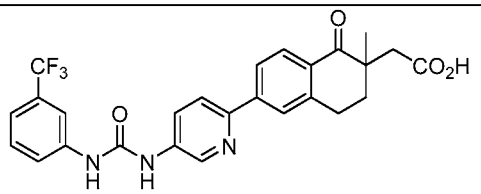
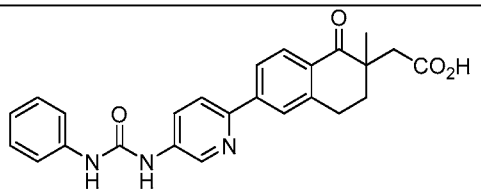
Ex	Structure	^{1}H NMR Data	Mass/purity
80		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (bs, 1H), 8.9 (bs, 1H), 7.9 (d, J = 7.5 Hz, 1H), 7.7-7.5 (m, 6H), 7.32 (s, 1H), 7.25 (m, 1H), 7.23 (t, J = 7.8 Hz, 1H), 6.8 (d, J = 7.8 Hz, 1H), 3.3-2.9 (m, 2H), 2.85 (d, J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 441 $(M-H)^-$; LCMS Purity: 92%.
81		^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, J = 8 Hz, 1H), 7.76 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.5 (s, 1H), 7.48-7.36 (m, 5H), 7.25 (t, J = 12 Hz, 1H), 6.95 (d, J = 8 Hz, 1H), 3.2-2.8 (m, 2H), 2.7-2.5 (m, 2H), 2.2 (d, J = 15 Hz, 1H), 1.75 (d, J = 12 Hz, 1H), 1.2 (s, 3H).	ESI-MS m/z = 463 $(M+H)^+$; HPLC Purity: 96%
82		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.85 (bs, 1H), 8.75 (bs, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.74-7.54 (m, 6H), 7.46 (d, J = 7.8 Hz, 2H),	ESI-MS m/z = 429 $(M+H)^+$; HPLC Purity: 97%.

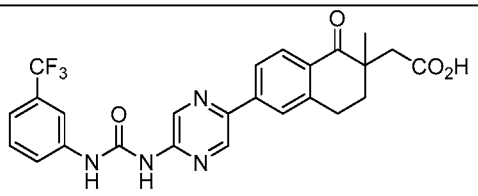
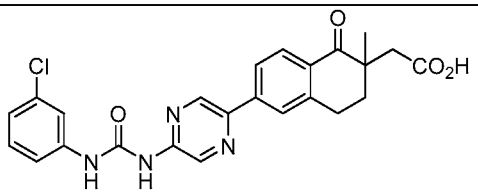
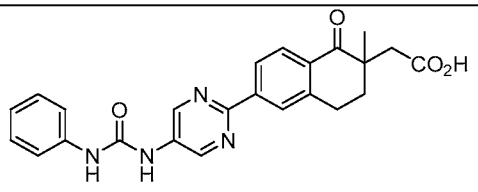
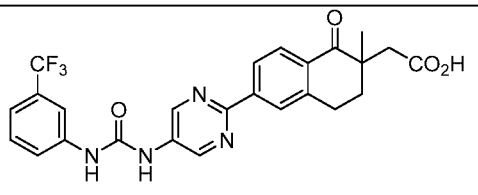
		7.3 (t, *J* = 7.5 Hz, 2H), 6.98 (t, *J* = 7.8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16 Hz, 1H), 2.4 (d, *J* = 16.2 Hz, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	
83		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.15 (bs, 1H), 9.05 (bs, 1H), 7.8 (d, *J* = 8 Hz, 2H), 7.75-7.55 (m, 5H), 7.2 (m, 2H), 6.95 (d, *J* = 6 Hz, 1H), 6.55 (m, 1H), 3.75 (s, 3H), 3.3-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 459 $(M+H)^+$; HPLC Purity: 97%.
84		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 7.8 (d, *J* = 8 Hz, 2H), 7.7 (d, *J* = 8.8 Hz, 2H), 7.65-7.55 (m, 3H), 7.5 (d, *J* = 12.4 Hz, 1H), 7.3 (q, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 6.8 (m, 1H), 3.2-2.85 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 447 $(M+H)^+$; HPLC Purity: 98%.
85		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.8-7.7 (d, *J* = 14.4 Hz, 1H), 7.58-7.3 (m, 6H), 7.18-7.08 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 6.9 Hz, 1H), 3.2-2.8 (m, 3H), 2.6 (m, 2H), 2.3 (s, 3H), 1.8 (m, 1H), 1.2 (s, 3H).	HPLC Purity: 98%
86		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (2s, 2H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.8 (m, 1H), 7.7 (bs, 1H), 7.48-7.26 (m, 6H), 7.05 (m, 1H), 3.2-2.8 (m, 3H), 2.35 (m, 2H), 1.9 (m, 1H), 1.25 (s, 3H).	HPLC Purity: 95%
87	 Chiral: enantiomer-1	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.12 (bs, 1H), 9.0 (bs, 1H), 8.02 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.75-7.5 (m, 8H), 7.3 (d, *J* = 7.8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.2 Hz, 1H), 2.4 (d, *J* = 15.9 Hz, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	HPLC Purity: 98%; Chiral HPLC purity: 99%

88	 Chiral: enantiomer-2	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.12 (bs, 1H), 9.0 (bs, 1H), 8.02 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.75-7.5 (m, 8H), 7.3 (d, J = 7.8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.2 Hz, 1H), 2.4 (d, J = 15.9 Hz, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	HPLC Purity: 98.7%; Chiral HPLC purity: 97.5%
89		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.54 (s, 1H), 8.85 (s, 1H), 8.25 (t, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H) 7.75-7.65 (m, 3H), 7.62-7.5 (m, 3H), 7.35 (m, 1H), 3.2-2.9 (m, 2H), 2.84 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 513 $(M-H)^-$. HPLC purity: 97.11%.
90		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.33 (s, 1H), 9.0 (s, 1H), 8.25 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 9.0 Hz, 1H) 7.75-7.65 (m, 4H), 7.6 (d, J = 8.4 Hz, 1H), 7.35-7.25 (m, 2H), 7.05 (t, J = 7.5 Hz, 1H), 3.2-2.9 (m, 2H), 2.83 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 481 $(M+H)^+$. HPLC purity: 97.55%.
91		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.24 (s, 1H), 8.8 (s, 1H), 8.27 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 8.8 Hz, 1H) 7.75-7.65 (m, 3H), 7.6 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 7.6 Hz, 2H), 7.3 (t, J = 7.6 Hz, 2H), 7.0 (t, J = 7.2 Hz, 1H), 3.2-2.9 (m, 2H), 2.82 (m, 1H), 2.35 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 445 $(M-H)^-$. HPLC purity: 95.51%.
92		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.35 (s, 1H), 8.76 (s, 1H), 8.3 (t, J = 8.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H) 7.7 (m, 3H), 7.6-7.5 (m, 1H), 7.35 (m, 1H), 7.1 (d, J = 7.6 Hz, 1H), 6.83 (m, 2H), 3.2-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 465 $(M+H)^+$. HPLC purity: 92.08%.

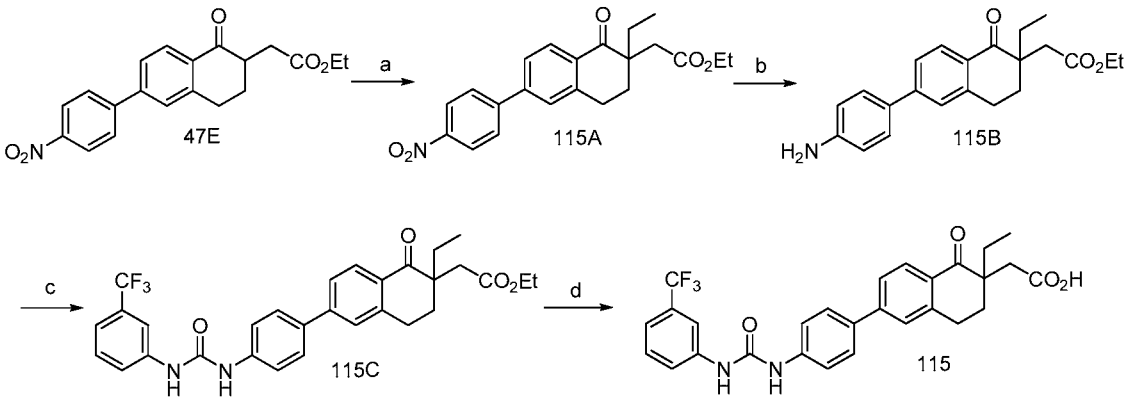
93		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.25 (s, 1H), 8.8 (s, 1H), 8.3 (t, J = 8.4 Hz, 1H), 7.9 (d, J = 8.8 Hz, 1H) 7.7 (m, 3H), 7.57 (d, J = 8.8 Hz, 1H), 7.2 (m, 2H), 6.95 (d, J = 9.2 Hz, 1H), 6.6 (dd, J = 2.0 Hz, 8.0 Hz, 1H), 3.75 (s, 3H), 3.2-2.9 (m, 2H), 2.81 (d, J = 16.4 Hz, 1H), 2.36 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 477 $(M+H)^+$. LCMS purity: 99.34%.
94		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.95 (bs,1), 8.65 (s, 1H), 8.3 (m, 1H), 8.1 (s, 1H), 7.95 -7.85 (m, 2H), 7.75-7.65 (m, 3H), 7.6-7.5 (m, 2H), 7.35 (d, J = 7.2 Hz, 1H), 3.2-2.8 (m, 2H), 2.6 (m, 1H), 2.3 (m, 2H), 1.9 (m, 1H), 1.3 (s, 3H).	HPLC purity: 95%.
95		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.5 (s, 1H), 9.0 (s, 1H), 8.2 (m, 1H), 7.9 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H), 7.6-7.5 (m, 3H), 7.4-7.2 (m, 2H), 7.1 (d, J = 8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16 Hz, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 499 $(M+H)^+$; HPLC Purity: 95.4%
96		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.42 (bs, 1H), 9.1 (bs, 1H), 8.16 (m, 1H), 7.95 (d, J = 8.4 Hz,, 1H), 7.6-7.4 (m, 5H), 7.3 (t, J = 7.6 Hz, 2H), 7.0 (t, J = 7.2 Hz, 1H), 3.3-2.9 (m, 2H), 2.8 (d, J = 16 Hz, 1H), 2.4 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	HPLC Purity: 93.4%
97		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.95 (bs, 1H), 8.85 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.45-7.3 (m, 6H), 7.15 (d, J = 8.4 Hz, 1H), 7.0 (m, 1H), 3.2-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 477 $(M+H)^+$; HPLC purity: 98.7%.
98		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.9 (2s, 2H), 7.9 (d, J = 7.6 Hz, 1H), 7.5-7.28 (m, 8H), 7.18 (d, J = 8.0 Hz, 1H), 7.0 (t, J = 7.2 Hz, 1H), 3.2-2.8 (m, 2H),	ESI-MS m/z = 445 $(M+H)^+$; HPLC purity: 95%.

		2.78 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 1.9 (m, 1H), 1.2 (s, 3H).	
99		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.6-9.0 (bs, 2H), 7.9 (d, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.4-7.25 (m, 4H), 7.12 (m, 2H), 7.0 (bs, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 3.2-2.95 (m, 2H), 2.85 (d, *J*=16.2 Hz, 1H), 2.56 (m, 2H), 2.3 (s, 3H), 2.26 (s, 3H), 1.8 (m, 1H), 1.2 (s, 3H);	ESI-MS *m/z* = 456 (M+H); HPLC Purity: 95%.
110		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.6-9.0 (bs, 2H), 8.08 (s, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.6 (m, 1H), 7.5 (m, 2H), 7.36-7.24 (m, 4H), 7.18 (m, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 (d, *J* = 16.2 Hz, 2H), 2.3 (s, 3H), 1.85 (m, 1H), 1.2 (s, 3H);	ESI-MS *m/z* = 510 $(M+H)^+$; HPLC purity: 96%.
101		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.6 (d, *J* = 8.1 Hz, 3H), 7.3 (m, 2H), 6.9 (m, 2H), 3.2-2.8 (m, 3H), 2.6 (m, 2H), 2.2 (s, 3H), 1.8 (m, 1H), 1.2(s, 3H);	ESI-MS *m/z* = 510 $(M+H)^+$; HPLC purity: 96.5%.
102		^{1}H NMR (400 MHz, DMSO-d_6): δ 7.9 (d, *J* = 8.4 Hz, 1H), 7.6 (m, 3H), 7.32-7.2 (m, 5H), 7.0 (bs, 1H), 3.2-2.9 (m, 3H), 2.4 (m, 2H), 2.2 (m, 3H), 1.8 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 477 $(M+H)^+$; HPLC purity: 92%.
103		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.2 (bs, 2H), 8.03 (s, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.64-7.48 (m, 6H), 7.38-7.24 (m, 2H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 515 $(M+H)^+$; HPLC Purity: 97%
104		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.2 (bs, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.7 (s, 1H), 7.6 (d, *J* = 14 Hz, 1H), 7.54-7.44 (m, 3H), 7.35-7.25 (m, 3H), 7.0 (m, 1H), 3.2-2.9 (m, 2H), 2.85 (d, *J* = 15.3 Hz, 1H), 2.4 (d, *J* = 16.2 Hz, 2H), 1.8 (m, 1H), 1.2 (s,	ESI-MS *m/z* = 481 $(M+H)^+$; HPLC Purity: 99%

		3H).	
105		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.4 (s, 1H), 8.04 (s, 1H), 7.94 (d, J = 8 Hz, 1H), 7.88 (bs, 1H), 7.62 (m, 1H), 7.5 (t, J = 7.6 Hz, 1H), 7.4-7.3 (m, 6H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	HPLC purity: 94%.
106		^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95 (d, J = 8.4 Hz, 2H), 7.7 (s, 1H), 7.4-7.3 (m, 6H), 7.2 (m, 1H), 7.0 (m, 1H), 3.2-2.8 (m, 3H), 2.3 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	HPLC purity: 95%.
107		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.15 (bs, 1H), 8.9 (bs, 1H), 8.1 (s, 1H), 8.0 (d, J = 7.5 Hz, 1H), 7.8 (m, 1H), 7.65-7.45 (m, 6H), 7.3 (t, J = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.2 (s, 3H).	ESI-MS m/z = 453 $(M+H)^+$; HPLC purity: 92%.
108		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.56 (s, 1H), 9.48 (s, 1H), 8.75 (s, 1H), 8.15-7.95 (m, 5H), 7.72 (s, 1H), 7.32 (m, 2H), 7.05 (s, 1H), 3.2-2.95 (m, 2H), 2.84 (m, 1H), 2.5-2.3 (m, 2H), 1.9 (m, 1H), 1.17 (s, 3H).	ESI-MS m/z = 464 $(M+H)^+$; HPLC purity: 96.3%.
109		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.48-9.45 (2bs, 2H), 8.76 (s, 1H), 8.2-7.95 (m, 6H), 7.63 (d, J = 8.4 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 3.2-2.95 (m, 2H), 2.84 (d, J = 16 Hz, 1H), 2.5-2.3 (m, 2H), 1.92 (m, 1H), 1.18 (s, 3H).	ESI-MS m/z = 498 $(M+H)^+$; HPLC purity: 93.9%.
110		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.6 (s, 1H), 9.22 (s, 1H), 8.79 (s, 1H), 8.2-7.95 (m, 5H), 7.48 (d, J = 8.0 Hz, 2H), 7.3 (t, J = 8.4 Hz, 2H), 7.0 (t, J = 7.2 Hz, 1H), 3.18-2.95 (m, 2H), 2.83 (d, J = 16.4 Hz, 1H), 2.5-2.3 (m, 2H), 1.9 (m, 1H), 1.18 (s, 3H).	ESI-MS m/z = 430 $(M+H)^+$; HPLC purity: 97.4%.

111		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H),10.06 (s, 1H), 9.91 (s, 1H), 9.19 (s, 1H), 9.02 (s, 1H), 8.1-7.95 (m, 4H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.4 (d, *J* = 7.2Hz, 1H), 3.2-2.95 (m, 2H), 2.85 (d, *J* = 16.0 Hz, 1H), 2.5-2.35 (m, 2H), 1.9 (m, 1H), 1.18 (s, 3H).	ESI-MS *m/z* = 497 $(M-H)^-$; HPLC purity: 95.7%.
112		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H),10.24 (bs, 1H), 9.98 (bs, 1H), 9.22 (s, 1H), 9.01 (s, 1H), 8.1-7.95 (m, 3H), 7.76 (s, 1H), 7.35 (m, 2H), 7.09 (m, 1H), 3.15-2.95 (m, 2H), 2.84 (d, *J* = 15.9 Hz, 1H), 2.5-2.35 (m, 2H), 1.9 (m, 1H), 1.18 (s, 3H).	ESI-MS *m/z* = 465 $(M+H)^+$; HPLC purity: 97.5%.
113		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 9.0 (s, 2H), 8.3 (m, 2H), 8.0 (d, *J* = 8.4 Hz, 1H), 7.5 (d, *J* = 7.8 Hz, 2H), 7.3 (t, *J* = 7.8 Hz, 2H), 7.0 (t, *J* = 7.2 Hz, 1H), 3.3 (m, 2H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.4 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	ESI-LCMS *m/z*: 431 (purity 91.3 %); HPLC purity 98 %.
114		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 10.0 (bs, 2H), 9.0 (s, 2H), 8.4 (m, 2H), 8.0 (m, 2H), 7.7 (d, *J* = 7.5 Hz, 1H), 7.5 (t, *J* = 7.8 Hz, 1H), 7.3 (d, *J* = 6.9 Hz, 1H), 3.1 (m, 3H), 2.8 (m, 1H), 2.4 (m, 1H), 1.9 (d, *J* = 12.6 Hz, 1H), 1.2 (s, 3H).	ESI-LCMS *m/z*: 498 (purity 98%). HPLC purity 98%.

Example-115

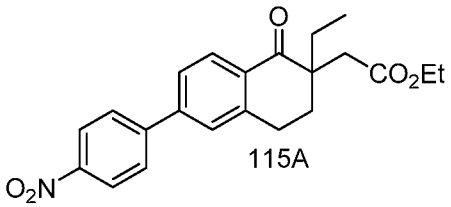


Reagents and conditions: a) EtI, KOH, Acetone, RT, 12 h; b)Fe-NH_4Cl, EtOH-H_2O, 85 °C, 2h; c) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; d) LiOH, THF-H_2O, RT, 12h.

Procedure:

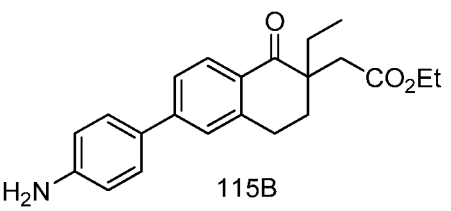
2-(2-Ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

Ethyl 2-(2-ethyl-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (115A):



Potassium hydroxide (0.57 g, 10.17 mmol) was added to a solution of product of Example 47E (1.2 g, 3.39 mmol) in acetone (20 mL) followed by ethyl iodide (2.57 g, 16.5 mmol), and the reaction mixture was stirred at room temperature for 12 h. Acetone was removed under reduced pressure, diluted with water and extracted with ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using 15% ethyl acetate in pet ether to afford title compound (0.43 g, 33%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.4 (d, J = 9.0 Hz, 2H), 8.2 (d, J = 8.4 Hz, 1H), 7.8 (d, J = 8.4 Hz, 2H), 7.6 (d, J = 7.6 Hz, 1H), 7.5 (s, 1H), 4.1 (m, 2H), 3.2-2.9 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.9 (t, J = 7.6 Hz, 3H).

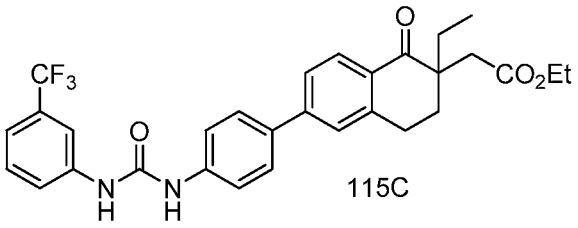
Ethyl 2-(6-(4-aminophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (115B):



Iron powder (0.189 g, 3.37 mmol) was added to a solution of product of Example 115A (0.43 g, 1.12 mmol) in 22 mL of ethanol-water mixture (2:1) followed by NH_4Cl (0.030 g, 0.55 mmol), and the mixture was refluxed for 2 h. The solvent was removed under reduced pressure, and residue

was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered, concentrated in vacuo and triturated with n-pentane to give title compound (0.35 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, J = 8.4 Hz, 1H), 7.8 (d, J = 8.4 Hz, 2H), 7.6-7.3 (m, 4H), 4.1 (m, 2H), 3.8 (bs, 2H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.6-2.4 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.3 (t, J = 7.6 Hz, 3H), 0.9 (t, J = 7.2 Hz, 3H).

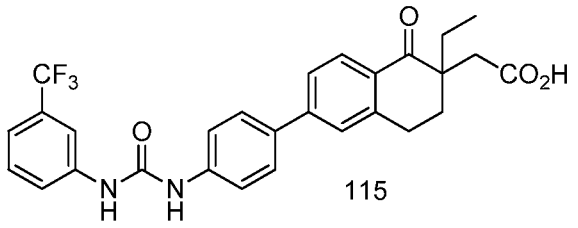
Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (115C):



115C

3-(Trifluoromethyl) phenyl isocyanate (0.084 mL, 0.56 mmol) was added to a solution of product of Example 115B (0.2 g, 0.56 mmol) and triethylamine (0.234 mL, 1.70 mmol) in THF (4 mL). The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 25-30% ethyl acetate in pet ether to afford title compound (0.25 g, 81%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, 8.4 Hz, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.5-7.3 (m, 9H), 7.1 (s, 1H), 4.1 (q, J = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.4-1.2 (m, 5H), 0.9 (t, J = 7.2 Hz, 3H).

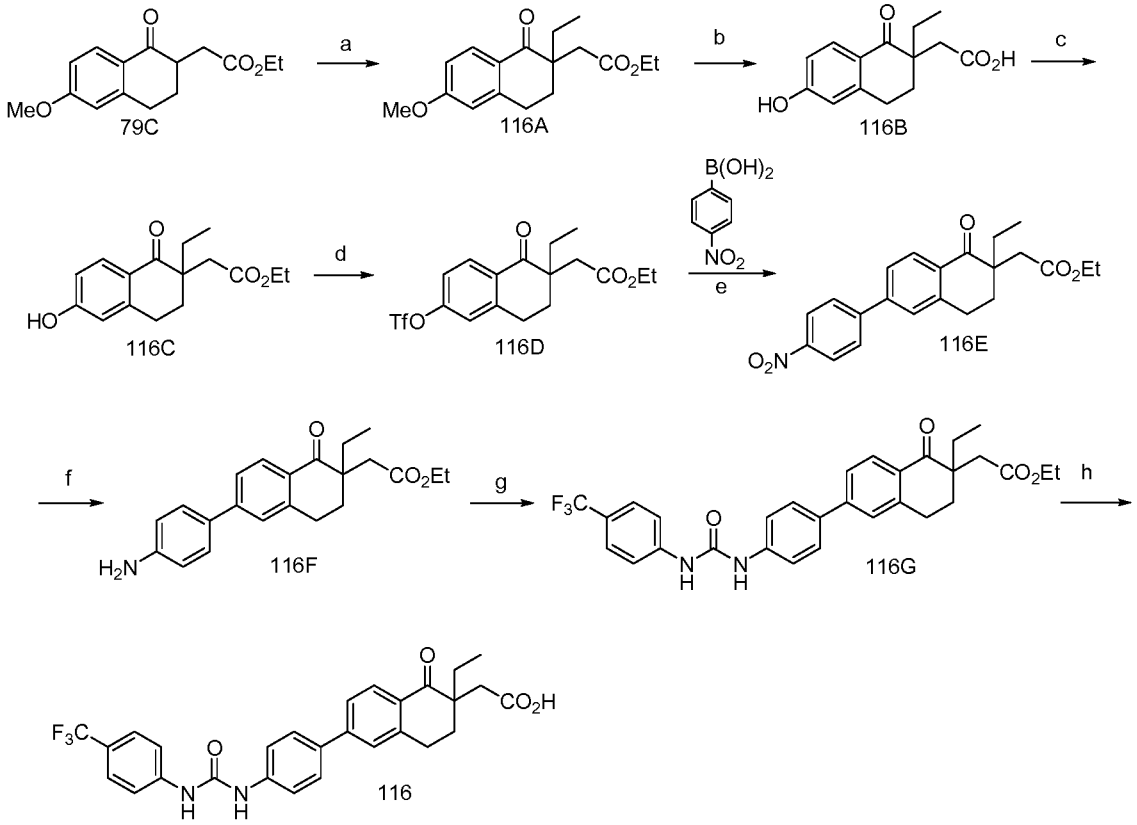
2-(2-Ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (115):



115

Lithium hydroxide (0.054 g, 1.38 mmol) was added to a solution of product of Example 115C (0.25 g, 0.46 mmol) in 3 mL of ethanol-water (2:1) mixture. The mixture was stirred at room temperature for 12 h. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solids were collected by filtration, triturated with n-pentane and diethyl ether and dried under vacuum to afford title compound (0.15 g, 63%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 8.1 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7 -7.5 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (t, J = 7.8 Hz, 3H); ESI-MS m/z: 511 $(M+H)^+$; HPLC purity: 95%.

Example-116

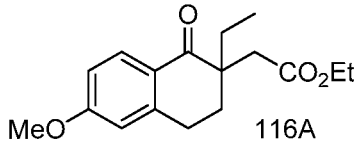


Reagents and conditions: a) EtI, NaH, DMF, RT, 5h; b) Aq. HBr, 100 °C, 3h; c) $MeSO_3H$, EtOH, RT, 16h; d) Tf_2O, CH_2Cl_2, Et_3N, RT, 2h; e) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 4h; f) Fe-NH_4Cl, EtOH-H_2O, 85 °C, 4h; g) 4-CF_3PhNCO, Et_3N, THF, RT, 12h; h) LiOH, THF-H_2O, RT, 12h.

Procedure:

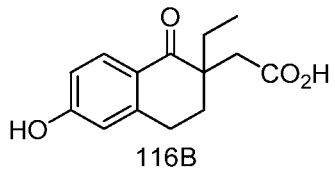
2-(2-Ethyl-1-oxo-6-(4-(3-(4-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

Ethyl 2-(2-ethyl-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (116A):



To an ice-cold solution of product of Example 79C (7 g, 26.8 mmol) in DMF (80 mL) was added NaH (1.93 g, 80.4 mmol) in portion wise, and the reaction mixture was stirred for 10 min. Ethyl iodide (20.91 g, 134.03 mmol) was then added, and the mixture was stirred for 5 h at room temperature. The reaction mixture was poured in to ice water and aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulphate, filtered and removed under vacuum to give title compound (7.8 g) as solid.

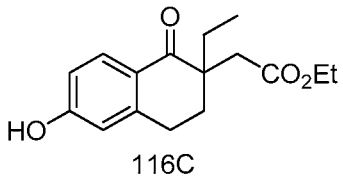
2-(2-Ethyl-6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (116B):



116B

Aqueous HBr (120 mL) was added to product of Example 116A (7.8 g, 26.9 mmol), and the reaction mixture was refluxed for 3 h. The reaction mixture was then brought to room temperature and extracted with ethyl acetate. The organic layers were dried over sodium sulphate, filtered and removed under reduced pressure to give crude product which was purified by flash chromatography using 30% ethyl acetate in pet ether to afford title compound (3.5 g, 53%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 10.3 (s, 1H), 7.8 (d, J = 8.4 Hz, 1H), 6.7 (d, J = 7.4 Hz, 1H), 6.6 (s, 1H), 3.0 (m, 1H), 2.7 (m, 2H), 2.4 (m, 2H), 1.9 (m, 1H), 1.7-1.5 (m, 2H), 0.9 (t, J = 7.6 Hz, 3H).

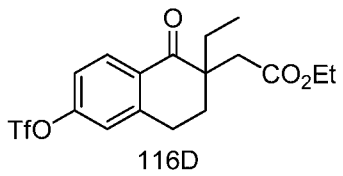
Ethyl 2-(2-ethyl-6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (116C):



116C

Methane sulphonic acid (6 mL) was added to a solution of product of Example 116B (3.5 g, 14.17 mmol) in ethanol (50 mL), and the reaction mixture was stirred at room temperature for 16 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and washed with brine solution. The organic layer was dried over sodium sulphate, filtered and removed under under reduced pressure to give crude product which was purified by flash chromatography using 20% ethyl acetate in pet ether to afford title compound (3.2 g, 82%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.2 (s, 1H), 8.0 (d, J = 8.4 Hz, 1H), 6.7 (d, J = 7.4 Hz, 1H), 6.6 (s, 1H), 4.0 (m, 2H), 3.2-2.7 (m, 3H), 2.5-2.3 (m, 2H), 2.2-1.9 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.8 (t, J = 7.6 Hz, 3H).

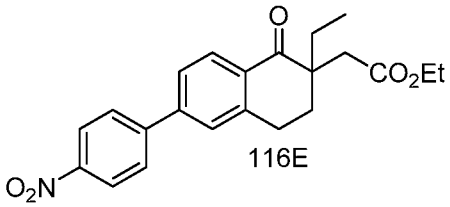
Ethyl 2-(2-ethyl-1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (116D):



116D

Triflic anhydride (3.28 g, 11.6 mmol) was added to an ice cold solution of product of Example 116C (3.2 g, 11.6 mmol) and pyridine (1.01 g, 12.7 mmol) in dichloromethane (40 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane and extracted with saturated aqueous solution of NaCl. The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 5% ethyl acetate in pet ether to give title compound (3 g, 63%) as syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.2 (d, J = 8.4 Hz, 1H), 7.3-7.2 (m, 2H), 4.2 (m, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 1.0 (t, J = 7.6 Hz, 3H).

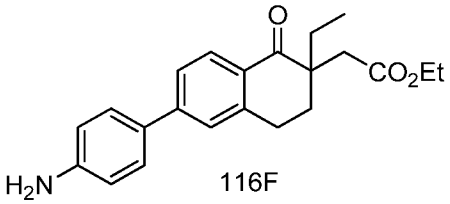
Ethyl 2-(2-ethyl-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (116E):



116E

$Pd(PPh_3)_4$ (0.02 g, 0.017 mmol) was added to a solution of product of Example 116D (0.6 g, 1.47 mmol) in 14 mL of 1,4 dioxane-H_2O (2:1) mixture under argon atmosphere, followed by cesium carbonate (1.44 g, 4.41 mmol) and 4-nitrophenyl boronic acid (0.246 g, 1.47 mmol). The reaction mixture was degassed for 5 min and refluxed for 4 h. Solvent was then removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 15% ethyl acetate in pet ether to afford title compound (0.5 g, 89%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.4 (d, J = 9.0 Hz, 2H), 8.2 (d, J = 8.4 Hz, 1H), 7.8 (d, J = 8.4 Hz, 2H), 7.6 (d, J = 7.6 Hz, 1H), 7.5 (s, 1H), 4.1 (m, 2H), 3.2-2.9 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.9 (t, J = 7.6 Hz, 3H).

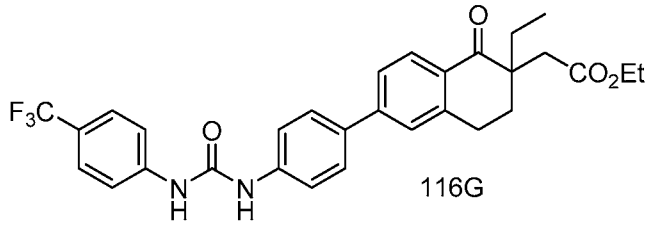
Ethyl 2-(6-(4-aminophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (116F):



116F

Iron powder (0.24 g, 4.3 mmol) was added to a solution of product of Example 116E (0.55 g, 1.44 mmol) in 30 mL of ethanol-water mixture (2:1) followed by NH_4Cl (0.039 g, 0.72 mmol). The reaction mixture was stirred and refluxed for 4 h. The solvent was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure, triturated with n-pentane to afford title compound (0.3 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, J = 8.4 Hz, 1H), 7.8 (d, J = 8.4 Hz, 2H), 7.6-7.3 (m, 4H), 4.1 (m, 2H), 3.8 (bs, 2H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.6-2.4 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.3 (t, J = 7.6 Hz, 3H), 0.9 (t, J = 7.2 Hz, 3H).

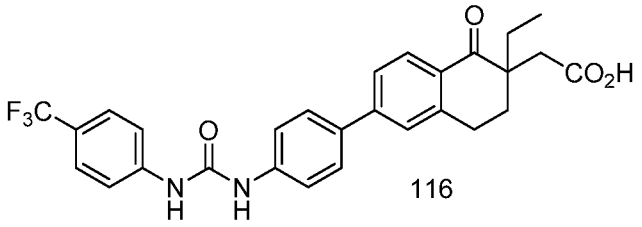
Ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(4-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (116G):



116G

4-(Trifluoromethyl) phenyl isocyanate (0.106 g, 0.57 mmol) was added to a solution of product of Example 116F (0.2 g, 0.56 mmol) and triethylamine (0.17 g, 1.68 mmol) in THF (5 mL). The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 25% ethyl acetate in pet ether to afford title compound (0.18 g, 58%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.0 (d, 8.4 Hz, 1H), 7.7 (bs, 1H), 7.52-7.42 (m, 5H), 7.38-7.32 (m, 2H), 7.28-7.20 (m, 4H), 4.1 (q, J = 7.2 Hz, 2H), 3.14-2.8 (m, 3H), 2.55-2.4 (m, 2H), 2.05 (m, 1H), 1.8-1.64 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H).

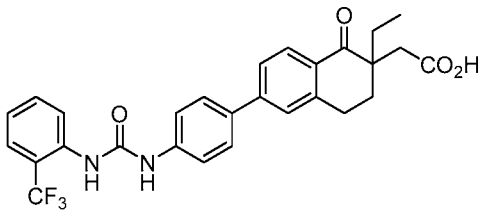
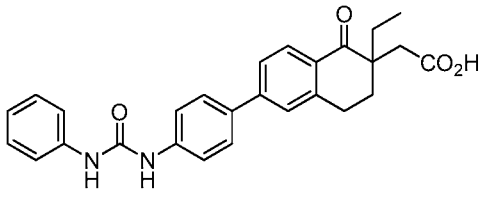
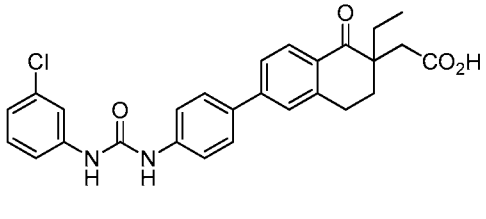
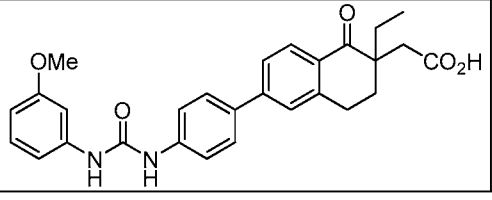
2-(2-Ethyl-1-oxo-6-(4-(3-phenylureido) phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (116):

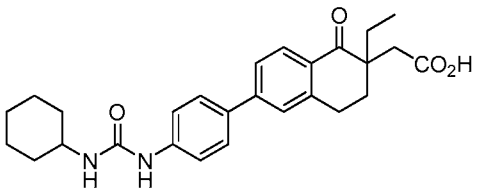
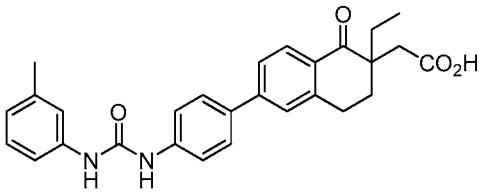
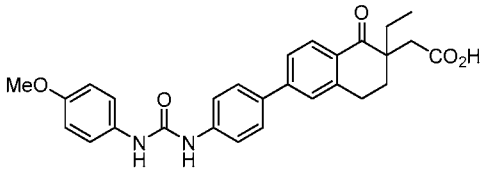
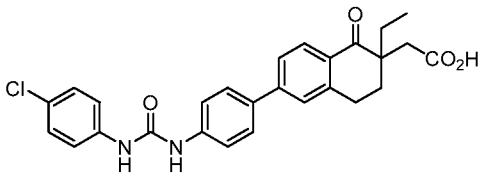
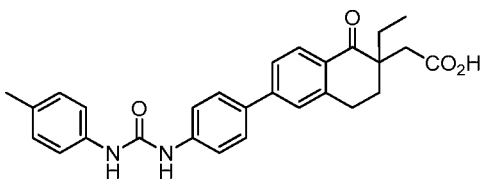


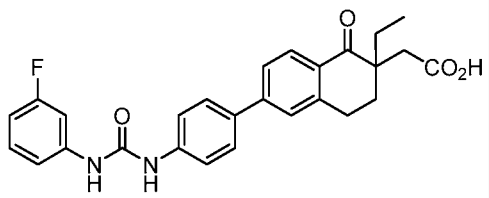
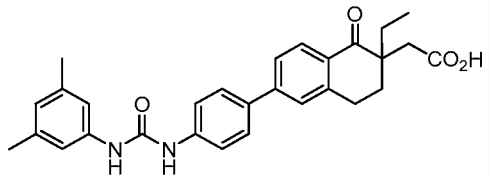
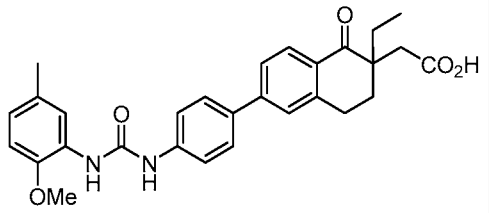
116

Lithium hydroxide (0.128 g, 2.28 mmol) was added to a solution of product of Example 116G (0.18 g, 0.76 mmol) in 6 mL of ethanol-water (2:1) mixture. The mixture was stirred at room temperature for 12 h. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solids were collected by filtration, triturated with n-pentane and dried under vacuum to afford title compound (0.1 g, 59%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.8-7.5 (m, 10H), 3.2-2.9 (m, 2H), 2.85-2.7 (d, J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1,8-1.45 (m, 2H), 0.95 (m, 3H); ESI-MS m/z: 511 $(M+H)^+$; HPLC purity: 94%.

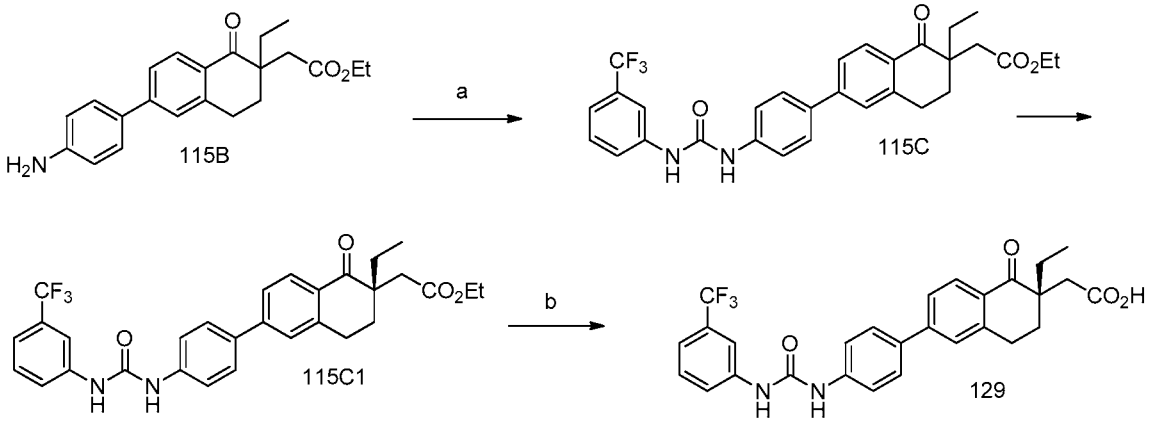
Examples 117 - 128 were prepared by the procedures analogous to those described in Example 116 using appropriate starting materials.

Ex	Structure	Analytical Data	$(M+H)^+$
117		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.7 (bs, 1H), 8.35 (bs, 1H), 7.9 (d, J = 8.4 Hz, 2H), 7.7-7.5 (m, 8H), 7.3 (t, J = 6.3 Hz, 1H), 3.3-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (m , 3H).	HPLC Purity: 92%
118		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.2-8.8 (m, 2H), 7.8 (d, J = 8.4 Hz, 1H), 7.7-7.55 (m, 6H), 7.45 (d, J = 8.4 Hz, 2H), 7.3 (t, J = 7.5 Hz, 2H), 6.95 (t, J = 7.5 Hz, 1H), 3.2-2.6 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, J = 7.8 Hz, 3H).	HPLC purity: 91%
119		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.0 (bs, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.73-7.56 (m, 6H), 7.3 (m, 3H), 7.02 (m, 1H), 3.2-2.7 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.75-1.45 (m, 2H), 0.9 (t, J = 7.5 Hz, 3H).	HPLC purity: 92%
120		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.6-9.0 (bs, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.66-7.48 (m, 6H), 7.26 (s, 1H), 7.16 (t, J = 8.4 Hz, 1H), 7.0 (d, J = 8.4	ESI-MS m/z = 473 $(M+H)^+$; HPLC purity:

		Hz, 1H), 6.56 (m, 1H), 3.8 (s, 3H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.4 Hz, 1H), 2.4 (m, 1H), 2.3 (d, *J* = 16.2 Hz, 1H), 2.0 (m, 1H), 1.78-1.5 (m, 2H), 0.85 (t, *J* = 6.9 Hz, 3H).	90%.
121		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.8 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.65-7.52 (m, 4H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.4 (bs, 1H), 3.5 (s, 1H), 3.2-2.8 (m, 2H), 2.6 (d, *J* = 16 Hz, 1H), 2.35 (d, *J* = 16 Hz, 1H), 2.0 (m, 1H), 1.9-1.5 (m, 8H), 1.4-1.0 (m, 5H), 0.85 (t, *J* = 7.6 Hz, 3H).	HPLC Purity: 90%.
122		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.0 (bs, 1H), 8.8 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.7-7.5 (m, 6H), 7.31 (s, 1H), 7.28-7.1 (m, 2H), 6.8 (d, *J* = 7.5 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 2.0 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t , *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 457 $(M+H)^+$; HPLC Purity: 98%.
123		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.8 (bs, 1H), 8.58 (bs, 1H), 7.9 (d, *J* = 7.8Hz, 1H), 7.7-7.66 (d, *J* = 8.4 Hz, 2H), 7.64-7.52 (m, 4H), 7.38 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.8 (s, 3H), 3.2-2.8 (m, 2H), 2.6 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (m, 3H).	ESI-MS *m/z* = 473 $(M+H)^+$; HPLC purity: 99%.
124		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 8.95 (2s, 2H), 7.9 (d, *J* = 7.8 Hz, 1H) , 7.7 (d, *J* = 8.4 Hz, 2H), 7.6 (m, 4H), 7.5 (d, *J* = 8.4 Hz, 2H), 7.3 (d, *J* = 8.4 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.5 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, *J* = 7.5 Hz, 3H).	ESI-MS *m/z* = 477 $(M+H)^+$; HPLC purity: 98%.
125		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.0-8.6 (bs, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.62-7.54 (m, 5H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.1 (d, *J* = 8.4 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.4 Hz, 1H), 2.4 (m, 2H), 2.25 (s, 3H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H).	HPLC purity: 98%

126		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7-7.4 (m, 7H), 7.3 (m, 1H), 7.15 (d, J = 8.4 Hz, 1H), 6.8 (t, J = 6.8 Hz, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 1.9 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t, J = 7.6 Hz, 3H).	HPLC purity: 91%.
127		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 8.92 (bs, 1H), 8.62 (bs, 1H), 7.9 (d, J = 8.0 Hz, 1H), 7.7-7.5 (m, 6H), 7.1 (m, 2H), 6.6 (m, 1H), 3.2-2.8 (m, 2H), 2.6 (d, J = 16.4 Hz, 1H), 2.4 (m, 2H), 2.2 (s, 6H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 470 $(M+H)^+$; HPLC purity: 90%.
128		^{1}H NMR (400 MHz, DMSO-d_6): δ 10.6 (bs, 1H), 8.8 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.8 (m, 2H), 7.6 -7.4 (m, 5H), 6.9 (d, J = 7.8 Hz, 1H), 6.8 (d, J = 7.5 Hz, 1H), 3.8 (s, 3H), 3.0-2.6 (m, 3H), 2.4 (m, 1H), 2.3 (s, 3H), 2.1 (m, 1H), 1.9 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (m, 3H).	HPLC purity: 90%.

Example-129

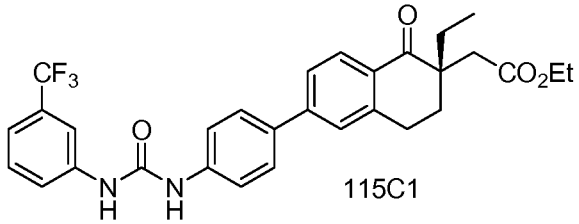


Reagents and conditions: a) 3-CF_3PhNCO, Et_3N, THF, RT, 6h; b) LiOH, Dioxane-H_2O, RT, 12h.

Procedures:

(S)-2-(2-Ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

(S)-ethyl 2-(2-ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (115C1):



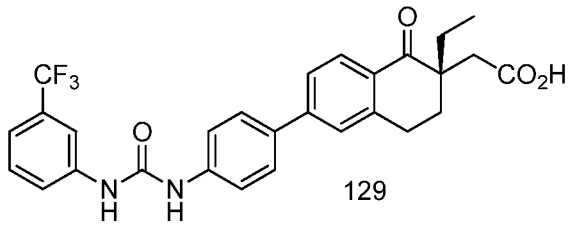
115C1

3-(Trifluoromethyl) phenyl isocyanate (0.185 g, 0.98 mmol) was added to a solution of product of Example 115B (0.29 g, 0.82 mmol) and triethylamine (0.25 g, 2.47 mmol) in THF (10 mL). The mixture was stirred at room temperature for 6 h. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 20% ethyl acetate in pet ether to afford Example 115C (0.34 g, 77%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, 8.4 Hz, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.5-7.3 (m, 9H), 7.1 (s, 1H), 4.1 (q, J = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.4-1.2 (m, 5H), 0.9 (t, J = 7.2 Hz, 3H).

Example **115C** (0.5 g, which derived from 0.32g obtained above and another batch of 180 mg using similar procedures as described for Example 115C) was racemic mixture with 1:1 enantiomeric ratio and was separated on chiral column to obtain single enantiomers of **115C1** (Rt 15.67 min) and **115C2** (Rt 20.16 min) using following conditions.
Column: CHIRAL PAK ODH (4.6x250 mm) 5μ
Mobile phase: A: Hexane, B: Ethanol
A: B(Iso) 85:15; Flow rate : 0.8 mL/min

115C1: 0.17 g, 15.67 min RT, Optical rotation +22 (c1 $CHCl_3$)
115C2: 0.168 g, 20.16 min RT, Optical rotation -22 (c1 $CHCl_3$)
Absolute configurations confirmed by VCD studies:
Absolute configuration of 115G1 is *S* and 115G2 is *R*.

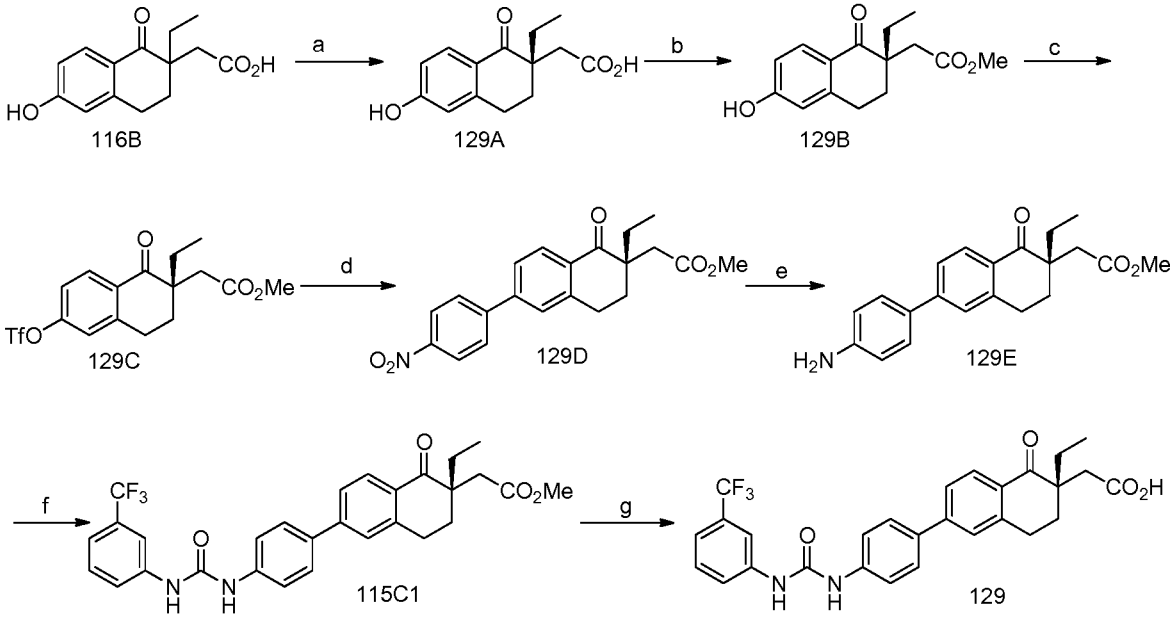
(S)-2-(2-Ethyl-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (129):



129

Lithium hydroxide (0.028 g, 0.67 mmol) was added to a solution of product of Example 115C1 (0.12 g, 0.22 mmol) in 4 mL of ethanol-water (3:1) mixture, and the reaction mixture was stirred at room temperature for 16 h. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration, triturated with n-pentane and dried under vacuum to afford title compound (0.08 g, 72%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.22 (bs, 1H), 9.09 (bs, 1H), 8.05 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.6-7.4 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (t, J = 5.7 Hz, 3H); ESI-MS *m/z*: 511 $(M+H)^+$.

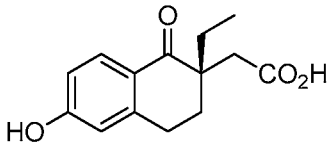
Alternative synthesis of Example 129:



Reagents and conditions: a) Cinchonidine, IPA-H_2O, 80 °C – RT, 24h then 6N HCl, RT; b) H_2SO_4, MeOH, 70 °C, 12h; c) Tf_2O, CH_2Cl_2, Et_3N, RT, 1h; d) 4-Nitrophenyl boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; e) Fe-NH_4Cl, EtOH-H_2O, 85 °C, 3h ; f) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; g) LiOH, THF-H_2O, RT, 12h.

Procedures:

(S)-2-(2-ethyl-6-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (129A):

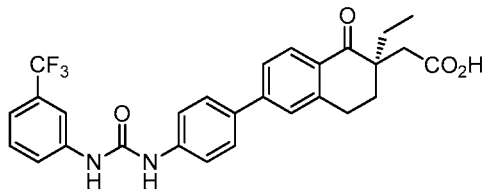
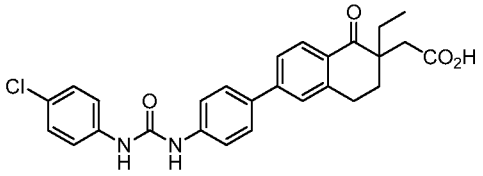
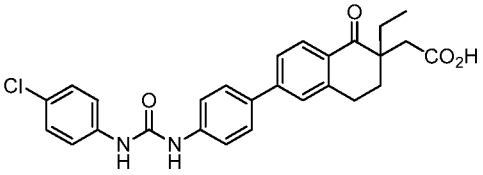
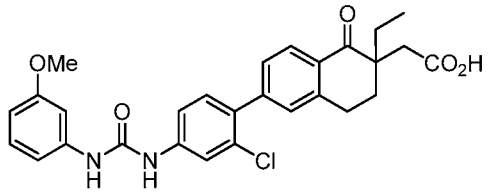


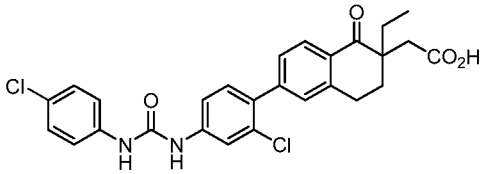
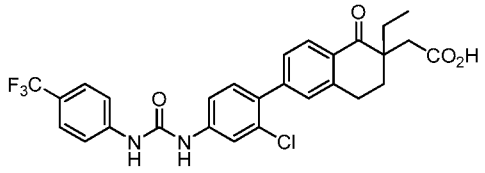
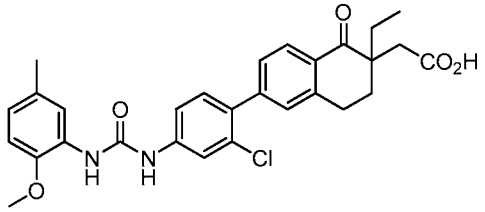
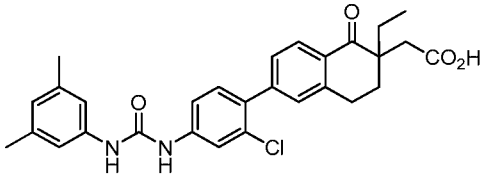
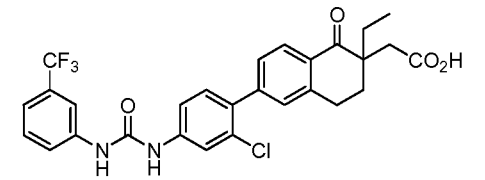
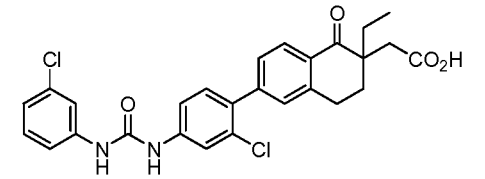
129A

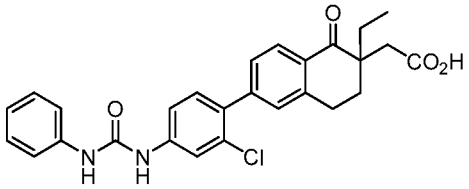
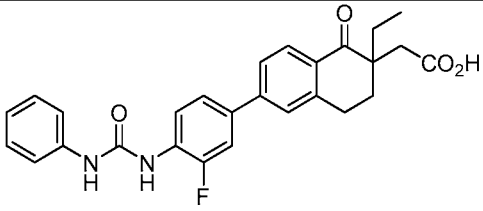
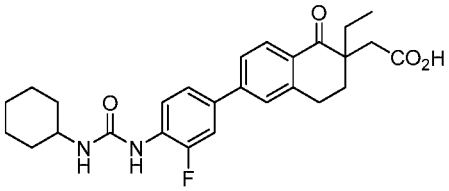
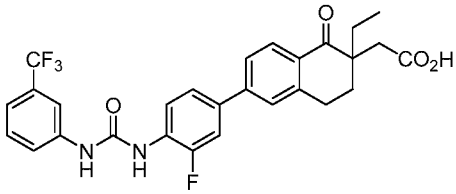
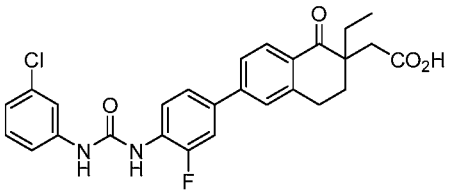
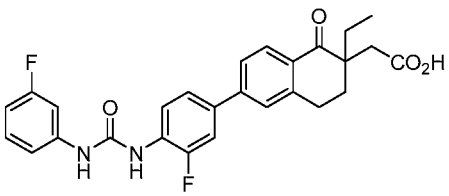
Cinchonidine (11.85 g, 40.3 mmol) was added to a solution of product of Example 116B (10 g, 40.3 mmol), in isopropyl alcohol (64 mL) and water (16 mL), and the mixture was heated to 80 °C 4 h. The resulting solution was stirred at room temperature for 16 h, and the salt was filtered and washed with a mixture of isopropyl alcohol (10 mL) and water (10 mL). The salt was dissolved in 6N HCl (40 mL) and extracted with ethyl acetate (2x50 mL). The organic layers were washed with water, brine solution, dried and concentrated to afford the title compound (1.3 g, 26%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 10.2 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 6.70 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.60 (d, J = 1.2 Hz, 1H), 3.0-2.88 (m, 1H), 2.77 (m, 1H), 2.7 (d, J = 16.8 Hz, 1H), 2.38 (m, 1H), 2.31 (d, J = 16.4 Hz, 1H), 1-95-1.85 (m, 1H), 1.62 (m, 1H), 1.48 (m, 1H), 0.8 (t, J = 7.2 Hz, 3H).

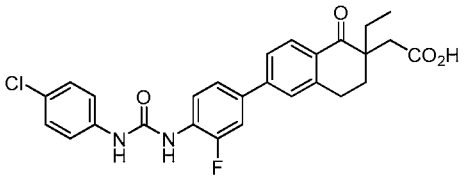
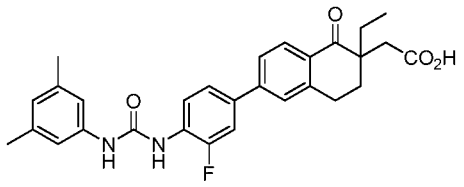
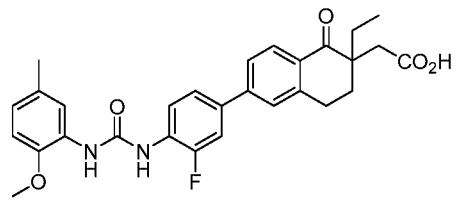
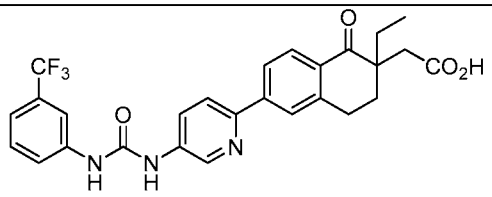
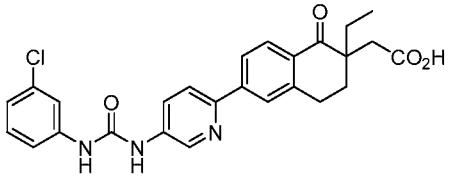
Examples 129B, 129C, 129D, 129E and 115C1 were synthesized from chiral 129A compound using the similar procedures as described for Example-116.

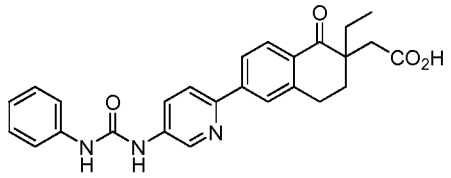
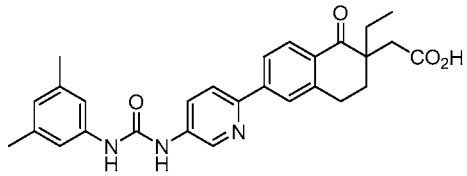
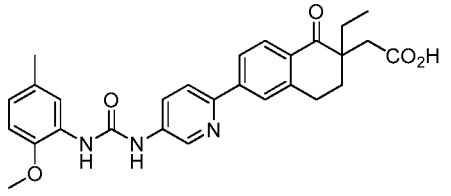
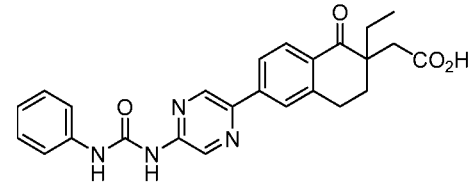
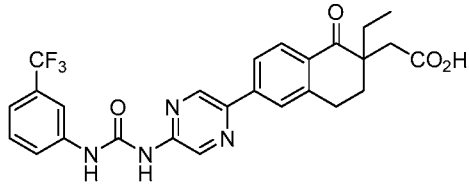
Examples 130- 172 were prepared by the procedures analogous to those described in Example 116 and 129 using appropriate starting materials. The requisite boronic acids (and appropriately functional-group-protected versions thereof) utilized herein were purchased if available commercially, were synthesized as described in the literature or by routine modifications thereof known by those skilled in the art, or were synthesized by alternative procedures known by those skilled in the art.

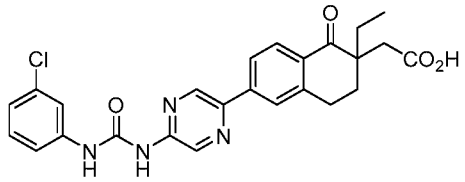
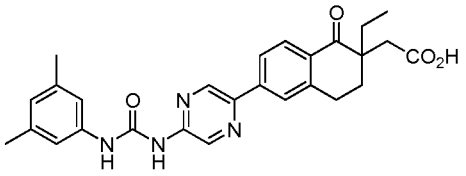
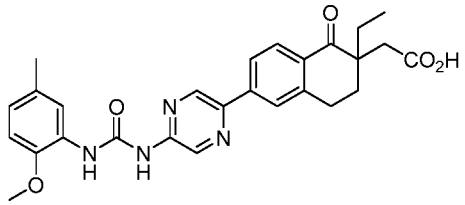
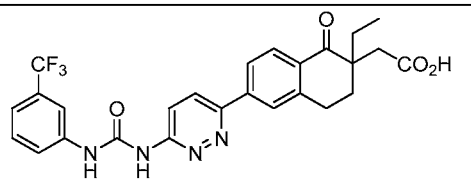
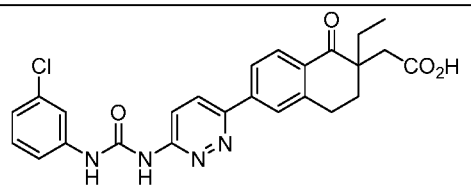
Ex	Structure	Analytical Data	$(M+H)^+$
130	 Chiral	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.22 (bs, 1H), 9.09 (bs, 1H), 8.05 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.6-7.4 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (t, J = 5.7 Hz, 3H).	HPLC purity: 97%
131	 Chiral: enantiomer-1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.1 (bs, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.7-7.54 (m, 6H), 7.5 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 3.2-2.9 (m, 2H), 2.79 (d, J = 16.8 Hz, 1H), 2.45 (m, 1H), 2.41 (d, J =16.4 Hz, 1H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, J = 7.2 Hz, 3H).	HPLC Purity: 99%
132	 Chiral: enantiomer-2	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.1 (bs, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.7-7.54 (m, 6H), 7.5 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 3.2-2.9 (m, 2H), 2.79 (d, J = 16.8 Hz, 1H), 2.45 (m, 1H), 2.41 (d, J = 16.4 Hz, 1H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, J = 7.2 Hz, 3H).	HPLC purity: 97%
133		^{1}H NMR (300 MHz, DMSO-d_6): δ δ 12.1 (bs, 1H), 9.1 (bs, 1H), 8.9 (bs, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.45-7.3 (m, 4H), 7.2 (m, 2H), 6.95 (d, J = 9.0 Hz, 1H), 6.6 (m, 1H), 3.78 (s, 3H), 3.3-2.9 (m, 2H), 2.8 (d, J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, J = 6.9 Hz, 3H).	ESI-MS m/z = 507 $(M+H)^+$; HPLC purity: 96%

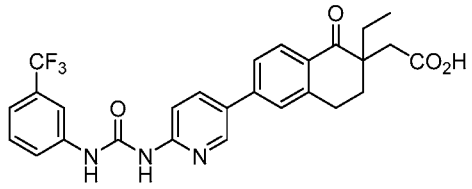
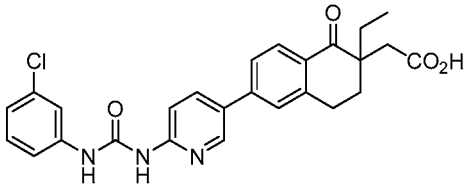
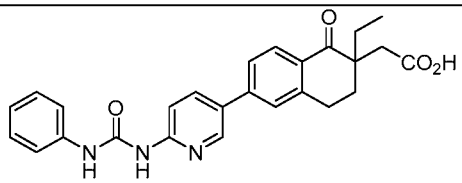
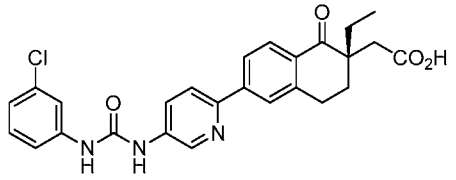
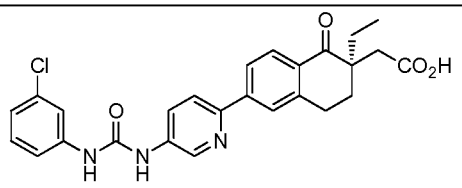
134		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 8.24 (s, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.64 (d, J = 9.3 Hz, 2H), 7.36-7.25 (m, 4H), 6.66 (m, 1H), 6.49 (m, 1H), 3.29-2.73 (m, 4H), 2.22 (m, 1H), 1.84 (m, 1H), 1.7-1.45 (m, 2H), 0.9 (t, J = 6.9 Hz, 3H).	HPLC purity: 98.89%.
135		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 8.02 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.7 (m, 3H), 7.6 (m 3H), 7.4 (m, 2H), 7.1 (m, 1H), 3.2-2.96 (m, 2H), 2.85 (d, J = 15.9 Hz, 1H), 2.6 (m, 1H), 2.3 (d, J = 16.8 Hz, 1H), 1.9 (m, 1H), 1.7-1.45 (m, 2H), 0.9 (t, J = 7.5 Hz, 3H).	ESI-MS m/z = 545 $(M+H)^+$; HPLC purity: 97.6%.
136		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.7 (bs, 1H), 8.8 (bs, 1H), 8.0-7.85 (m, 3H), 7.42-7.3 (m, 4H), 6.9 (m, 1H), 6.78 (m, 1H), 3.8 (s, 3H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.26 (s, 3H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (m, 3H).	ESI-MS m/z = 521 $(M+H)^+$; HPLC purity: 95.8%.
137		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.0 (bs, 1), 8.7 (bs, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.86 (s, 1H), 7.45-7.3 (m, 3H), 7.0 (m, 3H), 6.65 (s, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.4 (m, 2H), 2.26 (s, 6H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.85 (t, J = 6.9 Hz, 3H).	ESI-MS m/z = 505 $(M+H)^+$; HPLC purity: 97%.
138		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.3 (bs, 2H), 8.1 (s, 1H), 7.9 (m, 2H), 7.6-7.0 (m, 7H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.4 (m, 2H), 0.85 (m, 3H).	HPLC Purity: 90%.
139		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs,1), 9.15 (bs, 1H), 9.1 (bs, 1H), 7.95 (m, 1H), 7.85 (bs, 1H), 7.7 (s, 1H), 7.5-7.2 (m, 6H), 7.0 (s, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t, J = 6.9 Hz, 3H).	ESI-MS m/z = 510 $(M+H)^+$; HPLC purity: 90%.

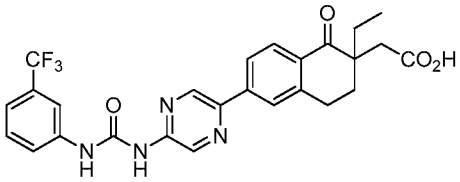
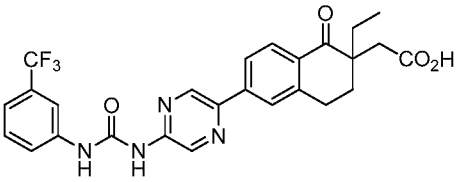
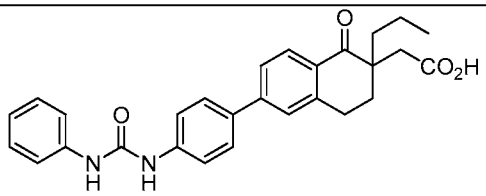
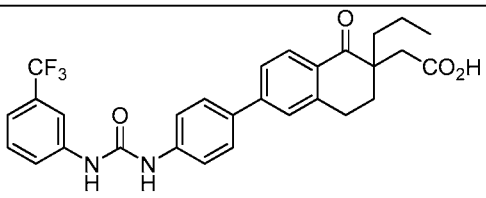
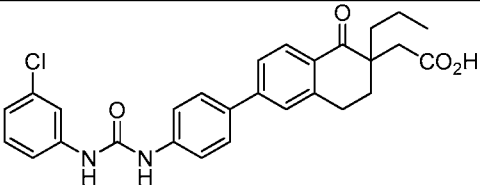
140		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.05 (bs, 1H), 8.95 (bs, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.6-7.2 (m, 8H), 7.0 (d, J = 7.8 Hz, 1H), 3.2-2.8 (m, 2H), 2.6 (d, J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.9-1.6 (m, 2H), 0.9 (t, J = 6.9 Hz, 3H).	HPLC purity: 97%.
141		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.6 (bs, 1H), 9.0 (bs, 1H), 8.2 (m, 1H), 7.9 (d, J = 8.1 Hz, 1H), 7.7-7.4 (m, 6H), 7.3 (t, J = 7.5 Hz, 2H), 7.0 (t, J = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (m, 1H), 2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (m, 3H).	ESI-MS m/z = 461 $(M+H)^+$; HPLC purity: 90%.
142		^{1}H NMR (300 MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.28 (t, J = 9 Hz, 1H), 7.9 (d, J = 8.1 Hz, 1H), 7.7-7.6 (m, 3H), 7.5 (d, J = 9.9 Hz, 1H), 6.7 (d, J = 6.9 Hz, 1H), 3.6-3.4 (m, 1H), 3.2-2.8 (m, 3H), 2.57 (d, J = 16.2 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 4H), 1.4-1.2 (m, 7H), 0.85 (t, J = 6.9 Hz, 3H).	HPLC purity: 97%.
143		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.6 (bs, 1H), 8.9 (bs, 1H), 8.25 (m, 1H), 8.05 (s, 1H), 7.9 (m, 1H), 7.72-7.5 (m, 6H), 7.36 (m, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 15.9Hz, 1H), 2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 528 $(M+H)^+$; HPLC purity: 95%.
144		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (s, 1H), 8.85 (s, 1H), 8.25 (m, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.8 -7.55 (m, 5H), 7.35-7.2 (m, 2H), 7.1 (t, J = 8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.2 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, J = 7.6 Hz, 3H).	ESI-MS m/z = 494 $(M+H)^+$; HPLC purity: 90%
145		^{1}H NMR (300 MHz, DMSO-d_6): δ 10.8 (bs, 1H), 10.4 (bs, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.56-7.40 (m, 5H), 7.29-7.13 (m, 2H), 6.74 (m, 1H), 3.2-2.7 (m, 3H), 2.6 (d, J = 16.2 Hz,	HPLC purity: 92%.

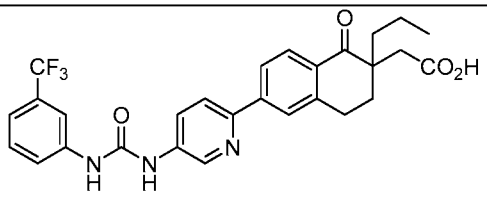
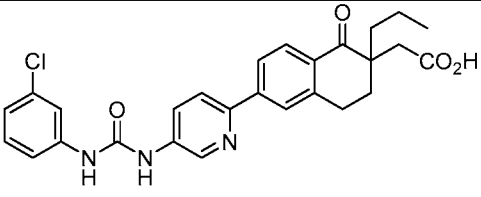
		1H), 2.2 (m, 2H), 1.7-1.5 (m, 2H), 0.9 (t, J = 6.9 Hz, 3H).	
146		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.26 (m, 1H), 8.76 (m, 1H), 8.27 (t, J = 9.0 Hz, 1H), 7.92 (d, J = 9.3 Hz, 1H), 7.74 - 7.56 (m, 4H), 7.54 (d, J = 6.4 Hz, 2H), 7.3 (d, J = 6.3 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.1 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.75-1.5 (m, 2H), 0.8 (t, J = 7.8 Hz , 3H).	HPLC purity: 96%.
147		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.05 (bs, 1H), 8.75 (s, 1H), 8.3 (m, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.72-7.62 (m, 3H), 7.58 (d, J = 8.4 Hz, 1H), 7.2 (s, 2H), 6.6 (s, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 6H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.8 (t, J = 7.8 Hz, 3H).	HPLC purity: 91%.
148		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 8.8 (bs, 1H), 8.3 (t, J = 8.4 Hz , 1H), 8.0 (s, 1H), 7.9 (d, J = 9 Hz, 1H), 7.7-7.65 (m, 3H), 7.54 (m, 1H), 6.9 (d, J = 8.4 Hz, 1H), 6.8 (d, J = 8.4 Hz, 1H), 3.8 (s, 3H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16 Hz, 1H), 2.35 (m, 2H), 2.25 (s, 3H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, J = 7.8 Hz , 3H).	HPLC purity: 92%.
149		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.50 (bs, 1H), 8.76 (s, 1H), 8.20-7.90 (m, 6H), 7.70-7.50 (m, 2H), 7.36-7.33 (m, 1H), 3.16-2.76 (m, 3H), 2.50-2.20 (m, 2H), 2.0-1.98 (m, 1H), 1.68-1.54 (m, 2H), 0.84 (m, 3H).	ESI-MS m/z = 512 $(M+H)^+$. HPLC purity: 95.3%.
150		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.78 (bs, 1H), 9.64 (bs, 1H), 8.80 (s, 1H), 8.15-8.06 (m, 2H), 8.0-7.95 (m, 3H), 7.72 (s, 1H), 7.3 (t, J = 8.4 Hz, 2H), 7.06-7.03 (m, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.8 Hz, 3H).	ESI-MS m/z = 478 $(M+H)^+$. HPLC purity: 95.66 %.

151		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.2 (bs, 1H), 8.9 (bs, 1H), 8.73 (s, 1H), 8.12-7.96 (m, 5H), 7.4 (d, J = 7.8 Hz, 2H), 7.3 (t, J = 8.4 Hz, 2H), 7.0 (m, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H).	ESI-MS m/z = 444 $(M+H)^+$. HPLC purity: 91.6 %.
152		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.4 (bs, 1H), 9.0 (bs, 1H), 8.74 (s, 1H), 8.15-7.95 (m, 5H), 7.1 (s, 2H), 6.64 (s, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.24 (s, 6H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.8 Hz, 3H).	HPLC purity: 94.4 %.
153		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.78 (bs, 1H), 8.7 (s, 1H), 8.35 (s, 1H), 8.15-7.95 (m, 6H), 6.9 (d, J = 8.1 Hz, 1H), 6.78 (dd, J_2 = 8.4 Hz, J_1 = 1.5 Hz, 1H), 3.85 (s, 3H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.24 (s, 3H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H).	HPLC purity: 98.67 %.
154		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.83 (bs, 1H), 9.81 (bs, 1H), 9.21 (s, 1H), 9.0 (s, 1H), 8.04-7.96 (m, 3H), 7.52 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.0 (t, J = 7.6 Hz, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.0 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.8 Hz, 3H).	ESI-MS m/z = 445 $(M+H)^+$; HPLC purity: 90 %.
155		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.95 (bs, 1H), 9.87 (bs, 1H), 9.17 (s, 1H), 9.03 (s, 1H), 8.05-7.9 (m, 4H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.4 (d, J = 7.8 Hz, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.2 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.8 Hz, 3H).	ESI-MS m/z = 513 $(M+H)^+$; HPLC purity: 91.59%.

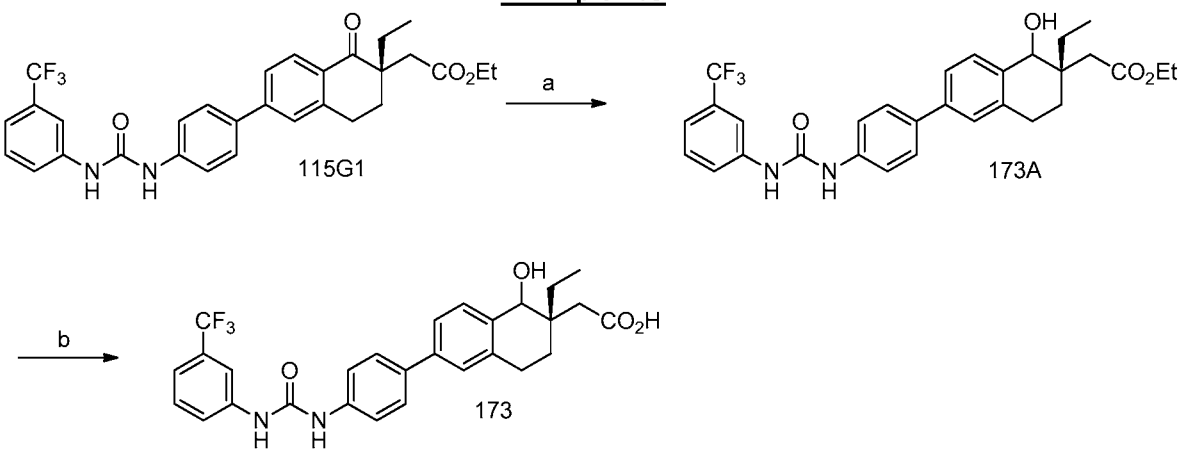
156		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.8 (bs, 1H), 9.7 (bs, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.04-7.89 (m, 3H), 7.76 (m, 1H), 7.36-7.28 (m, 2H), 7.11 (m, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 479 $(M+H)^+$; HPLC purity: 91.12 %.
157		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.05 (s, 1), 9.79 (bs, 1H), 9.62 (bs, 1H), 9.16 (s, 1H), 9.0 (s, 1H), 8.04-7.98 (m, 3H), 7.15 (s, 2H), 6.69 (s, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J*= 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.26 (s, 6H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (m, 3H).	HPLC purity: 91.88%.
158		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.05 (s, 1H), 10.29 (bs, 1H), 9.94 (bs, 1H), 9.0 (s, 2H), 8.04-7.98 (m, 4H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.89 (s, 3H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 16.2 Hz, 1H), 2.5-2.3 (m, 2H), 2.24 (s, 3H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 3H).	HPLC purity: 95.39%.
159		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 10.29 (m, 2H), 8.32 (d, *J* = 7.2 Hz, 1H), 8.25 (m, 1H), 8.07-7.98 (m, 4H), 7.64-7.57 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.8 Hz, 3H).	ESI-MS *m/z* =513 $(M+H)^+$; HPLC purity: 98.83%.
160		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs,1H), 10.29 (s, 1H), 9.95 (bs, 1H), 8.38-8.20 (m, 2H), 8.18-8.0 (m, 3H), 7.78 (s, 1H), 7.38 (m, 2H), 7.15 (s, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.0 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.8 Hz, 3H).	ESI-MS *m/z* =479(M+H) $^+$; HPLC purity: 93.4%

161		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 10.7 (s, 1H), 9.73 (s, 1H), 8.73 (s, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.08 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H) 7.68-7.53 (m, 4H), 7.56 (t, J = 8.4 Hz, 1H), 7.38 (d, J = 6.9 Hz, 1H), 3.1-2.9 (m, 2H), 2.8 (d, J = 16.2 Hz, 1H), 2.50-2.36 (m, 2H), 2.0 (m, 1H), 1.75-1.45 (m, 2H), 0.84 (m, 3H).	ESI-MS m/z = 512 $(M+H)^+$. HPLC purity: 95.8%.
162		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 11.45 (s, 1H), 8.35 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.88-7.8 (m, 2H), 7.65-7.5 (m, 4H), 7.25 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 3.15-2.75 (m, 4H), 2.1 (d, J = 15.6 Hz, 1H), 1.84 (m, 1H), 1.7-1.45 (m, 2H), 0.88 (t, J = 7.8 Hz, 3H).	ESI-MS m/z = 478 $(M+H)^+$. HPLC purity: 96.3%.
163		^{1}H NMR (300 MHz, DMSO-d_6): δ 10.4 (s, 1H), 9.9 (s, 1H), 8.7 (s, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.8-7.65 (m, 3H), 7.5 (d, J =7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.03 (t, J = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.76 (d, J = 16.8 Hz, 1H), 2.50-2.35 (m, 2H), 2.0 (m, 1H), 1.75-1.45 (m, 2H), 0.84 (t, J = 7.8 Hz, 3H).	ESI-MS m/z = 444 $(M+H)^+$. HPLC purity: 92.7%.
164	 Chiral	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (bs, 1H), 9.20 (bs, 1H), 8.75 (s, 1H), 8.15 (m, 1H), 8.03 (m, 4H), 7.74 (s, 1H), 7.34 (m, 2H), 7.07 (m, 1H), 3.13-3.02 (m, 2H), 2.8 (d, J = 16.4 Hz, 1H), 2.5-2.35 (m, 2H), 2.03 (m, 1H), 1.71-1.58 (m, 2H), 0.86 (t, J = 6.8 Hz, 3H).	ESI-MS m/z = 478 $(M+H)^+$. HPLC purity: 96.32 %.
165	 Chiral	^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (bs, 1H), 9.20 (bs, 1H), 8.75 (s, 1H), 8.15 (m, 1H), 8.03 (m, 4H), 7.74 (s, 1H), 7.34 (m, 2H), 7.07 (m, 1H), 3.13-3.02 (m, 2H), 2.8 (d, J = 16.4 Hz, 1H), 2.5-2.35 (m, 2H), 2.03 (m, 1H), 1.71-1.58 (m, 2H), 0.86 (t, J = 6.8 Hz, 3H).	ESI-MS m/z = 478 $(M+H)^+$. HPLC purity: 99.17 %.

166	 Chiral: enantiomer-1	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.08 (s, 1H), 10.0 (bs, 1H), 9.93 (bs, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.1-7.9 (m, 4H), 7.68 (d, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.4 (d, J = 6.3 Hz, 1H), 3.2-3.0 (m, 2H), 2.8 (d, J = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.68-1.55 (m, 2H), 0.84 (m, 3H).	ESI-MS m/z = 513 $(M+H)^+$; HPLC purity: 98%.
167	 Chiral: enantiomer-2	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.08 (s, 1H), 10.0 (bs, 1H), 9.93 (bs, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.1-7.9 (m, 4H), 7.68 (d, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.4 (d, J = 6.3 Hz, 1H), 3.2-3.0 (m, 2H), 2.8 (d, J = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.68-1.55 (m, 2H), 0.84 (m, 3H).	ESI-MS m/z = 513 $(M+H)^+$; HPLC purity: 97.5%.
168		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 9.1-8.9 (s, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.68-7.56 (m, 6H), 7.48-7.46 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 6.97 (t, J = 7.6 Hz, 1H), 3.08-2.92 (m, 2H), 2.80 (d, J = 16.4 Hz, 1H), 2.40 (m, 1H), 1.96 (m, 1H), 1.61 (m, 1H), 1.45-1.15 (m, 4H), 0.84 (m, 3H).	ESI-LCMS m/z: 457 (98%); HPLC purity: 98%.
169		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.8 (bs, 2H), 8.05 (s, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.6 (m, 8H), 7.3 (d, J = 7.5 Hz, 1H), 3.1 (m, 1H), 2.8 (m, 2H), 2.35 (d, J = 15.9 Hz, 1H), 2.0 (d, J = 12.6 Hz, 1H), 1.6 (m, 1H), 1.4 (m, 4H), 0.8 (t, J = 6.9 Hz, 3H).	ESI-LCMS m/z: 523 (purity 96%); HPLC purity: 94%.
170		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.35 (bs, 2H), 7.9 (d, J = 8.4 Hz, 1H), 7.75 (s, 1H), 7.6 (m, 6H), 7.3 (m, 2H), 7.0 (d, J = 5.7 Hz, 1H), 3.0 (m, 2H), 2.8 (m, 1H), 2.4 (d, J = 16.2 , 1H), 2.0 (d, J = 13.2 Hz, 1H), 1.6 (m, 1H), 1.5-1.2 (m, 4H), 0.8 (m, 3H).	ESI-LCMS m/z: 491 (purity 95%); HPLC purity: 96%.

171		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.5 (bs, 2H), 8.8 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8 (m, 5H), 7.65 (d, J = 8.4 Hz, 1H), 7.5 (t, J = 7.2 Hz, 1H), 7.35 (d, J = 6.9 Hz, 1H), 3.1-3.0 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.6 (m, 1H), 1.4 (m, 3H), 0.8 (m, 3H).	ESI-LCMS m/z: 526 (purity 92%); HPLC purity: 92.5%.
172		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.4 (s, 2H), 8.75 (s, 1H), 8.1 (d, J = 6.8 Hz, 1H), 8.0 (m, 4H), 7.7 (s, 1H), 7.3 (m, 2H), 7.0 (m, 1H), 3.1-2.9 (m, 3H), 2.8 (d, J = 16.4 Hz, 1H), 2.4 (m, 2H), 2.0 (d, J = 13.2 Hz, 1H), 1.6 (m, 1H), 1.4 (m, 2H), 0.8 (t, J = 7.2 Hz, 3H).	ESI-LCMS m/z: 492 (Purity 97%); HPLC purity: 98%.

Example-173

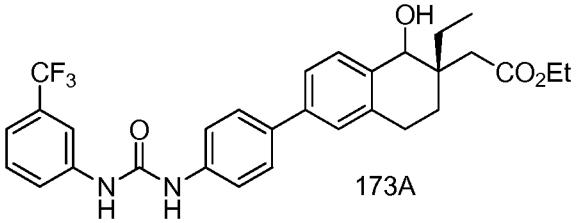


Reagents and conditions: a) $NaBH_4$, EtOH, RT, 5h; b) LiOH, Dioxane-H_2O, RT, 8h.

Procedures:

2-((2S)-2-Ethyl-1-hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

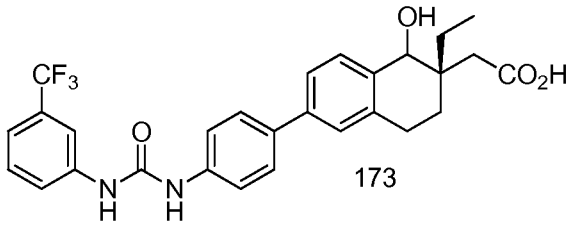
Ethyl 2-((2S)-2-ethyl-1-hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (173A):



Sodium borohydride (0.197 g, 5.18 mmol) was added portion wise to an ice cold solution of product of Example 115G1 (0.4 g, 0.74 mmol) in ethanol (10 mL), and the mixture was stirred at room temperature for 5 h. Ethanol was concentrated under reduced pressure and diluted with

water. The resulting solids were filtered, and crude product was purified by flash chromatography to afford title compound (0.22 g, 55%) as solid. ^{1}H NMR (300 MHz,$CDCl_3$): δ 7.68 (bs, 1H), 7.57 (m, 1H), 7.5 (d, J = 6.0 Hz, 1H), 7.4 (s, 1H), 7.32-7.27 (m, 2H), 7.23 (m, 2H), 7.09-7.02 (m, 3H), 4.67 (s, 1H), 4.15 (q, J = 6.9 Hz, 2H), 3.8 (bs, 1H), 2.78 (t, J = 6.3 Hz, 2H), 2.36 (q, J = 14.4 Hz, 2H), 1.8 (m, 1H), 1.67-1.6 (m, 2H), 1.45 (m, 1H), 1.29 (m, 3H), 0.92 (t, J = 7.2 Hz, 3H).

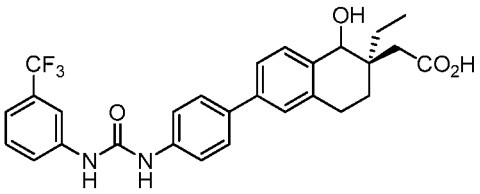
2-((2S)-2-Ethyl-1-hydroxy-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (173):



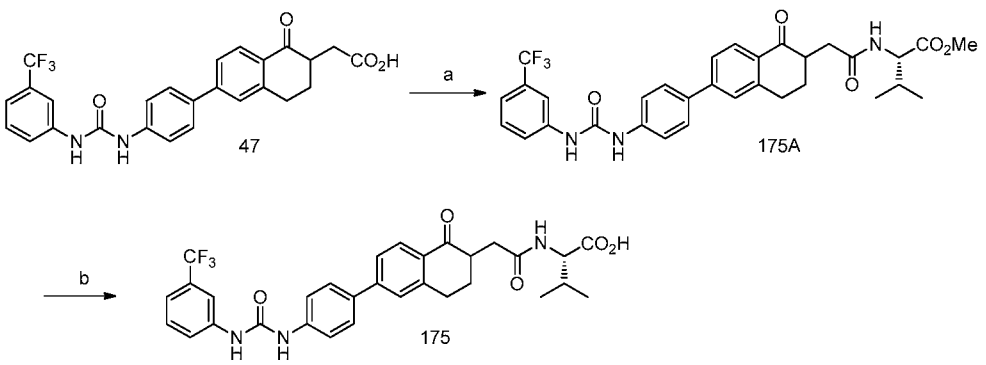
173

Lithium hydroxide (0.046 g, 1.09 mmol) was added to a solution of product of Example 173A (0.15 g, 0.27 mmol) in 4 mL of dioxane-water (3:1) mixture, and the reaction mixture was stirred at room temperature for 8 h. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.05 g, 36%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.7 (bs, 1H), 9.46 (bs, 1H), 8.05 (s, 1H), 7.63 (m, 3H), 7.54-7.4 (m, 4H), 7.36-7.26 (m, 3H), 4.5 (s, 1H), 2.6 (m, 2H), 2.2 (m, 2H), 1.8-1.55 (m, 3H), 1.3 (m, 1H), 1.0-0.8 (m, 3H). HPLC purity: 98%.

Examples 174 was prepared by the procedures analogous to those described in Example 173 using appropriate starting materials.

Ex	Structure	Analytical Data	$(M+H)^+$
174		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.7 (bs, 1H), 9.46 (bs, 1H), 8.05 (s, 1H), 7.63 (m, 3H), 7.54-7.4 (m, 4H), 7.36-7.26 (m, 3H), 4.5 (s, 1H), 2.6 (m, 2H), 2.2 (m, 2H), 1.8-1.55 (m, 3H), 1.3 (m, 1H), 1.0-0.8 (m, 3H).	HPLC purity: 99.8%

Example-175

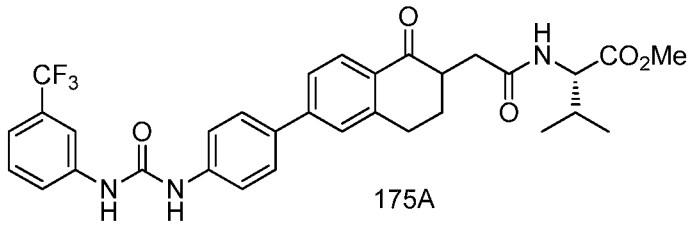


Reagents and conditions: a) HATU, THF, Valine methyl ester, RT, 8h; b) LiOH, THF-H_2O, RT, 12h.

Procedures:

(2S)-3-Methyl-2-(2-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamido)butanoic acid:

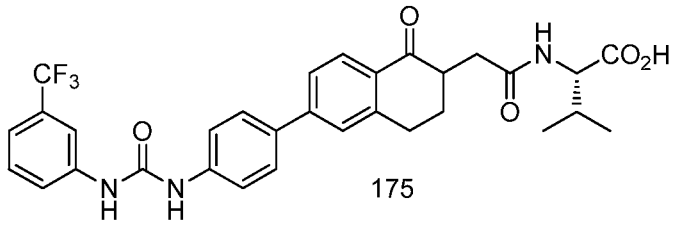
(2S)-Methyl 3-methyl-2-(2-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamido) butanoate (175A):



175A

HATU (0.19 g, 0.497 mmol) was added to a solution of product of Example 47A (0.2 g, 0.414 mmol) and N-ethyl diisopropylamine (0.16 g, 1.24 mmol) in THF (10 mL) followed by valine methyl ester (0.07 g, 0.413 mmol). The reaction mixture was stirred at room temperature for 8 h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated solution of NaCl, dried over sodium sulphate, filtered and concentrated. The residue obtained was purified by column chromatography using 25% ethyl acetate in hexane as eluent to afford title compound (0.12 g, 49%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.09 (bs, 1H), 8.97 (bs, 1H), 8.22 (m, 1H), 8.03 (bs, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.65-7.58 (m, 5H), 7.5 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 4.21 (m, 1H), 3.63 (s, 3H), 3.05-2.8 (m, 2H), 2.4-2.3 (m, 2H), 2.2-1.8 (m, 4H), 0.9 (s, 6H).

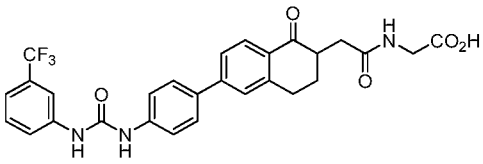
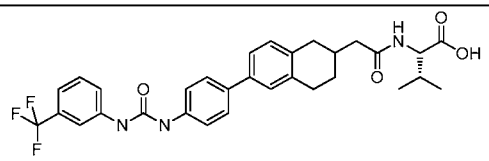
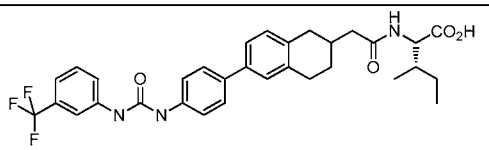
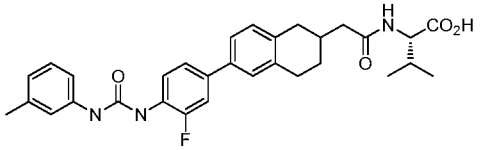
(2S)-3-Methyl-2-(2-(1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetamido)butanoic acid (175):

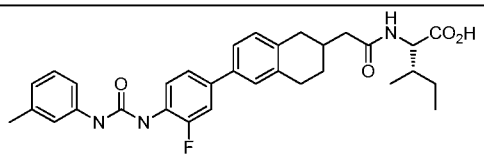
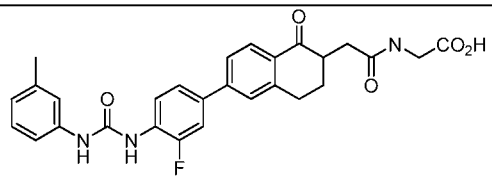


175

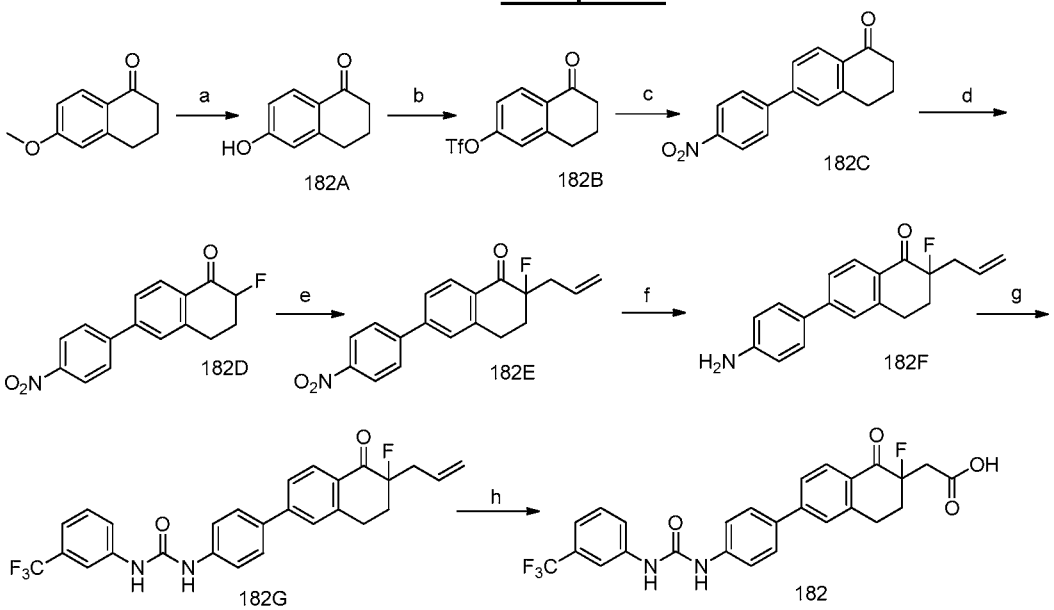
Lithium hydroxide (0.02 g, 0.5 mmol) was added to a solution of product of Example 175A (0.1 g, 0.16 mmol) in 4 mL of THF-water (3:1) mixture, and the reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.05 g, 51%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.5 (bs, 1H), 9.18 (bs, 1H), 9.04 (bs, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.9 (d, J = 7.6 Hz, 1H), 7.7 (d, J = 8.4 Hz, 2H), 7.66-7.5 (m, 6H), 7.32 (d, J = 8.4 Hz, 1H), 4.2 (m, 1H), 3.1-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 2.2-2.0 (m, 2H), 1.9 (m, 1H), 0.9 (m, 6H); HPLC purity: 94.8%.

Examples 176-181 were prepared by the procedures analogous to those described in Example 175 or routine variations thereof, starting from the requisite tetralone-2-acetic acid (e.g., Example 47) and amino acid, or appropriately functional-group protected versions thereof, followed by deprotection by procedures well-known to those skilled in the art.

Ex	Structure	Analytical Data	$(M+H)^+$
176		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.5 (bs, 1H), 8.17 (s, 1H), 8.11 (m, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.86-7.76 (m, 4H), 7.74-7.64 (m, 3H), 7.46 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 3.85 (m, 2H), 3.4 (m, 1H), 3.1-2.8 (m, 2H), 2.65 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	HPLC purity: 96.06%.
177		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.51 (bs, 1H), 9.31 (bs, 1H), 9.10 (bs, 1H), 8.04 (s, 1H), 7.97 (d, J = 8.1 Hz, 1H), 7.62-7.47 (m, 6H), 7.30 (m, 3H), 7.07 (d, J = 8.4 Hz, 1H), 4.18 (t, J = 6.3 Hz, 1H), 2.85-2.71 (m, 3H), 2.43 (m, 1H), 2.26 (d, J = 7.2 Hz, 2H), 2.08 (m, 2H), 1.90 (m, 1H), 1.45 (m, 1H), 0.9 (m, 6H).	ESI-MS m/z = 567 $(M+H)^+$; HPLC purity: 92%.
178		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.40 (bs, 1H), 9.06 (bs, 1H), 8.87 (bs, 1H), 8.02 (m, 2H), 7.59-7.49 (m, 6H), 7.33 (t, J = 7.6 Hz, 3H), 7.07 (d, J = 7.6 Hz, 1H), 4.22 (m, 1H), 2.88-2.79 (m, 3H), 2.45 (m, 1H), 2.25 (d, J = 6.4 Hz, 2H), 2.15 (m, 1H), 1.90-1.79 (m, 2H), 1.41 (m, 2H), 1.23 (m, 1H), 0.89 (m, 6H).	ESI-MS m/z = 582 $(M+H)^+$; HPLC purity: 90%.
179		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.40 (bs, 1H), 9.07 (bs, 1H), 8.64 (bs, 1H), 8.20 (t, J = 8.4 Hz, 1H), 7.96 (m, 1H), 7.52 (d, J = 12.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.37 (m, 2H), 7.31 (s, 1H), 7.25-7.15 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 4.16 (t, J = 6.4 Hz, 1H), 2.89-2.77 (m, 3 H), 2.32 (s, 3H), 2.28 (d, J = 7.2 Hz 2H), 2.14-2.05 (m, 3H), 1.89 (m, 1H), 1.40 (m, 1H), 0.85 (m, 6H).	ESI-MS m/z = 532 $(M+H)^+$; HPLC purity: 95%.

180		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.40 (bs, 1H), 9.06 (bs, 1H), 8.63 (bs, 1H), 8.20 (t, J = 8.4 Hz, 1H), 7.98 (bs, 1H), 7.52 (d, J=13.2 Hz, 1H), 7.43 (m, 3H), 7.31-7.15 (m, 3H) 7.08 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 4.20 (m, 1H), 2.98-2.79 (m, 3H), 2.28 (s, 3H), 2.24 (d, J = 6.8 Hz, 2H), 2.14 (m, 2H), 1.99-1.79 (m, 2H), 1.41 (m, 1H), 1.16 (m, 2H), 0.86 (m, 6H).	ESI-MS m/z = 546(M+H)$^+$; HPLC purity: 91%.
181		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.03 (bs, 1H), 8.70 (bs, 1H), 8.34-8.24 (m, 2H), 7.91 (d, J = 9.0 Hz, 1H), 7.73-7.66 (m, 3H), 7.59 (d, J = 8.7 Hz, 1H), 7.31 (bs, 1H), 7.26-7.15 (m, 2H), 6.82 (d, J = 7.2 Hz, 1H), 3.77 (m, 2H), 3.1-2.9 (m, 3H), 2.84-2.71 (m, 1H), 2.4 (m, 1H), 2.29 (s, 3H), 2.0 (m, 1H), 1.87 (m, 1H).	HPLC purity: 94%

Example-182

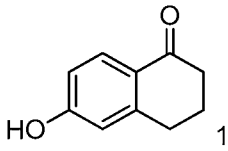


Reagents and conditions: a) Aq HBr Reflux, 12h; b) Tf_2O, DMAP, Py, RT, 1h; c) 4-NO_2 phenyl boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; d) select Fluor, MeOH, 80 °C, 4h; e) Allyl bromide, TBAI, KOH, RT, 18h; f) Fe/NH_4Cl, EtOH, H_2O, Reflux, 2h; g) 3-CF_3-PhNCO, Et_3N, THF, RT, 12h; h) LiOH, THF-H_2O, RT , 12h.

Procedures:

2-(2-Fluoro-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

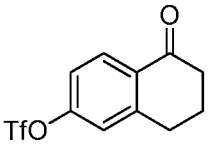
6-Hydroxy-3,4-dihydronaphthalen-1(2H)-one (182A):



182A

Aqueous HBr (100 mL) was added to 6-methoxy-1-tetralone (10.0 g, 56.8 mmol), and the reaction mixture was refluxed for overnight. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The crude product was purified using flash chromatography using 40% ethyl acetate in hexanes to afford title compound (8.0 g, 86%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.69 (s, 1H), 6.23 (bs, 1H), 2.9 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 6.0 Hz, 2H), 2.11 (m, 2H); ESI-MS m/z = 163 $(M+H)^+$.

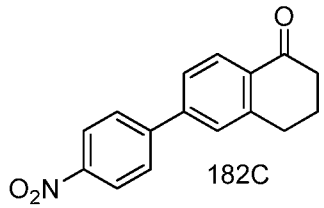
5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate (182B):



182B

Triflic anhydride (16.7 g, 59.2 mmol) was added to an ice cold solution of product of Example 182A (8.0 g, 49.3 mmol), DMAP (1.20 g, 9.83 mmol) and 2,6-lutidine (5.20 g, 49.3 mmol) in dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with dichloromethane (50 mL) and washed with saturated aqueous solution of NaCl (50 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 5% ethyl acetate in hexanes to give title compound (12 g, 85%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.4 Hz, 1H), 7.2 (m, 2H), 3.01 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 6.0 Hz, 2H), 2.18 (m, 2H); ESI-MS m/z = 295 $(M+H)^+$.

6-(4-Nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (182C):

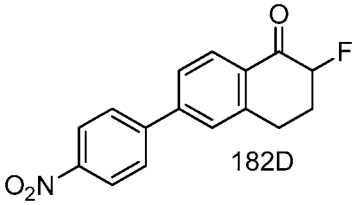


182C

$Pd(PPh_3)_4$ (0.023 g, 0.19 mmol) was added to a solution of product of Example 182B (5.0 g, 16.8 mmol) in 60 mL of 1,4 dioxane-H_2O (3:1) mixture under argon atmosphere, followed by cesium carbonate (13.7g, 42.0 mmol) and 4-nitro phenyl boronic acid (2.81 g, 16.8 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was then refluxed for 5 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography to afford title compound (3.5 g, 77%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34-8.30 (m, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.78-7.75 (m,

2H), 7.57-7.51 (m, 2H), 3.06 (t, J = 6.0 Hz, 2H), 2.71 (t, J = 6.0 Hz, 2H), 2.23-2.17 (m, 2H); ESI-MS m/z = 268 $(M+H)^+$.

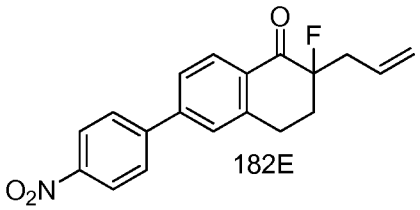
2-Fluoro-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (182D):



182D

Selectfluor (1.27 g, 3.58 mmol) was added to product of Example 182C (0.8 g, 2.99 mmol) in 20 mL of methanol. The reaction mixture was refluxed for 4 h, and the solvent was then removed under vacuum to obtain the residue. The residue was dissolved in dichloromethane. Insoluble materials were filtered, and filtrate was washed with water followed by brine solution. The organic layer was dried over sodium sulphate, filtered and concentrated to afford title compound (0.6 g, 70%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (m, 2H), 8.20 (d, J = Hz, 1H), 7.75(m, 2H), 7.65 (m, 1H), 7.52 (s, 1H), 5.30-5.10 (m, 1H), 3.30 (m, 2H), 2.65 (m, 1H), 2.40 (m, 1H); ESI-MS m/z = 286 $(M+H)^+$.

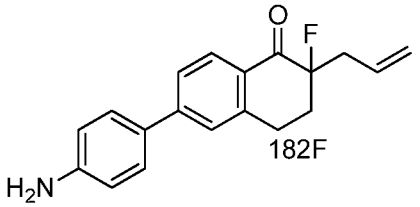
2-Allyl-2-fluoro-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (182E):



182E

Allyl bromide (1.89 g, 15.7 mmol) was added to a solution of product of Example 182D (3.0 g, 10.5 mmol), KOH (1.17 g, 21.0 mmol) and TBAI (0.77 g, 2.00 mmol) in Toluene (120 mL) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with water and ethyl acetate. The separated organic layer was washed with water, brine solution, dried over sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography using 10% ethyl acetate in hexanes to afford title compound (2.5 g, 73%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38-8.32 (m, 2H), 8.18 (d, J = 8.4 Hz, 1H), 7.80-7.75 (m, 2H), 7.61 (m, 1H), 7.50 (s, 1H), 5.86 (m, 1H), 5.23 (d, J =8.4 Hz, 2H), 3.25-3.09 (m, 2H), 2.77-2.25 (m, 4H); ESI-MS m/z = 326 $(M+H)^+$.

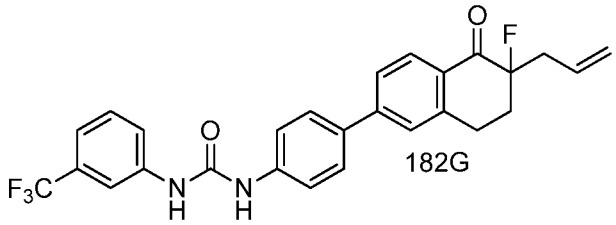
2-Allyl-6-(4-aminophenyl)-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (182F):



182F

Iron powder (0.214 g, 3.86 mmol) and NH_4Cl (0.040g, 0.74 mmol) was added to a solution of product of Example 182E (0.51g, 1.53 mmol) in 25 mL of ethanol-water (2:1) mixture. The reaction mixture was refluxed for 2 h, and solvent was removed under reduced pressure. The crude product was purified by flash chromatography using 2% methanol in chloroform to afford title compound (0.3 g, 66%) as solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.07 (d, J = 7.5 Hz, 1H), 7.53 (dd, J_1 = 1.2 Hz, J_2 = 8.1 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 (s, 1H), 6.75 (d, J = 8.4 Hz, 2H), 5.98-5.84 (m, 1H), 5.29-5.20 (m, 2H), 3.84 (bs, 2H), 3.16-2.97 (m, 2H), 2.80-2.54 (m, 2H), 2.46-2.33 (m, 2H); ESI-MS m/z = 296 $(M+H)^+$.

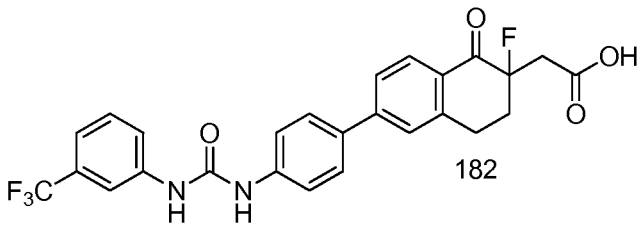
1-(4-(6-Allyl-6-fluoro-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)phenyl)-3-((trifluoromethyl)phenyl)urea (182G):



182G

3(Trifluoromethyl)phenyl isocyanate (0.158 g, 0.84 mmol) was added to a solution of product of Example 182F (0.25 g, 0.84 mmol) and triethylamine (0.128 g, 1.26 mmol) in THF (15 mL). The reaction mixture was stirred at room temperature overnight. The solvent was then removed under reduced pressure, and crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (0.2 g, 50%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 7.5 Hz, 1H), 7.67 (s, 1H), 7.62 (d, J = 7.8 Hz, 2H), 7.54- 7.44 (m, 5H), 7.40-7.28 (m, 4H), 5.90-5.80 (m, 1H), 5.29-5.20 (m, 2H), 3.40-2.98 (m, 2H), 2.60-2.50 (m, 2H), 2.48-2.30 (m, 2H); ESI-MS m/z = 483 $(M+H)^+$.

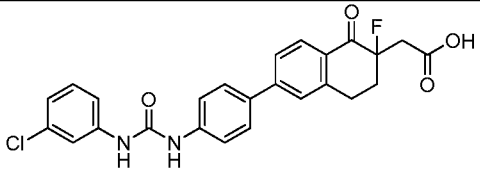
2-(2-Fluoro-1-oxo-6-(4-(3-(3-(trifluoromethyl) phenyl) ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (182):

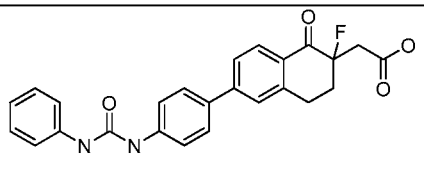


182

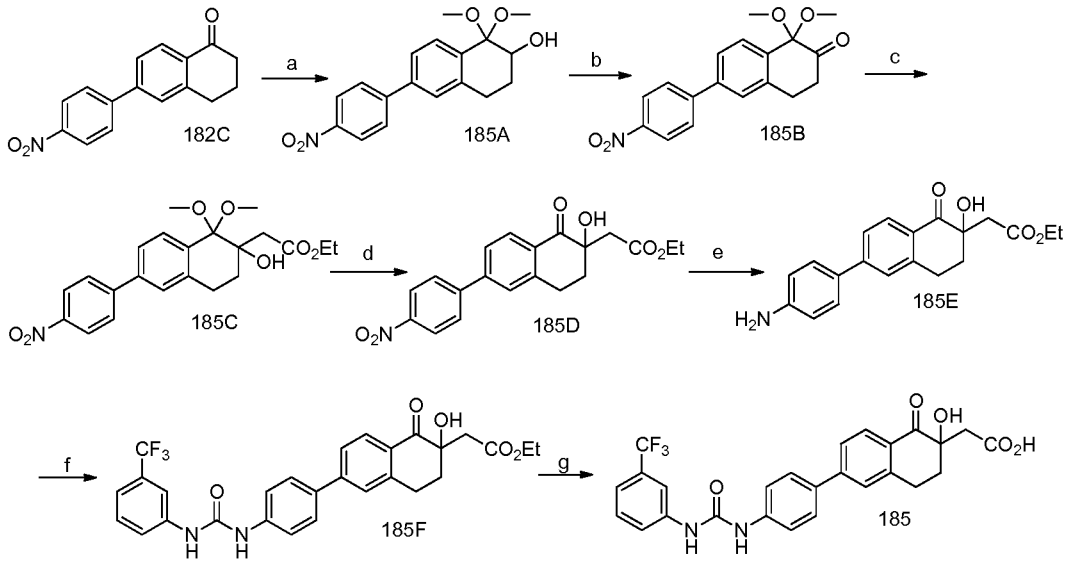
$KMnO_4$ (0.196 g, 1.24 mmol) was added to a solution of product of Example 182G (0.30 g, 0.62 mmol) and $NaIO_4$ (1.33 g, 6.2 mmol) in 30 mL of acetone-water (2:1) mixture. The reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure to obtain the crude product which was purified by the preparative HPLC to afford title compound (0.075 g, 25%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.5 (bs, 1H), 9.11 (bs, 1H), 9.01 (bs, 1H), 7.96 (m, 2H), 7.72 (t, J = 8.4 Hz, 4H), 7.62-7.50 (m, 4H), 7.32 (d, J = 7.6 Hz, 1H), 3.20-3.05 (m, 4H), 2.90 (m, 1H), 2.66 (m, 1H); ESI-MS m/z = 501 $(M+H)^+$; HPLC purity: 96%.

Examples 183-184 were prepared by the analogous procedures as described above in Example 182 using appropriate starting materials.

Ex	Structure	^{1}H NMR Data	Mass/purity
183		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.50 (bs, 1H), 8.96 (2s, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 8.8 Hz, 5H), 7.62 (d, J = 8.4 Hz, 2H), 7.33-7.27 (m, 2H), 7.03 (m, 1H), 3.20-3.02 (m, 4H), 2.90 (m, 1H), 2.67 (m, 1H).	MS m/z = 467 $(M+H)^+$; HPLC purity: 98%.

184		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.60 (bs, 1H), 8.88 (bs, 1H), 8.73 (bs, 1H), 7.95 (d, J = 8.4Hz, 1H), 7.71 (t, J = 8.8 Hz, 4H), 7.59 (d, J =8.4 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.17 (m, 2H), 3.16-3.04 (m, 2H), 2.93 (m, 1H), 2.89 (m, 1H).	ESI-MS m/z = 432 $(M+H)^+$; HPLC purity: 93%.

Example-185

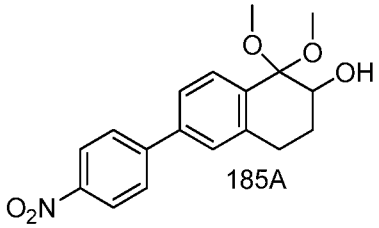


Reagents and conditions: a) $PhI(OAc)_2$, AcOH, RT, 16h; b) Pyridinium dichromate, Acetone, RT, 18h ; c) LiHMDS, EtOAc, THF, 0 °C to RT ,4h; d) 3N HCl, MeOH, RT, 18h; e) Pd/C, H_2, EtOH, RT, 3h; f) 3-CF_3PhNCO, Et_3N, THF, RT , 12h; g) NaOH, MeOH-THF-H_2O, RT, 18h.

Procedure:

2-(2-Hydroxy-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

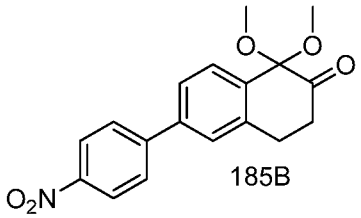
1,1-Dimethoxy-6-(4-nitrophenyl)-1,2,3,4-tetrahydronaphthalen-2-ol (185A):



KOH (4.40 g, 78.6 mmol) was added to an ice cold solution of product of Example 182C (7.0 g, 26.2 mmol) and $PhI(OAc)_2$ (8.44 g,26.2 mmol) in methanol (180 ml). The reaction mixture was stirred at room temperature for 16 h. The reaction solvent was removed under vacuum, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and concentrated. The product was washed with pentane to give title compound (7.0 g, 81%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (m, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.75-7.71 (m, 2H), 7.45 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.41 (s, 1H), 4.29 (t, J = 4.0 Hz,

1H), 3.45 (s, 3H), 3.12 (s, 3H), 3.0 (m,1H), 2.83 (m, 1H), 2.27-2.22 (m, 1H), 2.16-2.10 (m, 1H), 1.56 (m, 1H); ESI-MS *m/z* = 330 $(M+H)^+$.

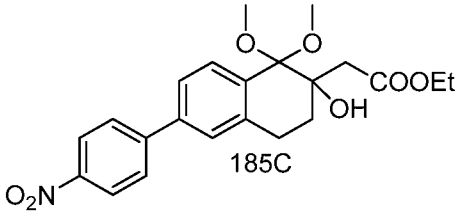
1,1-Dimethoxy-6-(4-nitrophenyl)-3,4-dihydronaphthalen-2(1H)-one (185B):



185B

Pyridinium dichromate (0.36 g, 0.97 mmol) was added to a solution of product of Example 185A (0.2 g, 0.6 mmol) and molecular sieves (3A, 0.5 g) in 10 mL dichloromethane under argon atmosphere, followed by acetic anhydride (0.1 mL). The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was then filtered, and the filtrate was washed with water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 20% ethyl acetate in hexane to afford title compound (0.12 g, 63%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.54 (dd, J_1 = 1.5 Hz, J_2 = 8.4 Hz, 1H), 7.46 (s, 1H), 3.38 (s, 6H), 3.25 (t, *J* = 6.0 Hz, 2H), 2.75 (t, *J* = 6.9 Hz, 2H). ESI-MS *m/z* = 328 $(M+H)^+$.

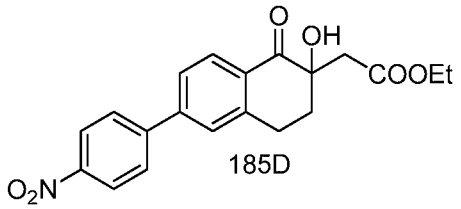
Ethyl-2-(2-hydroxy-1,1-dimethoxy-6-(4-nitrophenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (185C):



185C

Ethyl acetate (0.2 g, 2.29 mmol) was added to a solution of LiHMDS (0.63 g, 3.82 mmol) in 10 mL of THF at -78 ^{0}C, and the mixture was stirred for 15 min. The product of Example 185B (0.25 g, 0.76 mmol) was then added. The reaction mixture was performed at -78 °C to room temperature for 4 h and then quenched with 1N HCl. The reaction mixture was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 20% ethyl acetate in hexane to afford title compound (0.15 g, 48%) as off white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.82-7.72 (m, 3H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.4 (s, 1H), 4.2 (q, *J* = 6.9 Hz, 2H), 3.6 (s, 3H), 3.2 (s,3H), 3.0 (m, 2H), 2.75 (d, *J* = 14.7 Hz, 1H), 2.4 (d, *J* = 14.7 Hz, 1H), 2.3-2.1 (m, 2H), 1.3 (m, 3H). ESI-MS *m/z* = 416 $(M+H)^+$.

Ethyl 2-(2-hydroxy-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (185D):

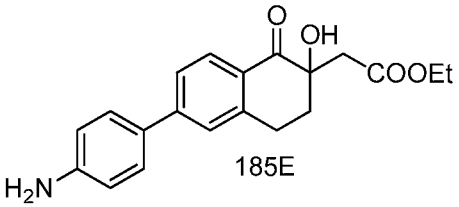


185D

3N HCl (2 mL) was added to a solution of product of Example 185C (0.15 g, 0.36 mmol) in 5 mL of ethanol at 0 °C and stirred for 18 h at RT. The reaction mixture was quenched with water, and

solid was collected by filtration to afford title compound (0.08 g, 61%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, J = 9.3 Hz, 2H), 8.04 (d, J = 9.3 Hz, 2H), 7.98 (s, 1H), 7.78 (m, 2H), 5.76 (bs, 1H), 4.02 (q, J = 7.8 Hz, 2H), 3.2 (m, 1H), 3.0-2.95 (m, 2H), 2.65 (d, J = 15.3 Hz, 1H), 2.39 (m, 1H), 2.16 (m, 1H), 1.15 (t, J = 6.9 Hz, 3H); ESI-MS m/z = 370 $(M+H)^+$.

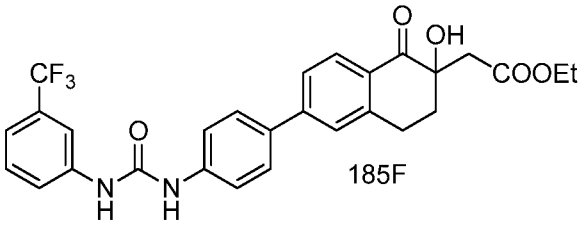
Ethyl 2-(6-(4-aminophenyl)-2-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (185E):



185E

Excess 10% Pd/C (0.04 g) was added to a solution of product of Example 185D (0.08 g, 0.21 mmol) in 5 mL of ethanol, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered over celite bed, and filtrate was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed in vacuum. The crude product was washed with Et_2O and pentane to afford title compound (0.05 g, 68%) as off white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 7.5 Hz, 2H), 7.55-7.35 (m, 4H), 6.75 (m, 1H), 4.53 (bs, 1H), 4.2 (m, 2H), 3.83 (bs, 2H), 3.18 (m, 2H), 2.67 (m, 2H), 2.40 (m, 1H), 2.25 (m, 1H), 1.28 (t, J = 6.9 Hz, 3H); ESI-MS m/z = 340 $(M+H)^+$.

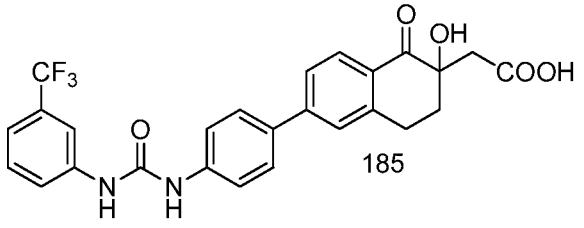
Ethyl-2-(2-hydroxy-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaph thalen-2-yl) acetate (185F):



185F

3-(Trifluoromethyl) phenyl isocyanate (0.12 g, 0.64 mmol) was added to a solution of product of Example 185E (0.2 g, 0.58 mmol) and triethylamine (0.17 g, 1.76 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 1% methanol in chloroform to afford title compound (0.14 g, 45%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.2 (bs, 1H), 9.0 (bs, 1H), 8.05 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.75-7.45 (m, 8H), 7.35 (d, J = 7.8 Hz, 1H), 5.7 (s, 1H), 4.0 (q, J = 7.2 Hz, 2H), 3.2 (m, 1H), 2.95 (m, 2H), 2.7 (d, J = 15.3 Hz, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 1.2 (t, J = 7.2 Hz, 3H); ESI-MS m/z =527 $(M+H)^+$.

2-(2-Hydroxy-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (185):

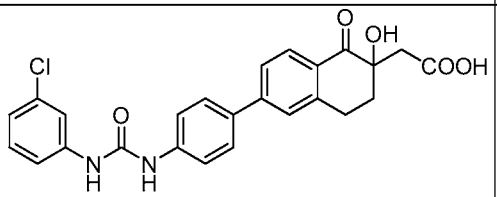
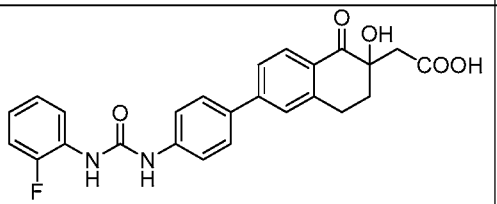
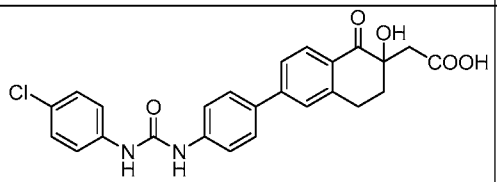
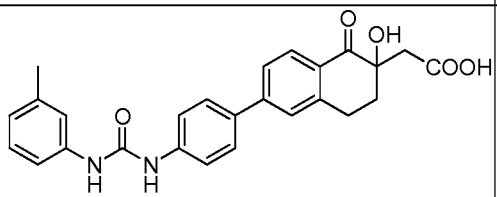


185

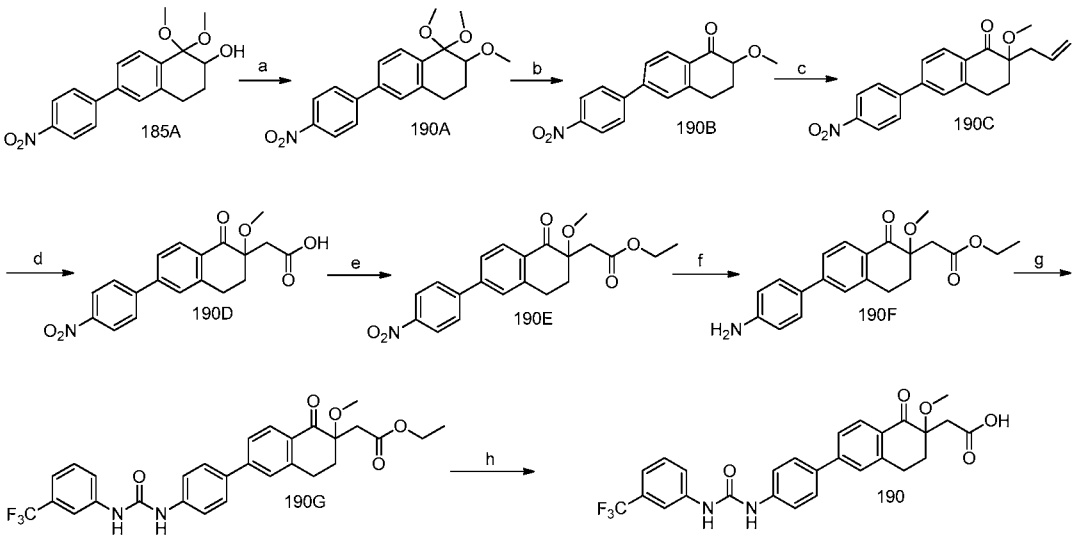
2N NaOH (0.031 g, 0.79 mmol) was added to a solution of product of Example 185F (0.14 g, 0.26 mmol) in 15 mL of THF-methanol (2:1) mixture, and the reaction mixture was stirred at room

temperature for 18 h. After the solvent was removed under vacuum, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was neutralized with 2N aq. HCl. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.09 g, 69%) as white-solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.4 (bs, 2H), 8.13 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 6.0 Hz, 1H), 7.62 (d, J = 6.4 Hz, 1H), 7.5-7.35 (m, 6H), 7.22 (d, J = 7.2 Hz, 1H), 6.0 (bs, 1H), 3.15 (m, 1H), 3.03 (d, J = 15.6 Hz, 1H), 2.85 (m, 1H), 2.5 (m, 1H), 2.35 (d, J = 15.6 Hz, 1H), 2.0 (m, 1H); ESI-MS m/z = 449 $(M+H)^+$. HPLC purity: 96.49%.

Examples 186-189 were prepared by the procedures analogous to those described in Example 185 using appropriate starting materials.

Ex	Structure	^{1}H NMR Data	Mass/purity
186		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.04 (s, 2H),7.92 (d, J = 8.0 Hz, 1H), 7.75-7.55 (m, 7H), 7.31 (m, 2H), 7.03 (d, J = 6.8 Hz, 1H), 5.63 (bs, 1H), 3.2 (m, 1H), 2.93 (m, 2H), 2.6-2.4 (m, 2H), 2.1 (m, 1H).	ESI-MS m/z = 465 $(M+H)^+$. HPLC purity: 97.5%.
187		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.36 (bs, 1H), 8.68 (bs, 1H),8.15 (t, J = 7.5 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.75-7.55 (m, 6H), 7.25 (m, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.03 (m, 1H), 3.2 (m, 1H), 2.95-2.8 (m, 2H), 2.5-2.35 (m, 2H), 2.1 (m, 1H).	ESI-MS m/z = 449 $(M+H)^+$; HPLC purity: 93.3%.
188		^{1}H NMR (300 MHz, DMSO-d_6): δ 9.49 (bs, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.7-7.45 (m, 8H), 7.32 (d, J = 8.4 Hz, 2H), 3.2 (m, 1H), 2.95-2.8 (m, 2H), 2.5-2.4 (m, 2H), 2.1 (m, 1H).	ESI-MS m/z = 465 $(M+H)^+$. LCMS purity: 92%.
189		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.16 (bs,1H), 8.94 (bs, 1H),7.92 (d, J = 7.8 Hz, 1H), 7.75-7.55 (m, 6H), 7.35-7.25 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 6.8 (d, J = 6.9 Hz, 1H), 3.39 (m, 1H), 3.21 (m, 1H), 2.92 (d, J = 15.3 Hz, 2H), 2.55 (m, 1H), 2.28 (s, 3H), 2.12 (m, 1H).	ESI-MS m/z = 445 $(M+H)^+$. LCMS purity: 91.88%.

Example 190

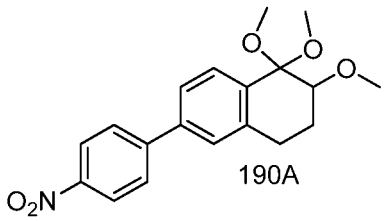


Reagents and conditions: a) NaH, MeI, THF, RT, 16h; b) 3N HCl, EtOH, RT, 3h; c) Allyl bromide, TBAI, KOH, toluene, RT, 16h; d) $KMnO_4$, $NaIO_4$, RT, 16h; e) $MeSO_3H$, EtOH, RT, 12h; f) Fe-NH_4Cl, EtOH-H_2O, 90 °C, 2h; g) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; h) LiOH, THF-H_2O, RT, 12h.

Procedures:

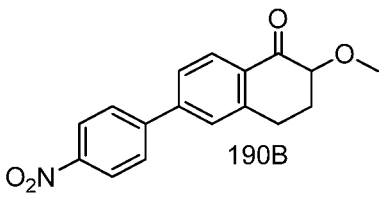
2-(2-Methoxy-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

1,1,2-Trimethoxy-6-(4-nitrophenyl)-1,2,3,4-tetrahydronaphthalene (190A):



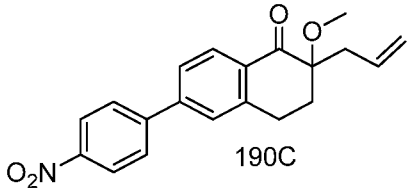
Methyl iodide (15.1 g, 106.1 mmol) was added to an ice cold solution of product of Example 185A (2.0 g, 6.1 mmol) and NaH (0.76 g, 31.91 mmol) in THF (120 mL)). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with ice cold water and extracted with ethyl acetate. The separated organic layer was dried over Na_2SO_4, filtered and removed under reduced pressure to give title compound (6.0 g, 83%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.25 (m, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.73-7.69 (m, 2H), 7.45 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.37 (s, 1H), 3.87 (m, 1H), 3.42 (s, 6H), 3.07 (s, 3H), 2.95 (m, 1H), 2.83-2.77 (m, 1H), 2.28-2.19 (m, 2H)); ESI-MS m/z = 344 $(M+H)^+$.

2-Methoxy-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (190B):



3N HCl (60 mL) was added to an ice cold solution of product of Example 190A (6.0 g, 17.4mmol) in ethanol (150 mL), and the reaction mixture was stirred at room temperature for 3 h. The residue was partitioned between ethyl acetate and water. The solvent was removed under reduced pressure, and water added until the compound was precipitated out. Solid was collected by filtration and dried. The product was washed with pentane to give title compound (5.0 g, 96%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (m, 2H), 8.15 (d, J = 8.4 Hz, 1H), 7.75 (m, 2H), 7.55 (m, 1H), 7.50 (s, 1H), 4.00 (m, 1H), 3.60 (s, 3H), 3.25 (s, 1H), 3.10 (m, 1H), 2.40 (m, 1H), 2.30 (m, 1H); ESI-MS m/z = 298 $(M+H)^+$

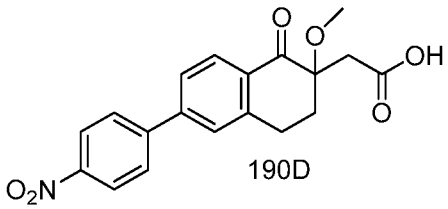
2-Allyl-2-methoxy-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (190C):



190C

Allyl bromide (3.63 g, 30.6 mmol) was added to an ice cold solution of product of Example 190B (6.0 g, 20.2 mmol) KOH (2.82 g, 50.5 mmol) and TBAI (2.98 g, 8.0 mmol) in toluene (120 mL), and the reaction mixture was stirred at room temperature for 16 h. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over Na_2SO_4, filtered and removed under reduced pressure. The product was purified by flash chromatography using 10% ethyl acetate in hexanes to afford to give title compound (4.46g , 64%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.35 (m, 2H), 8.16 (d, J = 8.4 Hz, 1H), 7.75 (m, 2H), 7.55 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.5 (s, 1H), 5.83 (m, 1H), 5.16 (d, J = 12.0 Hz, 2H), 3.32 (m, 1H), 3.24 (s, 3H), 2.95-2.79 (m, 1H), 2.75 (m, 1H), 2.52-2.42 (m, 2H), 2.35-2.06 (m, 1H); ESI-MS m/z = 338 $(M+H)^+$

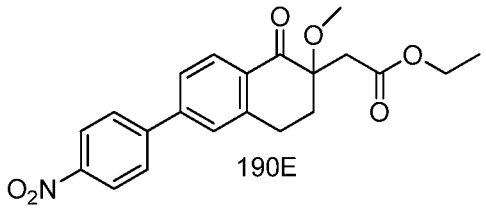
2-(2-Methoxy-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (190D):



190D

$KMnO_4$ (0.187 g, 1.18 mmol) was added to an ice cold solution of product of Example 190C (0.20 g, 0.59 mmol) and $NaIO_4$ (1.26 g, 5.90 mmol) in acetone-water (2:1) mixture. The reaction mixture was stirred at room temperature for 16 h. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over Na_2SO_4, filtered and removed under reduced pressure to afford title compound (0.14 g, 69%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.35-8.31 (m, 3H), 8-16-7.99 (m, 3H), 7.77 (d, J = 7.2 Hz, 1H), 3.35 (m, 1H), 3.25 (m, 1H), 3.19 (s, 3H), 2.92 (m, 1H), 2.73 (d, J = 16.8 Hz, 1H), 2.45 (m, 2H); ESI-MS m/z = 356 $(M+H)^+$.

Ethyl 2-(2-methoxy-6-(4-nitrophenyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (190E):

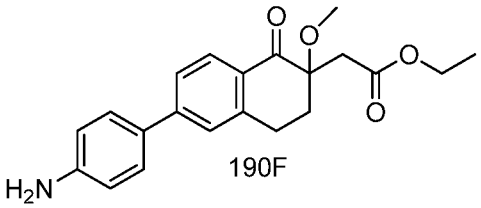


190E

Methane sulphonic acid (0.5ml) was added to a solution of product of Example 190D (0.26 g, 0.18 mmol) in ethanol (15 mL), and the reaction mixture was stirred at room temperature overnight.

The solvent was removed under reduced pressure, and product was purified by flash chromatography using 10% ethyl acetate in hexanes to afford title compound (0.07 g, 46%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.38-8.31 (m, 2H) , 8.16 (d, J = 8.4 Hz, 1H), 7.80-7.75 (m, 2H), 7.56 (m, 1H), 7.48 (s, 1H), 4.2 (q, J = 7.5 Hz, 2H), 3.45 (m, 1H), 3.25 (s, 3H), 2.95-2.73 (m, 3H), 2.5 (m, 2H), 1.25 (t, J = 6.9 Hz, 3H); ESI-MS m/z = 384 $(M+H)^+$

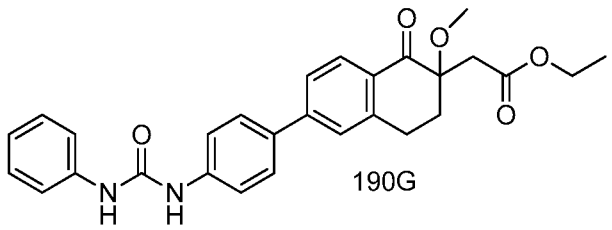
Ethyl 2-(6-(4-aminophenyl)-2-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (190F):



190F

Iron powder (0.182 g, 3.26 mmol) and NH_4Cl (0.034g, 0.65 mmol) was added to a solution of product of Example 190E (0.5 g, 1.30 mmol) in 30 mL of ethanol-water (2:1) mixture. The reaction mixture was refluxed for 2 h. Solvent was removed under reduced pressure, and product was purified by flash chromatography using 2% methanol in chloroform to afford title compound (0.4 g, 86%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 8.1 Hz, 1H), 7.47-7.43 (m, 3H), 7.38 (s, 1H), 6.73 (m, 2H), 4.15 (q, J = 7.5 Hz, 2H), 3.80 (bs, 2H), 3.42-3.35 (m, 1H), 3.3 (s, 3H), 2.94-2.79 (m, 3H), 2.53-2.36 (m, 2H), 1.2 (t, J = 6.9 Hz, 3H); ESI-MS m/z = 354 $(M+H)^+$.

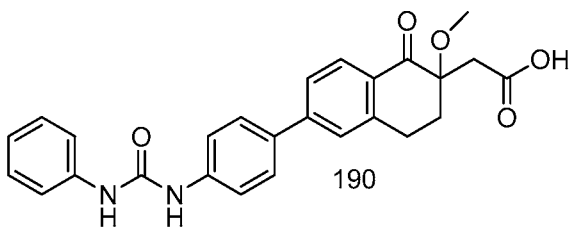
Ethyl2-(2-methoxy-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (190G):



190G

Phenyl isocyanate (0.067 g, 0.56 mmol) was added to a solution of product of Example 190F (0.200 g, 0.56 mmol) and triethylamine (0.178 g, 1.68 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 10% in hexane to afford title compound (0.2g, 76%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.86 (bs, 1H), 8.72 (bs, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.69 (m, 2H), 7.64-7.57 (m, 4H), 7.46 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 6.9 Hz, 2H), 6.98 (t, J = 7.5 Hz, 1H), 4.07 (q, J = 6.9 Hz, 2H), 3.23 (m, 1H), 3.13 (s, 3H), 2.93 (m, 1H), 2.86 (d, J = 15.3 Hz, 2H), 2.43 (m, 2H), 1.18 (t, J = 7.8 Hz,3H); ESI-MS m/z = 473 $(M+H)^+$.

2-(2-Methoxy-1-oxo-6-(4-(3-phenylureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (190):

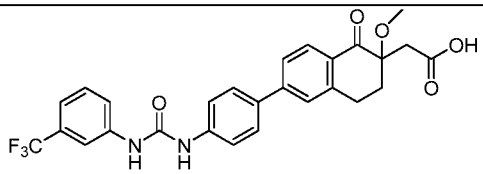
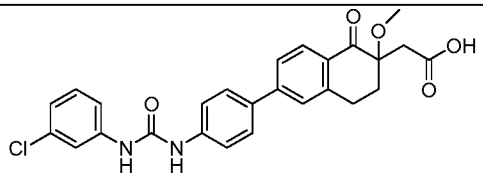
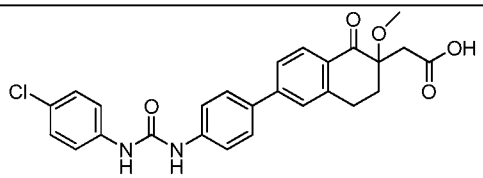
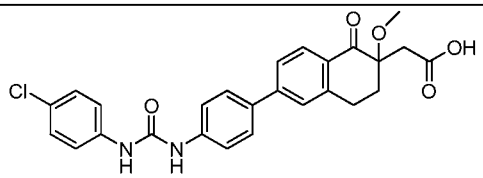
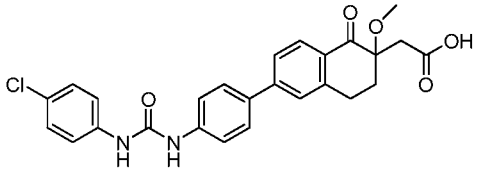


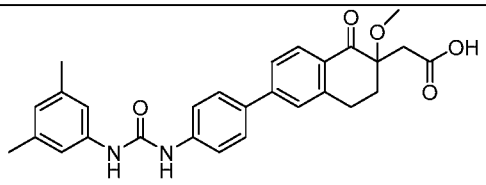
190

Lithium hydroxide (0.088 g, 2.11 mmol) was added to a solution of product of Example 190G (0.2 g, 0.42 mmol) in 12 mL of THF-water (3:1) mixture. The reaction mixture was stirred at room

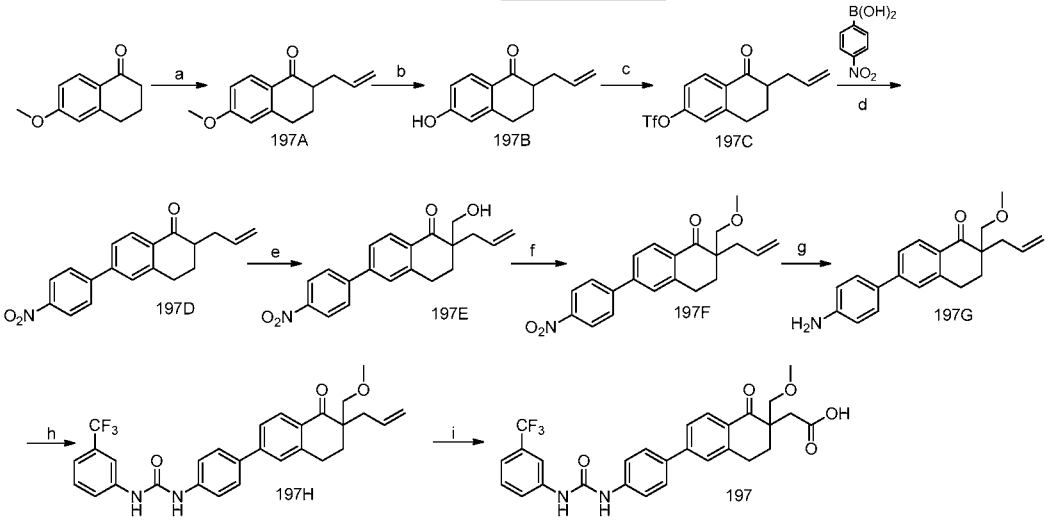
temperature overnight. After the solvent was removed in vacuum, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C and solids were collected by filtration and dried under vacuum to afford title compound (0.05 g, 26%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.0 (bs, 1H), 8.87 (bs, 1H), 8.74 (bs, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.59 (m, 3H), 7.47 (d, J = 8.0 Hz, 2H), 7.29 (t, J = 8.0 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.23-3.15 (m, 1H), 3.12 (s, 3H), 2.90 (d, J = 15.2 Hz, 2H), 2.68 (m,1H), 2.46 (m, 2H); ESI-MS m/z = 445 $(M+H)^+$; HPLC purity: 90%.

Examples –191- 196 were prepared by the procedures analogous to those described in Example 190 using appropriate starting materials. Enantiomers were separated from racemic mixtures using similar procedures as described in Example 129.

Ex	Structure	^{1}H NMR Data	Mass/purity
191		^{1}H NMR (400MHz, DMSO-d_6): δ 12.20 (bs, 1H), 9.10 (bs, 1H), 8.99 (bs, 1H), 8.03 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.71(d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.60 (m, 4H), 7.52 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 3.24-3.15 (m, 1H), 3.13 (s, 3H), 2.91 (m, 2H), 2.69 (m, 1H), 2.50-2.39 (m, 2H).	ESI-MS m/z = 513 $(M+H)^+$; HPLC purity:98 %.
192		^{1}H NMR (400MHz, DMSO-d_6): δ 12.20 (bs, 1H), 8.94 (bs, 2H), 7.94 (d, J = 11.2 Hz, 1H), 7.70 (d, J = 11.3 Hz, 3H), 7.66-7.57 (m, 4H), 7.34-7.26 (m, 2H), 7.05-7.01 (m, 1H), 3.23 (m, 1H), 3.12 (s, 3H), 2.90 (m, 2H), 2.72 (m, 1H), 2.44 (m, 2H).	ESI-MS m/z = 479(M+H)$^+$; HPLC purity: 98%.
193		^{1}H NMR (400MHz, DMSO-d_6): δ 12.20 (bs, 1H), 8.92 (2s, 2H), 7.94 (d, J = 7.8 Hz, 1H), 7.72-7.66 (m, 2H), 7.63-7.57 (m, 4H), 7.50 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 3.23 (m, 1H), 3.13 (s, 3H), 2.90 (d, J = 15.3 Hz, 2H), 2.74 (m, 1H), 2.43 (m, 2H).	ESI-MS m/z = 479(M+H)$^+$; HPLC purity: 90%.
194	 Chiral: enantiomer-2	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.90 (2s, 2H), 7.94 (d, J = 8.4 Hz, 1H), 7.72-7.56 (m, 6H), 7.50 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 3.23 (m, 1H), 3.12 (s, 3H), 2.90 (d, J = 10.5 Hz, 2H), 2.70 (s, 1H), 2.44 (m, 2H).	ESI-MS m/z = 479 $(M+H)^+$; HPLC purity: 96%.
195	 Chiral: enantiomer-1	^{1}H NMR (300MHz, DMSO-d_6): δ 12.20 (bs, 1H), 8.90 (2s, 2H), 7.94 (d, J = 8.4 Hz, 1H), 7.72-7.56 (m, 6H), 7.50 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H), 3.23 (m, 1H), 3.12 (s, 3H), 2.90 (d, J = 10.5 Hz,	ESI-MS m/z = 479 $(M+H)^+$; HPLC purity:

		2H), 2.70 (m, 1H), 2.44 (m, 2H).	96%
196		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.68 (bs, 1H), 8.60 (bs, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.70-7.56 (m, 6H), 7.09 (s, 2H), 6.62 (s, 1H), 3.18 (m, 1H), 3.12 (s, 3H), 2.90 (d, J = 15.6 Hz, 2H), 2.73 (m, 1H), 2.43 (m, 2H), 2.24 (s, 6H).	ESI-MS m/z = 473 $(M+H)^+$; HPLC purity:96 %

Example-197

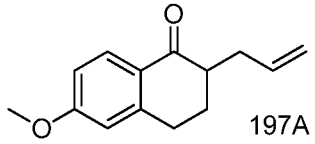


Reagents and conditions: a) Allyl bromide, KOtBu, THF, RT, 18h; b) BBr_3, CH_2Cl_2, RT, 12h; c) Tf_2O, Py, CH_2Cl_2, RT, 3h; d) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 3h; e) HCHO, 2N NaOH, THF, RT, 3h; f) NaH, MeI, THF, RT, 18h; g) Fe-NH_4Cl, EtOH-H_2O, 90 °C, 2h; h) 3-CF_3PhNCO, Et_3N, THF, RT, 12h; i) $KMnO_4$, $NaIO_4$, Acetone-H_2O, RT, 18h.

Procedures:

2-(2-(Methoxymethyl)-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

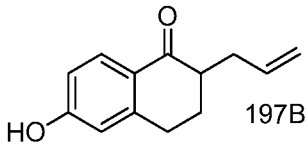
2-Allyl-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (197A) :



Allyl bromide (5.4 g, 45.0 mmol) was added to a solution of 6-methoxy-1-tetralone (10.0 g, 56.0 mmol) and potassium tert-butoxide in THF (50 mL), and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with ethyl acetate. The separated organic layer was washed with water, brine solution, dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 4% ethyl acetate in hexanes to afford title compound (2.0 g, 15%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H), 6.80 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 6.68 (m, 1H), 5.89-5.79

(m, 1H), 5.12 (t, J = 17.2 Hz, 2H) 3.85 (s, 3H), 2.95 (m, 2H), 2.93-2.72 (m, 1H), 2.53-2.46 (m, 1H), 2.29-2.17 (m, 2H), 1.89-1.79 (m, 1H).

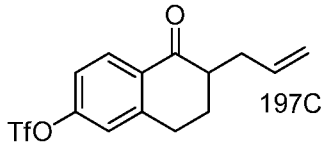
2-Allyl-6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (197B):



197B

BBr_3 was added slowly drop wise to product of Example 197A (2.0 g, 9.00 mmol) at -78 °C in dichloromethane (75 mL), and the reaction mixture was stirred for overnight. The reaction mixture was then quenched with ice cold water and extracted with dichloromethane (2X100 mL). The organic layer was dried over sodium sulphate, filtered and removed under vacuum. The residue was purified by flash chromatography using 15% ethyl acetate in hexanes to afford title compound (0.9 g, 60%) as liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 8.4 Hz, 1H), 6.76 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 6.66 (m, 1H), 5.90-5.77 (m, 1H), 5.12-5.04 (m, 2H), 2.92 (m, 2H), 2.78-2.70 (m, 1H), 2.56-2.46 (m, 1H), 2.31-2.15 (m, 2H), 1.91-1.78 (m, 1H).

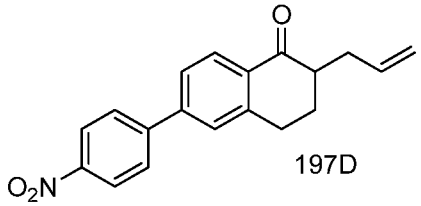
6-Allyl-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate (197C):



197C

Triflic anhydride (1.5 g, 5.34 mmol) was added to an ice cold solution of product of Example 197B (0.9 g, 4.45 mmol) and pyridine (0.421 g, 5.34 mmol) in dichloromethane (20 mL), and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with dichloromethane (50 mL) and washed with saturated aqueous solution of NaCl (50 mL). The organic layer was dried over sodium sulphate, filtered and removed under vacuum. The residue was purified by flash chromatography using 10% ethyl acetate in hexanes to give title compound (1.1 g, 61%) as solid.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 8.1 Hz, 1H), 7.21-7.16 (m, 2H), 5.90-5.75 (m, 1H), 5.14-5.07 (m, 2H), 3.04 (m, 2H), 2.79-2.70 (m, 1H), 2.62-2.52 (m, 1H), 2.32-2.22 (m, 2H), 1.96-1.82 (m, 1H).

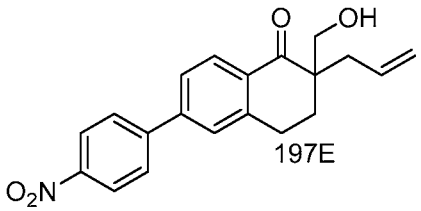
2-Allyl-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (197D):



197D

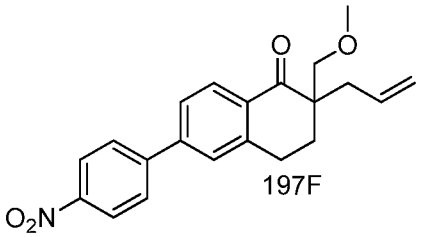
$Pd(PPh_3)_4$ (0.04 g, 0.035 mmol) was added to a solution of product of Example 197C (1.0 g, 2.99 mmol) in 20 mL of 1,4 dioxane-H_2O (4:1) mixture under Argon atmosphere, followed by cesium carbonate (2.42 g, 7.48 mmol) and 4-nitrophenyl boronic acid (0.6 g, 3.59 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was then refluxed for 3 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 10% ethyl acetate in hexanes to give title compound (0.9 g, 61%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (m, 2H), 8.14 (d, J = 8.0 Hz, 1H), 7.77 (m, 2H), 7.55 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.49 (s, 1H), 5.91-5.80 (m, 1H), 5.10 (t, J = 16.0 Hz, 2H), 3.07 (m, 2H), 2.80-2.75 (m, 1H), 2.63-2.56 (m, 1H), 2.34-2.26 (m, 2H), 1.97-1.86 (m, 1H).

2-Allyl-2-(hydroxymethyl)-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (197E):



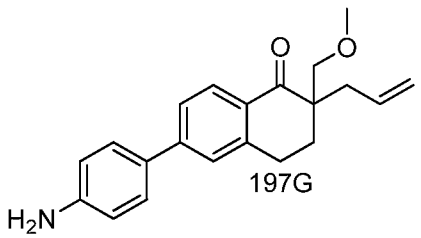
37% Formaldehyde solution (5 mL) was added to a solution of product of Example 197D (0.9 g, 2.92 mmol) in 7 mL of THF under argon atmosphere, followed by 2N NaOH solution (2 mL) at RT. The reaction mixture was stirred for 3 h, and solvent removed under reduced pressure. The residue was acidified with 2N HCl and partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under vacuum to give crude product was purified by flash chromatography using 15% ethyl acetate in hexanes to give title compound (0.62 g, 61%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.33 (d, J = 8.4 Hz, 2H), 8.06-7.93 (m, 3H), 7.76-7.73 (m, 2H), 5.79-5.65 (m, 1H), 5.05 (m, 2H), 3.77 (d, J = 5.7 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 3.11-3.01 (m, 2H), 2.44 (m, 1H), 2.30-2.14 (m, 2H), 2.03-1.94 (m, 1H).

2-Allyl-2-(methoxymethyl)-6-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2H)-one (197F):



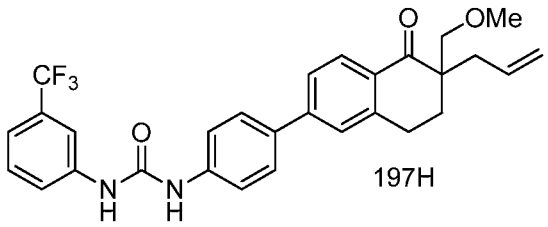
Methyl iodide (1.29 g, 9.15 mmol) was added to an ice cold solution of product of Example 197E (0.6 g, 1.83 mmol) and NaH (0.146 g, 3.67 mmol) in THF (20 mL), and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (60 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 10% ethyl acetate in hexanes to give title compound (0.3 g, %) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 5.2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.55 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.47 (s, 1H), 5.80-5.71 (m, 1H), 5.13-5.07 (m, 2H), 3.74 (d, J = 9.2 Hz, 1H), 3.42 (d, J = 9.6 Hz, 1H), 3.33 (s, 3H), 3.11-3.05 (m, 2H), 2.53-2.48 (m, 1H), 2.38 (m, 2H), 2.16-2.10 (m, 1H).

2-Allyl-6-(4-aminophenyl)-2-(methoxymethyl)-3,4-dihydronaphthalen-1(2H)-one (197G):



Iron powder (0.09g, 1.7 mmol) and NH_4Cl (0.023 g, 0.427 mmol) was added to a solution of 197F (0.3 g, 0.847 mmol) in 25 mL of ethanol-water (2:1) mixture. The reaction mixture was refluxed for 2 h, and solvent was removed under reduced pressure and extracted with ethyl acetate (40 mL). The organic layer was washed with water. , dried over sodium sulphate, filtered and removed under reduced pressure to give title compound (0.22 g, %) as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.83 (d, J = 8.4 Hz, 1H), 7.53-7.44 (m, 4H), 6.64 (d, J = 9.0 Hz, 2H), 5.75-5.65 (m, 1H), 5.42 (s, 2H), 5.09-5.03 (m, 2H), 3.62 (d, J = 9.0 Hz, 1H), 3.21 (s, 3H), 2.99-2.5 (m, 2H), 2.44-2.27 (m, 1H), 2.25-2.12 (m, 2H), 2.00-1.94 (m, 2H).

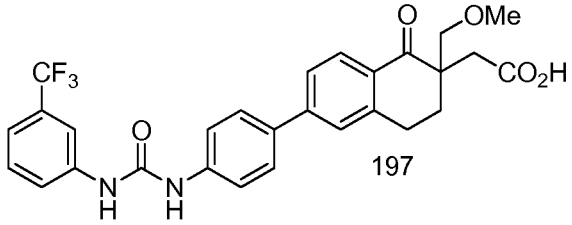
1-(4-(6-allyl-6-(methoxymethyl)-5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)phenyl)-3-(3-(trifluoromethyl) phenyl)urea (197H):



197H

3-(Trifluoromethyl) phenyl isocyanate (0.256 g, 1.37 mmol) was added to a solution of product of Example 197G (0.26 g, 1.21 mmol) and triethylamine (0.138 g, 1.37 mmol) in THF (5 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 1% methanol in chloroform to give title compound (0.46 g, 31%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.10 (s, 1H), 8.98 (s, 1H), 8.03 (s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.72-7.69 (m, 2H), 7.64-7.43 (m ,6H), 7.32 (d, J = 7.8 Hz, 1H), 5.77-5.68 (m, 1H), 5.09-5.04 (m, 2H), 3.63 (d, J = 9.0 Hz, 1H), 3.33 (m, 1H), 3.21 (s, 3H), 2.5 (m, 2H), 2.45 -2.38 (m, 1H), 2.3-2.15 (m, 2H), 2.04-1.95 (m, 1H).

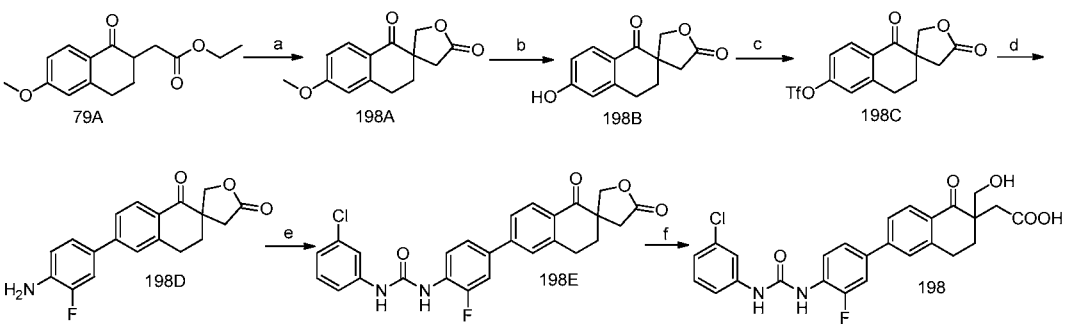
2-(2-(Methoxymethyl)-1-oxo-6-(4-(3-(3-(trifluoromethyl)phenyl)ureido)phenyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (197):



197

$KMnO_4$ (0.015 g, 0.35 mmol) was added to a solution of product of Example 197H (0.45 g, 0.11 mmol) and $NaIO_4$ in 15 mL of acetone-water (3:1) mixture. The reaction mixture was stirred at room temperature for 18 h. After the solvent was removed in vacuo, the residue was dissolved in water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The residue was purified by the preparative HPLC to afford title compound (30 mg). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.12 (s, 1H), 9.00 (s, 1H), 8.03 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.72-7.68 (m, 2H), 7.61-7.49 (m, 6H), 7.32 (d, J = 7.8 Hz, 1H), 3.61 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 3.22 (s, 3H), 3.11 (m, 1H), 2.99 (m, 1H), 2.88-2.82 (m, 1H), 2.44 (m, 2H), 2.27-2.18 (m, 1H); ESI-MS m/z = 527 $(M+H)^+$; HPLC purity: 98.63 %.

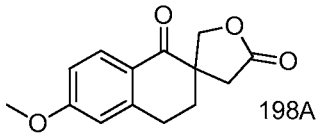
Example 198



Reagents and conditions: a) HCHO, 2N NaOH, THF, RT, 3h; b) Aq HBr, 100 °C, 1h; c) Tf_2O, Py, CH_2Cl_2, RT, 3h; d) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 3h; e) 3-ClPhNCO, Et_3N, THF, RT, 4h; f) LiOH, THF-H_2O, RT, 4h.

2-(6-(4-(3-(3-Chlorophenyl) ureido)-3-fluorophenyl)-2-(hydroxymethyl)-1-oxo-1,2,3,4-tetrahydro naphthalen-2-yl)acetic acid:

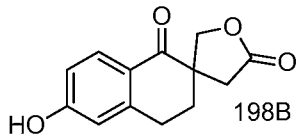
6'-Methoxy-3',4'-dihydro-1'H,2H-spiro[furan-3,2'-naphthalene]-1',5(4H)-dione (198A):



198A

37% Formaldehyde solution (15 mL) was added to a solution of product of Example 79A (2.0 g, 7.0 mmol) in 20 mL of THF under argon atmosphere, followed by 2N aqueous solution of NaOH (0.06 g, 15.0 mmol) at room temperature. The reaction mixture was stirred for 3 h, solvent was removed under vacuum, and residue was acidified with 2N HCl. Aqueous layer was extracted with ethyl acetate and separated organic layer was dried over sodium sulphate, filtered and concentrated to afford the crude title compound (0.6 g, 31%) as gummy material. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.87 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.89 (s, 1H), 4.45 (d, J = 8.8 Hz, 1H), 4.25 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 2.98-2.91 (m, 2H), 2.70 (m, 2H), 2.22 (m, 2H).

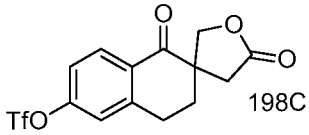
6'-Hydroxy-3',4'-dihydro-1'H,2H-spiro[furan-3,2'-naphthalene]-1',5(4H)-dione (198B):



198B

Aqueous HBr (20 mL) was added to product of Example 198A (0.6 g, 2.43 mmol), and the reaction mixture was refluxed for 1 h. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The separated organic layer dried over sodium sulphate, filtered and removed under reduced pressure to afford title compound (0.37 g, 65%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.67 (s, 1H), 5.51 (s, 1H), 4.58 (d, J = 8.8 Hz, 1H), 4.22 (d, J = 8.0 Hz, 1H), 3.1-2.98 (m, 3H), 2.50-2.46 (m, 1H), 2.26 (t, J = 6.4 Hz, 2H).

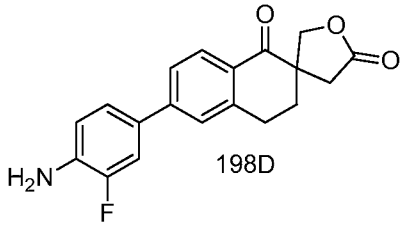
1',5-Dioxo-3',4,4',5-tetrahydro-1'H,2H-spiro[furan-3,2'-naphthalene]-6'-yl trifluoromethanesulfonate (198C):



198C

Triflic anhydride (0.493 g, 1.75 mmol) was added to an ice cold solution of product of Example 198B (0.37 g, 1.59 mmol) and pyridine (0.138 g, 1.75 mmol) in dichloromethane (15 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with dichloromethane (50 mL) and extracted with saturated aqueous solution of NaCl (50 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 20% ethyl acetate in hexanes to give title compound (0.46 g, 79%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 9.6 Hz, 1H), 7.59 (s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 4.53 (d, J = 8.8 Hz, 1H), 4.25 (d, J = 9.2 Hz, 1H), 3.05 (t, J = 6.0 Hz, 2H), 2.75 (d, J = 7.6 Hz, 2H), 2.29 (m, 2H).

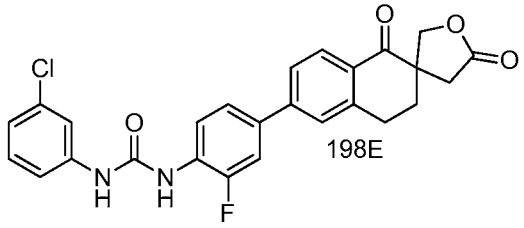
6'-(4-Amino-3-fluorophenyl)-3',4'-dihydro-1'H,2H-spiro[furan-3,2'-naphthalene]-1',5(4H)-dione (198D):



198D

$Pd(PPh_3)_4$ (0.011 g, 0.009 mmol) was added to a solution of product of Example 198C (0.3 g, 0.824 mmol) in 12 mL of 1,4 dioxane-H_2O (4:1) mixture under Argon atmosphere, followed by cesium carbonate (0.67 g, 2.06 mmol) and 4-amino 2-fluoro phenyl boronic acid (0.234 g, 0.989 mmol). The reaction mixture was degassed for 15 min. The reaction mixture was then refluxed for 3 h, and solvent was removed under vacuum. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered andremoved under reduced pressure. The crude product was purified by flash chromatography using 20% ethyl acetate in hexane to afford title compound (1.3 g, 72%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, J = 8.4 Hz, 1H), 7.48-7.43 (m, 2H), 7.27 (t, J = 8.8 Hz, 1H), 6.48 (dd, J_1 = 2.4 Hz, J_2 = 8.4 Hz, 1H), 6.42 (dd, J_1 = 2.4 Hz, J_2 = 16.4 Hz, 1H), 5.74 (s, 2H), 4.50 (d, J = 9.2 Hz, 1H), 4.28 (d, J = 9.2 Hz, 1H), 3.05 (m, 2H), 2.73 (d, J = 9.6 Hz, 2H), 2.26 (m, 2H).

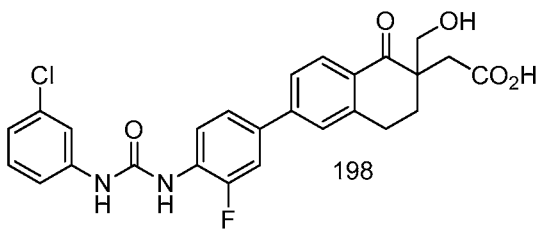
3-Chloro-N-(4-(1',5-dioxo-3',4,4',5-tetrahydro-1'H,2H-spiro [furan-3,2'-naphthalene]-6'-yl)-2-fluoro phenyl)benzamide (198E):



198E

3-Chlorophenyl isocyanate (0.052 g, 0.338 mmol) was added to a solution of product of Example 198D (0.1 g, 0.307 mmol) and triethylamine (0.034 g, 0.338 mmol) in THF (5 mL), and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 40% ethyl acetate in hexanes to afford title compound (0.09 g, 31%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.31 (s, 1H), 8.78 (m, 1H), 8.28 (t, J = 8.4 Hz, 1H), 7.98 (d, J = 5.7 Hz, 1H), 7.75-7.71 (m, 4H), 7.63-7.60 (m, 1H), 7.36-7.23 (m, 2H), 7.07-7.04 (m, 1H), 4.51 (d, J = 9.0 Hz, 1H), 4.3 (d, J = 9.3 Hz, 1H), 3.16 (d, J = 4.8 Hz, 1H), 3.06 (m, 1H), 2.75 (d, J = 4.2 Hz, 2H), 2.28 (t, J = 5.7 Hz, 2H).

2-(6-(4-(3-(3-Chlorophenyl) ureido)-3-fluorophenyl)-2-(hydroxymethyl)-1-oxo-1,2,3,4-tetrahydro naphthalen-2-yl)acetic acid (198):

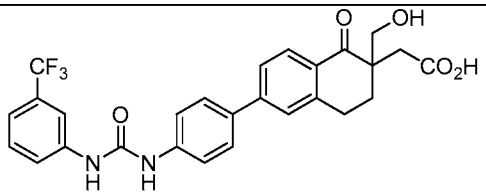
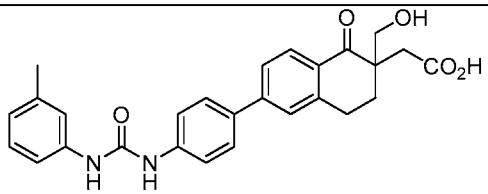


198

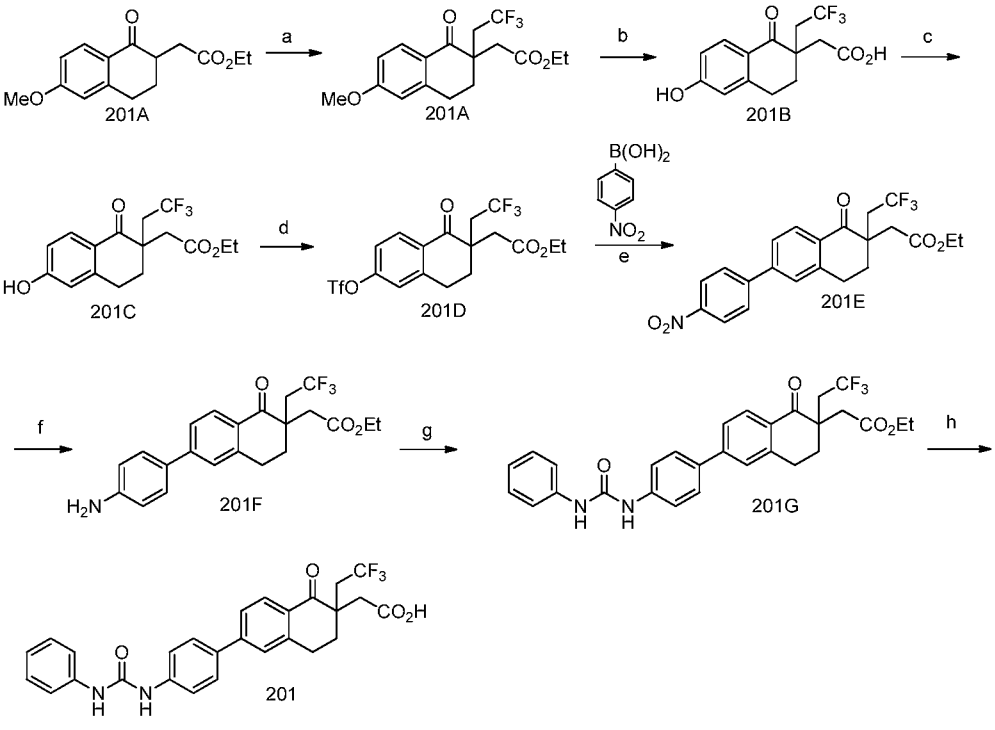
Lithium hydroxide (0.023 g, 0.564 mmol) was added to a solution of product of Example 198E (0.09 g, 0.188 mmol) in 15 mL of THF-water (2:1) mixture, and the reaction mixture was stirred at room temperature for 4h. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous

solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, solids were collected by filtration and dried under vacuum to afford title compound (0.05 g, 53%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.70 (bs, 1H), 9.11 (bs, 1H), 8.20 (t, J = 8.1 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H) 7.76 (s, 1H),7.68-7.64 (m, 3H), 7.57 (d, J = 9.0 Hz, 1H) 7.32-7.28 (m, 2H), 7.03 (m, 1H), 3.15-2.90 (m, 4H), 2.74-2.67 (m, 1H), 2.44-2.34 (m, 1H), 2.28-2.16 (m, 1H), 2.00 (m, 1H); ESI-MS m/z = 466 (M-CH_2OH).

Examples 199 - 200 were prepared by the procedures analogous to those described in Example 198 using appropriate starting materials.

Ex	Structure	^{1}H NMR Data	Mass/Purity
199		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 2H), 8.14 (s, 1H), 7.96 (m, 1H), 7.80 (m, 1H), 7.66 (m, 1H) 7.47-7.40 (m, 2H),7.33 (m, 4H), 7.20 (d, J = 7.6 Hz, 1H), 3.09 (m, 1H), 2.94 (m, 3H), 2.33 (m, 2H), 2.02 (m, 2H).	ESI-MS m/z = 481 (M-CH_2OH); HPLC purity: 95.09 %.
200		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.12 (bs, 2H), 7.90 (d, J = 8.1 Hz, 1H), 7.70-7.55 (m, 6H), 7.35 (s, 1H), 7.25 (m, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.80 (d, J = 6.9 Hz, 1H), 3.20-3.02 (m, 2H), 2.97-2.86 (m, 2H), 2.70 (m, 2H) 2.30 (s, 3H), 2.20-2.12 (m, 1H), 2.08-1.90 (m, 1H).	ESI-MS m/z = 429 (M-CH_2OH); HPLC purity: 95.33 %.

Example-201

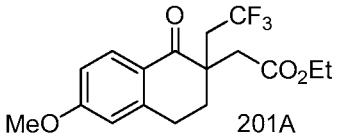


Reagents and conditions: a) CF_3CH_2I, NaH, DMF, RT, 4h; b) Aq. HBr, 100 °C, 12h; c) $MeSO_3H$, EtOH, RT, 5h; d) Tf_2O, CH_2Cl_2, Et_3N, RT, 1h; e) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; f) Fe-NH_4Cl, EtOH-H_2O, 80 °C, 3h; g) PhNCO, Et_3N, THF, RT, 12h; h) LiOH, THF-H_2O, RT, 12h.

Procedure:

2-(1-Oxo-6-(4-(3-phenylureido)phenyl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

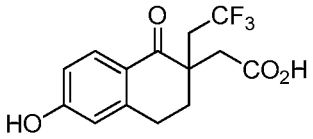
Ethyl 2-(6-methoxy-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (201A):



201A

A solution of ethyl 2-(6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (3 g, 11.4 mmol) in DMF (10 mL) was added over a period of 30 min to an ice cold solution of NaH (1.14 g, 28.5 mmol) in DMF (20 mL), and the reaction mixture was stirred for 10 min. Trifluoroethyl iodide (5.9 g, 28.22 mmol) was then added, and the mixture was stirred for 2 h at room temperature. The reaction was then brought to 0 °C, excess NaH was quenched with ice water and extracted with ethyl acetate (2X50 mL). The combined organic layers were dried over sodium sulphate, filtered and removed under vacuum to give title compound (1.5 g, 38%) as solid. ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, J = 9.3 Hz, 1H), 6.85 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 4.1 (q, J = 6.9 Hz, 2H), 3.86 (s, 3H), 3.05-2.9 (m, 4H), 2.6-2.4 (m, 4H), 1.23 (t, J = 6.9 Hz, 3H); ESI-MS m/z: 345 $(M+H)^+$

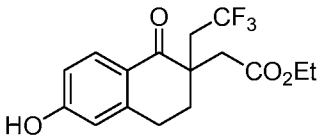
2-(6-Hydroxy-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (201B):



201B

Aqueous HBr (15 mL) was added to product of Example 201A (1.5 g, 4.36 mmol), and the reaction mixture was refluxed for overnight. The reaction mixture was then brought to room temperature and extracted with ethyl acetate (2X100 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure to afford crude compound (1.2 g) as solid, which was carried on to the next step without further purification.

Ethyl 2-(6-hydroxy-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (201C):

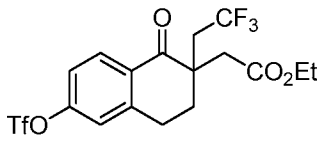


201C

Methane sulphonic acid (2 mL) was added to a solution of product of Example 201B (1.2 g, 3.97 mmol) in ethanol (15 mL), and the reaction mixture was stirred at room temperature for 12 h. Ethanol was removed from reaction mixture under reduced pressure, and residue was diluted with ethyl acetate and washed with brine solution. The organic layer was dried over sodium sulphate, filtered, and solvent was removed under reduced pressure. The crude product was purified by flash

chromatography using 20% ethyl acetate in hexanes to give title compound (0.9 g, 62%) as syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 9.2 Hz, 1H), 6.75 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 4.1 (q, J = 6.8 Hz, 2H), 3.0-2.8 (m, 4H), 2.62-2.5 (m, 2H), 2.4 (m, 1H), 2.3 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H); ESI-MS *m/z*: 329 $(M-H)^-$

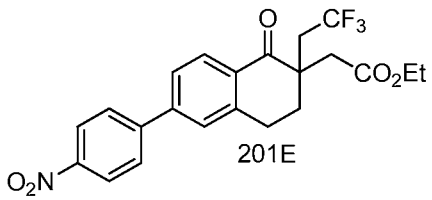
Ethyl 2-(1-oxo-2-(2,2,2-trifluoroethyl)-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (201D):



201D

Triflic anhydride (1.33 g, 4.71 mmol) was added to an ice cold solution of product of Example 201C (1.3 g, 3.93 mmol) and pyridine (0.34 g, 4.72 mmol) in dichloromethane (15 mL), and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane (100 mL) and washed with saturated aqueous solution of NaCl (25 mL). The organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography using 5% ethyl acetate in hexanes to give title compound (1.1 g, 61%) as syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 9.0 Hz, 1H), 7.28-7.18 (m, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.09 (t, J = 6.3 Hz, 2H), 2.95-2.8 (m, 2H), 2.66-2.45 (m, 3H), 2.34 (m, 1H), 1.24 (t, J = 6.9 Hz, 3H).

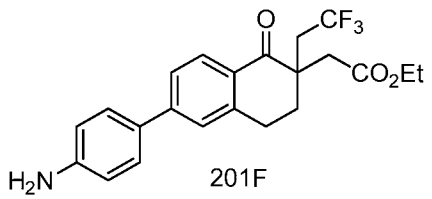
Ethyl 2-(6-(4-nitrophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (201E):



201E

$Pd(PPh_3)_4$ (0.022 g, 0.02 mmol) was added to a solution of product of Example 201D (0.9 g, 1.94 mmol) in 13 mL of 1,4 dioxane-H_2O (3:1) mixture under argon atmosphere, followed by cesium carbonate (1.9 g, 5.8 mmol) and 4-nitro phenyl boronic acid (0.35 g, 2.09 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 4 h, and solvent was then removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography to afford title compound (0.4 g, 47%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 8.8 Hz, 2H), 8.17 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.8 Hz, 2H), 7.6 (m, 1H), 7.5 (s, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.13 (t, J = 6.0 Hz, 2H), 2.95-2.85 (m, 2H), 2.7-2.58 (m, 2H), 2.5 (m, 1H), 2.4 (m, 1H), 1.25 (t, J = 6.8 Hz, 3H). ESI-MS *m/z*: 436 $(M+H)^+$

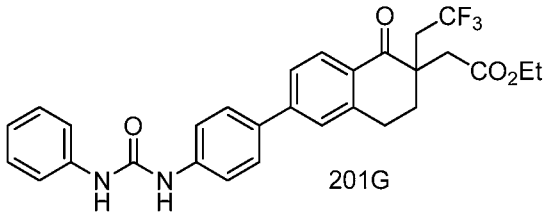
Ethyl 2-(6-(4-aminophenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (201F):



201F

Iron powder (0.12 g, 2.3 mmol) was added to a solution of product of Example 201E (0.4 g, 0.9 mmol) in 15 mL of ethanol-water mixture (2:1) followed by NH_4Cl (0.024 g, 0.45 mmol), and the reaction mixture was refluxed for 4 h. The solvent was removed under reduced pressure, and residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed in vacuo to give title compound (0.2 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.86 (d, J = 8.4 Hz, 1H), 7.6-7.45 (m, 4H), 6.65 (d, J = 9.0 Hz, 2H), 5.44 (bs, 2H), 4.03 (q, J = 7.2 Hz, 2H), 3.1-2.8 (m, 4H), 2.75-2.6 (m, 2H), 2.38 (m, 1H), 2.15 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H). ESI-MS m/z: 406 $(M+H)^+$

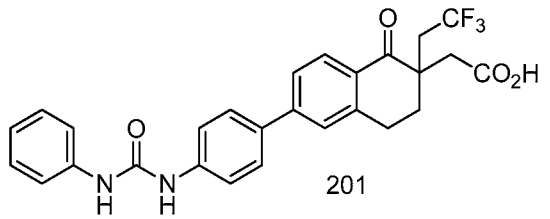
Ethyl 2-(1-oxo-6-(4-(3-phenylureido)phenyl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl) acetate (201G):



201G

Phenyl isocyanate (0.035 g, 0.3 mmol) was added to a solution of product of Example 201F (0.12 g, 0.3 mmol) and triethylamine (0.06 g, 0.6 mmol) in THF (5 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (0.08 g, 66%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, 8.4 Hz, 1H), 7.6-7.45 (m, 5H), 7.42-7.35 (m, 5H), 7.19 (m, 1H), 6.6 (s, 1H), 6.5 (s, 1H), 4.1 (q, J = 7.2 Hz, 2H), 3.1 (m, 2H), 2.9 (m, 2H), 2.63 (m, 2H), 2.5-2.3 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H); ESI-MS m/z: 526 $(M+H)^+$

2-(1-Oxo-6-(4-(3-phenylureido)phenyl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (201):

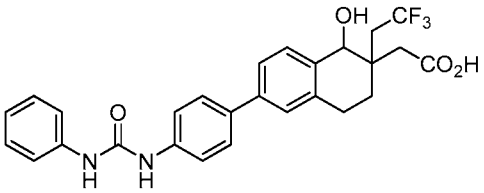
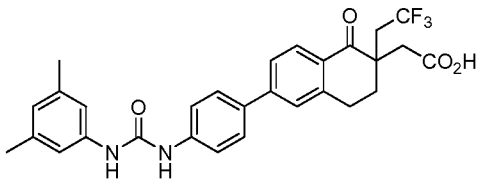
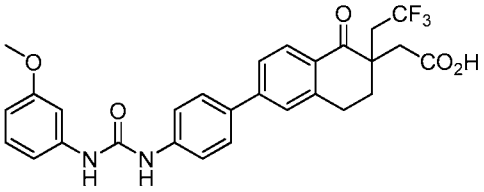
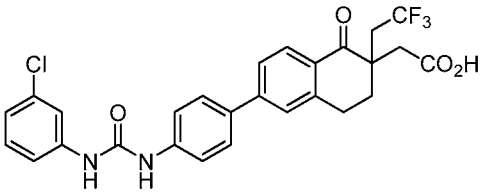
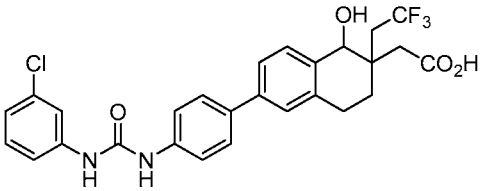
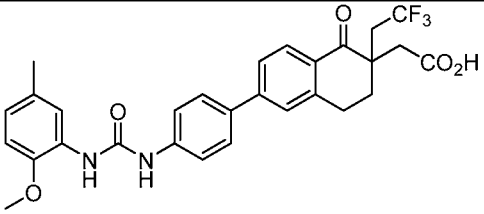


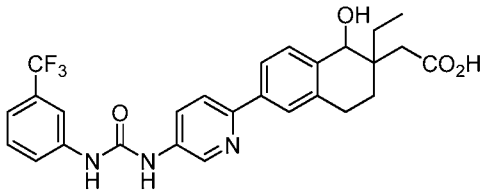
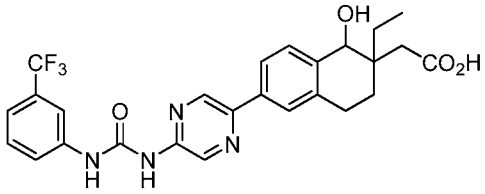
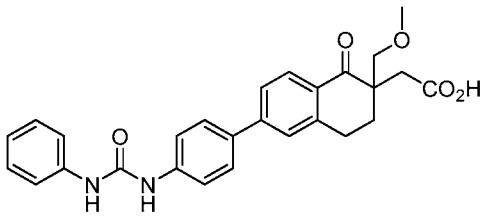
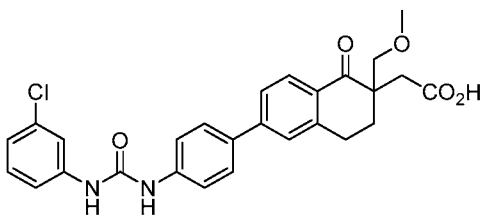
201

Lithium hydroxide (0.025 g, 0.61 mmol) was added to a solution of product of Example 201G (0.08 g, 0.15 mmol) in 4 mL of THF-water (3:1) mixture, and the reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, solids were collected by filtration and dried under vacuum to afford title compound (0.05 g, 66%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.15 (bs, 1H), 8.95 (bs, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.7 -7.62 (m, 4H), 7.57 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 3.2-2.9 (m, 3H), 2.83-2.67 (m, 2H), 2.6-2.45 (m, 2H), 2.15 (m, 1H); ESI-MS m/z: 495 $(M-H)^-$; HPLC purity: 95%.

Examples 202 - 211 were prepared by the procedures analogous to those described in Examples 173, 197 and 201 using appropriate starting materials.

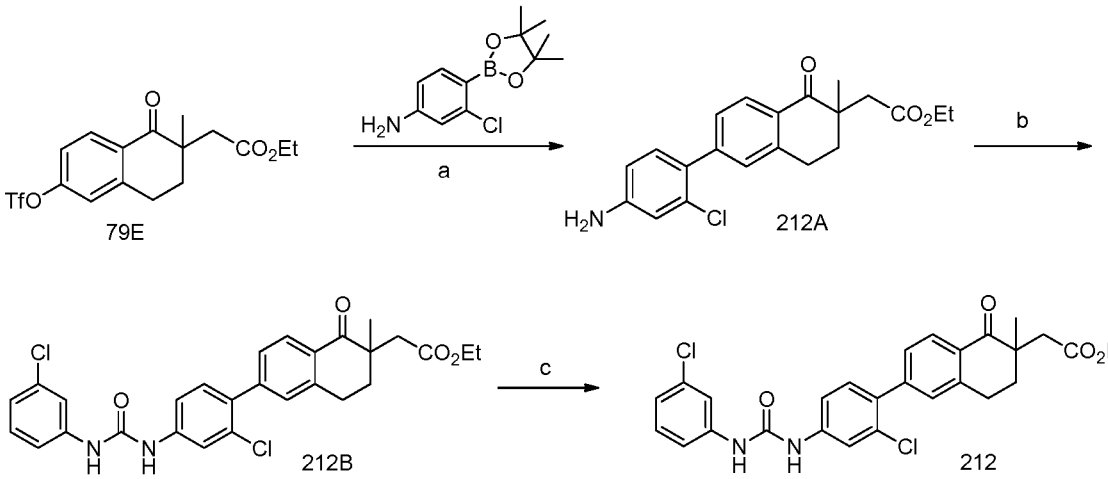
Exp	Structure	Analytical Data	$(M+H)^+$

202		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.78 (s, 1H), 8.7 (s, 1H), 7.6-7.52 (m, 4H), 7.5-7.4 (m, 3H), 7.38-7.26 (m, 4H), 6.97 (t, *J* = 7.5 Hz, 1H), 5.5 (d, *J* = 6.3 Hz, 1H), 4.5 (d, *J* = 5.4 Hz, 1H), 2.9-2.55 (m, 4H), 2.4-2.2 (m, 2H), 1.94 (m, 2H).	ESI-MS *m/z*: 499 $(M+H)^+$; HPLC purity: 99%.
203		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.16 (bs, 1H), 8.9 (bs, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.7-7.55 (m, 6H), 7.1 (s, 2H), 6.6 (s, 1H), 3.2-2.9 (m 3H), 2.84-2.7 (m, 2H), 2.55 (m, 1H), 2.45 (m, 1H), 2.24 (s, 6H), 2.16 (m, 1H).	ESI-MS *m/z*: 525 $(M+H)^+$; HPLC purity: 97%.
204		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.9 (bs, 1H), 8.8 (bs, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.72-7.55 (m, 6H), 7.24-7.16 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 6.3 Hz, 1H), 3.74 (s, 3H), 3.2-2.9 (m, 3H), 2.85-2.65 (m, 3H), 2.55 (m, 1H), 2.17 (m, 1H).	ESI-MS *m/z*: 525 $(M-H)^-$; HPLC purity: 98%.
205		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.2 (bs, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.74 -7.64 (m, 5H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.32-7.28 (m, 2H), 7.02 (m, 1H), 3.2-2.9 (m, 3H), 2.82 (d, J = 16.4 Hz, 1H), 2.7 (m, 1H), 2.56 (m, 1H), 2.45 (m, 1H), 2.18 (m, 1H).	ESI-MS *m/z*: 529 $(M-H)^-$; LCMS purity: 98%.
206		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.32 (bs, 1H), 9.24 (bs, 1H), 7.74 (s, 1H), 7.65 -7.52 (m, 4H), 7.5-7.35 (m, 3H), 7.3 (m, 2H), 7.0 (m, 1H), 4.54 (s, 1H), 2.95-2.8 (m, 4H), 2.5-2.2 (m, 2H), 1.9 (m, 2H).	ESI-MS *m/z*: 531 $(M-H)^-$; LCMS purity: 93%.
207		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.51 (s, 1H), 8.23 (s, 1H), 8.0 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.75-7.55 (m, 6H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 3.85 (s, 3H), 3.2-2.9 (m 3H), 2.84-	ESI-MS *m/z*: 541 $(M+H)^+$; LCMS purity: 93%.

		2.65 (m, 2H), 2.55 (m, 1H), 2.45 (m, 1H), 2.24 (s, 3H), 2.18 (m, 1H).	
208		^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (bs, 1H), 9.31 (bs, 1H), 8.73 (bs, 1H), 8.1 (d, J = 8.4 Hz, 1H), 8.0 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.76 (s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 7.2 Hz, 1H), 4.42 (s, 1H), 2.81 (m, 2H), 2.13 (m, 2H), 1.84 (m, 1H), 1.7 (m, 1H), 1.56 (m, 1H), 1.4 (m, 1H), 0.9 (t, J = 6.8 Hz, 3H).	ESI-MS m/z: 512 $(M+H)^+$; LCMS purity: 96%.
209		^{1}H NMR (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 10.0 (bs, 1H), 9.8 (bs, 1H), 9.1 (s, 1H), 8.9 (s, 1H), 8.05 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.8 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 4.5 (s, 1H), 2.81 (m, 2H), 2.26 (m, 2H), 1.85 (m, 1H), 1.7 (m, 1H), 1.6 (m, 1H), 1.45 (m, 1H), 0.9 (t, J = 7.2 Hz, 3H).	ESI-MS m/z: 513 $(M+H)^+$; LCMS purity: 90%.
210		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 8.85 (s, 1H), 8.7 (s, 1H), 7.9 (d, J = 7.5 Hz, 1H), 7.7 (d, J = 8.4 Hz, 2H), 7.65-7.55 (m, 4H), 7.45 (d, J = 7.8 Hz, 2H), 7.3 (t, J = 7.5 Hz, 2H), 7.0 (m, 1H), 3.6 (d, J = 9.3 Hz, 1H), 3.36 (d, J = 9.9 Hz, 1H), 3.22 (s, 3H), 3.12-2.89 (m, 2H), 2.85 (m, 1H), 2.42 (m, 2H), 2.18 (m, 1H).	HPLC purity: 92%.
211		^{1}H NMR (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 8.95 (s, 2H), 7.9 (d, J = 7.5 Hz, 1H), 7.7 (d, J = 9.0 Hz, 2H), 7.63-7.57 (m, 4H), 7.34-7.29 (m, 2H), 7.03 (m, 1H), 3.6 (d, J = 9.3 Hz, 1H), 3.36 (d, J = 9.9 Hz, 1H), 3.22 (s, 3H), 3.18-2.9 (m, 2H), 2.85 (m, 1H), 2.42 (m, 2H), 2.15 (m,	ESI-MS m/z: 491 $(M-H)^-$; HPLC purity: 91%.

		1H).	

Example-212

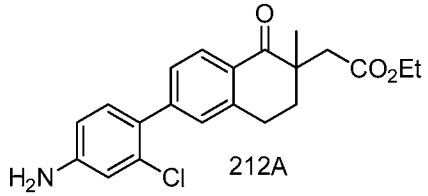


Reagents and conditions: a) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; b) 3-ClPhNCO, Et_3N, THF, RT, 12h; c) LiOH, THF-H_2O, RT, 12h.

Procedures:

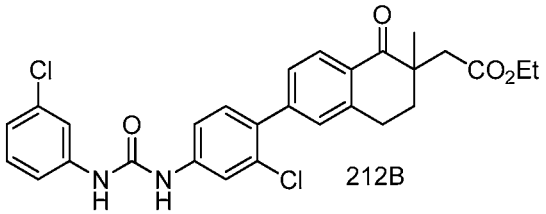
2-(6-(2-Chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

Ethyl 2-(6-(4-amino-2-chlorophenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (212A):



$Pd(PPh_3)_4$ (0.088 g, 0.076 mmol) was added to a solution of product of Example 79E (2.5 g, 6.34 mmol) in 35 mL of 1,4 dioxane-H_2O (5:1) mixture under Argon atmosphere, followed by cesium carbonate (6.2 g, 19.02 mmol) and 4-Amino-2-chlorophenylboronic acid, pinacol ester (1.607 g, 6.34 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 5 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and removed under reduced pressure. The product was purified by flash chromatography to afford title compound (2 g, 85%) as solid. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 1H), 7.38-7.36 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.28 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 6.64-6.61 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 4.1 (q, J = 6.8 Hz, 2H), 3.8 (bs, 2H), 3.1 (m, 1H), 2.95 (m, 2H), 2.5 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.25 (m, 3H).

Ethyl 2-(6-(2-chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (212B):

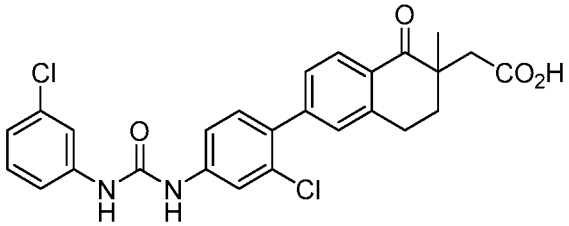


212B

1-Chloro-3-isocyanatobenzene (0.892 g, 5.81 mmol) was added to a solution of product of Example 212A (1.8 g, 4.84 mmol) and triethylamine (2.024 g, 14.52 mmol) in THF (25 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 12% ethyl acetate in hexanes to afford title compound (1.2 g, 47.2%) as solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H), 8.02 (s, 1H), 7.48 (m, 2H), 7.36 (m, 1H), 7.29 (m, 1H), 7.21 (m, 1H), 7.11-7.03 (m, 5H), 4.11 (q, *J* = 7.5 Hz, 2H), 3.12-2.89 (m, 3H), 2.44 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, *J* = 7.2 Hz, 3H).

Compound **212B** (0.88g) was racemic mixure with 1:1 enantiomeric ratio and was separated on chiral column to obtain single enantiomers of **212B1** (Rt 17.32 min) and **212B2** (Rt 19.06 min) using following conditions:
Column: CHIRAL PAK IA 4.6 X 250mm, 5µ
Column ID: ANL_CHIRAL IA_141
Mobile Phase: A= n-HEXANE, C=Ethanol; ISOCRATIC: 90:10; Flow rate: 1.0 mL/min

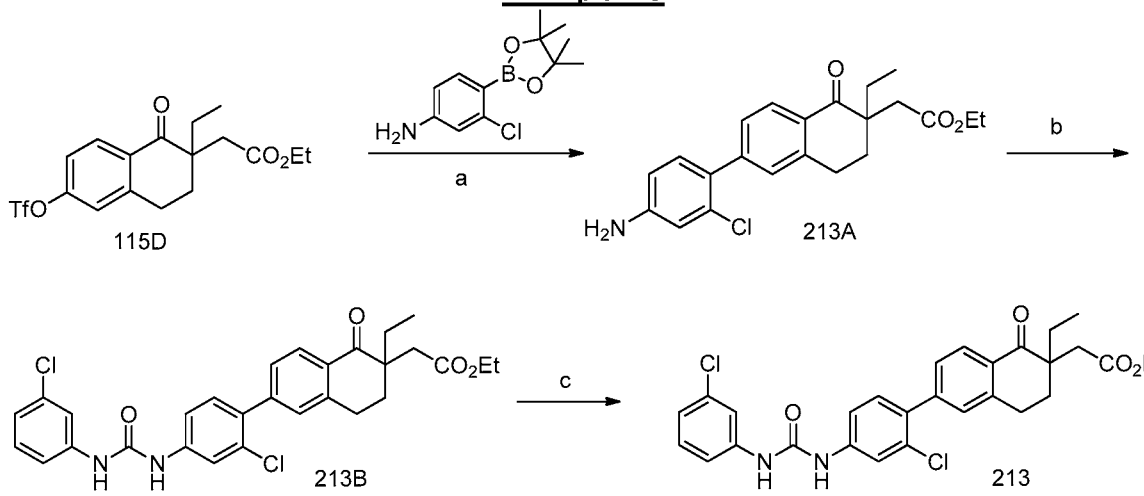
2-(6-(2-chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (212):



Chiral: enantiomer-1

Lithium hydroxide (0.08 g, 1.903 mmol) was added to a solution of product of Example 212B1 (0.25 g, 0.476 mmol) in 10 mL of dioxane-water (4:1) mixture, and the reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.19 g, 80%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.1 (bs, 1H), 9.03 (bs, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.8 (d, *J* = 1.8 Hz, 1H), 7.7 (m, 1H), 7.43-7.39 (m, 4H), 7.32-7.3 (m, 2H), 7.06-7.03 (m, 1H), 3.11-2.98 (m, 2H), 2.87 (d, *J* = 15.6 Hz, 1H), 2.5 (m, 1H), 2.4 (d, J = 16.5 Hz, 1H), 1.87 (m, 1H), 1.2 (s, 3H); ESI-MS *m/z* = 495 $(M-H)^-$; HPLC Purity: 95%.

Example 213

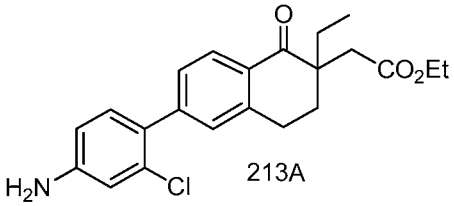


Reagents and conditions: a) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; b) 3-ClPhNCO, Et_3N, THF, RT, 12h; c) LiOH, THF-H_2O, RT, 12h.

Procedures:

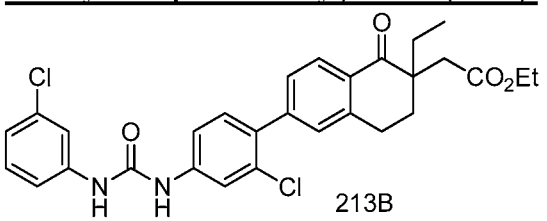
2-(6-(2-chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

Ethyl 2-(6-(4-amino-2-chlorophenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (213A):



$Pd(PPh_3)_4$ (0.085 g, 0.073 mmol) was added to a solution of product of Example 115D (3 g, 7.35 mmol) in 40 mL of 1,4 dioxane-H_2O (3:1) mixture under argon atmosphere, followed by cesium carbonate (7.18 g, 22.04 mmol) and 3-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.862 g, 7.35 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 3 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The separated organic layer was dried over sodium sulphate, filtered and concentrated under reduced pressure to give curde product which was purified by flash chromatography to afford title compound (3 g, 58%) as solid. ^{1}H NMR (400MHz, DMSO- d_6): δ 8.07 (d, J = 7.6 Hz, 1H), 7.36 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.26 (m, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 2 Hz, 1H), 6.62 (dd, J_1 = 2 Hz, J_2 = 8.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.13-3.07 (m, 1H), 3.00-2.88 (m, 2H), 2.52-2.38 (m, 2H), 2.09-2.03 (m, 1H), 1.82-1.6 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.8 Hz, 3H).

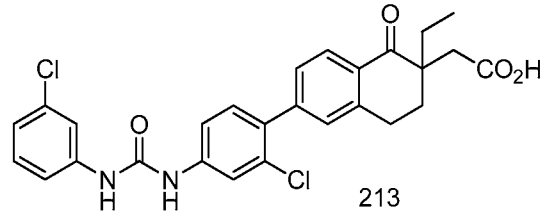
Ethyl 2-(6-(2-chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (213B):



3-Chloro-3-isocyanatobenzene (0.944 mL, 7.77 mmol) was added to a solution of product of Example 213A (3 g, 7.77 mmol) and triethylamine (2.18 mL, 15.55 mmol) in THF (10 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (1 g, 14%) as yellow solid. ^{1}H NMR (300 MHz , DMSO-d_6): δ 9.13 (s, 1H), 9.06 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.72 (s, 1H), 7.46-7.28 (m, 6H), 7.06-7.02 (m, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.31-2.8 (m, 3H), 2.5-2.34 (m, 2H), 2.03-1.99 (m, 1H), 1.73-1.53 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H).

Compound **213B (**1 g) was racemic mixture with 1:1 enantiomeric ratio and was separated on chiral column to obtain single enantiomers of **213B1** (Rt 15.15 min) and **213B2** (Rt 16.97 min) using following conditions:
Column: CHIRAL PAK IA 4.6 X 250mm, 5µ
Column ID: ANL_CHIRAL IA_141
Mobile Phase: D= n-HEXANE (0.1% DEA), C=Ethanol; ISOCRATIC: 90:10; Flow rate: 1.0 mL/min.

2-(6-(2-Chloro-4-(3-(3-chlorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (213):

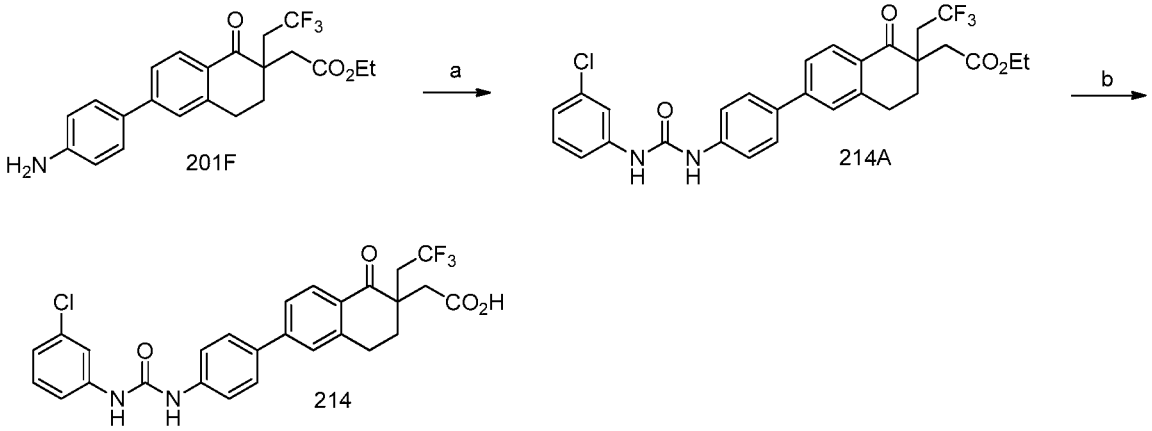


213

Chiral: enantiomer-1

Lithium hydroxide (0.136 g, 3.24 mmol) was added to a solution of product of Example 213B1 (0.35 g, 0.649 mmol) in 12 mL of THF-water (5:1) mixture, and the reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, solids were collected by filtration and dried under vacuum to afford title compound (0.24 g, 71%) as white solid. ^{1}H NMR (300 MHz , DMSO-d_6) : δ 12.16 (bs, 1H) , 9.21 (bs, 2H), 7.93 (d, J = 8.1 Hz, 1H), 7.87 (s, 1H), 7.72 (s, 1H), 7.41-7.27 (m, 6H), 7.08-7.0 (m, 1H), 3.07-3.03 (m, 1H), 2.94-2.79 (m, 2H), 2.50-2.34 (m, 2H), 2.00-1.95 (m, 1H), 1.72-1.49 (m, 2H), 0.85 (t, J = 7.5 Hz, 3H); LCMS : 98.6% m/z = 511 $(M+H)^+$; HPLC purity: 94%.

Example-214

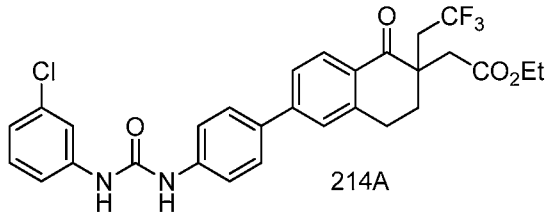


Reagents and conditions: a) 3-ClPhNCO, Et_3N, THF, RT, 12h; b) LiOH, THF-H_2O, RT, 12h.

Procedures:

2-(6-(4-(3-(3-Chlorophenyl)ureido)phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

Ethyl 2-(6-(4-(3-(3-chlorophenyl)ureido)phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (214A):

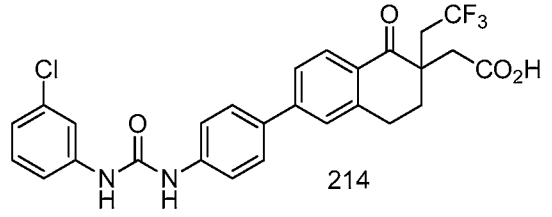


214A

3-Chlorophenyl isocyanate (0.604 g, 3.95 mmol) was added to a solution of product of Example 201F (1.6 g, 3.95 mmol) and triethylamine (0.79 g, 7.89 mmol) in THF (10 mL), and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and product was purified by flash chromatography using 20% ethyl acetate in hexanes to afford title compound (1.6 g, 64.5%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (bs, 2H), 7.93 (d, J = 8.1 Hz, 1H), 7.73-7.57 (m, 7H), 7.31-7.29 (m, 2H), 7.05-7.02 (m, 1H), 4.04 (q, J = 7.3 Hz, 2H), 2.91-2.85 (m, 4H), 2.72-2.64 (m, 2H), 2.39 (m, 2H), 1.15 (t, J = 7.2 Hz, 3H). Yield= 64.5 %.

Compound **214A** was racemic mixture with 1:1 enantiomeric ratio and was separated on chiral column to obtain single enantiomers of **214A1** (Rt 5.832 min) and **214A2** (Rt 6.469 min) using following prep conditions:
Column: CHIRAL PAK IA 4.6 X 250mm, 5µ
Column ID: ANL_CHIRAL IA_110
Mobile Phase: A= n-HEXANE, C=Ethanol; ISOCRATIC: 60:40; Flow rate: 1.0 mL/min

2-(6-(4-(3-(3-Chlorophenyl)ureido)phenyl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (214):

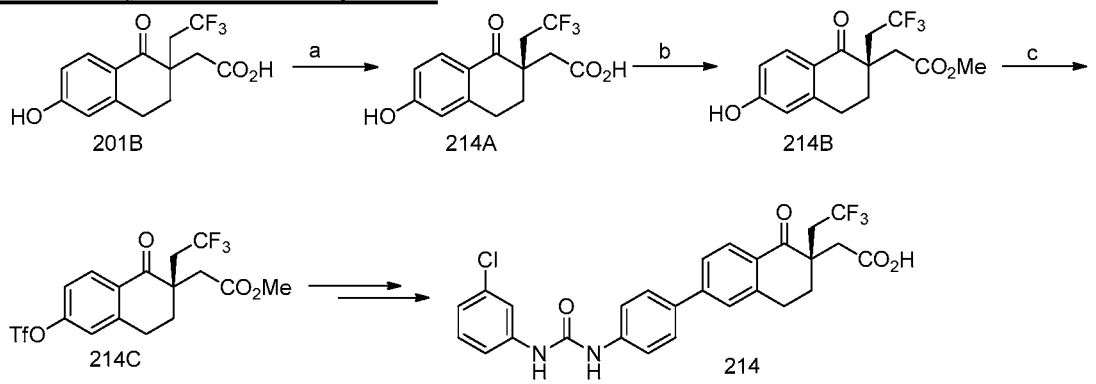


214

Chiral: enantiomer-1

Lithium hydroxide (0.131 g, 3.13 mmol) was added to a solution of product of Example 214A1 (0.35 g, 0.626 mmol) in 10 mL of THF-water (4:1) mixture, and the reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, solids were collected by filtration and dried under vacuum to afford title compound (0.22 g, 65%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.8 (bs, 1H), 9.8 (bs, 2H), 7.95 (d, J = 8 Hz, 1H), 7.75 (m, 1H), 7.7 -7.5 (m, 6H), 7.36-7.26 (m, 2H), 7.0 (d, J = 7.2 Hz, 1H), 3.16-2.96 (m, 3H), 2.95-2.78 (m, 2H), 2.54 (m, 1H), 2.46 (m, 1H), 2.16-2.12 (m, 1H); ESI-MS m/z: 495 $(M-H)^-$; HPLC purity: 95%.

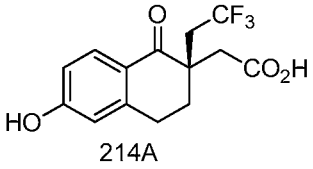
Alternative synthesis of Example 214:



Reagents and conditions: a) Cinchonidine, IPA-H_2O, 80 °C – RT, 24h then 5N HCl, RT; b) H_2SO_4, MeOH, 70 °C, 12h; c) Tf_2O, CH_2Cl_2, Et_3N, RT, 1h.

Procedures:

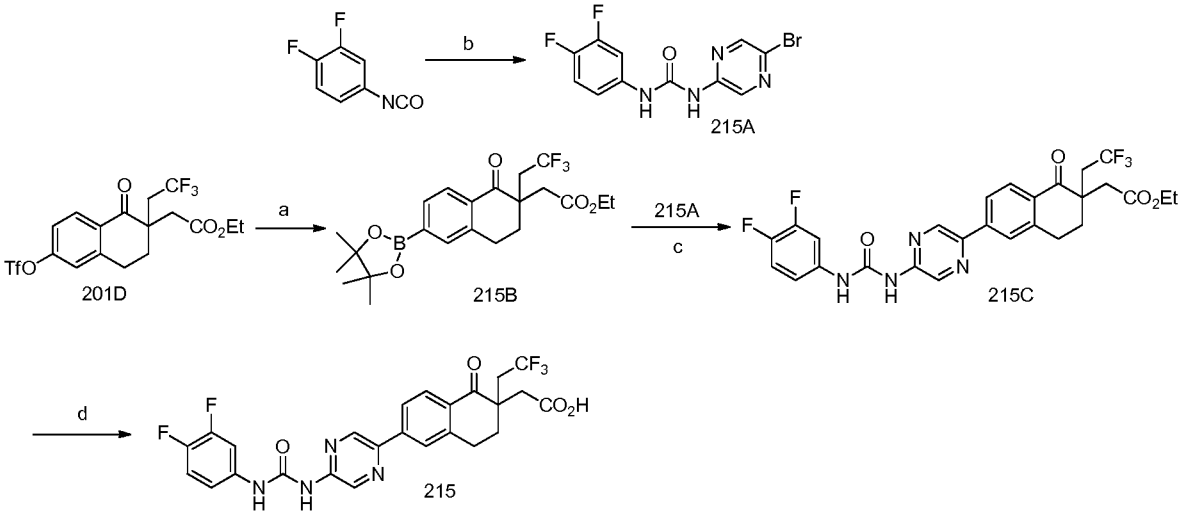
(S)-2-(6-hydroxy-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:



Cinchonidine (0.97 g, 3.31 mmol) was added to a solution of product of Example 201B (1 g, 3.31 mmol), in isopropyl alcohol (9 mL) and water (3 mL), and the reaction mixture was heated to 80 °C 4 h. The resulting solution was stirred at room temperature for 16 h, and the salt was filtered and washed with a mixture of isopropyl alcohol (2 mL) and water (2 mL). The salt was dissolved in 5N HCl (5 mL), extracted with ethyl acetate (25 mL), dried and concentrated to afford the title compound (0.18 g, 18%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 10.4 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 6.74 (dd, J_1 = 2.1 Hz, J_2 = 8.1 Hz, 1H), 6.64 (s, 1H), 3.05-2.80 (m, 3H), 2.75-2.60 (m, 2H), 2.45 (m, 1H), 2.35 (m, 1H), 2.15-2.0 (m, 1H).

Compounds 214B, 214C and 214 may be synthesized from chiral 214A compound using the procedures analogous to those described for Example-201 and 214.

Example-215

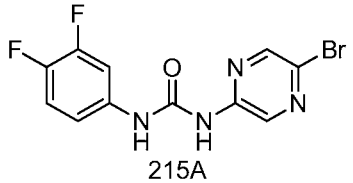


Reagents and conditions: e) $PdCl_2(dppf)$, KOAc, Dioxane, 100 °C, 5h; b) 2-amino-4-bromo pyrazine, Et_3N, Toluene, 120 °C, 12h ; c) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; d) LiOH, EtOH-H_2O, RT, 12h.

Procedures:

2-(6-(5-(3-(3,4-Difluorophenyl)ureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

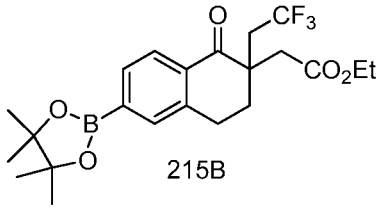
1-(5-Bromopyrazin-2-yl)-3-(3,4-difluorophenyl)urea (215A):



215A

3,4-Difluorophenyl isocyanate (8.8 g, 56.9 mmol) was added to a solution of 2-amino-4-bromo pyrazine (9 g, 51.72 mmol) and triethyl amine (3.98 mL, 28.4 mmol) in toluene (100 mL), and the reaction mixture was stirred at 120 °C for 12 hr. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 20% ethyl acetate in hexane to afford title compound (10 g, 59%) as solid. ^1H NMR (300 MHz, DMSO-d_6): δ 9.69 (s, 1H), 9.46 (s, 1H), 8.93 (d, J = 1.2 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 7.74-7.64 (m, 1H), 7.46-7.32 (m, 1H), 7.22-7.14 (m, 1H).

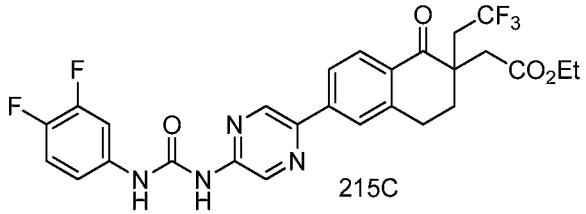
Ethyl 2-(1-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (215B):



215B

$PdCl_2(dppf)$-CH_2Cl_2 adduct (0.58 g, 0.71 mmol) was added to a solution of Example 201D (6.6 g, 14.27 mmol) in 50 mL of 1,4 dioxane in argon atmosphere, followed by potassium acetate (4.19 g, 42.85 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.62 g, 14.27 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 5 hr, cooled to room température and filtered over celite bed. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography using 10% ethyl acetate in hexane to afford title compound (5.6 g, 89%) as viscous liquid.: ^1HNMR (400MHz, $CDCl_3$): δ 8.02 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 4.14-4.09 (q, J = 7.2 Hz, 2H), 3.06-3.03 (m, 2H), 2.89-2.82 (m, 2H), 2.63-2.56 (m, 2H), 2.42-2.29 (m, 2H), 1.35-1.31 (m, 3H), 1.24-1.19 (m, 12H).

Ethyl 2-(6-(5-(3-(3,4-difluorophenyl)ureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (215C):



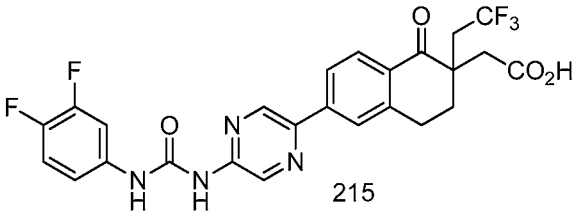
215C

$Pd(PPh_3)_4$ (0.3 g, 0.26 mmol) was added to a solution of Example 215B (2.3 g, 3.22 mmol) in 60 mL of 1,4 dioxane-H_2O (5:1) mixture under argon atmosphere, followed by cesium carbonate (5.11 g, 15.67 mmol) and compound 215A (2.063 g, 6.27 mmol). The reaction mixture was

degassed for 30 min. The reaction mixture was refluxed for 16 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water, organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash chromatography using 18% ethyl acetate in hexane to afford title compound (1 g, 32%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.82 (s, 1H), 9.75 (s, 1H), 9.16 (d, J = 1.5 Hz, 1H), 9.03 (d, J = 1.5 Hz, 1H), 8.10-7.95 (m, 3H), 7.78-7.68 (m, 1H), 7.48-7.35 (m, 1H), 7.26-7.18 (m, 1H), 4.08-3.98 (q, J = 7.2 Hz, 2H), 3.26-3.10 (m, 2H), 3.08-2.85 (m, 2H), 2.80-2.64 (m, 2H), 2.48-2.36 (m, 1H), 2.28-2.15 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H). ESI-MS m/z = 563 (M+1).

Compound **215C** was racemic mixture with 1:1 enantiomeric ratio and was separated on chiral column to obtain single enantiomers of **215C1** (Rt 9.394 min) and **215C2** (Rt 12.342 min) using following prep conditions:
Column: CHIRAL PAK IA 4.6 X 250mm, 5µ
Mobile Phase: A= n-HEXANE, C=isopropanol; ISOCRATIC: 70:30; Flow rate: 1.0 mL/min

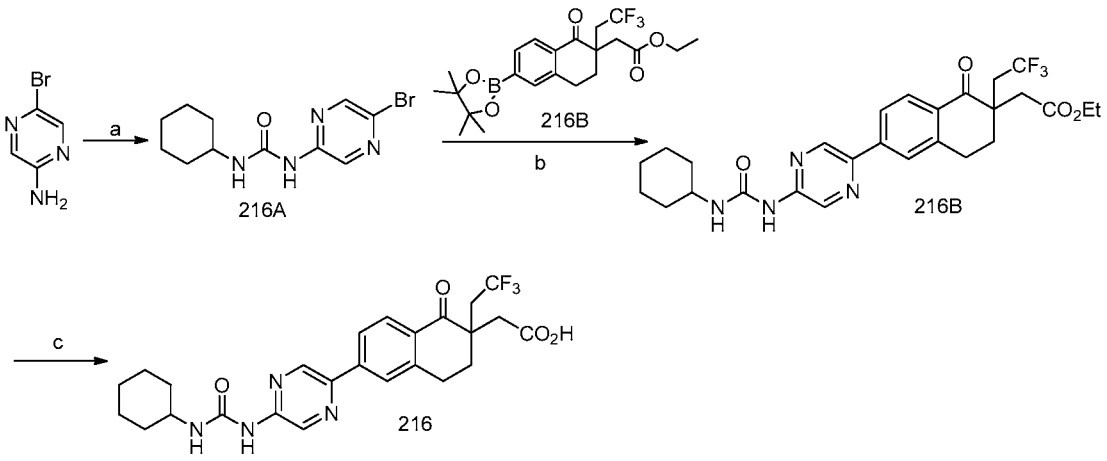
2-(6-(5-(3-(3,4-Difluorophenyl)ureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (215):



Chiral: enantiomer-1

Lithium hydroxide (0.075 g, 3.11 mmol) was added to a solution of product of Example 215C (0.35 g, 0.62 mmol) in 30 mL of ethanol-water (5:1) mixture, and the reaction mixture was stirred at room temperature overnight. After the solvent was removed in vacuo, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of 2N aqueous solution of HCl until pH 2 was attained. The resulting solution was cooled to 0 °C, and solids were collected by filtration and dried under vacuum to afford title compound (0.255 g, 76%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.42 (bs, 1H), 9.83 (s, 1H), 9.77 (s, 1H), 9.16 (d, J = 1.2 Hz, 1H), 9.02 (d, J = 1.5 Hz, 1H), 8.1-7.94 (m, 3H), 7.78-7.68 (m, 1H), 7.46-7.35 (m, 1H), 7.24 (m, 1H), 3.41-3.35 (m, 1H), 3.20-2.95 (m, 2H), 2.88-2.80 (m, 2H), 2.65-2.55 (m, 1H), 2.50-2.42 (m, 1H), 2.24-2.14 (m, 1H). ESI-MS m/z = 535 {$(M+H)^+$}. HPLC purity: 98.87%.

Example-216

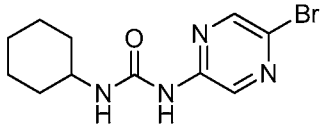


Reagents and conditions: a) cyclohexyl isocyanate, Et_3N, Toluene, 120 °C, 12h ; b) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 5h; c) LiOH, Dioxane-H_2O, RT, 12h.

Procedures:

2-(6-(5-(3-cyclohexylureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

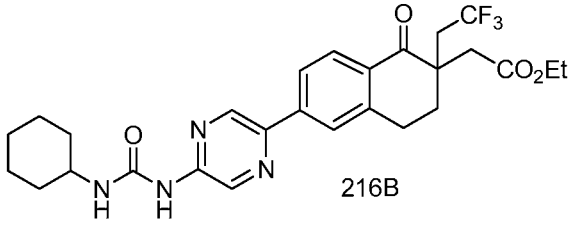
1-(5-bromopyrazin-2-yl)-3-cyclohexylurea (216A):



216A

Isocyanatocyclohexane (2.158 g, 17.24 mmol) was added to a solution of 2-amino-4-bromo pyrazine (3 g, 17.24 mmol) and triethylamine (1 mL, 7.17 mmol) in 20 mL toluene and stirred at 120 °C for 5 h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography using 15% ethyl acetate in hexane to afford title compound (1.60 g, 31%) as solid. ^{1}HNMR (300MHz, $CDCl_3$): δ 9.6 (bs, 1H), 8.38 (bs, 1H), 8.2 (m, 2H), 3.8 (m, 1H), 2.04-1.95 (m, 2H), 1.75-1.58 (m, 3H), 1.49-1.13 (m, 5H).

Ethyl 2-(6-(5-(3-cyclohexylureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (216B):



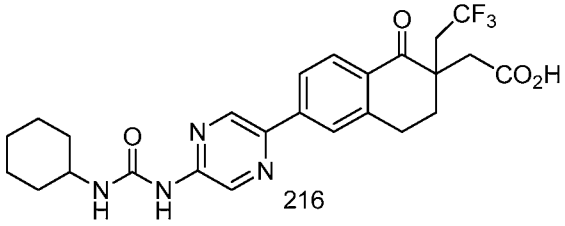
216B

$Pd(Ph_3P)_4$ (0.07 g, 0.06 mmol) was added to a solution of Example 216A (1.50 g, 5.01 mmol) in 15 mL of 1,4 dioxane-H_2O (3:1) mixture under argon atmosphere, followed by cesium carbonate (4.90 g, 15.04 mmol) and Example 216B (2.2 g, 5.01 mmol). The reaction mixture was degassed for 5 min. The reaction mixture was refluxed for 5 hr, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water, organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash chromatography using 30% ethyl acetate in hexane to afford title compound (0.88 g, 33%) as solid. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.8 (bs, 2H), 8.6 (s, 1H), 8.39 (bs, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 7.9-7.85 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.85 (m, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.9-2.85 (m, 2H), 2.67-2.60 (m, 2H), 2.4-2.3 (m, 2H), 2.0 (m, 2H), 1.7-1.6 (m, 3H), 1.4-1.2 (m, 8H).

Compound **216B** (0.88g) was racemic mixture with 1:1 enantiomeric ratio and was separated in chiral column to obtain single enantiomers of **216B1** (Rt 11.1 min) and **216B2** (Rt 15.1 min) using following conditions:

Column: Chiralpak IA (4.6X250mm) 5μ
Mobile Phase D= n-Hexane (0.1%TFA) B= IPA; Isocratic: D: B = 80:20; Flow Rate: 1.0 mL/min

2-(6-(5-(3-cyclohexylureido)pyrazin-2-yl)-1-oxo-2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (216):

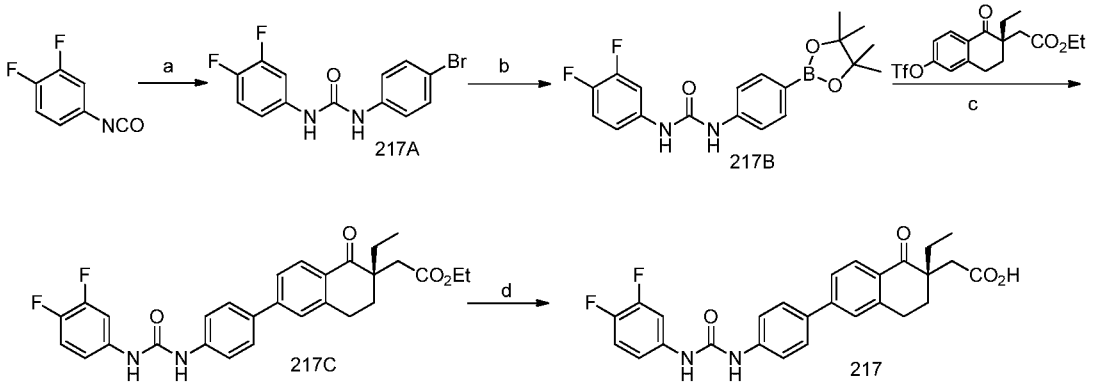


216

Chiral: enantiomer-1

LiOH (40.5 mg, 1.69 mmol) was added to a solution of Example 216B1 (300 mg, 0.563 mmol) in 7 mL of 1,4-dioxane-H_2O (3:1) mixture, and the reaction mixture was stirred at room temperature for 12 hr. After the solvent was removed in vacuum, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of saturated citric acid solution until pH 2 was attained. The resulting solution was cooled to 0 °C, solids were collected by filtration and dried under vacuum to afford title compound (0.220 g, 77%) as white solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.56 (bs, 1H), 9.04 (s, 1H), 8.9 (s, 1H), 8.06-7.95 (m, 3H), 7.4 (d, J = 7.2 Hz, 1H), 3.56 (m, 1H), 3.16-2.69 (m, 5H), 2.5-2.37 (m, 2H), 2.13 (m, 1H), 1.8 (m, 2H), 1.65-1.5 (m, 3H), 1.39-1.2 (m, 5H); LCMS m/z = 505 $(M+H)^+$; HPLC PURITY = 97.8%.

Example-217



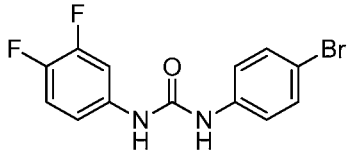
217A 217B 217C 217

Reagents and conditions: a) 4-bromo aniline, THF, RT, 12h ; b) $PdCl_2$(dppf), bis-pinacolato diborane, KOAc, DMF, 85 °C, 6h; c) $Pd(PPh_3)_4$, Cs_2CO_3, Dioxane-H_2O, 80 °C, 12h; d) LiOH, Dioxane-H_2O, RT, 12h.

Procedures:

(S)-2-(6-(4-(3-(3,4-Difluorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid:

1-(4-bromophenyl)-3-(3,4-difluorophenyl)urea (217A):

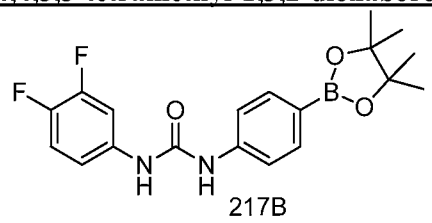


217A

3,4-Difluorophenyl isocyanate (0.74 g, 4.8 mmol) was added to a solution of 4-bromo aniline (0.75 g, 4.36 mmol) in THF (20 mL) and stirred at room temperature for 2 hr. The solvent was removed under reduced pressure and the residue was triturated with chloroform (60 mL) to afford title

compound (0.6 g, 42%) as solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.9 (s, 1H), 8.87 (s, 1H), 7.64 (m, 1H), 7.47-7.41 (m, 4H), 7.39 (m, 1H), 7.2 (m, 1H).

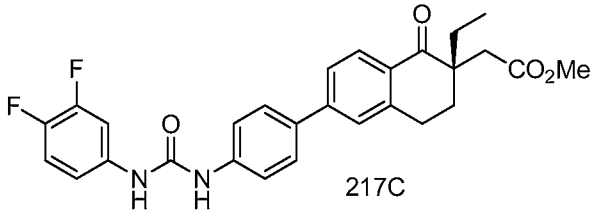
1-(3,4-difluorophenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (217B):



217B

$PdCl_2(dppf)CH_2Cl_2$ (0.125 g, 0.153 mmol) was added to a solution of Example 217A (1.0 g, 3.06 mmol) in 15 mL of DMF, followed by potassium acetate (0.6 g, 6.11 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.932 g, 3.67 mmol), and the solution was degassed for 30 min using argon. The reaction mixture was stirred at 85 °C for 6 h and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash chromatography using 15% ethyl acetate in DCM to afford title compound (0.6 g, 52%) as solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ8.9 (m, 2H), 7.7 (m, 1H), 7.63-7.59 (m, 2H), 7.5-7.42 (m, 2H), 7.4-7.3 (m, 1H), 7.1 (m, 1H), 1.3 (s, 12H). ESI-MS *m/z* = 375 $(M+H)^+$.

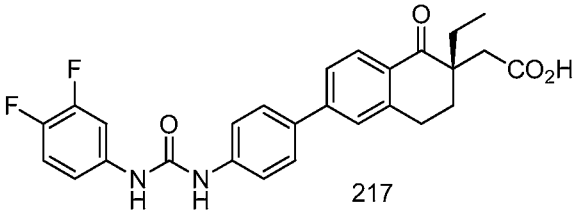
(S)-Methyl 2-(6-(4-(3-(3,4-difluorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (217C):



217C

$Pd(PPh_3)_4$ (0.018 g, 0.015 mmol) was added to a solution of (*S*)-ethyl 2-(2-ethyl-1-oxo-6-(trifluoromethylsulfonyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl)acetate (129C, 0.3 g, 0.761 mmol) in 10 mL 1,4 dioxane-H_2O (4:1) mixture under argon atmosphere, followed by cesium carbonate (0.74 g, 2.28 mmol) and Example 217B (0.313 g, 0.837 mmol). The reaction mixture was degassed for 30 min. The reaction mixture was refluxed for 12 h, and solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash chromatography using 20% ethyl acetate in hexane to afford title compound (0.15 g, 40%) as solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 8.03 (s, 1H), 7.44-7.37 (m, 3H), 7.35-7.31 (m, 4H), 7.18 (m, 1H), 7.08-6.97 (m, 2H), 3.67 (s, 3H), 3.14 (m, 1H), 3.04 (d, *J* = 16 Hz, 1H), 2.90 (m, 1H), 2.5 (d, *J* = 16 Hz, 1H), 2.45 (m, 1H), 2.05 (m, 1H), 1.79-1.6 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H); ESI-MS *m/z* = 493 $(M+H)^+$.

(S)-2-(6-(4-(3-(3,4-Difluorophenyl)ureido)phenyl)-2-ethyl-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetic acid (217):



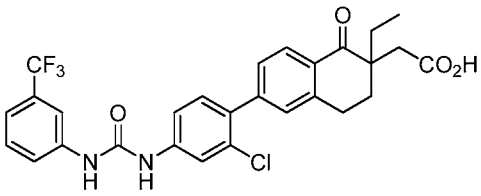
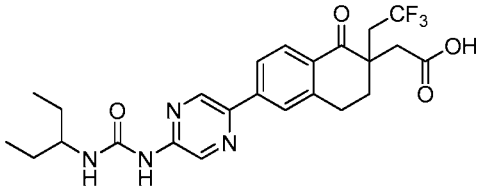
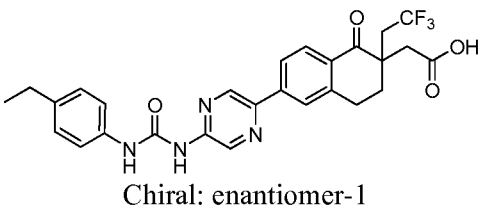
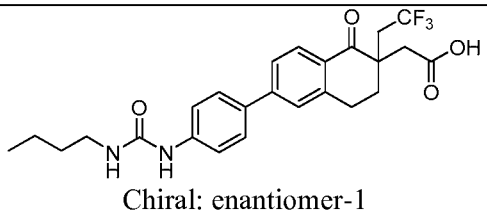
217

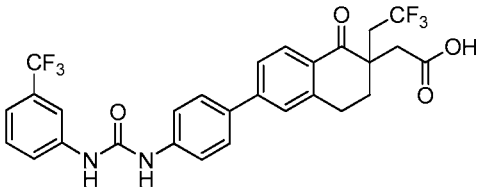
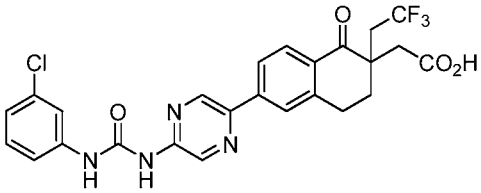
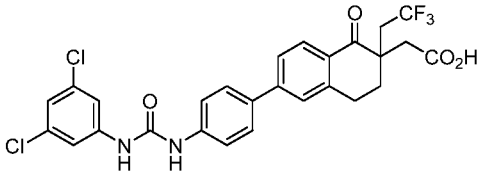
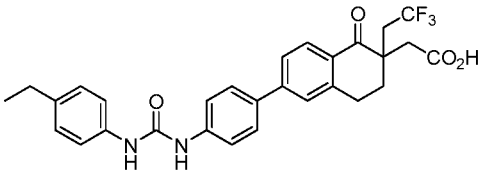
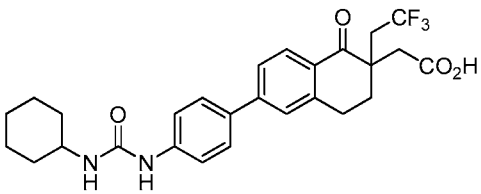
Chiral

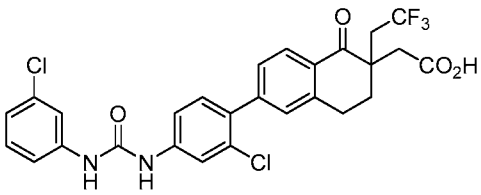
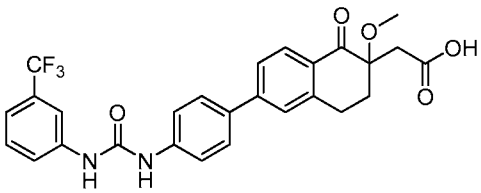
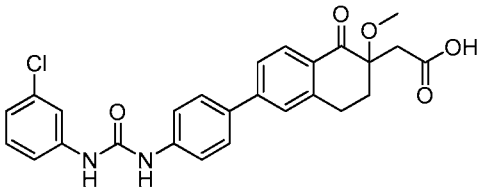
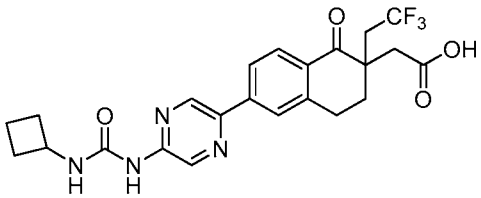
LiOH (17.9 mg, 0.426 mmol) was added to a solution of Example 217C (70 mg, 0.142 mmol) in 5 mL of 1,4-dioxane-H_2O (4:1) mixture, and the reaction mixture was stirred at room temperature

for 12 hr. After the solvent was removed in vacuum, the residue was dissolved in water and washed with ethyl acetate. The aqueous layer was acidified with addition of saturated citric acid solution until pH 2 was attained. The resulting solution was cooled to 0 ^{0}C, and solids were collected by filtration and dried under vacuum to afford title compound (0.035 g, 51%) as pale yellow solid. ^{1}H NMR (400MHz, DMSO-d_6): δ 12.05 (bs, 1H), 8.95 (s, 1H), 8.9 (s, 1H), 7.92 (d, J = 8 Hz, 1H), 7.7-7.65 (m, 3H), 7.63-7.56 (m, 4H), 7.35 (q, J = 8 Hz, 1H), 7.15 (m, 1H), 3.07 (m, 1H), 2.96 (m, 1H), 2.8 (d, J = 16.8 Hz, 1H), 2.44 (m, 1H), 2.4 (d, J = 16 Hz, 1H), 1.9 (m, 1H), 1.68 (m, 1H), 1.54 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); LCMS m/z = 479 $(M+H)^+$; PURITY = 95%.

Examples 218 - 230 were prepared by procedures analogous to those described in Examples 190, and 212-217 using appropriate starting materials. The requisite boronic acids (and appropriately functional-group-protected versions thereof) utilized herein were purchased if available commercially, were synthesized as described in the literature or by routine modifications thereof known by those skilled in the art, or were synthesized by alternative procedures known by those skilled in the art.

Exp	Structure	Analytical Data	$(M+H)^+$
218	 Chiral: enantiomer-1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.23 (s, 1H), 9.18 (s, 1H), 8.02 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.63-7.58 (m, 1H), 7.56-7.51 (m, 1H), 7.46-7.32 (m, 5H), 3.14-3.04 (m, 1H), 2.97-2.89 (m, 1H), 2.84-2.77 (m, 1H), 2.48-2.36 (m, 2H), 2.02-1.96 (m, 1H), 1.74-1.62 (m, 1H), 1.58-1.50 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H).	ESI-MS m/z: 545 $(M+H)^+$; HPLC purity: 99%.
219	 Chiral: enantiomer-1	^{1}H NMR (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.52 (bs, 1H), 9.04 (s, 1H), 8.92 (s, 1H), 8.04-7.95 (m, 3H), 7.23 (d, J = 8.4 Hz, 1H), 3.55 (m, 1H), 3.15-2.96 (m, 3H), 2.75 (m, 2H), 2.50-2.40 (m, 2H), 2.15 (m, 1H), 1.6-1.35 (m, 4H), 0.9 (t, J = 7.6 Hz, 6H).	ESI-MS m/z: 493 $(M+H)^+$; HPLC purity: 99%.
220	 Chiral: enantiomer-1	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.9 (bs , 1H), 9.7 (bs, 1H), 9.18 (d, J = 1.5 Hz, 1H), 8.99 (d, J = 1.2 Hz, 1H), 8.07-7.97 (m, 3H) 7.43 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.2-2.7 (m, 6H), 2.6-2.50 (m, 2H), 2.46 (m, 1H), 2.18 (m, 1H), 1.15 (t, J = 7.5 Hz, 3H).	ESI-MS m/z: 525 $(M-H)^-$; HPLC purity: 98%.
221	 Chiral: enantiomer-1	^{1}H NMR (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 8.85 (bs, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.66-7.58 (m, 4H), 7.5 (d, J = 8.8 Hz, 2H), 6.44 (bs, 1H), 3.12–2.9 (m, 5H), 2.85-2.65	ESI-MS m/z: 477 $(M+H)^+$; HPLC purity: 95%.

		(m, 2H), 2.5-2.4 (m, 2H), 2.12 (m, 1H), 1.45 -1.25 (m, 4H), 0.9 (t, J = 7.2 Hz, 3H).	
222	 Chiral: enantiomer-1	^{1}HNMR (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.22 (bs, 1H), 9.1 (bs, 1H), 8.03 (s, 1H) ,7.93 (d, J = 7.6 Hz, 1H), 7.72-7.58 (m, 7H), 7.53 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 3.2-2.65 (m, 5H), 2.6-2.44 (m, 2H), 2.18 (m, 1H).	ESI-MS m/z: 565 $(M+H)^+$; HPLC purity: 98%.
223	 Chiral: enantiomer-1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.87 (s, 1H), 9.83 (s, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.12-7.96 (m, 3H), 7.77 (s, 1H), 7.36 (d, J = 4.8 Hz, 2H), 7.1 (m, 1H), 3.24-2.92 (m, 3H), 2.83 (d, J = 16.4 Hz, 1H), 2.8-2.65 (m, 1H), 2.57 (d, J = 16.0 Hz, 1H), 2.50-2.42 (m, 1H), 2.24-2.15 (m, 1H).	ESI-MS m/z: 531 $(M-H)^-$; HPLC purity: 99%
224	 Chiral: enantiomer-1	^{1}H NMR (300 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.32 (bs, 1H), 9.26 (bs, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.75-7.5 (m, 8H), 7.16 (s, 1H), 3.20-2.90 (m, 3H), 2.85-2.64 (m, 2H), 2.6-2.4 (m, 2H), 2.19-2.08 (m, 1H).	ESI-MS m/z: 565 $(M+H)^+$; HPLC purity: 99%.
225	 Chiral: enantiomer-1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.3 (bs, 1H), 8.85 (s, 1H), 8.65 (s, 1H), 7.93 (d, J = 8 Hz, 1H), 7.71-7.57 (m, 6H), 7.37 (d, J = 8 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 3.2-2.92 (m, 3H), 2.84-2.65 (m, 2H), 2.60-2.40 (m, 4H), 2.21-2.10 (m, 1H), 1.16 (t, J = 7.2 Hz, 3H).	ESI-MS m/z: 525 $(M+H)^+$; HPLC purity: 99%.
226	 Chiral: enantiomer-1	^{1}H NMR (400 MHz, DMSO–d_6): δ 12.4 (bs, 1H), 8.5 (bs, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.63 (m, 4H), 7.49 (d, J = 8.4 Hz, 2H), 6.14 (d, J = 7.2 Hz, 1H), 3.46 (m, 1H), 3.15-2.9 (m, 3H), 2.85-2.6 (m, 2H), 2.55-2.40 (m, 2H), 2.17-2.10 (m, 1H), 1.88-1.60 (m, 4H), 1.53 (m, 1H), 1.40-1.12 (m, 5H).	ESI-MS m/z: 503 $(M+H)^+$; HPLC purity: 99%.

227	 Chiral: enantiomer-1	^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (bs , 1H), 9.12 (bs, 1H), 9.05 (bs, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.46-7.37 (m, 4H), 7.34-7.30 (m, 2H), 7.05 (m, 1H), 3.2-2.9 (m, 3H), 2.85 (d, J = 16 Hz, 1H), 2.76-2.66 (m, 1H), 2.59 (d, J = 16 Hz, 1H), 2.50-2.44 (m, 1H), 2.17 (m, 1H).	ESI-MS m/z: 565 $(M+H)^+$; HPLC purity: 99%.
228	 Chiral: enantiomer-1	1H NMR (300MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.13 (s, 1H), 9.01 (s, 1H), 8.03 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.75-7.48 (m, 8H), 7.32 (d, J = 7.8 Hz, 1H), 3.28-3.15 (m, 1H), 3.13 (s, 3H), 2.90 (d, J = 15.6 Hz, 2H), 2.72 (d, J = 15.3 Hz, 1H), 2.42-2.38 (m, 2H).	ESI-MS m/z: 512 $(M+H)^+$; HPLC purity: 98%.
229	 Chiral: enantiomer-1	1H NMR (400MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.95 (s, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.73-7.56 (m, 7H), 7.32-7.28 (m, 2H), 7.05-7.01 (m , 1H), 3.28-3.15 (m, 1H), 3.13 (s, 3H), 2.94-2.86 (m, 2H), 2.71 (d, J = 16 Hz, 1H), 2.48-2.38 (m, 2H).	ESI-MS m/z: 479 $(M+H)^+$; HPLC purity: 99%.
230	 Chiral: enantiomer-1	^{1}H NMR (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.51 (bs, 1H), 9.04 (d, J = 1.6 Hz, 1H), 8.92 (d, J = 1.2 Hz, 1H), 8.05-7.95 (m, 3H), 7.23 (d, J = 7.6 Hz, 1H), 4.19 (m, 1H), 3.18-2.90 (m, 3H), 2.85-2.6 (m, 2H), 2.50-2.40 (m, 2H), 2.3-2.1 (m, 3H), 1.9 (m, 2H), 1.65 (m, 2H).	ESI-MS m/z: 477 $(M+H)^+$; LCMS purity: 98%.

Biological Assay

Inhibition of human DGAT1 activity in vitro

Human DGAT1 was expressed in Sf9 insect cells using a baculovirus expression system. Microsomes were prepared and used as enzyme for in vitro inhibition testing in either of two formats measuring production of coenzyme A or tridecanoylglycerol product, respectively. All

steps were performed at 21-23°C. All data for DGAT1 inhibition by test compounds were collected under conditions where product formation was linear with reaction time.

For inhibition of CoA product formation, test compounds were prepared in 100% DMSO, diluted 100-fold into assay buffer, and 10 uL added to 96-well half-area plates (Greiner 675076). An equal volume (10 uL) of 3X enzyme in buffer was added and the components incubated for 30 minutes pre-reaction incubation to allow enzyme and test compounds to attain binding equilibrium. The 3X enzyme mixture contained 30 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid for fully inhibited control wells. Some assays were performed with inclusion of didecanoylglycerol in the pre-reaction incubation of test compound and enzyme. DGAT reactions (30 uL) were initiated upon addition of 10 uL of 3X substrate solution. Final reaction conditions consisted of 20 mM HEPES pH 7.5, 2 mM $MgCl_2$, 1 mM CHAPS, 50 uM didecanoylglycerol, 3 uM decanoyl-CoA, 1 ug/mL microsomal protein, and 1% DMSO. Following a 60 minute reaction incubation, reactions were stopped and CoA product derivatized with 30 uL of buffer containing 10 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid and 50 uM 7-diethylamino-3-(4'-maleimidylphenyl)-4-methylcoumarin (CPM). Fluorescence was read using Envision reader at Ex 405 nm/Em 480 nm about 30 minutes after addition of final solution. Inhibition was normalized to controls containing DMSO or 10 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid. IC_{50}s were fitted using GraphPad Prism to a sigmoidal dose response.

For inhibition of triacylglycerol product formation, 11 uL reactions were run in white Polyplate-384 (PerkinElmer6007300) starting with a 30 minute pre-reaction incubation of 5 uL of 2.2X enzyme and 1 uL of 100% DMSO containing test compound or control compound, {4-[4-(4-amino-7,7-dimethyl-7*H*-pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid. Some assays were performed with inclusion of didecanoylglycerol in the pre-reaction incubation of test compounds and enzyme. Reactions were initiated after 30 minute pre-reaction incubation via addition of 5 uL of 2.2X substrate. Final reaction conditions consisted of 50 mM HEPES pH 7.5, 2 mM $MgCl_2$, 1 mM CHAPS, 25 uM didecanoylglycerol, 0.5 uM decanoyl-CoA, 0.3 nCi/uL [^{14}C]-decanoyl-CoA or 0.5 nCi/uL [^{3}H]-decanoyl-CoA, 0.05-4 ug/mL microsomal protein, and 1% DMSO. Following 60 minute reaction incubation, reactions were stopped with 40 uL of 45% isopropanol and 50 mM sodium carbonate in water and mixed. Extraction of tridecanoylglycerol product was accomplished via addition of 30 uL Microscint-E (Perkin Elmer) and 2 hours of incubation (sealed). Plates were read on a Microbeta Microplate reader. Inhibition was normalized to controls containing DMSO or 10 uM {4-[4-(4-amino-7,7-dimethyl-7*H*-

pyrimido[4,5-*b*][1,4]oxazin-6-yl)phenyl]cyclohexyl}acetic acid. IC_{50}s were fitted using GraphPad Prism to a sigmoidal dose response.

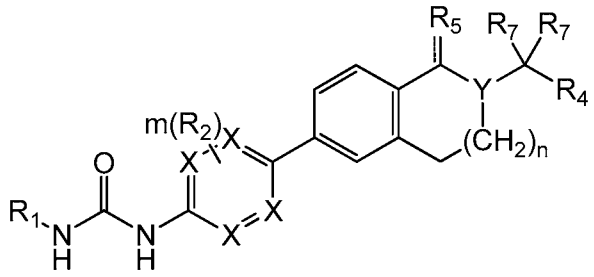
Biological Data

Exemplified compounds of the present invention were tested at one or more DGAT assays described above and were found to be inhibitors of DGAT1 with IC_{50} < 10 uM or % inhibition >50 at 10 uM. Data for some specific examples tested at the human DGAT1 fluorescene (CPM) assay are listed below.

Example #	hDGAT IC_{50} (nM)	Example #	hDGAT IC_{50} (nM)	Example #	hDGAT IC_{50} (nM)
1	1880.0	143	11.2	219	5955.0
20	586.0	144	5.8	220	0.3
40	357.0	154	47.8	223	0.7
42	60.0	164	4.5	224	2.8
47	180.5	173	10.8	225	1.2
68	503.0	182	48.0	226	6.1
69	113.6	185	32.0	228	6.9
76	112.0	190	67.6	229	5.2
79	35.4	192	10.6	230	27.5
81	18.8	197	2.3		
90	12.0	198	55.0		
109	14.2	201	2.6		
115	2.9	202	6.5		
116	18	205	3.5		
129	3.1	212	32.8		
130	138.3	213	5.9		
131	2.5	214	0.6		
139	10.8	215	1.8		
140	31.8	216	2.7		
141	9.4	218	7.4		

Claims:

1. A compound of Formula (I):



(I)

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl and heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

R_5 is hydrogen, hydroxyl, or oxo;

each R_7 is independently H or C_1-C_3alkyl;

each X is independently C or N, provided that at least two X's are C;

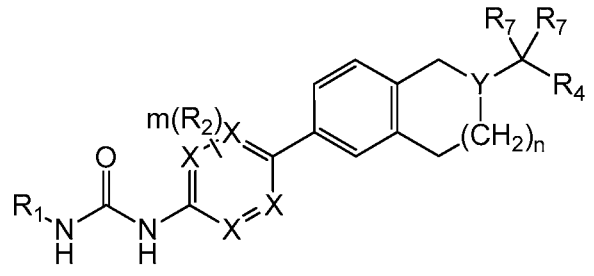
Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

n is 0-1, provided that when n is 0, Y is CR_3;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, which is represented by Formula (I)(A)



(I)(A);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

each R_7 is independently H or C_1-C_3alkyl;

each X is independently C or N, provided that at least two X's are C;

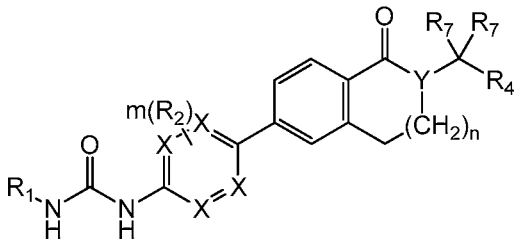
Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

n is 0-1, provided that when n is 0, Y is CR_3;

or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1, which is represented by Formula (I)(B),



(I)(B);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

each R_7 is independently H or C_1-C_3alkyl;

each X is independently C or N, provided that at least two X's are C;

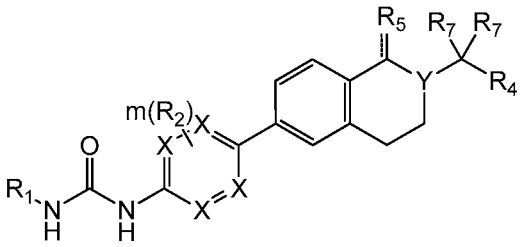
Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

n is 0-1, provided that when n is 0, Y is CR_3;

or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1, which is represented by Formula (I)(C):



(I)(C);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

R_5 is hydrogen, hydroxyl, or oxo;

each R_7 is independently H or C_1-C_3alkyl;

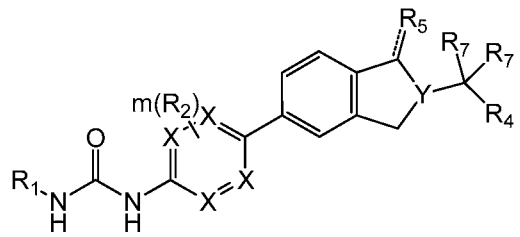
each X is independently C or N, provided that at least two X's are C;

Y is N or CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

or a pharmaceutically acceptable salt thereof.

5. A compound of claim 1, which is represented by Formula (I)(D):



(I)(D);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

R_5 is hydrogen, hydroxyl, or oxo;

each R_7 is independently H or C_1-C_3alkyl;

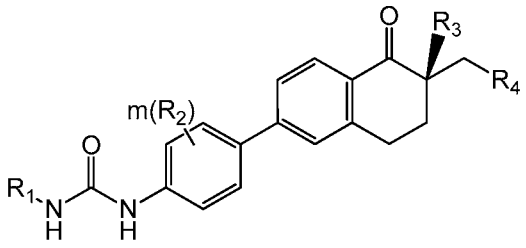
each X is independently C or N, provided that at least two X's are C;

Y is CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

or a pharmaceutically acceptable salt thereof.

6. A compound of claim 1, which is reprented by Formula (I)(F):



(I)(F);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

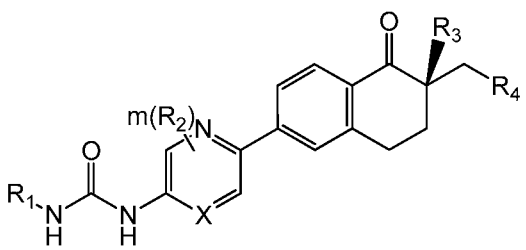
R_4 is CH_2COOH, COOH, ester, or amide;

R_3 is C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-3;

or a pharmaceutically acceptable salt thereof.

7. A compound of claim 1, which is represented by Formula (I)(H):



(I)(H);

wherein R_1 is C_1-C_6alkyl, C_3-C_7cycloalkyl, aryl or heteroaryl, wherein said aryl or heteroaryl may be substituted with one to three groups selected from the group consisting of acyl, C_1-C_6alkyl, alkylsulfonyl, alkoxy, alkoxycarbonyl, cyano, halo, urea, amide, hydroxyl, SF_5, oxo, and nitro;

R_2 is selected from the group consisting of H, C_1-C_6alkyl, alkoxy, cyano, halo, urea, amide, hydroxyl, oxo, and nitro;

R_4 is CH_2COOH, COOH, ester, or amide;

X is independently C or N;

R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, wherein said C_1-C_6alkyl may be further substituted with one to three groups selected from halo, hydroxyl, alkoxy, COOH, and ester;

m is 0-2;

or a pharmaceutically acceptable salt thereof.

8. A compound of claim 1, wherein R_5 is hydroxyl, or a pharmaceutically acceptable salt thereof.

9. A compound of any one of claims 1-5 and7, wherein X's are C, or a pharmaceutically acceptable salt thereof.

10. A compound of any one of claims 1-7, wherein R_1 is phenyl which may be substituted with one to three groups selected from the group consisting of methyl, ethyl, OCF_3, -OCF_2H, trifluoromethyl, methoxy, ethoxy, cyano, Cl, or F, or a pharmaceutically acceptable salt thereof.

11. A compound of any one of claims 1-7, wherein R_1 is C_1-C_6alkyl, or a pharmaceutically acceptable salt thereof.

12. A compound of any one of claims 1-7, wherein R_2 is C_1-C_3alkyl, F, Cl, or CN, or a pharmaceutically acceptable salt thereof.

13. A compound of any one of claims 1-5 wherein Y is CR_3, wherein R_3 is H, C_1-C_6alkyl, hydroxyl, halo, or alkoxy, or a pharmaceutically acceptable salt thereof.

14. A compound of any one of claims 1-5, wherein Y is CR_3, wherein R_3 is methyl, CH_2CF_3, CH_2OCH_3 or ethyl; or a pharmaceutically acceptable salt thereof.

15. A compound of any one of claims 1-5, wherein Y is N, or a pharmaceutically acceptable salt thereof.

16. A compound of any one of claims 1-7, wherein m is 0.

17. A compound of any one of claims 1-7, wherein R_4 is $-CH_2COOH$ or COOH, or a pharmaceutically acceptable salt thereof.

18. A method of treating obesity comprising administering to a human in need thereof an effective amount of a compound according to any one of the above claims.

19. A pharmaceutical composition comprising a compound according to any one of claims 1-17, and a pharmaceutically acceptable carrier.

20. The compound according to any one of claims 1-17.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038520

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/17 (2012.01)
USPC - 514/598
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)
IPC(8) - A61K 31/17, 4418, 444, 472, 4725, 4965, 497 (2012.01)
USPC - 514/255.05, 255.06, 307, 309, 352, 353, 596, 598

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 practicable, search terms used)
PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CURTIN et al. Isoindolinone ureas: a novel class of KDR kinase inhibitors. Bioorganic & Medicinal Chemistry Letters 14 (2004). Pgs. 4505–4509. entire document	1-17
A	US 2007/0249620 A1 (KURATA et al) 25 October 2007 (25.10.2007) entire document	1-17
A	US 2010/0041590 A1 (BOUILLOT) 18 February 2010 (18.02.2010) entire document	1-17
A, P	US 2011/0245247 A1 (BRAJE et al) 06 October 2011 (06.10.2011) entire document	1-17
A, P	WO 2011/080718 A1 (JADHAV et al) 07 July 2011 (07.07.2011) entire document This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
27 July 2012	26 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038520

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.: 18-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

2. ☐ As all searchable claims could be searched without effort justifying 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.:

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.

COMPUESTOS NOVEDOSOS COMO INHIBIDORES DE DIACILGLICEROL ACILTRANSFERASA

CAMPO DE LA INVENCIÓN

Esta invención se refiere a compuestos novedosos que son inhibidores de acil coenzima A : diacilglicerol aciltransferasa 1 (DGAT-1), a composiciones farmacéuticas que los contienen, a procedimientos para su preparación, y a su uso en terapia para la prevención o tratamiento de enfermedades relacionadas con disfunción de DGAT-1, o en donde la modulación de la actividad de DGAT-1 puede tener un beneficio terapéutico, que incluyen, sin limitación, obesidad, trastornos relacionados con la obesidad, hipertrigliceridemia, hiperlipoproteinemia, quilomicronemia, dislipidemia, esteatohepatitis no alcohólica, diabetes, resistencia a la insulina, síndrome metabólico, infección por virus de hepatitis C y acné u otros trastornos de la piel.

ANTECEDENTES DE LA INVENCIÓN

La obesidad es una enfermedad que está alcanzando proporciones epidémicas entre los humanos en varios países de todo el mundo. Es una afección que también está asociada con, o induce, otras enfermedades o afecciones que interrumpen las actividades de la vida y los

estilos de vida. La obesidad es reconocida como un factor de riesgo serio para otras enfermedades y afecciones como diabetes, hipertensión y arteriosclerosis. También se sabe que el aumento de peso corporal debido a la obesidad puede poner una carga sobre las articulaciones, como las articulaciones de la rodilla, causando artritis, dolor y rigidez.

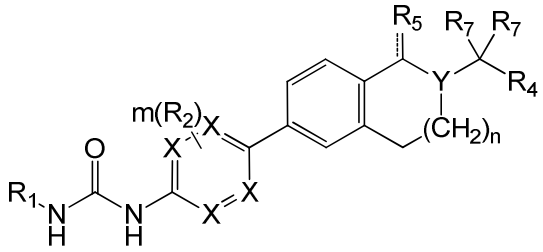
Como la sobrealimentación y la obesidad se han convertido en un problema en la población general, ahora muchos individuos están interesados en perder peso, reducir su peso y mantener un peso corporal sano y un estilo de vida conveniente. Una propuesta para tratar la obesidad es reducir la ingestión de alimento y/o la hiperlipidemia. Se ha sugerido que las moléculas que se desarrollan para prevenir la acumulación de triglicéridos no solo reducen la obesidad, sino que también tienen el efecto beneficioso adicional de reducir la resistencia a la insulina, un factor primario que contribuye al desarrollo de la diabetes.

La acil coenzima A : diacilglicerol aciltransferasa 1 (DGAT-1) es una de dos enzimas DGAT conocidas que cataliza el paso final de la síntesis de triglicérido en los mamíferos. La DGAT-1 es una enzima que está implicada en el desarrollo tanto de diabetes como de resistencia a la insulina. Los estudios de ratones deficientes en DGAT-1 muestran que la deficiencia en DGAT-1 protege contra la resistencia a la insulina y la obesidad; véase Chen, H.C. *et al., J Clin Invest*., 109(8), 1049-1055 (2002). Por lo tanto los inhibidores de DGAT-1 serían útiles para el tratamiento de trastornos metabólicos, por ejemplo, la obesidad, diabetes de tipo 2y síndrome de

resistencia a la insulina (o síndrome metabólico),y otras enfermedades y afecciones asociadas o relacionadas.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

Esta invención se refiere a los compuestos de fórmula (I):



(I)

en donde:

R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dichos arilo y heteroarilo pueden estar sustituidos con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

R_5 es hidrógeno, hidroxilo, u oxo;

cada R_7 es independientemente H o alquilo de C_1-C_3;

cada X es independientemente C o N, siempre que por lo menos

dos X sean C;

Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH, y éster;

m es 0-3;

n es 0-1, con la condición de que cuando n es 0, Y es CR_3;

o una sal farmacéuticamente aceptable de los mismos.

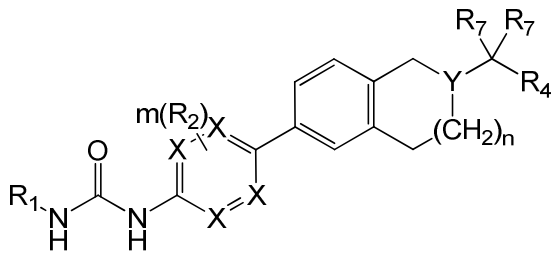
Esta invención también se refiere a una composición farmacéutica que comprende un compuesto de fórmula (I) y un vehículo farmacéuticamente aceptable.

Esta invención también se refiere a un método de tratamiento de la obesidad, que comprende administrar a un humano en necesidad del mismo una cantidad eficaz de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo en una composición farmacéutica.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Esta invención se refiere a los compuestos de la fórmula (I) que se define arriba.

Esta invención también se refiere a los compuestos de fórmula (I)(A):



(I)(A)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

cada R_7 es independientemente H o alquilo de C_1-C_3;

cada X es independientemente C o N, siempre que por lo menos dos X sean C;

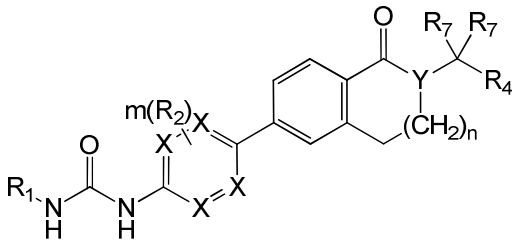
Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-3;

n es 0-1, con la condición de que cuando n es 0, Y es CR_3;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I)(B):



(I)(B)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

cada R_7 es independientemente H o alquilo de C_1-C_3;

cada X es independientemente C o N, siempre que por lo menos dos X sean C;

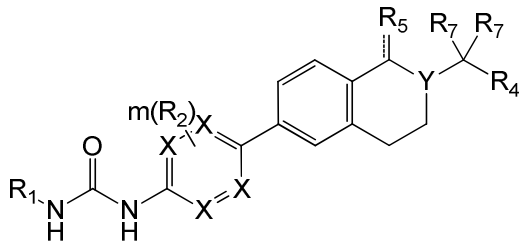
Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionado de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-3;

n es 0-1, con la condición de que cuando n es 0, Y es CR_3;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I)(C):



(I)(C)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

R_5 es hidrógeno, hidroxilo, u oxo;

cada R_7 es independientemente H o alquilo de C_1-C_3;

cada X es independientemente C o N, siempre que por lo menos dos X sean C;

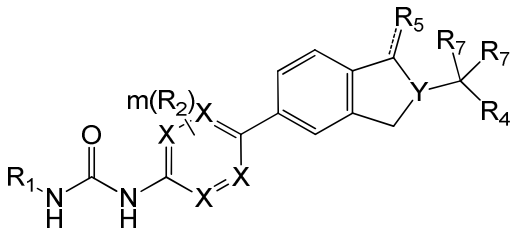
Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo,

halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-3;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I)(D):



(I)(D)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

R_5 es hidrógeno, hidroxilo, u oxo;

cada R_7 es independientemente H o alquilo de C_1-C_3;

cada X es independientemente C o N, siempre que por lo menos

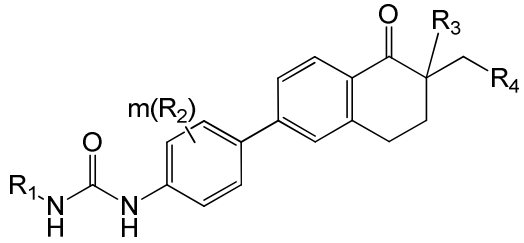
dos X sean C;

Y es CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-3;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I)(E):



(I)(E)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

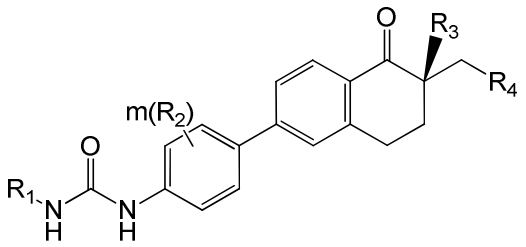
R_3 es alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde

dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-3;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I)(F):



(I)(F)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

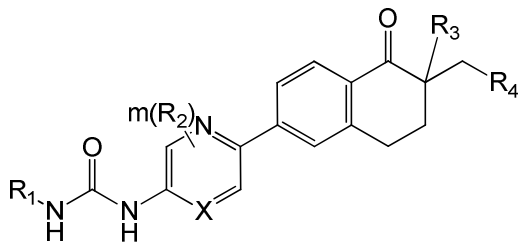
R_4 es CH_2COOH, COOH, éster, o amida;

R_3 es alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-3;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I)(G):



(I)(G)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

X es independientemente C o N;

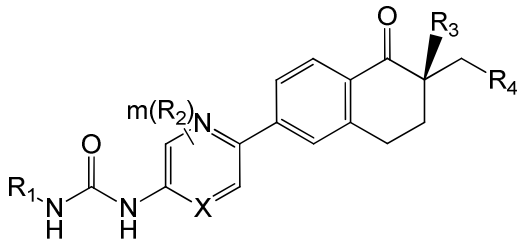
R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionado de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-2;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula

(I)(H):



(I)(H)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro;

R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro;

R_4 es CH_2COOH, COOH, éster, o amida;

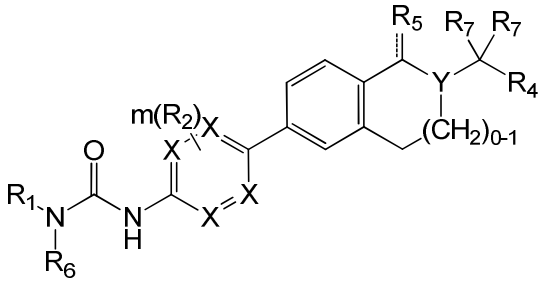
X es independientemente C o N;

R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionado de halógeno, hidroxilo, alcoxi, COOH y éster;

m es 0-2;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención se refiere a los compuestos de fórmula (I)(K):



(I)(K)

en donde R_1 es cicloalquilo de C_3-C_7, arilo o heteroarilo, que puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en: acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro,

y R_6 es H o alquilo de C_1-C_3,

o R_1 y R_6, junto con el N al que están unidos, forman un anillo mono- o bicíclico que puede contener 0-3 heteroátomos y puede estar sustituido con uno a tres halógenos, alquilos de C_1-C_3, o alcoxi,

R_2 se selecciona del grupo que consiste en: H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro,

R_4 es CH_2COOH, COOH, éster, o amida,

R_5 es hidrógeno, hidroxilo, u oxo,

cada R_7 es independientemente H o alquilo de C_1-C_3,

cada X es independientemente C o N, siempre que por lo menos dos X sean C,

Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo,

halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de: halógeno, hidroxilo, alcoxi, ácido carboxílico y éster,

m es 0-3;

o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), en donde R_5 es hidroxilo, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(G) o (I)(H),en donde los X son C, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C) o (I)(D), en donde X es independientemente C o N, y dos X son N, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(E), (I)(F), (I)(G) o (I)(H), en donde R_1 es fenilo que puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en metilo, etilo, OCF_3, -OCF_2H, trifluorometilo, metoxi, etoxi, ciano, Cl o F, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G) o (I)(H), en donde R_1 es alquilo de C_1-C_6, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula

(I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(E), (I)(F), (I)(G) o (I)(H), en donde R_2 es alquilo de C_1-C_3, F, Cl, o CN, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), o (I)(F), (I)(G) o (I)(H), en donde Y es CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C) o (I)(D), en donde Y es CR_3, en donde R_3 es metilo, CH_2CF_3, CH_2OCH_3 o etilo, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C) o (I)(D), en donde Y es N, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(E), (I)(F), (I)(G) o (I)(H), en donde m es 0.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(E), (I)(F), (I)(G) o (I)(H), en donde R_4 es CH_2COOH o COOH, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C) o (I)(D), en donde Y es CR_3, en donde R_3 es H, metilo, etilo, propilo, isopropilo, hidroxilo, halógeno, alcoximetilo, hidroxialquilo o alcoxi, o una sal farmacéuticamente aceptable de los mismos.

Esta invención también se refiere a los compuestos que se ejemplifican en la sección experimental.

Los compuestos específicos de esta invención incluyen:

ácido 2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidroisoquinolin-2-il}acético;

ácido 2-{1-oxo-6-[4-({[4-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidroisoquinolin-2-il}acético;

ácido 2-[6-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidroisoquinolin-2-il]acético;

ácido 2-{1-oxo-6-[4-({[4-(trifluorometoxi)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidroisoquinolin-2-il}acético;

ácido 2-{6-[4-({[3-metil-5-(trifluorometil)fenil]carbamoil}-amino)fenil]-1-oxo-1,2,3,4-tetrahidroisoquinolin-2-il}acético;

ácido 3-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidroisoquinolin-2-il}propanoico;

ácido 3-{1-oxo-6-[4-({[4-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidroisoquinolin-2-il}propanoico;

ácido 3-[6-(4-{[(2-metoxi-5-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidroisoquinolin-2-il]propanoico;

ácido 2-{[6-(4-{[(2-metoxi-5-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidroisoquinolin-2-il]metil}pentanodioico;

ácido 2-(6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{6-[2-({[3-(trifluorometil)fenil]carbamoil}amino)pirimidin-5-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(2-{[(3-metilfenil)carbamoil]amino}pirimidin-5-il)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[4-({[3-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[4-({[3,5-bis(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-fluorofenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(4-fluorofenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-cianofenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-nitrofenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[4-({[2-(trifluorometoxi)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[4-({[4-fluoro-3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[4-({[3-(trifluorometoxi)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[4-({[3-(pentafluoro-λ⁶-sulfanil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[4-({[2-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(2-metoxi-5-metilfenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[4-({[4-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(4-metilfenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-metoxifenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[4-({[3-(difluorometoxi)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido rel-2-[(2R)-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 1);

ácido rel-2-[(2R)-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 2);

ácido 2-{6-[3-fluoro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[3-fluoro-4-({[4-fluoro-3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(3-fluoro-4-{[(3-metilfenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3,5-dimetilfenil)carbamoil]amino}fenil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[5-({[3-(trifluorometil)fenil]carbamoil}amino)piridin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[5-({[3-(trifluorometil)fenil]carbamoil}amino)pirazin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(5-{[(3-clorofenil)carbamoil]amino}pirazin-2-il)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{2-hidroxi-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{2-hidroxi-6-[4-({[4-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{2-etil-1-oxo-5-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2,3-dihidro-1H-inden-2-il}acético;

ácido 2-{1-oxo-5-[4-({[3-(trifluorometil)fenil]carbamoil}amino)fenil]-2,3-dihidro-1H-inden-2-il}acético;

ácido 2-{1-oxo-5-[4-({[4-(trifluorometil)fenil]carbamoil}amino)fenil]-

2,3-dihidro-1H-inden-2-il}acético;

ácido 2-[5-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-2,3-dihidro-1H-inden-2-il]acético;

ácido 2-[5-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-2,3-dihidro-1H-inden-2-il]acético;

ácido 2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{1-oxo-6-[4-({[4-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{1-oxo-6-[4-({[2-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(2-metoxi-5-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(4-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{1-oxo-6-[4-({[2-(trifluorometoxi)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{6-[3-fluoro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(3-fluoro-4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(6-{3-fluoro-4-[(fenilcarbamoil)amino]fenil}-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(3-fluoro-4-{[(3-fluorofenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-3-fluorofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(3-fluoro-4-{[(3-metoxifenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3,5-dimetilfenil)carbamoil]amino}-3-fluorofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(3-fluoro-4-{[(2-fluoro-5-metilfenil)carbamoil]amino}-fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-cianofenil)carbamoil]amino}-3-fluorofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[2-fluoro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(2-fluoro-4-{[(2-metoxi-5-metilfenil)carbamoil]amino}-fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(6-{2-fluoro-4-[(fenilcarbamoil)amino]fenil}-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{1-oxo-6-[5-({[3-(trifluorometil)fenil]carbamoil}-

amino)pirimidin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{1-hidroxi-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 3-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}propanoico;

ácido 3-(1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)propanoico;

ácido 3-[6-(4-{[(2-metoxi-5-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]propanoico;

ácido 3-[6-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]propanoico;

ácido 3-{6-[3-fluoro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}propanoico;

ácido 3-[6-(3-fluoro-4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]propanoico;

ácido 3-[6-(4-{[(3-clorofenil)carbamoil]amino}-3-fluorofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]propanoico;

ácido 2-metil-2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}propanoico;

ácido 2-metil-2-(1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)propanoico;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]-2-metilpropanoico;

ácido 2-{2-metil-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[2-metil-6-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-metil-1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(4-{[(3-metoxifenil)carbamoil]amino}fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-fluorofenil)carbamoil]amino}fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(2-fluoro-4-{[(3-metilfenil)carbamoil]amino}fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(2-cloro-4-{[(3-clorofenil)carbamoil]amino}fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-2-metil-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 1);

ácido rel-2-[(2R)-2-metil-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 2);

ácido 2-{6-[3-fluoro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-3-fluorofenil)-2-

metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(6-{3-fluoro-4-[(fenilcarbamoil)amino]fenil}-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(3-fluoro-4-{[(3-fluorofenil)carbamoil]amino}fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(3-fluoro-4-{[(3-metoxifenil)carbamoil]amino}fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[3-cloro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-2,5-difluorofenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(6-{2,5-difluoro-4-[(fenilcarbamoil)amino]fenil}-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-2-metilfenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-metil-6-{2-metil-4-[(fenilcarbamoil)amino]fenil}-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[2-metil-6-(2-metil-4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{2-metil-6-[2-metil-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{2-metil-6-[2-metil-4-({[4-(trifluorometil)fenil]carbamoil}-amino)fenil]-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(4-clorofenil)carbamoil]amino}-2-metilfenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[2-fluoro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-2-fluorofenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[2-cloro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-(6-{2-cloro-4-[(fenilcarbamoil)amino]fenil}-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-(6-{2-ciano-4-[(fenilcarbamoil)amino]fenil}-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(5-{[(3-clorofenil)carbamoil]amino}piridin-2-il)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{2-metil-1-oxo-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)piridin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-(2-metil-1-oxo-6-{5-[(fenilcarbamoil)amino]piridin-2-il}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{2-metil-1-oxo-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)pirazin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(5-{[(3-clorofenil)carbamoil]amino}pirazin-2-il)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-metil-1-oxo-6-{5-[(fenilcarbamoil)amino]pirimidin-2-il}-

1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{2-metil-1-oxo-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)pirimidin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{2-etil-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{2-etil-1-oxo-6-[4-({[4-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{2-etil-1-oxo-6-[4-({[2-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-(2-etil-1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(4-{[(3-metoxifenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(6-{4-[(ciclohexilcarbamoil)amino]fenil}-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[2-etil-6-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(4-{[(4-metoxifenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(4-clorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(4-{[(4-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(4-{[(3-fluorofenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3,5-dimetilfenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(4-{[(2-metoxi-5-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[(2S)-2-etil-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[(2R)-2-etil-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(4-{[(4-clorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 1);

ácido rel-2-[(2R)-6-(4-{[(4-clorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 2);

ácido 2-[6-(2-cloro-4-{[(3-metoxifenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(2-cloro-4-{[(4-clorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[2-cloro-4-({[4-(trifluorometil)fenil]carbamoil}-amino)fenil]-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(2-cloro-4-{[(2-metoxi-5-metilfenil)carbamoil]amino}-

fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(2-cloro-4-{[(3,5-dimetilfenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{6-[2-cloro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(2-cloro-4-{[(3-clorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(6-{2-cloro-4-[(fenilcarbamoil)amino]fenil}-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-(2-etil-6-{3-fluoro-4-[(fenilcarbamoil)amino]fenil}-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-(6-{4-[(ciclohexilcarbamoil)amino]-3-fluorofenil}-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{2-etil-6-[3-fluoro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1-oxo-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-3-fluorofenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(3-fluoro-4-{[(3-fluorofenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(4-clorofenil)carbamoil]amino}-3-fluorofenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3,5-dimetilfenil)carbamoil]amino}-3-fluorofenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(3-fluoro-4-{[(2-metoxi-5-metilfenil)carbamoil]-amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{2-etil-1-oxo-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)piridin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(5-{[(3-clorofenil)carbamoil]amino}piridin-2-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-etil-1-oxo-6-{5-[(fenilcarbamoil)amino]piridin-2-il}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(5-{[(3,5-dimetilfenil)carbamoil]amino}piridin-2-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(5-{[(2-metoxi-5-metilfenil)carbamoil]amino}-piridin-2-il)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-etil-1-oxo-6-{5-[(fenilcarbamoil)amino]pirazin-2-il}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{2-etil-1-oxo-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)pirazin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(5-{[(3-clorofenil)carbamoil]amino}pirazin-2-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(5-{[(3,5-dimetilfenil)carbamoil]amino}pirazin-2-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-etil-6-(5-{[(2-metoxi-5-metilfenil)carbamoil]amino}-pirazin-2-il)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{2-etil-1-oxo-6-[6-({[3-(trifluorometil)fenil]carbamoil}-

amino)piridazin-3-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(6-{[(3-clorofenil)carbamoil]amino}piridazin-3-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{2-etil-1-oxo-6-[6-({[3-(trifluorometil)fenil]carbamoil}-amino)piridin-3-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(6-{[(3-clorofenil)carbamoil]amino}piridin-3-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-etil-1-oxo-6-{6-[(fenilcarbamoil)amino]piridin-3-il}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[(2S)-6-(5-{[(3-clorofenil)carbamoil]amino}piridin-2-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[(2R)-6-(5-{[(3-clorofenil)carbamoil]amino}piridin-2-il)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-2-etil-1-oxo-6-[5-({[3-(trifluorometil)fenil]-carbamoil}amino)pirazin-2-il]-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 1);

ácido rel-2-[(2R)-2-etil-1-oxo-6-[5-({[3-(trifluorometil)fenil]-carbamoil}amino)pirazin-2-il]-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 2);

ácido 2-(1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-2-propil-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{1-oxo-2-propil-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-1-oxo-2-propil-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{1-oxo-2-propil-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)piridin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(5-{[(3-clorofenil)carbamoil]amino}piridin-2-il)-1-oxo-2-propil-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(1R,2S)-2-etil-1-hidroxi-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(1R,2S)-2-etil-1-hidroxi-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido (2S)-3-metil-2-(2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acetamido)butanoico;

ácido 2-(2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acetamido)acético;

ácido (2S)-3-metil-2-(2-{6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acetamido)butanoico;

ácido (2S)-3-metil-2-(2-{6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acetamido)pentanoico;

ácido (2S)-2-{2-[6-(3-fluoro-4-{[(3-metilfenil)carbamoil]amino}-fenil)-1,2,3,4-tetrahidronaftalen-2-il]acetamido}-3-metilbutanoico;

ácido (2S)-2-{2-[6-(3-fluoro-4-{[(3-metilfenil)carbamoil]amino}-fenil)-1,2,3,4-tetrahidronaftalen-2-il]acetamido}-3-metilpentanoico;

ácido 2-{2-[6-(3-fluoro-4-{[(3-metilfenil)carbamoil]amino}fenil)-1-

oxo-1,2,3,4-tetrahidronaftalen-2-il]acetamido}acético;

ácido 2-{2-fluoro-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-fluoro-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-fluoro-1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{2-hidroxi-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(2-fluorofenil)carbamoil]amino}fenil)-2-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(4-clorofenil)carbamoil]amino}fenil)-2-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-hidroxi-6-(4-{[(3-metilfenil)carbamoil]amino}fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(2-metoxi-1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-{2-metoxi-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(4-clorofenil)carbamoil]amino}fenil)-2-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(4-{[(4-clorofenil)carbamoil]amino}fenil)-2-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 2);

ácido rel-2-[(2R)-6-(4-{[(4-clorofenil)carbamoil]amino}fenil)-2-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético (enantiómero 1);

ácido 2-[6-(4-{[(3,5-dimetilfenil)carbamoil]amino}fenil)-2-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-(metoximetil)-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-3-fluorofenil)-2-(hidroximetil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-(hidroximetil)-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[2-(hidroximetil)-6-(4-{[(3-metilfenil)carbamoil]amino}-fenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-(1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-(1-hidroxi-6-{4-[(fenilcarbamoil)amino]fenil}-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético;

ácido 2-[6-(4-{[(3,5-dimetilfenil)carbamoil]amino}fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-metoxifenil)carbamoil]amino}fenil)-1-oxo-2-

(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-1-hidroxi-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(2-metoxi-5-metilfenil)carbamoil]amino}fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-{2-etil-1-hidroxi-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)piridin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-{2-etil-1-hidroxi-6-[5-({[3-(trifluorometil)fenil]carbamoil}-amino)pirazin-2-il]-1,2,3,4-tetrahidronaftalen-2-il}acético;

ácido 2-[2-(metoximetil)-1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-(metoximetil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(2-cloro-4-{[(3-clorofenil)carbamoil]amino}-fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(2-cloro-4-{[(3-clorofenil)carbamoil]amino}-fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(5-{[(3,4-difluorofenil)carbamoil]amino}pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-{5-[(ciclohexilcarbamoil)amino]pirazin-2-il}-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido 2-[(2S)-6-(4-{[(3,4-difluorofenil)carbamoil]amino}fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-[2-cloro-4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-1-oxo-6-(5-{[(pentan-3-il)carbamoil]amino}-pirazin-2-il)-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(5-{[(4-etilfenil)carbamoil]amino}pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-{4-[(butilcarbamoil)amino]fenil}-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-1-oxo-2-(2,2,2-trifluoroetil)-6-[4-({[3-(trifluorometil)fenil]carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(5-{[(3-clorofenil)carbamoil]amino}pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(4-{[(3,5-diclorofenil)carbamoil]amino}fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(4-{[(4-etilfenil)carbamoil]amino}fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-{4-[(ciclohexilcarbamoil)amino]fenil}-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(2-cloro-4-{[(3-clorofenil)carbamoil]amino}-fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-2-metoxi-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-2-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético;

ácido rel-2-[(2R)-6-{5-[(ciclobutilcarbamoil)amino]pirazin-2-il}-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético;

o una sal farmacéuticamente aceptable de los mismos.

Una persona con conocimientos medios en la materia reconoce que los compuestos de la presente invención pueden tener nombres alternativos al usar un software de nomenclatura diferente.

Los siguientes compuestos ejemplificados tienen los nombres químicos alternativos ilustrados en el siguiente cuadro.

Ejemplo #	Nombre químico	Nombre químico alternativo
1	ácido 2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidroisoquinolin-2-il}acético	ácido 2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-3,4-dihidroisoquinolin-2(1H)-il)acético
10	ácido 2-(6-{4-[(fenilcarbamoil)-amino]fenil}1,2,3,4-tetrahidronaftalen-2-il)acético	ácido 2-(6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
40	ácido 2-{2-hidroxi-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(2-hidroxi-6-(4-(3-(3-(trifluorometil) fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
42	ácido 2-{2-etil-1-oxo-5-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-2,3-dihidro-1H-inden-2-il}acético	ácido 2-(2-etil-1-oxo-5-(4-(3-(3-(trifluorometil) fenil) ureido)fenil)-2,3-dihidro-1H-inden-2-il) acético

Ejemplo #	Nombre químico	Nombre químico alternativo
47	ácido 2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
68	ácido 2-{1-hidroxi-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(1-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
69	ácido 3-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}propanoico	ácido 3-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)propanoico
76	ácido 2-metil-2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}propanoico	ácido 2-metil-2-(1-oxo-6-(4-(3-(3-(trifluorometil) fenil)ureido) fenil)-1,2,3,4-tetrahidronaftalen-2-il)propanoico
79	ácido 2-{2-metil-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(2-metil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
115	ácido 2-{2-etil-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(2-etil-1-oxo-6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
116	ácido 2-{2-etil-1-oxo-6-[4-({[4-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(2-etil-1-oxo-6-(4-(3-(4-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
129	ácido 2-[(2S)-2-etil-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido (*S*)-2-(2-etil-1-oxo-6-(4-(3-fenilureido) fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

Ejemplo #	Nombre químico	Nombre químico alternativo
173	ácido rel-2-[(1R,2S)-2-etil-1-hidroxi-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-((2S)-2-etil-1-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
175	ácido (2S)-3-metil-2-(2-{1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acetamido)butanoico	ácido (2S)-3-metil-2-(2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetamido)butanoico
182	ácido 2-{2-fluoro-1-oxo-6-[4-({[3-(trifluorometil)fenil]carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(2-fluoro-1-oxo-6-(4-(3-(3-(trifluorometil) fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
185	ácido 2-{2-hidroxi-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}-amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il}acético	ácido 2-(2-hidroxi-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
190	ácido 2-(2-metoxi-1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-1,2,3,4-tetrahidronaftalen-2-il)acético	ácido 2-(2-metoxi-1-oxo-6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
197	ácido 2-[2-(metoximetil)-1-oxo-6-[4-({[3-(trifluorometil)fenil]-carbamoil}amino)fenil]-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-(2-(metoximetil)-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético
198	ácido 2-[6-(4-{[(3-clorofenil)carbamoil]amino}-3-fluorofenil)-2-(hidroximetil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-(6-(4-(3-(3-clorofenil) ureido)-3-fluorofenil)-2-(hidroximetil)-1-oxo-1,2,3,4-tetrahidro naftalen-2-il)acético
201	ácido 2-(1-oxo-6-{4-[(fenilcarbamoil)amino]fenil}-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético	ácido 2-(1-oxo-6-(4-(3-fenilureido)fenil)-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético

Ejemplo #	Nombre químico	Nombre químico alternativo
212	ácido rel-2-[(2R)-6-(2-cloro-4-{[(3-clorofenil)carbamoil]amino}-fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-(6-(2-cloro-4-(3-(3-clorofenil)ureido)fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético:
213	ácido rel-2-[(2R)-6-(2-cloro-4-{[(3-clorofenil)carbamoil]amino}-fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-(6-(2-cloro-4-(3-(3-clorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético
214	ácido rel-2-[(2R)-6-(4-{[(3-clorofenil)carbamoil]amino}fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-(6-(4-(3-(3-clorofenil)ureido)fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético
215	ácido rel-2-[(2R)-6-(5-{[(3,4-difluorofenil)carbamoil]amino}pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-(6-(5-(3-(3,4-difluorofenil)ureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético
216	ácido rel-2-[(2R)-6-{5-[(ciclohexilcarbamoil)amino]pirazin-2-il}-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido 2-(6-(5-(3-ciclohexilureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético
217	ácido 2-[(2S)-6-(4-{[(3,4-difluorofenil)carbamoil]amino}-fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il]acético	ácido (S)-2-(6-(4-(3-(3,4-difluorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (I)(E), (I)(F), (I)(G), (I)(H), (I)(K), o cualquiera de los compuestos ejemplificados, o sus sales farmacéuticamente aceptables, para usarse como un medicamento.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G), (I)(H), (I)(K), o cualquiera de los compuestos ejemplificados, o sus sales farmacéuticamente aceptables, para usarse en el tratamiento de la obesidad.

Esta invención también se refiere a los compuestos de fórmula (I), (I)(A), (I)(B), (I)(C), (I)(D), (IE), (I)(F), (I)(G), (I)(H), (I)(K), o cualquiera de los compuestos ejemplificados, o sus sales farmacéuticamente aceptables, en la fabricación de un medicamento para el tratamiento de la obesidad.

Típicamente, aunque no absolutamente, las sales de la presente invención son sales farmacéuticamente aceptables. Las sales abarcadas dentro del término “sales farmacéuticamente aceptables” se refieren a sales inocuas de los compuestos de esta invención. Las sales de los compuestos descritos que contienen amina básica u otro grupo funcional básico se pueden preparar mediante cualquier método adecuado conocido, que incluye el tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico y similares, o con un ácido orgánico, tal como ácido acético, ácido trifluoroacético, ácido maleico, ácido succínico, ácido mandélico, ácido fumárico, ácido malónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, ácido piranosidílico como ácido glucorónico o ácido galacturónico, alfa-hidroxiácido como ácido cítrico o ácido tartárico, aminoácido como ácido aspártico o ácido glutámico, ácido aromático como ácido benzoico o ácido cinámico, ácido sulfónico como ácido p-toluenosulfónico, ácido

metanosulfónico, ácido etanosulfónico, o similares. Ejemplos de sales farmacéuticamente aceptables incluyen sulfatos, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, cloruros, bromuros, yoduros, acetatos, propionatos, decanoatos, caprilatos, acrilatos, formiatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, sebacatos, fumaratos, maleatos, butino-1,4-dioatos, hexino-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, dinitrobenzoatos, hidroxibenzoatos, metoxienzoatos, ftalatos, fenilacetatos, fenilpropionatos, fenilbutiratos, citratos, lactatos, γ-hidroxibutiratos, glicolatos, tartratos mandelatos y sulfonatos tales como xilenosulfonatos, metanosulfonatos, propanosulfonatos, naftaleno-1-sulfonatos y naftaleno-2-sulfonatos.

Las sales de los compuestos descritos que contienen un ácido carboxílico u otro grupo funcional ácido se pueden preparar haciéndolo reaccionar con una base adecuada. Esta sal farmacéuticamente aceptable se puede hacer con una base que produce un catión farmacéuticamente aceptable, que incluye sales de metal alcalino (especialmente sodio y potasio), sales de metal alcalinotérreo (especialmente calcio y magnesio), sales de aluminio y sales de amonio, y también sales hechas de bases orgánicas fisiológicamente aceptables, tales como trimetilamina, trietilamina, morfolina, piridina, piperidina, picolina, diciclohexilamina, N,N'-dibenciletilenediamina, 2-hidroxietilamina, bis-(2-hidroxietil)amina, tri-(2-hidroxietil)amina, procaína, dibencilpiperidina, dehidroabietilamina, N,N'-bisdehidroabietilamina, glucamina, N-metilglucamina, colidina, colina, quinina,

quinolina, y aminoácido básico como lisina y arginina.

Otras sales que no son farmacéuticamente aceptables pueden ser útiles en la preparación de los compuestos de esta invención y se considera que forman un aspecto adicional de la invención. Estas sales, tales como oxálico o trifluoroacetato, aunque por sí solas no son farmacéuticamente aceptables, pueden ser útiles como intermediarios en la preparación de sales útiles para obtener los compuestos de la invención y sus sales farmacéuticamente aceptables.

Como se usa aquí, el término “un compuesto de fórmula (I)” o “el compuesto de fórmula (I)” se refiere a uno o más compuestos de acuerdo con la fórmula (I). Los compuestos de fórmula (I) pueden existir en forma sólida o líquida. En estado sólido pueden existir en forma cristalina o no cristalina, o como una mezcla de los mismos. El experto en la materia apreciará que se pueden formar solvatos farmacéuticamente aceptables para compuestos cristalinos o no cristalinos. En los solvatos cristalinos, las moléculas de disolventes se incorporan en la red cristalina durante la cristalización. Los solvatos pueden incluir disolventes no acuosos tales como por ejemplo, sin limitación, etanol, isopropanol, DMSO, ácido acético, etanolamina o acetato de etilo, o pueden incluir agua como el disolvente que se incorpora en la red cristalina. Los solvatos en donde el agua es el disolvente que se incorpora en la red cristalina típicamente son referidos como “hidratos”. Los hidratos incluyen hidratos estequiométricos, así como también composiciones que contienen cantidades variables de agua. La invención incluye todos estos

solvatos.

El experto en la materia apreciará además que algunos compuestos de la invención que existen en forma cristalina, que incluyen los diversos solvatos de los mismos, pueden exhibir polimorfismo (es decir, la capacidad de ocurrir en diferentes estructuras cristalinas). Estas formas cristalinas diferentes son conocidas típicamente como “polimorfos”. La invención incluye todos estos polimorfos. Los polimorfos tienen la misma composición química pero difieren en empaquetamiento, disposición geométrica y otras propiedades descriptivas del estado sólido cristalino. Por lo tanto, los polimorfos pueden tener diferentes propiedades físicas, tales como forma, densidad, dureza, deformabilidad, estabilidad y propiedades de disolución. Típicamente los polimorfos exhiben diferentes puntos de fusión, espectros de IR y patrones de difracción de rayos x en polvo, que se pueden usar para identificación. El experto en la materia apreciará que se pueden producir diferentes polimorfos, por ejemplo cambiando o ajustando las condiciones de reacción o reactivos usados en la preparación del compuesto. Por ejemplo, los cambios de temperatura, presión o disolvente pueden producir polimorfos. Además, un polimorfo puede convertirse espontáneamente en otro polimorfo bajo algunas condiciones.

El compuesto de fórmula (I) o una sal del mismo pueden existir en formas estereoisoméricas (por ejemplo, contienen uno o más átomos de carbono asimétricos). Los estereoisómeros individuales (enantiómeros y diasterómeros) y mezclas de estos están incluidos dentro del alcance de la

presente invención. Similarmente, se entiende que un compuesto o sal de fórmula (I) puede existir en formas tautoméricas diferentes de las que se muestran en la fórmula, y éstas también se incluyen dentro del alcance de la presente invención. Se entiende que la presente invención incluye todas las combinaciones y subgrupos de los grupos particulares anteriormente definidos. El alcance de la presente invención incluye mezclas de estereoisómeros y también enantiómeros purificados o mezclas enriquecidas enantioméricamente/diasteroméricamente. Se entiende que la presente invención incluye todas las combinaciones y subgrupos de los grupos particulares definidos aquí anteriormente.

La presente invención también incluye los compuestos marcados con isótopo que son idénticos a los citados en la fórmula (I) y siguientes, excepto por el hecho de que uno o más átomos están reemplazados por un átomo que tiene una masa atómica o número de masa diferente de la masa atómica o número de masa encontrado más comúnmente en la naturaleza. Los ejemplos de los isótopos que se pueden incorporar en los compuestos de la invención y sus sales farmacéuticamente aceptables, incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, azufre, flúor, yodo y cloro, tales como ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I y ^{125}I.

Los compuestos de la presente invención y las sales farmacéuticamente aceptables de dichos compuestos que contienen los isótopos anteriormente mencionados, u otros isótopos de otros átomos, están dentro del alcance de la presente invención. Los compuestos de la presente

invención marcados con isótopo, por ejemplo aquellos en los que se han incorporado isótopos radioactivos tales como ^{3}H o ^{14}C, son útiles en pruebas de distribución de fármaco y/o substrato en el tejido. Los isótopos tritiados, esto es, ^{3}H, y de carbono 14, esto es, ^{14}C, son particularmente preferidos por su facilidad de preparación y detección. Los isótopos de ^{11}C y ^{18}F son particularmente útiles en la PET (tomografía de emisión de positrones), y los isótopos de ^{125}I son particularmente útiles en la SPECT (tomografía computarizada de emisión de un solo fotón), todos útiles en los estudios de imágenes del cerebro. Además, la sustitución con isótopos más pesados como deuterio, es decir, ^{2}H, puede producir algunas ventajas terapéuticas que se originan de su mayor estabilidad metabólica, por ejemplo mayor vida media *in vivo,* o reducción de las dosis requeridas, y por lo tanto pueden ser preferidos en algunas circunstancias. Los compuestos de fórmula I y siguientes de esta invención marcados con isótopo generalmente se pueden preparar efectuando los procedimientos descritos en los esquemas y/o los ejemplos que se dan más abajo, sustituyendo un reactivo no marcado con isótopo con un reactivo marcado con isótopo fácilmente disponible.

Definiciones

Los términos se usan dentro de sus significados aceptados. Las siguientes definiciones tienen la intención de aclarar, más no de limitar, los términos definidos.

Como se usa en la presente, a menos que se defina de otra

manera, el término “alquilo” (o “alquileno”) se refiere a un alquilo de cadena recta o ramificada que tiene preferiblemente de uno a doce átomos de carbono, que puede estar saturado o insaturado, no sustituido o sustituido con múltiples grados de sustitución, preferiblemente una, dos o tres, incluidas en la presente invención. Los sustituyentes adecuados se seleccionan del grupo que consiste en halógeno, amino, amino sustituido, ciano, hidroxilo, alcoxi, éster, ácido carboxílico y alquiltio. Los ejemplos del “alquilo” usado en la presente incluyen, sin limitación, metilo, trifluorometilo, etilo, propilo, isopropilo, isobutilo, n-butilo, t-butilo, isopentilo, n-pentilo, etcétera, y también versiones sustituidas de los mismos.

Como se define en la presente, a menos que se defina de otra manera, el término “cicloalquilo” se refiere a un anillo no aromático mono- o policíclico, sustituido o no sustituido, que incluye opcionalmente un enlazador alquileno a través del cual puede estar unido el cicloalquilo. Los grupos “cicloalquilo” ejemplares incluyen, sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, etcétera, y también versiones sustituidas y no sustituidas de los mismos.

Como se usa en la presente, a menos que se defina de otra manera, el término “alcoxi” se refiere al grupo $-OR^a$, en donde R^a es alquilo de C_1-C_4 o cicloalquilo como se define arriba.

Como se usa en la presente, el término “amida” se refiere al grupo $–C(O)NR^cR^d$, en donde R^c y R^d son, cada uno independientemente, H, alquilo de C_1-C_6, o cicloalquilo de C_3-C_6, o R^c es la porción restante de un

aminoácido natural o no natural.

Como se usa en la presente, el término “heterociclo” o “heterociclilo” se refiere a un sistema de anillo no aromático mono- o policíclico, sustituido o no sustituido, que contiene uno o más heteroátomos. Los heteroátomos preferidos incluyen N, O y S, incluso N-óxidos, óxidos y dióxidos de azufre. Preferiblemente el anillo es de tres a ocho miembros y está completamente saturado o tiene uno o más grados de insaturación. En la presente definición se incluyen grados múltiples de sustitución. Los ejemplos de grupos “heterocíclicos” incluyen, sin limitación, tetrahidrofuranilo, piranilo, 1,4-dioxanilo, 1,3-dioxanilo, piperidinilo, pirrolidinilo, morfolinilo, azetidinilo, piperazinilo, pirrolidinonilo, piperazinonilo, pirazolidinilo, y sus diversos tautómeros.

Como se usa en la presente, el término “arilo”, a menos que se defina de otra manera, significa un sistema de anillo de hidrocarburo aromático. El sistema de anillo puede ser monocíclico o policíclico fusionado (por ejemplo, bicíclico, tricíclico, etc.), sustituido o no sustituido. En sus diversas modalidades, el anillo de arilo monocíclico es de C5-C10, o C5-C7, o C5-C6, en donde estos números de carbono se refieren al número de átomos de carbono que forman el sistema de anillo. Un sistema de anillo de C6, es decir, un anillo de fenilo, es un grupo arilo adecuado. En varias modalidades, el anillo policíclico es un grupo arilo bicíclico, en donde los grupos arilo bicíclicos adecuados son de C8-C12, o C9-C10. Un anillo de naftilo, que tiene 10 átomos de carbono, es un grupo arilo policíclico adecuado. Los

sustituyentes adecuados para arilo se describen más abajo en la definición de "sustituido opcionalmente".

Como se usa en la presente, el término "heteroarilo", a menos que se defina de otra manera, significa un sistema de anillo aromático que contiene carbono y por lo menos un heteroátomo. El heteroarilo puede ser monocíclico o policíclico, sustituido o no sustituido. Un grupo heteroarilo monocíclico puede tener de 1 a 4 heteroátomos en el anillo, mientras que un heteroarilo policíclico puede contener de 1 a 10 heteroátomos. Un anillo de heteroarilo policíclico puede contener uniones de anillo fusionado, espiro o de puente, por ejemplo un heteroarilo bicíclico es un heteroarilo policíclico. Los anillos de heteroarilo bicíclico pueden contener de 8 a 12 átomos miembros. Los anillos de heteroarilo monocíclico pueden contener de 5 a 8 átomos miembros (carbonos y heteroátomos). Los grupos heteroarilo ejemplares incluyen, sin limitación: benzofurano, benzotiofeno, furano, imidazol, indol, isotiazol, oxazol, pirazina, pirazol, piridazina, piridina, pirimidina, pirrol, quinolina, quinazolina, quinoxalina, tiazol y tiofeno. Los sustituyentes adecuados para heteroarilo se describen más abajo en la definición de "sustituido opcionalmente".

Como se usa en la presente, el término "ciano" se refiere al grupo –CN.

Como se usa en la presente, el término "acilo" se refiere al grupo $-C(O)R^b$, en donde R^b es alquilo, cicloalquilo, o heterociclilo, como se definen en la presente.

Como se usa en la presente, el término “éster” se refiere al grupo -C(O)OR^e, en donde R^e es alquilo de C_1-C_6 o cicloalquilo de C_3-C_6.

Como se usa en la presente, el término “urea” se refiere al grupo -NR^{c}C(O)NR^d, en donde R^c y R^d son, cada uno independientemente H, alquilo de C_1-C_6 o cicloalquilo de C_3-C_6.

Como se usa en la presente, el término “opcionalmente” significa que el evento descrito puede o no ocurrir, e incluye tanto eventos que ocurren como eventos que no ocurren.

Como se usa en la presente, a menos que se defina de otra manera, el término “sustituidoopcionalmente” o variaciones del mismo denotan una sustitución opcional, que incluye múltiples grados de sustitución, con uno o más grupos sustituyentes, preferiblemente uno, dos o tres. El término no se debe considerar como duplicado de las sustituciones aquí descritas y representadas. Los grupos sustituyentes opcionales ejemplares incluyen acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno urea, amida, hidroxilo, oxo y nitro.

Composiciones farmacéuticas

La invención provee, además, una composición farmacéutica (denominada también formulación farmacéutica) que comprende un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo, y uno o más excipientes (denominados también vehículos y/o diluentes en las ciencias farmacéuticas). Los excipientes son aceptables en el sentido de ser

compatibles con los otros ingredientes de la formulación e inocuos para el receptor de los mismos (es decir, el paciente).

De acuerdo con otro aspecto de la invención se provee un procedimiento para la preparación de una composición farmacéutica, que comprende mezclar (o incorporar) un compuesto de fórmula I o sal del mismo con al menos un excipiente.

Las composiciones farmacéuticas pueden estar en forma de dosis unitarias que contienen una cantidad predeterminada de ingrediente activo por dosis unitaria. Esta unidad puede contener una dosis terapéuticamente eficaz del compuesto de fórmula I o una sal del mismo, o una fracción de una dosis terapéuticamente eficaz, de tal manera que se puedan administrar múltiples formas de dosis unitarias en un tiempo dado para obtener la dosis terapéuticamente eficaz deseada. Las formulaciones de dosis unitarias preferidas son las que contienen una dosis o subdosis diaria como se menciona arriba, o una fracción apropiada de la misma, de un ingrediente activo. Además, estas composiciones farmacéuticas se pueden preparar mediante cualquiera de los métodos bien conocidos en las ciencias farmacéuticas.

Las composiciones farmacéuticas pueden ser adaptadas para administración mediante cualquier vía apropiada, por ejemplo, mediante las vías oral (incluyendo bucal o sublingual), rectal, nasal, tópica (incluyendo bucal, sublingual o transdérmica), vaginal o parenteral (incluyendo subcutánea, intramuscular, intravenosa o intradérmica). Dichas

composiciones pueden prepararse mediante cualquier método conocido en la técnica de farmacia, por ejemplo, poniendo en asociación el ingrediente activo con el excipiente o los excipientes.

Cuando son adaptadas para administración oral, las composiciones farmacéuticas pueden estar en unidades discretas tales como tabletas o cápsulas; polvos o gránulos; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas o batidos comestibles; emulsiones líquidas de aceite en agua o emulsiones líquidas de agua en aceite. El compuesto o sal del mismo de la invención o la composición farmacéutica de la invención puede incorporarse también en un dulce, una oblea, y/o formulación de cinta lingual para administración como un medicamento “de disolución rápida”.

Por ejemplo, para administración oral en la forma de una tableta o cápsula, el componente de fármaco activo puede combinarse con un vehículo inerte oral, no tóxico farmacéuticamente aceptable tal como etanol, glicerol, agua, y similares. Polvos o gránulos se preparan triturando el compuesto hasta un tamaño fino apropiado y mezclando con un vehículo farmacéutico triturado de igual manera, tal como un carbohidrato comestible como por ejemplo almidón o manitol. Pueden estar presentes también agentes saborizantes, conservadores, dispersantes y colorantes.

Las cápsulas se obtienen preparando una mezcla de polvo, como se describió anteriormente, y vaciándola en las cubiertas de gelatina o no gelatinosas formadas. Deslizantes y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio o polietilenglicol sólido

pueden añadirse a la mezcla de polvo antes de la operación de llenado. Un agente de desintegración o solubilizador tal como agar-agar, carbonato de calcio o carbonato de sodio puede añadirse también para mejorar la disponibilidad del medicamento cuando la cápsula es ingerida.

Además, cuando se desee o sea necesario, aglutinantes, lubricantes, agentes de desintegración y agentes colorantes adecuados, pueden incorporarse también en la mezcla. Aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas tales como acacia, tragacanto, alginato de sodio, carboximetilcelulosa, polietilenglicol, ceras, y similares. Los lubricantes usados en estas formas de dosis incluyen oleato de sodio, estearato de sodio, estearato de magnesio, benzoato de sodio, acetato de sodio, cloruro de sodio, y similares. Los desintegradores incluyen, sin limitación, almidón, metilcelulosa, agar, bentonita, goma de xantano, y similares.

Las tabletas se formulan, por ejemplo, preparando una mezcla de polvo, granulando o formando bolitas, añadiendo un lubricante y desintegrador, y prensando en tabletas. Una mezcla de polvo se prepara mezclando el compuesto, triturado convenientemente con un diluente o base como se describió anteriormente, y opcionalmente, con un aglutinante tal como carboximetilcelulosa y alginato, gelatina o polivinilpirrolidona, un retardador de solución tal como parafina, un acelerador de resorción tal como una sal cuaternaria, y/o un agente de absorción tal como bentonita, caolín o

fosfato dicálcico. La mezcla de polvo puede granularse mojando un aglutinante tal como jarabe, pasta de almidón, mucílago de acacia, o soluciones de materiales celulósicos o poliméricos y forzando a través de un tamiz. Como una alternativa a la granulación, la mezcla de polvo puede pasar a través de la máquina tableteadora, y el resultado son bolitas imperfectas que se rompen en gránulos. Los gránulos pueden ser lubricados para prevenir que se adhieran a los dados que forman las tabletas por medio de la adición de ácido esteárico, una sal de estearato, talco o aceite mineral. La mezcla lubricada es comprimida entonces en tabletas. El compuesto o sal de la presente invención puede combinarse también con un vehículo inerte de flujo libre y puede ser comprimido en tabletas directamente, sin pasar a través de los pasos de granulación o formación de bolitas. Puede proveerse también un recubrimiento protector opaco claro que consista de una cubierta de sellado o laca, un recubrimiento de azúcar o material polimérico y un recubrimiento de pulimento de cera. Pueden añadirse colorantes a estos recubrimientos para distinguir diferentes dosificaciones.

Fluidos orales tales como soluciones, jarabes y elíxires pueden prepararse en forma de dosis unitaria, de modo que una cantidad dada contenga una cantidad predeterminada de ingrediente activo. Pueden prepararse jarabes disolviendo el compuesto o sal del mismo de la invención en una solución acuosa convenientemente saborizada, mientras que se preparan elíxires usando un vehículo alcohólico inocuo. Pueden formularse suspensiones dispersando el compuesto o sal de la invención en un vehículo

inocuo. Pueden añadirse también solubilizadores y emulsionantes, tales como alcoholes isoestearílicos etoxilados y éteres de polioxietileno sorbitol, conservadores, aditivos de sabor tales como aceite de menta, edulcorantes naturales, sacarina u otros edulcorantes artificiales, y similares.

En donde sea apropiado, pueden microencapsularse formulaciones de dosis unitarias para administración oral. La formulación puede prepararse también para prolongar o sostener la liberación, por ejemplo, recubriendo o incluyendo material de partículas en polímeros, cera, o similares.

En la presente invención se prefieren las tabletas y cápsulas para el suministro de la composición farmacéutica.

Como se usa en la presente, el término “tratamiento” incluye la profilaxis, y se refiere al alivio de la afección especificada, eliminación o reducción de uno o más síntomas de la afección, retardo o eliminación de la progresión de la afección, y prevención o retardo la recidiva de la afección en un paciente o sujeto previamente enfermo o diagnosticado. La profilaxis (o prevención o retardo del inicio de la enfermedad) se logra típicamente administrando un fármaco de la misma manera, o de manera similar, que para un paciente con la enfermedad o afección desarrollada.

La presente invención provee un método de tratamiento de un mamífero, especialmente un humano, que sufre de obesidad, diabetes, hipertensión, depresión, ansiedad, adición a fármacos, adición a sustancias, o una combinación de los mismos. Dicho tratamiento comprende el paso de

administrar una cantidad terapéuticamente eficaz de un compuesto de fórmula I o sal del mismo a dicho mamífero, en particular un humano. El tratamiento puede comprender también el paso de administrar una cantidad terapéuticamente eficaz de una composición farmacéutica que contenga un compuesto de fórmula I o sal del mismo a dicho mamífero, en particular un humano.

Como se usa en la presente, el término “cantidad eficaz” significa aquella cantidad de un fármaco o agente farmacéutico que inducirá la respuesta biológica o médica de un tejido, sistema, animal o humano que está siendo buscada, por ejemplo, por un investigador o médico clínico.

El término “cantidad terapéuticamente eficaz” significa cualquier cantidad que, en comparación con un sujeto correspondiente que no ha recibido dicha cantidad, resulta en el tratamiento, curación, mejora o prevención mejorado de una enfermedad, trastorno o efecto secundario, o una disminución en el ritmo de avance de una enfermedad o trastorno. El término incluye también dentro de su alcance cantidades eficaces para mejorar la función fisiológica normal. Para su uso en terapia, las cantidades terapéuticamente eficaces de un compuesto de fórmula I, así como sales del mismo, pueden administrarse como el compuesto químico bruto. Además, el ingrediente activo puede presentarse como una composición farmacéutica.

Aunque es posible que, para su uso en terapia, una cantidad terapéuticamente eficaz de un compuesto de fórmula I o sal del mismo pueda administrarse como el compuesto químico bruto, se presenta típicamente

como el ingrediente activo de una composición o formulación farmacéutica.

La cantidad terapéuticamente eficaz precisa de un compuesto o sal del mismo de la invención dependerá de muchos factores que incluyen, sin limitación, la edad y el peso del sujeto (paciente) que está siendo tratado, el trastorno preciso que requiere tratamiento y su severidad, la naturaleza de la formulación/composición farmacéutica, y la vía de administración, y finalmente será a la criterio del médico o veterinario a cargo. Típicamente, un compuesto de fórmula I o sal del mismo se dará para el tratamiento en la escala de aproximadamente 0.1 a 100 mg/kg de peso corporal del receptor (paciente, mamífero) por día, y más usualmente en la escala de 0.1 a 10 mg/kg de peso corporal por día. Dosificaciones diarias aceptables pueden ser de aproximadamente 1 a aproximadamente 1000 mg/día, y de preferencia de aproximadamente 1 a aproximadamente 100 mg/día. Esta cantidad puede darse en una sola dosis por día o en muchas (tales como dos, tres, cuatro, cinco o más) subdosis por día, de modo que la dosis diaria total sea la misma. Una cantidad eficaz de una sal del mismo puede determinarse como una proporción de la cantidad eficaz del compuesto de fórmula I *per se*. Dosificaciones similares deben ser apropiadas para el tratamiento (incluyendo profilaxis) de las otras condiciones referidas en la presente para tratamiento. En general, la determinación de la dosificación apropiada puede ser lograda fácilmente por el experto en medicina o la técnica de farmacia.

Además, la presente invención comprende un compuesto de fórmula I o sal del mismo o una composición farmacéutica del mismo con por

lo menos algún otro fármaco antiobesidad y/o por lo menos un fármaco antidiabetes. Dichos fármacos antiobesidad pueden incluir, por ejemplo, metformina (o glucofage), antagonistas de los receptores CB1, agonistas de GLP-1, antagonistas de opioides e inhibidores de la reabsorción de neurotransmisores. Cuando un compuesto de la invención se usa en combinación con otro fármaco antiobesidad o fármaco antidiabetes, los expertos en la materia apreciarán que la dosis de cada compuesto o fármaco de la combinación puede diferir de aquella cuando el fármaco o compuesto se usa solo. Las dosis apropiadas serán fácilmente apreciadas y determinadas por los expertos en la materia. Las dosis apropiadas del compuesto de fórmula I o sal del mismo y los otros agentes terapéuticamente activos y las horas de administración relativas, se seleccionarán para lograr el efecto terapéutico combinado deseado, y están dentro de la experiencia y la discreción del médico o médico clínico a cargo.

Preparación de los compuestos

Esquemas de síntesis genéricos

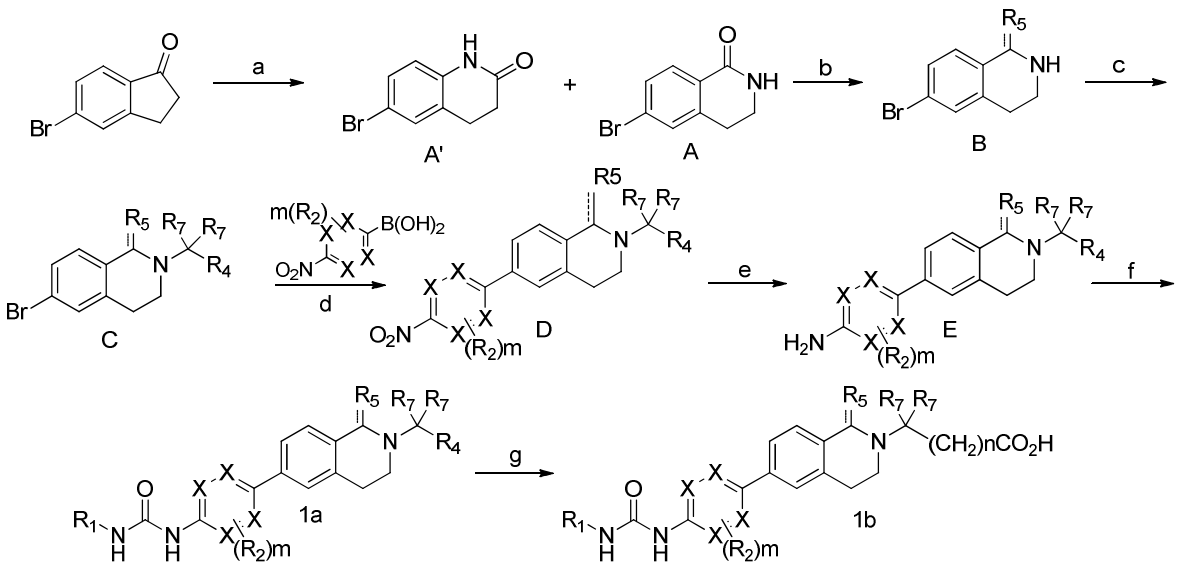
Los compuestos de esta invención pueden obtenerse mediante una variedad de métodos, que incluyen métodos de síntesis estándar bien conocidos. Métodos de síntesis generales ilustrativos se exponen a continuación, y entonces se preparan compuestos específicos de la invención en los ejemplos de trabajo. El experto en la técnica apreciará que si un sustituyente descrito en la presente no es compatible con los métodos de

síntesis descritos en la presente, el sustituyente puede ser protegido con un grupo protector adecuado que sea estable a las condiciones de reacción. El grupo protector puede quitarse en un punto conveniente de la secuencia de reacciones para proveer un compuesto objetivo o intermediario deseado. En todos los esquemas descritos a continuación, se usan grupos protectores para grupos sensibles o reactivos en donde sea necesario de acuerdo con los principios generales de la química de síntesis. Los grupos protectores se manipulan de acuerdo con los métodos estándar de síntesis orgánica (véase T.W. Green y P.G. M. Wuts (1991),"Protecting Groups in Organic Synthesis", John Wiley & Sons, cita incorporada en la presente como referencia con respecto a los grupos protectores). Estos grupos se remueven en una etapa conveniente de la síntesis de los compuestos usando métodos que son fácilmente evidentes para los expertos en la materia. La selección de los procedimientos, así como las condiciones de reacción y el orden de su ejecución, serán consistentes con la preparación de los compuestos de la presente invención.

La síntesis de los compuestos de la fórmula (I) general y derivados farmacéuticamente aceptables y sales de los mismos, puede ser lograda como se esboza a continuación en los esquemas 1 a 15 por los expertos en la materia. En la siguiente descripción, los grupos son como se definieron anteriormente para los compuestos de fórmula (I), a menos que se indique de otra manera. Los materiales de partida están disponibles comercialmente o se obtienen de materiales de partida disponibles

comercialmente usando métodos conocidos por los expertos en la materia.

ESQUEMA 1

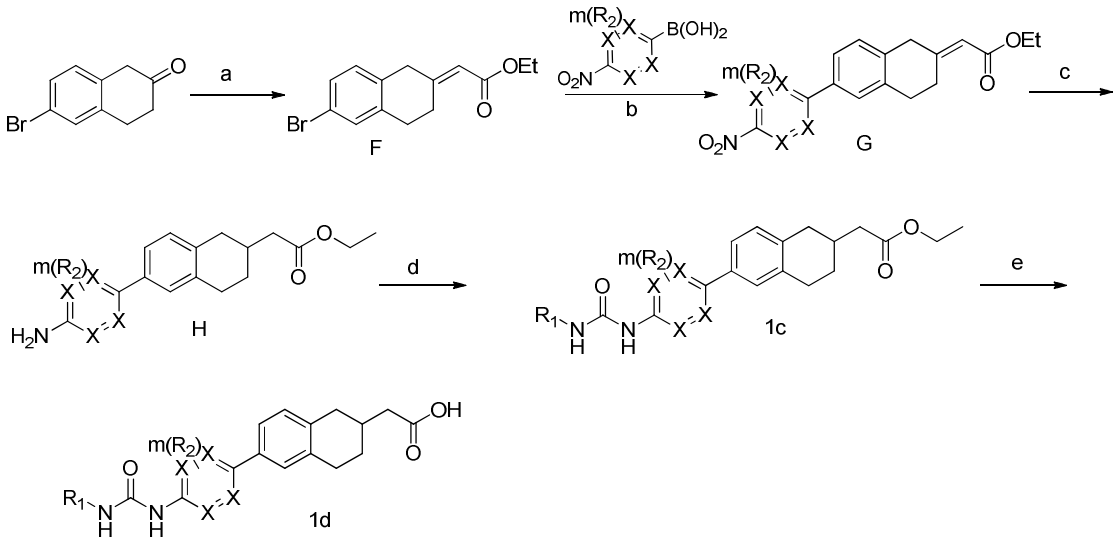


Reactivos y condiciones: a) NaN_3, $MeSO_3H$, CH_2Cl_2, t.a.; b) BH_3:SMe_2, THF, 60ºC; c) X-C(R_7)(R_7)R_4, Et_3N, CH_2Cl_2, t.a.; d) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80ºC; e) Pd a 10%/C, EtOH, H_2, t.a.; f) R_1NCO, Et_3N, THF, t.a.; g) LiOH, THF-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 1. El intermediario A puede obtenerse mediante una reacción de trasposición de 5-bromo-1-indanona con NaN_3 en $MeSO_3H$ en disolventes tales como CH_2Cl_2. La reducción del intermediario A con un agente reductor tal como BH_3:SMe_2 en disolventes tales como THF, da el intermediario B (R_5=H), el cual puede ser alquilado usando un halogenuro de alquilo

apropiadamente sustituido (X-C(R_7)(R_7)R_4) y una base tal como Et_3N bajo condiciones estándares conocidas por los expertos en la materia, para formar C. El intermediario A puede ser alquilado también directamente con un halogenuro de alquilo apropiadamente sustituido bajo condiciones similares para formar el intermediario C, en donde R_5 es oxo. El acoplamiento de Suzuki catalizado por paladio del intermediario C con un éster o ácido borónico apropiadamente sustituido en presencia de una base tal como Cs_2CO_3 bajo condiciones estándar, da el intermediario D. La reducción del grupo funcional nitro en D bajo condición de reducción e hidrogenación estándar, provee el intermediario de anilina E. El acoplamiento de E con un isocianato apropiadamente sustituido da los compuestos de urea de fórmula (I) (1a, en donde R_5 es H). En el compuesto 1a, en donde R_4 es –$CH_2C(O)OR^e$ o -$C(O)OR^e$, la hidrólisis del grupo éster con una base tal como LiOH provee otro compuesto de fórmula (I)(1b),en donde R_4es –$CH_2C(O)OH$ o –C(O)OH, respectivamente.

ESQUEMA 2

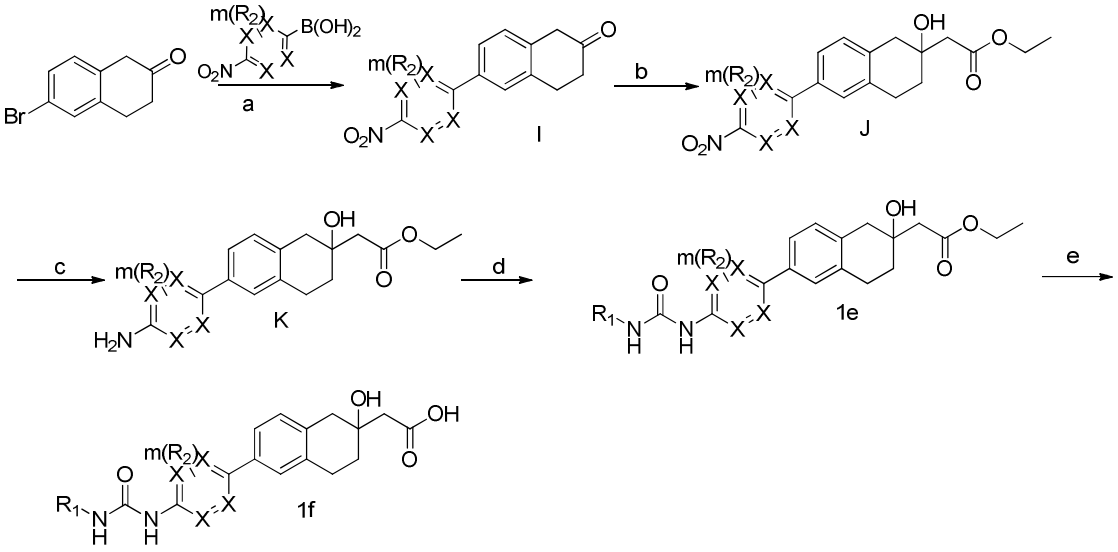


Reactivos y condiciones: a) $Ph_3P=CHCO_2Et$, NaH, DMF, t.a.; b) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; c) Pd/C, MeOH, H_2, t.a.; d) R_1NCO, Et_3N, THF, t.a.; e) LiOH, THF-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 2. El intermediario F puede prepararse a partir de la 6-bromo-2-tetralona usando condiciones de reacción de Wittig estándar tal como $Ph_3P=CHCO_2Et$ con una base tal como NaH en un disolvente tal como DMF. El acoplamiento de Suzuki catalizado por paladio de F con un éster/ácido borónico apropiadamente sustituido en presencia de una base tal como Cs_2CO_3, da el intermediario nitro G. La reacción de reducción e hidrogenación estándar convierte G hasta la anilina H, la cual puede ser acoplada con un isocianato apropiadamente sustituido (R_1NCO),para formar el compuesto de

fórmula (I) (1c). El éster en 1c puede ser hidrolizado adicionalmente bajo condiciones básicas tales como LiOH en THF-H_2O hasta otro compuesto de fórmula (I) (1d).

ESQUEMA 3

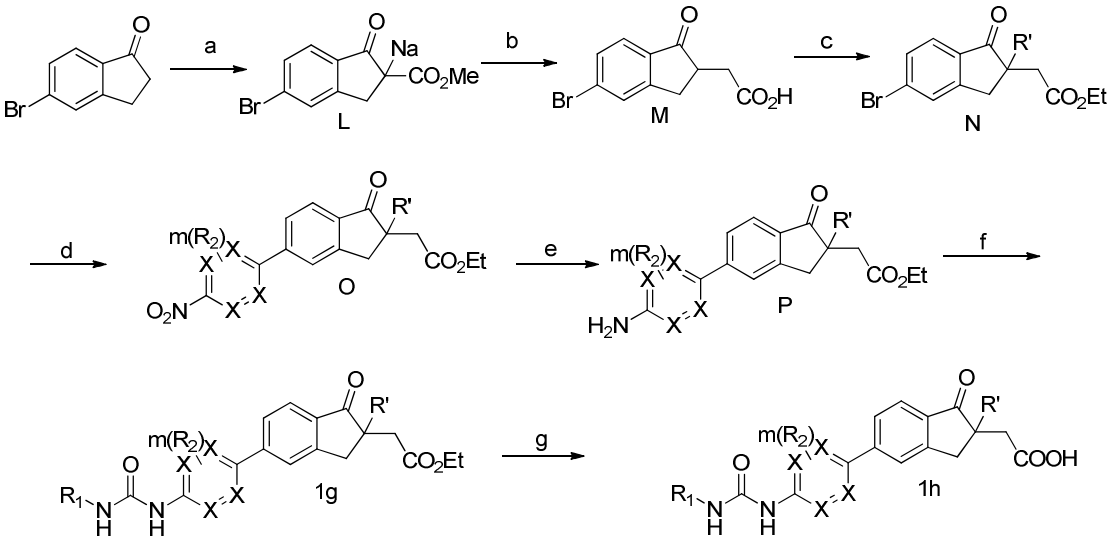


Reactivos y condiciones: a) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; b) EtOAc, LiHMDS, THF, -78°Chasta t.a.; c) Pd/C, MeOH, H_2, t.a.; d) R_1NCO, Et_3N, THF, t.a.; e) NaOH, MeOH-THF-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 3. El acoplamiento de Suzuki catalizado por paladio de la 6-bromo-2-tetralona con un éster/ácido borónico apropiadamente sustituido da el intermediario I, el cual puede ser convertido al intermediario J en presencia de acetato de etilo en Li-HMDS en un disolvente tal como THF. La reducción

del grupo nitro en J usando condiciones de hidrogenación estándar provee la anilina K, la cual puede ser acoplada con un isocianato apropiadamente sustituido (R_1NCO),para proveer el compuesto de fórmula (I) (1e).Más hidrólisis del grupo éster en 1e con una base tal como NaOH en un disolvente tal como MeOH-THF-H_2O, da otro compuesto de fórmula (I) (1f).

ESQUEMA 4

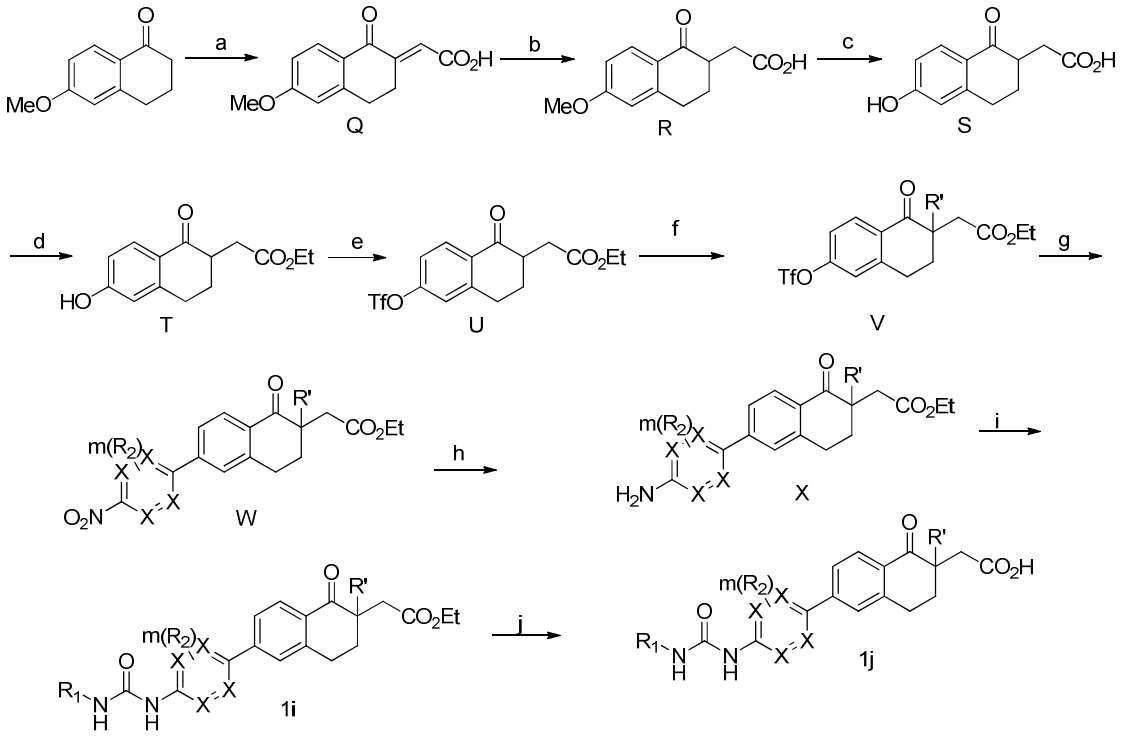


Reactivos y condiciones: a) $CO(OMe)_2$, NaH, THF, 75°C; b) $BrCH_2COOEt$, THF, 75°C; c) NaH, R'-X, DMF, t.a.; d) éster/ácido borónico sustituido, $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; e) Fe/NH_4Cl, EtOH-H_2O, 85°C; f) R_1NCO, Et_3N, THF, t.a.; g) LiOH, dioxano-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 4. La 5-bromo-indanona puede ser convertida al intermediario L en presencia de NaH y carbonato de dimetilo. El intermediario L puede ser

convertido al intermediario M con bromoacetato de etilo seguido de condiciones de descarboxilación. La alquilación de M con un agente de alquilación apropiadamente sustituido tal como halogenuro de alquilo (por ejemplo R'-X, en donde R' puede ser alquilo de C_1-C_3 sustituido, y X puede ser halógeno tal como yodo), provee el intermediario N, el cual puede ser convertido a los compuestos de fórmula (I) (1g, 1h) usando acoplamiento de Suzuki, reducción del nitro, formación de urea y/o condiciones de hidrólisis subsiguientes, como se describe en el esquema 1-2. El intermediario M puede sufrir también transformación química similar (acoplamiento de Suzuki, reducción del nitro, formación de urea y/o condición de hidrólisis subsiguiente), para formar compuestos de fórmula (I) (1g, 1h),en donde R' es H.

ESQUEMA 5

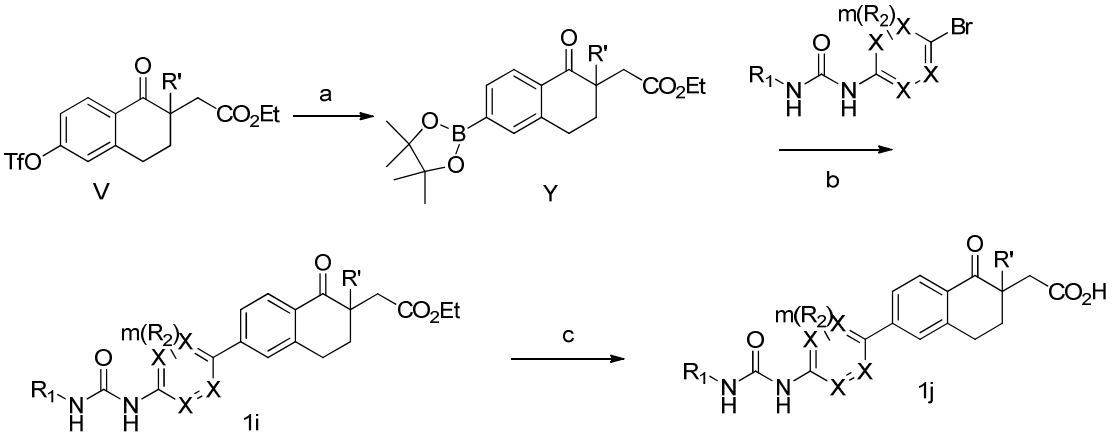


Reactivos y condiciones: a) ácido glioxálico, H_2SO_4, diglima, 85°C; b) Zn, AcOH, 80°C; c) HBr acuoso, 100°C; d) $MeSO_3H$, EtOH, t.a.; e) Tf_2O, CH_2Cl_2, Et_3N, t.a.; f) R'-X, NaH, DMF, t.a.; g) éster/ácido borónico sustituido, $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; h) Pd/C, H_2, EtOH, t.a.; i) R_1NCO, Et_3N, THF, t.a.; j) LiOH, EtOH-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 5. La 6-metoxitetralona puede ser convertida al intermediario Q usando ácido glioxálico seguido de ácido sulfúrico en diglima bajo condición de calentamiento. La reducción de la olefina en presencia de condición

reductora tal como Zn en AcOH da el intermediario R, el cual puede ser desmetilado usando HBr acuoso, para proveer el compuesto de fenol S. La esterificación de S bajo condiciones estándar provee el éster T, en donde el grupo funcional fenol puede ser protegido como el triflato U usando anhídrido de triflato bajo condiciones básicas. La alquilación de U con un halogenuro de alquilo apropiadamente sustituido (R'-X) tal como yoduro de metilo, yoduro de etilo, yoduro de propilo o yoduro de trifluoroetilo provee el intermediario V, el cual puede ser convertido a los compuestos de fórmula (I) (1i, 1j) usando acoplamiento de Suzuki, reducción del nitro, formación de urea y/o condiciones de hidrólisis subsiguientes como se describe en el esquema 1-2. El intermediario U puede sufrir también transformación química similar (acoplamiento de Suzuki, reducción del nitro, formación de urea y/o condición de hidrólisis subsiguiente), para formar compuestos de fórmula (I) (1i, 1j), en donde R' es H.

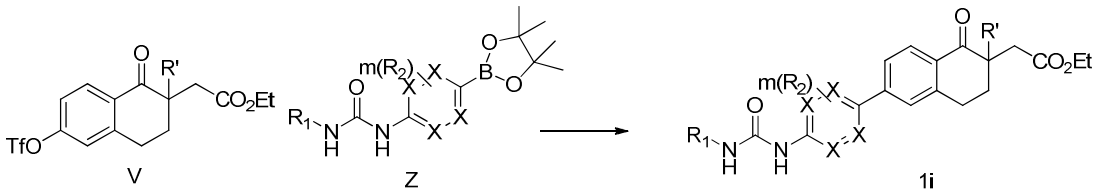
ESQUEMA 6



Reactivos y condiciones: a) 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano, $PdCl_2(dppf)$, KOAc, dioxano, 100°C; b) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; c) LiOH, EtOH-H_2O, t.a.

En forma alternativa, pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 6. El intermediario V puede ser convertido a éster borónico, el cual puede sufrir entonces reacción de Suzuki catalizada por paladio con el halogenuro de arilo o heteroarilo apropiadamente sustituido, para formar compuestos de fórmula (I) (1i). Pueden prepararse halogenuros de arilo o heteroarilo apropiadamente sustituidos usando condiciones de reacción conocidas por los expertos en la materia, por ejemplo, mediante el acoplamiento de aminas apropiadamente sustituidas con isocianatos apropiadamente sustituidos. El compuesto 1i puede ser convertido posteriormente hasta otros compuestos de fórmula (I) (1j) mediante condiciones de hidrólisis estándar.

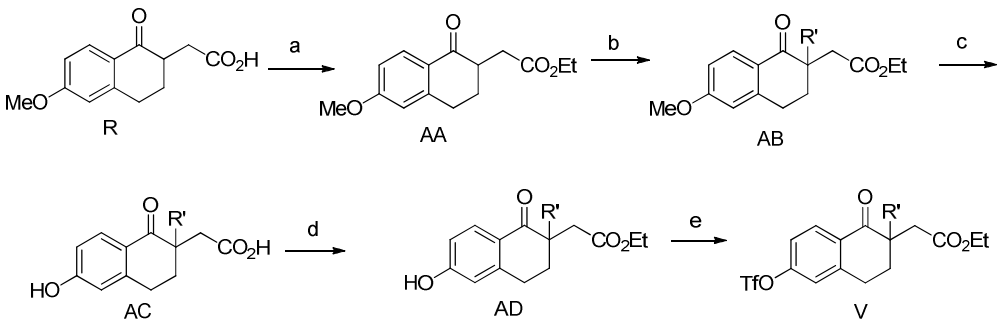
ESQUEMA 7



En forma alternativa, pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 7, invirtiendo los miembros de acoplamiento

como en el esquema 6. El intermediario V puede ser acoplado con el éster borónico Z apropiadamente sustituido, para formar compuestos de fórmula (I) (1i) usando condiciones de acoplamiento de Suzuki catalizado por paladio. El éster borónico Z apropiadamente sustituido puede prepararse usando condiciones de reacción conocidas por los expertos en la materia, por ejemplo, convirtiendo los halogenuros de arilo o heteroarilo apropiadamente sustituidos hasta ésteres borónicos usando bis-pinacolato diborano en presencia de KOAc y una cantidad catalítica de $PdCl_2$(dppf) en un disolvente tal como DMF bajo condiciones calentadas.

ESQUEMA 8



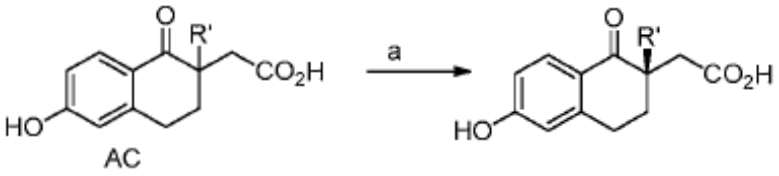
Reactivos y condiciones: a) $MeSO_3H$, EtOH, t.a.; b) R'-X, NaH, DMF, t.a.; c) HBr acuoso, 100°C; d) $MeSO_3H$, EtOH, t.a.; e) Tf_2O, CH_2Cl_2, Et_3N, t.a.

El intermediario V puede prepararse también como se ilustra en el esquema 8. La esterificación de R provee el éster AA, el cual puede ser alquilado con un halogenuro de alquilo apropiadamente sustituido (R'-X) tal

como MeI, EtI y yoduro de trifluoroetilo, para dar el intermediario AB. La desmetilación de AB provee el fenol AC, el cual puede ser esterificado para dar AD. El grupo fenol puede ser protegido entonces como triflato para formar el intermediario V. El intermediario V puede ser convertido a compuestos de fórmula (I) usando los esquemas 5 a 7 descritos anteriormente.

Pueden obtenerse compuestos enantioméricos enriquecidos mediante la separación quiral de intermediarios o compuestos de fórmula (I) apropiados. Por ejemplo, para la mezcla racémica de los compuestos 1i, pueden separarse enantiómeros puros en la columna quiral usando columnas quirales tales como CHIRAL PAKIA (4.6x250 mm) 5 µ y fases móviles apropiadas, para dar los compuestos de 1i enantioméricos enriquecidos. Los compuestos enantioméricos enriquecidos de 1i pueden sufrir entonces una transformación química adicional tal como hidrólisis del éster, para proveer los compuestos enantioméricos enriquecidos de 1j.

ESQUEMA 9

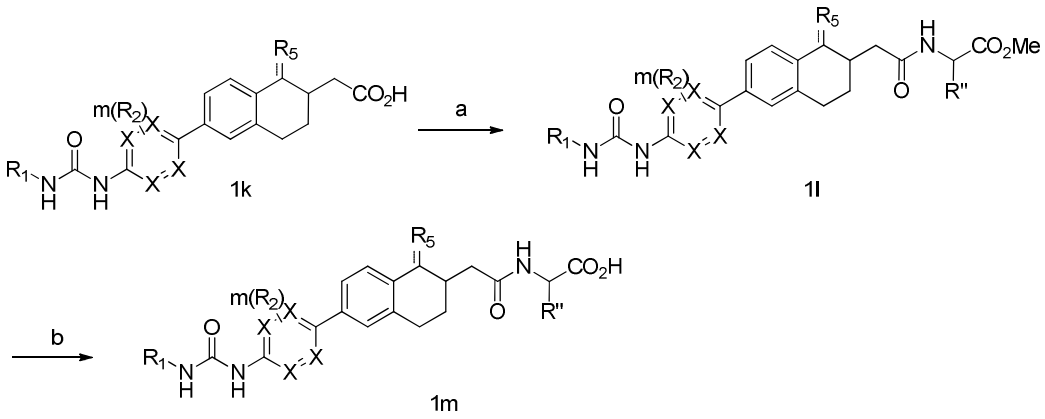


AC enantiomérico enriquecido

Reactivos y condiciones: a) cinconidina, IPA-H_2O, 80°C – t.a., 24h,luego HCl6N.

En forma alternativa, pueden obtenerse compuestos enantioméricos enriquecidos mediante la resolución química de una mezcla de compuestos racémicos. Por ejemplo, como se muestra en el esquema 9, el intermediario racémico AC puede ser resuelto hasta el AC puro enantiomérico usando cinconidina en presencia de disolventes tales como IPA-H_2O. El intermediario AC enantiomérico enriquecido puede ser convertido entonces hasta los compuestos enantioméricos enriquecidos de fórmula (I) (1i, 1j),usando reacciones de igual manera que las descritas en los esquemas 5 a 8.

ESQUEMA 10

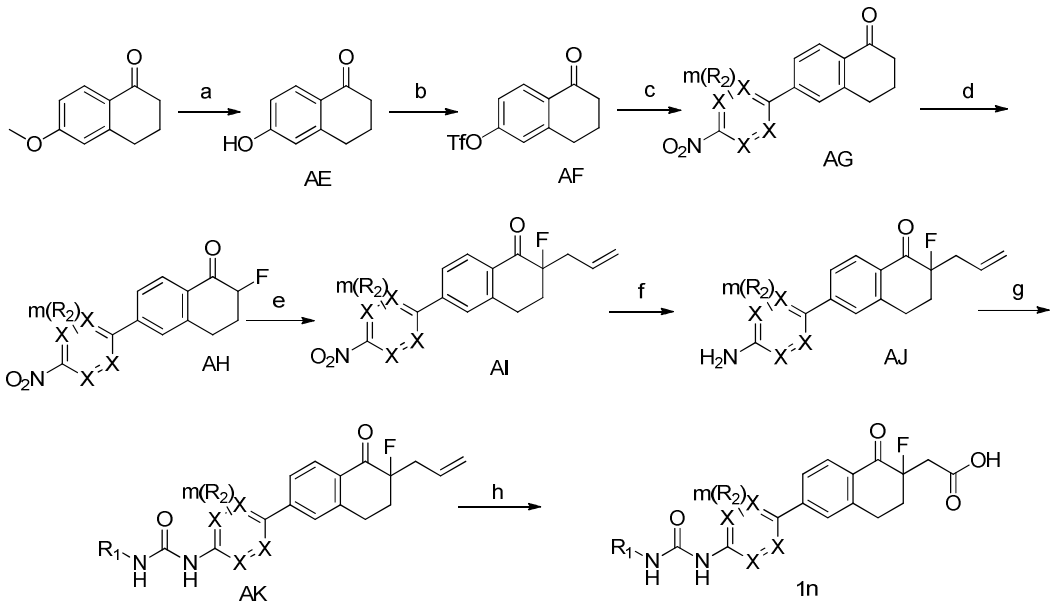


Reactivos y condiciones: a) HATU, THF, éster metílico de aminoácido (NH_2-CH(R")CO_2Me), t.a.; b) LiOH, THF-H_2O, t.a.

El compuesto de fórmula (I) puede ser convertido a otro compuesto de fórmula (I) usando una transformación química conocida por los

expertos en la materia. Por ejemplo, como se muestra en el esquema 10, el compuesto de fórmula (I) (1k) puede ser acoplado con éster metílico de aminoácido (NH_2-CH(R")CO_2Me) bajo condiciones de acoplamiento conocidas por los expertos en la materia, hasta otro compuesto de formula I (1l), el cual puede ser hidrolizado entonces para formar el compuesto de fórmula (I) (1m).

ESQUEMA 11

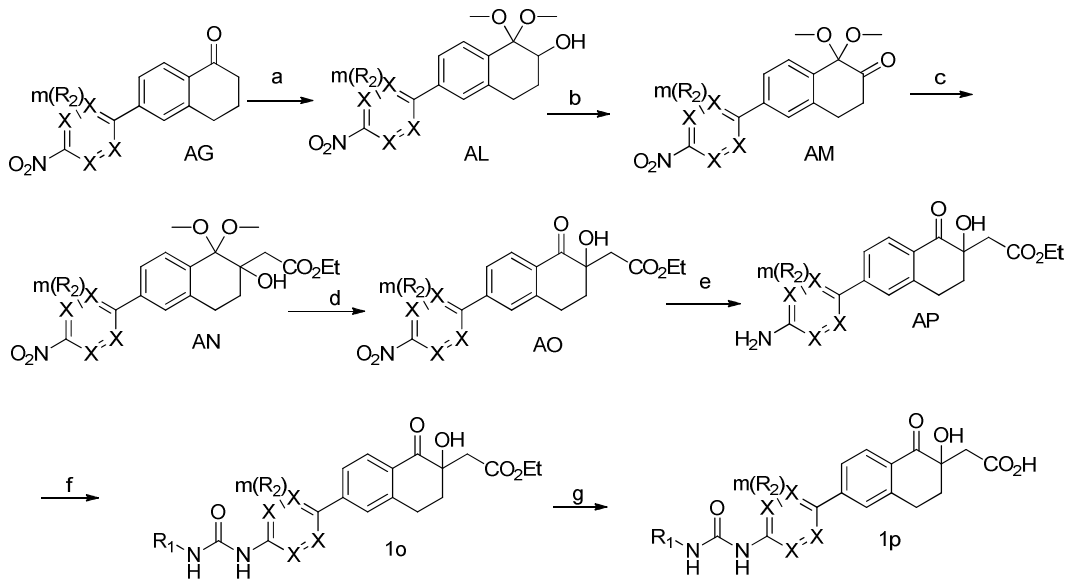


Reactivos y condiciones: a) HBr acuoso, reflujo; b) Tf_2O, DMAP, Py, t.a.; c) éster o ácido aril/heteroaril borónico sustituido, $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; d) SelectFluor, MeOH, 80°C; e) bromuro de alilo, TBAI, KOH, t.a.; f) Fe/NH_4Cl, EtOH, H_2O, reflujo; g) R_1NCO, Et_3N, THF, t.a.; h) $KMnO_4$, $NaIO_4$, acetona-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en

el esquema 11. La 6-metoxi-1-tetralona puede ser desmetilada para dar el fenol AE, el cual es protegido entonces como el triflato AF. El acoplamiento de Suzuki catalizado por paladio de AF con un éster o ácido aril/heteroaril borónico apropiadamente sustituido da AG, el cual puede ser fluorado para dar AH. La alquilación con bromuro de alilo provee AI, el cual puede ser reducido mediante condiciones de hidrogenación para proveer AJ. El acoplamiento de AJ con un isocianato apropiadamente sustituido da AK. La oxidación de AK con agentes oxidantes tales como $KMnO_4$ y $NaIO_4$ en disolventes tales como acetona-agua, provee el compuesto de fórmula (I) (1n).

ESQUEMA 12

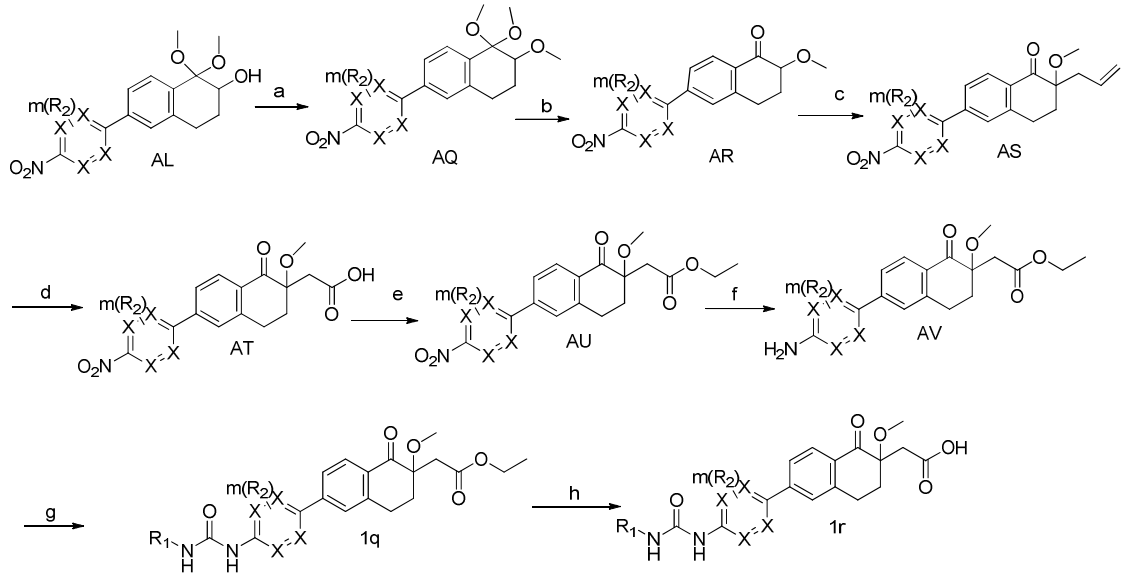


Reactivos y condiciones: a) $PhI(OAc)_2$, KOH, MeOH, t.a.; b) dicromato de piridinio, AcOH, CH_2Cl_2, t.a.; c) LiHMDS, EtOAc, THF, 0°C hasta t.a.; d) HCl 3N, MeOH, t.a.; e) Pd/C, H_2, EtOH, t.a.; f) R_1NCO, Et_3N, THF, t.a.;

g) LiOH, MeOH-THF-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 12. La hidroxilación de AG provee AL, el cual puede ser oxidado hasta la cetona AM. La adición de EtOAc en LiHMDS a la cetona AM da AN, el cual reacciona entonces con HCl 3N para proveer AO. La hidrogenación del grupo nitro en AO da la anilina AP, la cual puede reaccionar con un isocianato apropiadamente sustituido para proveer el compuesto de urea de fórmula (I) (1o). La hidrólisis de 1o provee otro compuesto de fórmula (I) (1p).

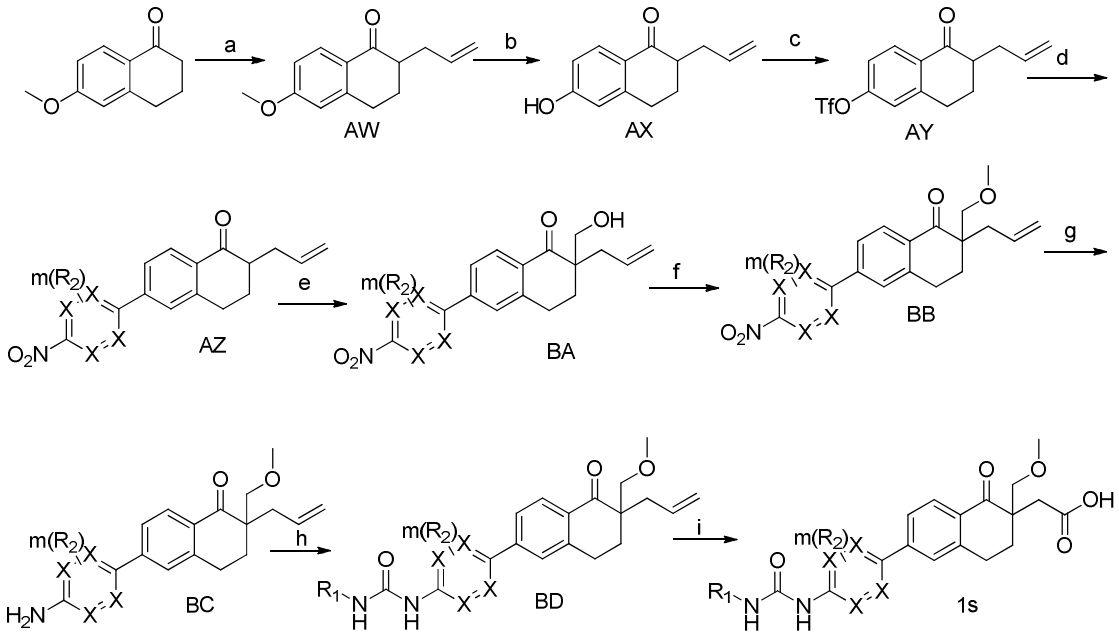
ESQUEMA 13



Reactivos y condiciones: a) NaH, MeI, THF, t.a.; b) HCl 3N, EtOH, t.a.; c) bromuro de alilo, TBAI, KOH, tolueno, t.a.; d) $KMnO_4$, $NaIO_4$, t.a.; e) $MeSO_3H$, EtOH, t.a.; f) Fe-NH_4Cl, EtOH-H_2O, 90°C; g) R_1NCO, Et_3N, THF, t.a.; h) LiOH, THF-H_2O, t.a., 12h.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 13. La alquilación del intermediario AL con un agente de alquilación tal como MeI bajo condición básica provee AQ, el cual reacciona entonces con HCl para proveer la cetona AR. La alquilación de AR con bromuro de alilo da AS, el cual puede ser oxidado hasta el ácido AT. La esterificación de AT provee AU, el cual sufre entonces reducción y formación de urea para formar el compuesto de fórmula (I) (1q). La hidrólisis subsiguiente de 1q provee otro compuesto de fórmula (I) (1r).

ESQUEMA 14

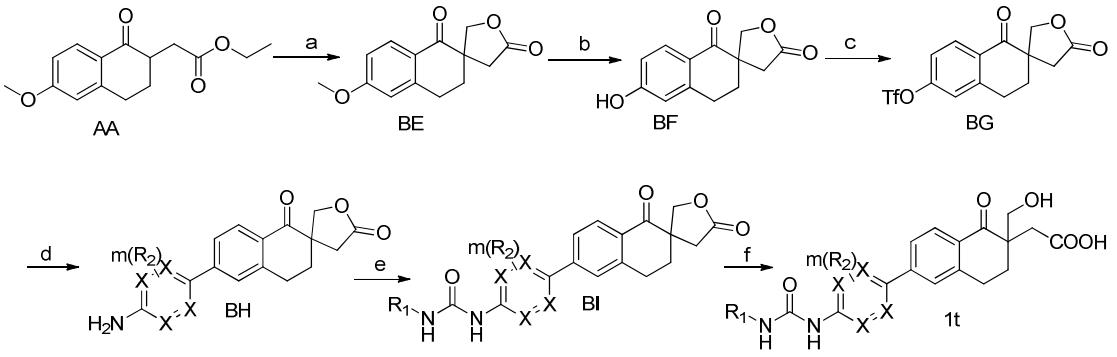


Reactivos y condiciones: a) bromuro de alilo, KOtBu, THF, t.a.; b) BBr_3, CH_2Cl_2, t.a.; c) Tf_2O, Py, CH_2Cl_2, t.a.; d) éster/ácido aril/heteroaril

borónico sustituido, $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; e) HCHO, NaOH 2N, THF, t.a.; f) NaH, MeI, THF, t.a.; g) Fe-NH_4Cl, EtOH-H_2O, 90°C; h) R_1NCO, Et_3N, THF, t.a.; i) $KMnO_4$, $NaIO_4$, acetona-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 14. La alquilación de la 6-metoxi-1-tetralona con bromuro de alilo bajo condición básica, da AW. La desmetilación de AW da el fenol AX, el cual forma el triflato AY usando condiciones estándar conocidas por los expertos en la materia. El acoplamiento Suzuki de AY con un éster o ácido borónico apropiadamente sustituido provee el intermediario nitro AZ, el cual reacciona entonces con formaldehído para formar el alcohol BA. La alquilación del alcohol con un agente de alquilación tal como yoduro de metilo, provee BB. La hidrogenación del grupo nitro en BB da la anilina BC, la cual puede reaccionar entonces con un isocianato apropiadamente sustituido, para formar el compuesto de urea BD. La oxidación de la olefina en BC provee el compuesto de fórmula (I) (1s).

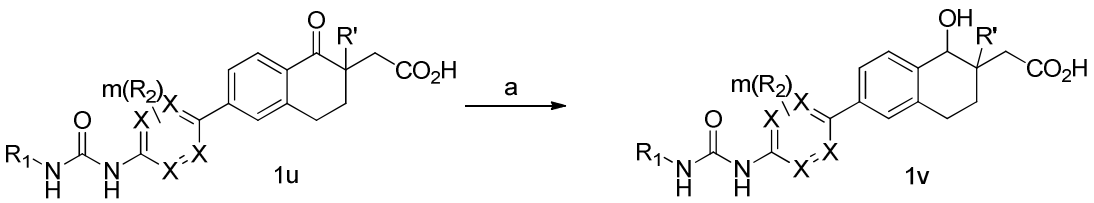
ESQUEMA 15



Reactivos y condiciones: a) HCHO, NaOH 2N, THF, t.a.; b) HBr acuoso, 100°C; c) Tf_2O, Py, CH_2Cl_2, t.a.; d) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C; e) R_1NCO, Et_3N, THF, t.a.; f) LiOH, THF-H_2O, t.a.

Pueden prepararse compuestos de fórmula (I) como se ilustra en el esquema 15. El éster cíclico BE puede formarse a partir del intermediario AA usando formaldehído en NaOH y THF como disolvente. La desmetilación de BE con HBr acuoso da el fenol BF, el cual puede ser convertido al triflato BG usando anhídrido de triflato y piridina. El acoplamiento de Suzuki de BG con un éster o ácido borónico apropiadamente sustituido, da la anilina BH. El acoplamiento de BH con un isocianato apropiadamente sustituido provee la urea BI, la cual puede ser hidrolizada para formar el compuesto de fórmula (I) (1t).

ESQUEMA 16



Reactivos y condiciones: a) $NaBH_4$, MeOH, t.a.

El compuesto de fórmula (I) puede ser convertido a otro compuesto de fórmula (I). Por ejemplo, como se ilustra en el esquema 16, el compuesto de fórmula (I) (1u) puede ser reducido bajo condiciones de reducción estándar conocidas por los expertos en la materia, hasta el alcohol como en el compuesto 1v.

SECCIÓN EXPERIMENTAL

Los siguientes ejemplos ilustran la invención. No se pretende que estos ejemplos limiten el alcance de la presente invención, sino más bien provean una guía para los expertos en la materia para preparar y usar los compuestos, composiciones y métodos de la presente invención. Mientras que se describen modalidades particulares de la presente invención, los expertos en la materia apreciarán que pueden hacerse varios cambios y modificaciones sin que se aparten del espíritu y alcance de la invención. A

menos que se indique de otra manera, los reactivos están disponibles comercialmente o se preparan de acuerdo con los procedimientos en la literatura. Los símbolos y convenciones usados en la descripción de los procedimientos, esquemas y ejemplos son consistentes con los usados en la literatura científica contemporánea, por ejemplo, *TheJournal of the American Chemical Society* o *The Journal of Biological Chemistry*.

En los ejemplos:

Los desplazamientos químicos se expresan en unidades de partes por millón (ppm). Las constantes de acoplamiento (J) están en unidades de hertz (Hz). Los patrones de desdoblamiento describen multiplicidades evidentes y se designan como s (singulete), d (doblete), t (triplete), q (cuarteto), dd (doble doblete), dt (doble triplete), m (banda múltiple) y br (ancha).

Se llevó a cabo cromatografía en columna de vaporización instantánea sobre gel de sílice.

Los programas de nomenclatura usados son ACDLABs 11.0 Namebatch, ACD IUPAC o Chem Draw.

<u>Abreviaturas</u>

BH_3:SMe_2 borano: sulfuro de dimetilo

CH_2Cl_2 diclorometano

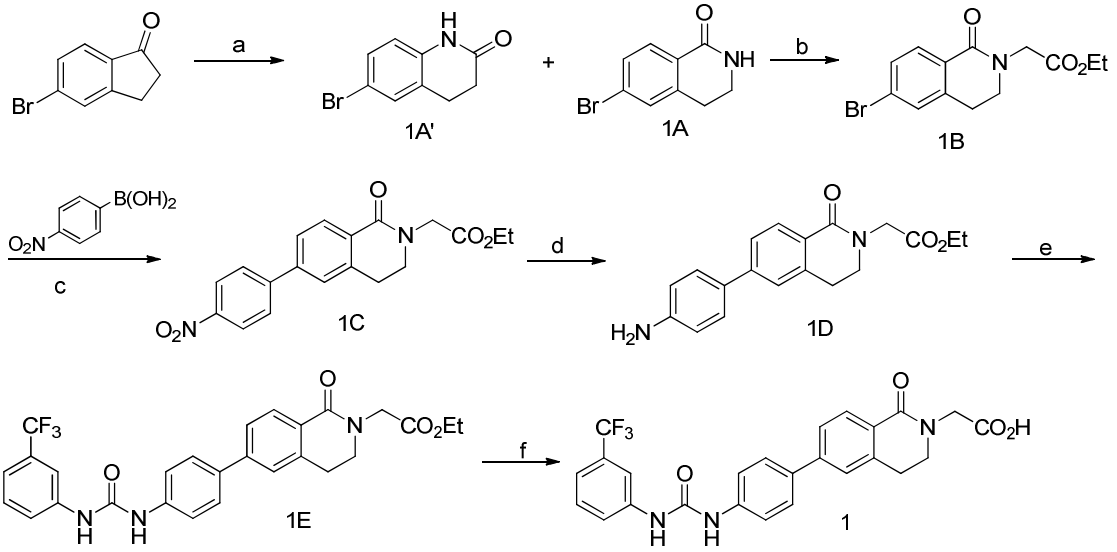
$CHCl_3$ cloroformo

Cs_2CO_3 carbonato de cesio

DMAP	4-(dimetilamino)piridina
DMF	*N*,*N*-dimetilformamida
DMSO	sulfóxido de dimetilo
Et_3N	trietilamina
EtOAc	acetato de etilo
EtOH	etanol
Fe	fierro
h	horas
H_2	hidrógeno gaseoso
H_2O	agua
HATU	hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio
HBr	ácido bromhídrico
HCl	ácido clorhídrico
KOH	hidróxido de potasio
$KMnO_4$	permanganato de potasio
LiHMDS	hexametildisilazida de litio
LiOH	hidróxido de litio
NaH	hidruro de sodio
$NaIO_4$	peryodato de sodio
NaN_3	azida de sodio
NH_4Cl	cloruro de amonio
MeI	yoduro de metilo

MeOH	metanol
$MeSO_3H$	ácido metanosulfónico
Pd/C	paladio sobre carbón
$Pd(PPh_3)_4$	tetraquis(trifenilfosfina)paladio(0)
Py	piridina
t.a.	temperatura ambiente
TBAI	yoduro de tetrabutilamonio
THF	tetrahidrofurano
Tf_2O	anhídrido tríflico

EJEMPLO 1



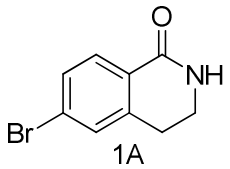
Reactivos y condiciones: a) NaN_3, $MeSO_3H$, CH_2Cl_2, t.a., 8h; b) $BrCH_2CO_2Et$, NaH, THF, t.a., 3h; c) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80°C, 5h; d) Pdal 10%/C, EtOH, H_2, t.a., 4h; e) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; f)

LiOH, THF-H_2O, t.a., 14h.

Procedimientos

Ácido 2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-3,4-dihidroisoquinolin-2(1H)-il)acético

6-Bromo-3,4-dihidroisoquinolin-1(2H)-ona (1A):

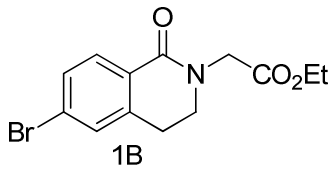


1A

Se añadió NaN_3 (6.2 g, 94.78 mmol) a una solución de 5-bromo-1-indanona (10 g, 47.39 mmol) en 40 mL de una mezcla de ácido metanosulfónico y diclorometano (1:1) en porciones a 0℃-5℃. La mezcla resultante se agitó por 8 horas a temperatura ambiente. La mezcla de reacción se enfrió a 0℃ en un baño de hielo, se neutralizó con NaOH acuoso al 5%, y se extrajo la capa acuosa con acetato de etilo (2x100 mL). La capa orgánica combinada se lavó con solución de salmuera y agua, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró al vacío y se purificó por cromatografía en columna de vaporización instantánea de gel de sílice, usando acetato de etilo al 30% en hexano, para dar el compuesto del título como un sólido (6.4 g, 60%).

^{1}H RMN (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 1H), 7.5 (d, *J* = 8.4 Hz, 1H), 7.4 (s, 1H), 6.1 (bs, 1H), 3.6 (t, *J* = 6.8 Hz, 2H), 3 (t, *J* = 6.4 Hz, 2H).

2-(6-Bromo-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1B):

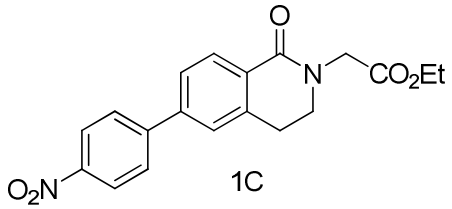


1B

Se añadió NaH (0.42 g, 17.7 mmol) a una solución enfriada en hielo del producto del ejemplo 1A (2 g, 8.8 mmol) en THF (40 ml) en porciones, y la mezcla se agitó por 15 minutos. Entonces se añadió bromoacetato de etilo (2.2 g, 13.2 mmol) a la solución, y la mezcla se agitó a temperatura ambiente por 3 horas. La mezcla de reacción se extinguió con agua enfriada en hielo y se diluyó con acetato de etilo. La capa orgánica se separó, se lavó con salmuera, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró al vacío, para dar el compuesto del título como un sólido (3.3 g, 80%).

^{1}H RMN (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.36 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.65 (t, *J* = 7.2 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.2 Hz, 3H).

2-(6-(4-Nitrofenil)-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1C):

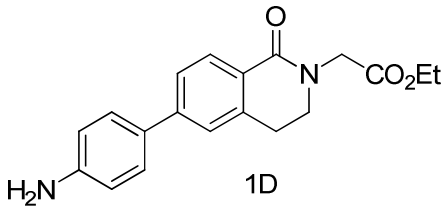


1C

Se añadió $Pd(PPh_3)_4$ (0.133 g, 0.115 mmol) a una solución del producto del ejemplo 1B (3 g, 9.6 mmol) en 35 mL de una mezcla de 1,4 dioxano-H_2O (5:1) bajo una atmósfera de argón, seguido de carbonato de cesio (9.38 g, 28.7 mmol) y ácido 4-nitrofenilborónico (1.6 g, 9.6 mmol).La mezcla de reacción se desgasificó durante 10 minutos. La mezcla de reacción se puso entonces a reflujo por 5 horas, y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio y se filtró. El filtrado se concentró bajo presión reducida y se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al30% en hexano, para dar el compuesto del título como un sólido (2 g, 64%).

^{1}H RMN (300 MHz, $CDCl_3$): δ 8.33-8.3 (m, 2H), 8.2 (d, J = 7.5 Hz, 1H), 7.79-7.75 (m, 2H), 7.61 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 7.45 (s, 1H), 4.39 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.72 (t, J = 6.9 Hz, 2H), 3.16 (t, J = 6.9 Hz, 2H), 1.3 (t, J = 6.9 Hz, 3H).

2-(6-(4-Aminofenil)-1-oxo-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1D):

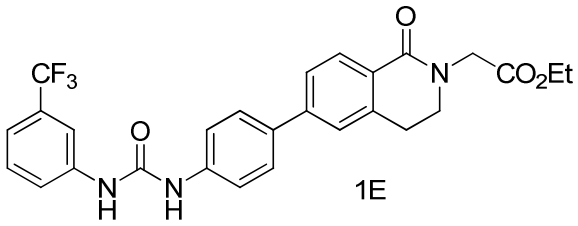


1D

Se añadió exceso de Pd al 10%/C (0.5 g) a una solución del producto del ejemplo 1C (1.1 g, 3.09 mmol) en 20 mL de etanol, y la mezcla se agitó bajo atmósfera de H_2 a temperatura ambiente durante 4 horas. La mezcla de reacción se filtró sobre un lecho de celite y el filtrado se separó bajo presión reducida y se trituró con éter dietílico y pentano, para dar el compuesto del título como un sólido (0.97 g, 97%).

^{1}H RMN (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.0 Hz, 1H), 7.43 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.39 (m, 2H), 7.27 (s, 1H), 6.7 (m, 2H), 4.28 (s, 2H), 4.15 (q, J = 6.8 Hz, 2H), 3.69 (bs, 2H), 3.61 (t, J = 6.4 Hz, 2H), 3.03 (t, J = 6.8 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H).

2-(1-Oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-3,4-dihidroisoquinolin-2(1H)-il)acetato de etilo (1E):

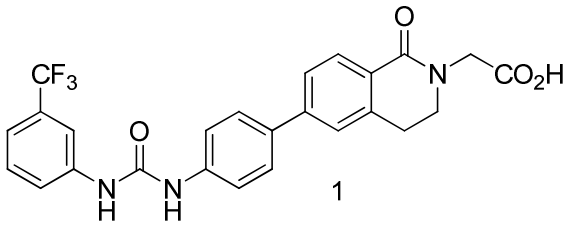


1E

Se añadió isocianato de 3-(trifluorometil)fenilo (0.14 g, 0.769 mmol) a una solución del producto del ejemplo 1D(0.25 g, 0.76 mmol) y trietilamina (0.23 g, 2.3 mmol) en THF (10 mL), y la mezcla se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se trituró con éter dietílico y pentano, para dar el compuesto del título como un sólido (0.26 g, 66%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 9.1 (bs, 1H), 8.97 (bs, 1H), 8.03 (s, 1H), 7.9 (d, J = 7.5 Hz, 1H), 7.71-7.5 (m, 8H), 7.34 (d, J = 7.5 Hz, 1H), 4.31 (s, 2H), 4.17 (q, J = 7.5 Hz, 2H), 3.67 (t, J = 6.3 Hz, 2H), 3.07 (t, J = 6.3 Hz, 2H), 1.22 (t, J = 6.9 Hz, 3H).

Ácido 2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-3,4-dihidroisoquinolin-2(1H)-il)acético (1):



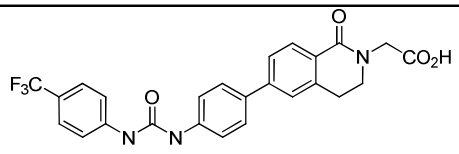
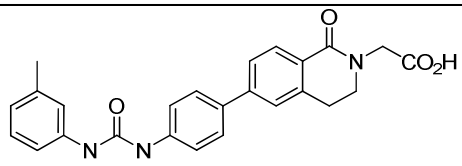
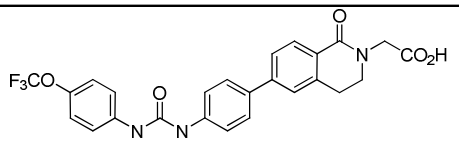
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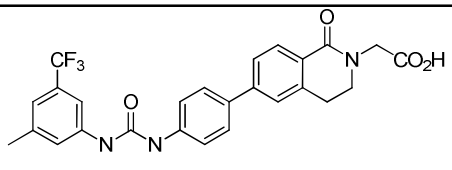
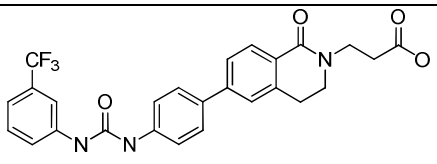
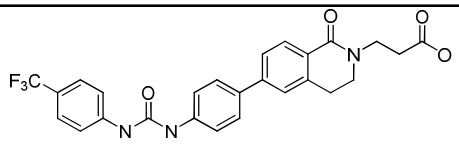
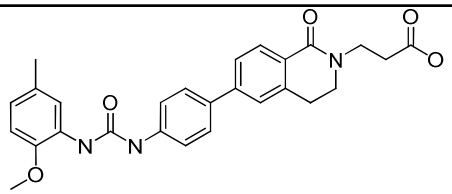
Se añadió hidróxido de litio (0.054 g, 1.17 mmol) a una solución del producto del ejemplo 1E(0.2 g, 0.39 mmol) en 10 mL de una mezcla de THF-agua (4:1), y la mezcla se agitó a temperatura ambiente durante la noche. Después de que el disolvente se eliminó en vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó

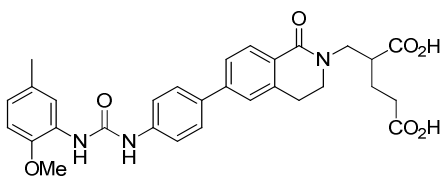
agregando una solución acuosa de HCl 2N hasta que se alcanzara un pH de 2. La solución resultante se enfrió hasta 0°C y el sólido se recogió por filtración y se secó al vacío, para dar el compuesto del título como un sólido (0.15 g, 79%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 9.2 (bs, 1H), 9.0 (bs, 1H), 8.05 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.68 (m, 3H), 7.64-7.58 (m, 4H), 7.52 (m, 1H), 7.0 (m, 1H), 4.2 (s, 2H), 3.65 (m, 2H), 3.05 (m, 2H); ESI-MS m/z = 482 (M-H); pureza HPLC: 96%.

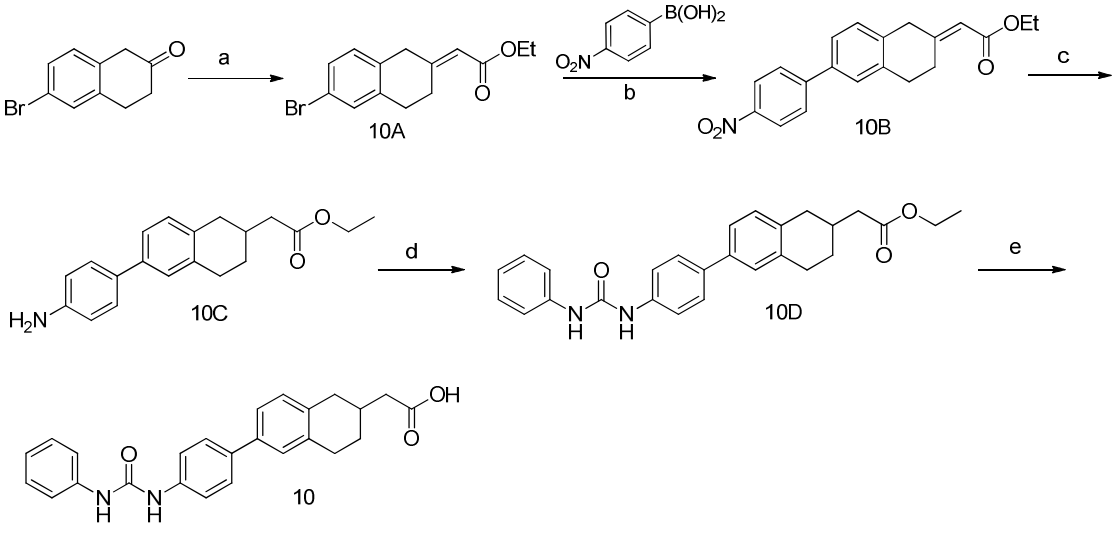
Los ejemplos 2-9 se prepararon usando procedimientos análogos a los que se describen en el ejemplo 1, con los materiales iniciales apropiados.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/Pureza
2		^{1}H-RMN (300 MHz, DMSO-d_6): δ 10.6 (bs, 1H), 7.9-7.78 (m, 4H), 7.6-7.3 (m, 7H), 4.0 (s, 2H), 3.7 (m, 2H), 3.0 (m, 2H).	ESI-MS m/z = 482 $(M-H)^-$; pureza HPLC: 98.5%.
3		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.8 (bs, 1H), 9.2 (bs, 1H), 8.9 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.72-7.56 (m, 6H), 7.36-7.12 (m, 2H), 7.06 (t, 1H), 6.8 (d, J = 7.4 Hz, 1H), 4.2 (s, 2H), 3.65 (t, J = 6.8 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H), 2.26 (s, 3H).	ESI-MS m/z = 428 $(M-H)^-$; pureza HPLC: 99%.
4		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.7 (bs, 1H), 9.1 (bs, 1H), 9.06 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.76-7.56 (m, 8H), 7.3 (m, 2H), 4.2 (s, 2H), 3.65 (t, J = 6.6 Hz, 2H), 3.05 (t, J = 6.6 Hz, 2H).	ESI-LCMS m/z: 500 $(M+H)^+$; (pureza 97%).

Ej.	Estructura	Datos ^{1}H-RMN	Masa/Pureza
5		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.8 (bs, 1H), 9.7 (bs, 1H), 9.6 (bs, 1H), 7.9 (d, *J* = 8.1, 1H), 7.85 (s, 1H), 7.7-7.6 (m, 6H), 7.5 (s, 1H), 7.1 (s, 1H), 4.1 (s, 2H), 3.7 (m, 2H), 3.1 (m, 2H), 2.3 (s, 3H).	ESI-LCMS *m/z*: 497 (pureza 96 %); pureza HPLC 99%.
6		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.47 (bs, 1H), 9.32 (bs, 1H), 8.05 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.67-7.56 (m, 7H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 6.8 Hz, 2H), 3.0 (t, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H).	ESI-LCMS *m/z*: 498 (pureza 95%); pureza HPLC 93%.
7		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.59 (bs, 1H), 9.39 (bs, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.71-7.57 (m, 10H), 3.69 (m, 2H), 3.62 (m, 2H), 3.0 (m, 2H), 2.54 (m, 2H).	ESI-LCMS *m/z*: 498 (pureza 95 %); pureza HPLC 96.6%.
8		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.50 (s, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.89 (d, *J* = 8 Hz, 1H), 7.68-7.55 (m, 6H), 6.90 (d, *J* = 8 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.68 (t, *J* = 7.2 Hz, 2H), 3.61 (t, *J* = 6.8 Hz, 2H), 3.0 (t, *J* = 6.0 Hz, 2H), 2.54 (m, 2H), 2.24 (s, 3H).	ESI-LCMS *m/z*: 474 (pureza 98.5 %); pureza HPLC 98%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/Pureza
9		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.40 (s, 1H), 8.21 (s, 1H), 7.99 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.57-7.55 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.75 (m, 1H), 3.57 (t, *J* = 6.0 Hz, 2H), 3.51 (m, 1H), 3.0 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 1H), 2.4-2.25 (m, 2H), 2.23 (s, 3H), 1.7 (q, *J* = 7.6 Hz, 2H).	ESI-LCMS *m/z*: 546 $(M+H)^+$; pureza HPLC: 96%.

EJEMPLO 10



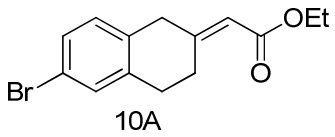
Reactivos y condiciones: a) $Ph_3P=CHCO_2Et$, NaH, DMF, t.a., 18h; b) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 ^{0}C, 6h; c) Pd/C, MeOH, H_2, t.a.,

18h; d) PhNCO, Et_3N, THF, t.a., 12h; e) LiOH, THF-H_2O, t.a., 12h.

Procedimiento:

Acido 2-(6-(4-(3-(3,5-bis(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

2-(6-Bromo-3,4-dihidronaftalen-2(1*H*)-iliden)acetato de etilo (10A):

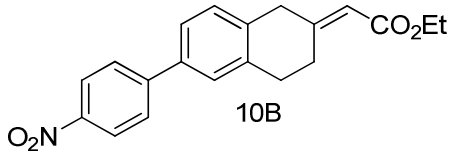


10A

A una solución enfriada en hielo de 6-bromo-2-tetralona (5.0 g, 22.22 mmol) y NaH (0.69 g, 28.88 mmol) en DMF (40 mL), se le agregó $Ph_3P=CHCO_2Et$ (5 g, 22.22 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. La mezcla de reacción se diluyó con agua (20 mL) y se extrajo con éter dietílico (2X100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida para dar un producto crudo que se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 2% en hexano, para producir el compuesto del título como un sólido (4.0 g, 61%) .

^{1}H-RMN (300 MHz, $CDCl_3$): δ7.28 (m, 2H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.33 (s, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.22 (s, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 7.8 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ESI-MS *m/z* = 297 $(M+H)^+$.

2-(6-(4-Nitrofenil)-3,4-dihidronaftalen-2(1*H*)-iliden)acetato de etilo (10B):

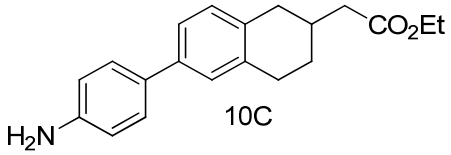


10B

A una solución del producto del ejemplo 10A (4.0 g, 13.55 mmol) en 80 mL de una mezcla de 1,4-dioxano-H_2O (3:1),bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$ (0.18 g, 0.16 mmol), seguido por carbonato de cesio (8.8 g, 27.11 mmol) y ácido 4-nitrofenil-borónico (2.25 g, 13.55 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 6 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea usando acetato de etilo al 12% en hexano para producir el compuesto del título como un sólido (4.0 g, 87%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.3 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.40 (m, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.41 (s, 1H), 4.19 (q, *J* = 7.8 Hz, 2H), 3.25 (s, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 1.28 (t, *J* = 6.9 Hz, 3H).

2-(6-(4-Aminofenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (10C):

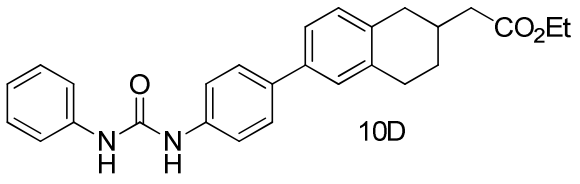


10C

A una solución del producto del ejemplo 10B (4.0 g, 11.86 mmol) en 30 mL de etanol se le agregó un exceso de Pd 10% /C (1.0 g). La mezcla se agitó bajo una atmósfera de H_2 a temperatura ambiente durante 18 h. La mezcla de reacción se filtró sobre una almohadilla de celite, el filtrado se separó bajo presión reducida, y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó al vacío. El producto crudo se lavó con éter dietílico y pentano para producir el compuesto del título como un sólido (3.2 g, 87%).

^{1}H-RMN (400 MHz, DMSO- d_6): δ7.40 (d, J = 8.4 Hz, 2H), 7.26 (m, 2H), 7.05 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 8.8 Hz, 1H), 4.10 (q, J = 7.2 Hz, 2H), 2.86-2.78 (m, 3H), 2.50-2.35 (m, 3H), 2.12 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H), 1.20 (t, J = 6.8 Hz, 3H). ESI-MS m/z = 310 $(M+H)^+$.

2-(6-(4-(3-Fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (10D):

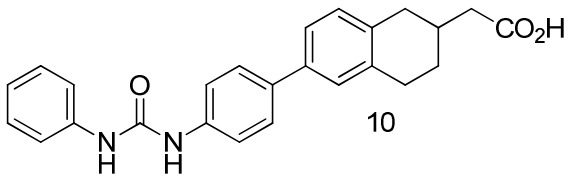


10D

A una solución del producto del ejemplo 10C(0.2 g, 0.64 mmol) y trietilamina (0.098 g, 0.96 mmol) en THF (10 mL)se le agregó isocianato de fenilo (0.084 g, 0.71 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea usando metanol al 1% en cloroformo para producir el compuesto del título como un sólido (0.14 g, 50%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.75 (bs, 1H), 8.65 (bs, 1H), 7.60-7.40 (m, 6H), 7.3-7.21 (m, 4H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.95 (m, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 2.9 (m, 3H), 2.45 (m, 3H), 2.15 (m, 1H), 1.90 (m, 1H), 1.45 (m, 1H), 1.2 (t, *J* = 7.2 Hz, 3H); ESI-MS *m/z* = 429 $(M+H)^+$.

Acido 2-(6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (10):



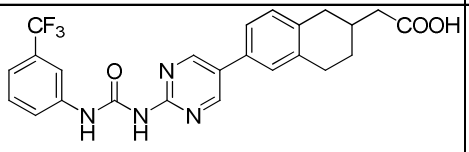
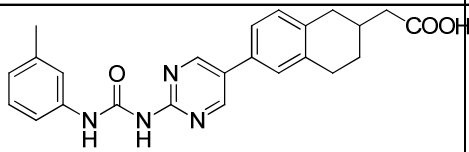
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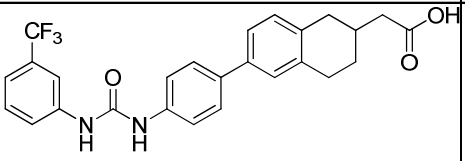
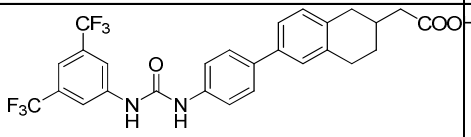
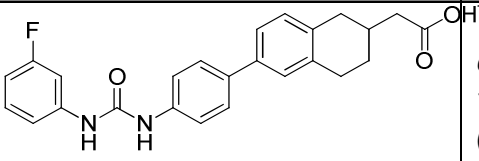
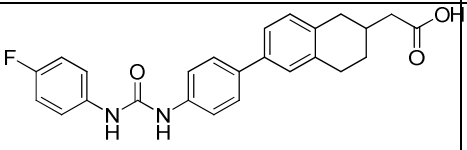
A una solución del producto del ejemplo 10D(0.14 g, 0.327 mmol) en 10 mL de THF-agua (3:1)se le agregó hidróxido de litio (0.068 g, 1.62 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se

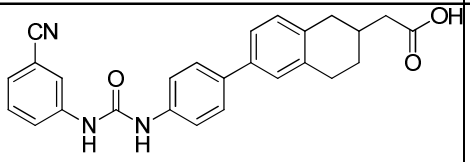
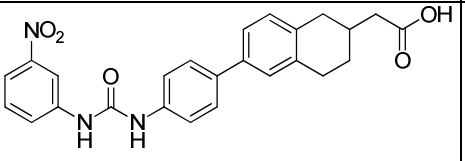
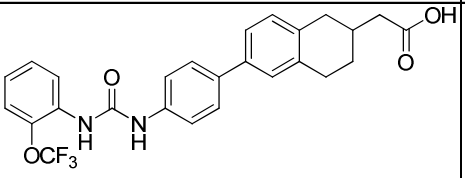
disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 ºC y el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.1 g, 76%).

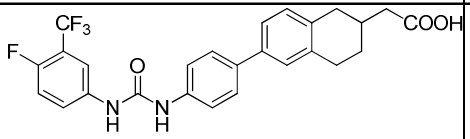
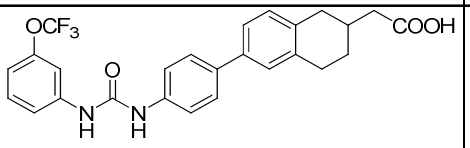
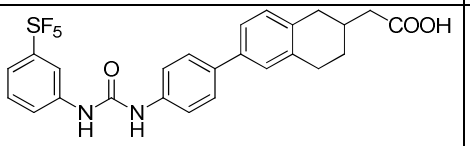
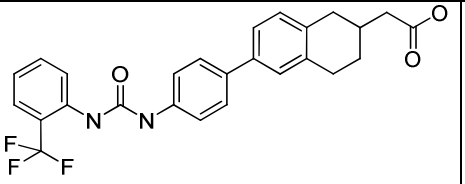
^{1}H-RMN (300 MHz, DMSO-d_6): δ12.13 (bs, 1H), 7.56-7.42 (m, 6H), 7.40-7.24 (m, 4H), 7.10 (d, J = 8.4 Hz, 1H), 7.0-6.94 (m, 1H), 2.90-2.71 (m, 3H), 2.45 (m, 1H), 2.29 (d, J = 6.9 Hz, 2H), 2.10 (m, 1H), 1.91 (m, 1H), 1.42 (m, 1H); ESI-MS m/z = 401 $(M+H)^+$; pureza HPLC: 90%.

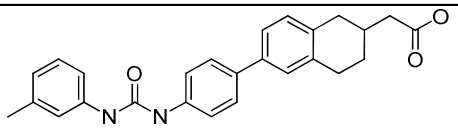
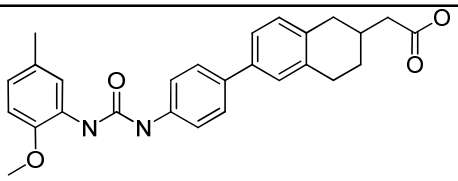
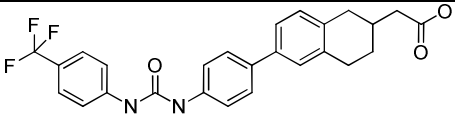
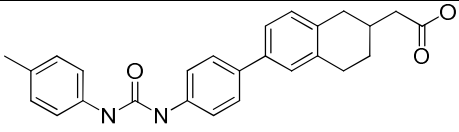
Los ejemplos 11-39 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 10, usando los materiales iniciales apropiados. Los compuestos quirales se separaron usando procedimientos análogos a los que se describen en el ejemplo 129.

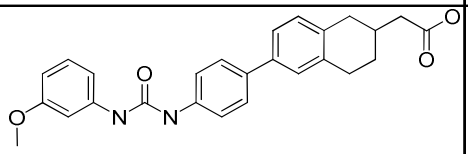
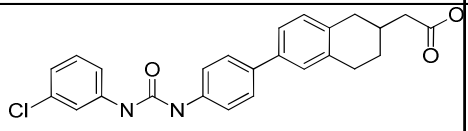
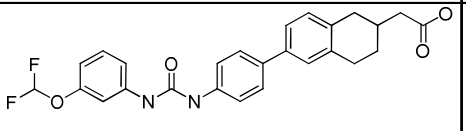
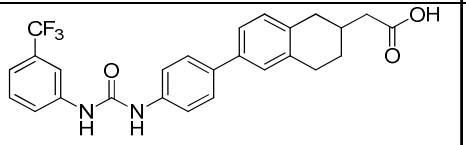
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
11		^{1}H-RMN (400 MHz, DMSO-d_6): δ 11.8 (s, 1H), 10.46 (s, 1H), 9.02 (s, 2H), 8.09 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.5-7.45 (m, 3H), 7.2 (d, J = 8.0 Hz, 1H), 2.95-2.8 (m, 4H), 2.28 (d, J = 7.2 Hz, 2H), 2.12 (m, 1H), 1.94 (m, 1H), 1.45 (m, 1H).	ESI-MS m/z = 471 $(M+H)^+$; pureza HPLC: 92%.
12		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H),11.5 (s, 1H), 10.23 (s, 1H), 9.0 (s, 2H), 7.5-7.4 (m, 4H), 7.3-7.1 (m, 2H), 6.88 (d, J = 7.2 Hz, 1H), 2.95-2.8 (m, 4H), 2.3 (m, 5H), 2.12 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS m/z = 417 $(M+H)^+$; pureza HPLC: 92%.

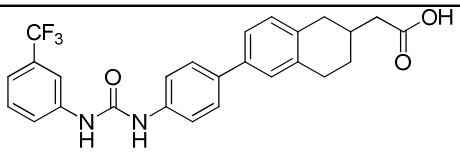
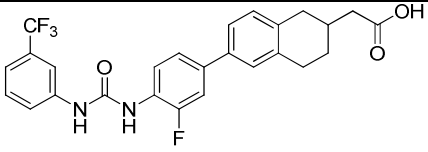
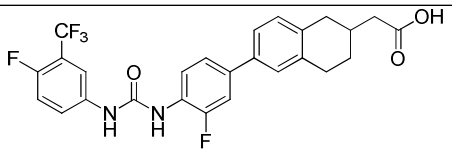
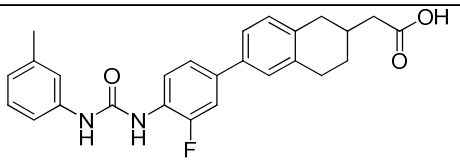
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
13		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.46 (bs, 1H), 9.20 (bs, 1H), 8.04 (s, 1H), 7.63-7.47 (m, 6H), 7.36-7.27 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 1H), 2.90-2.72 (m, 3H), 2.45 (m, 1H), 2.28 (d, *J* = 7.2 Hz, 2H), 2.13 (m, 1H), 1.92 (m, 1H), 1.43 (m, 1H).	ESI-MS *m/z* = 469 $(M+H)^+$. pureza HPLC: 95.96%.
14		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.11 (s, 1H), 9.61 (s, 1H), 9.19 (s, 1H), 8.14 (s, 2H), 7.64 (s, 1H), 7.65-7.52 (m, 4H), 7.35 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 2.9-2.80 (m, 3H), 2.45 (m, 1H), 2.30 (d, *J* = 6.8 Hz, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 537 $(M+H)^+$; pureza HPLC: 98.4%.
15		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.19 (s, 1H), 9.07 (s, 1H), 7.58-7.45 (m, 5H), 7.35-7.25 (m, 3H), 7.18-7.05 (m, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 2.9-2.8 (m, 3H), 2.42 (m, 1H), 2.28 (d, *J* = 6.8 Hz, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.50-1.40 (m, 1H).	ESI-MS *m/z* = 419 $(M+H)^+$. pureza HPLC: 94.4%.
16		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 8.9 (m, 2H), 7.58-7.45 (m, 6H), 7.35-7.31 (m, 2H), 7.1 (m, 3H), 2.91-2.70 (m, 3H), 2.42 (m, 1H), 2.29 (d, *J* = 7.2 Hz, 2H), 2.1 (m, 1H), 1.9 (m, 1H), 1.50 (m, 1H).	ESI-MS *m/z* = 419 $(M+H)^+$. pureza HPLC: 96.14%.

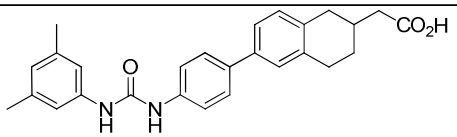
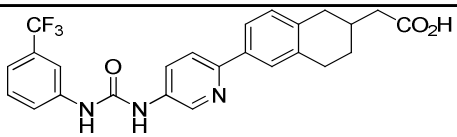
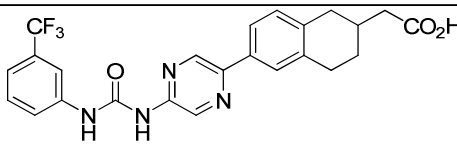
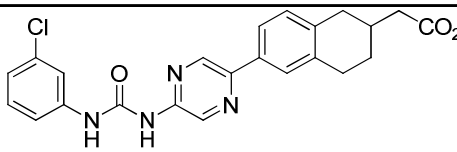
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
17		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.28 (bs, 1H), 9.10 (bs, 1H), 7.99 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60-7.45 (m, 5H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.34 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 2.9-2.8 (m, 3H), 2.45 (m, 1H), 2.30 (d, *J* = 6.8 Hz, 2H), 2.11 (m, 1H), 1.91 (m, 1H), 1.41 (m, 1H).	ESI-MS *m/z* = 426 $(M+H)^+$. pureza HPLC: 93.67%
18		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.67 (bs, 1H), 9.28 (bs, 1H), 8.55 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.54 (m, 5H), 7.33 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 2.90-2.80 (m, 3H), 2.45 (m, 1H), 2.28 (d, *J* = 6.9 Hz, 2H), 2.10 (m, 1H), 1.88 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 446 $(M+H)^+$. pureza HPLC: 93.25%.
19		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.89 (bs, 1H), 9.00 (bs, 1H), 8.22 (d, *J* = 8.4 Hz, 1H), 7.55 (m, 4H), 7.38-7.30 (m, 4H), 7.12-7.05 (m, 2H), 2.91-2.72 (m, 3H), 2.45 (m, 1H), 2.19 (m, 2H), 2.11 (m, 1H), 1.91 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 484 $(M+H)^+$. pureza HPLC: 94.0%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
20		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.19 (s, 1H), 9.0 (s, 1H), 8.02 (s, 1H), 7.64 (m, 1H), 7.6-7.5 (m, 4H), 7.44 (m, 1H), 7.33 (m, 2H), 7.1 (d, *J* = 8.4 Hz, 1H), 2.95-2.75 (m, 3H), 2.5-2.35 (m, 1H), 2.35 (d, *J* = 6.8 Hz, 2H), 2.2 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 487 $(M+H)^+$; pureza HPLC: 90%.
21		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1bs, 1H), 9.05 (s, 1H8.87 (s, 1H), 7.7 (s, 1H), 7.54 (m, 4H), 7.45-7.25 (m, 4H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 2.95-2.75 (m, 3H), 2.5-2.35 (m, 1H), 2.3 (d, *J* = 7.2 Hz, 2H), 2.15 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 485 $(M+H)^+$. LCMS pureza: 96%.
22		^{1}H-RMN (300MHz, DMSO-d_6): δ 12.2 (bs, 1H), 10.12 (bs, 1H9.78 (bs, 1H), 8.3 (s, 1H), 7.65-7.45 (m, 9H), 7.1 (m, 1H), 2.95-2.75 (m, 3H), 2.45-2.25 (m, 3H), 2.0 (m, 2H), 1.43 (m, 1H).	ESI-MS *m/z* = 527 $(M+H)^+$; pureza HPLC: 96%.
23		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 9.44 (bs, 1H), 8.08 (bs, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.69-7.62 (m, 2H), 7.54 (m, 4H), 7.35-7.26 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 1H), 2.90- 2.80 (m, 3H), 2.45 (m, 1H), 2.32 (d, *J* = 6.8 Hz, 2H), 2.10 (m, 1H), 1.92 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 469 $(M+H)^+$; pureza HPLC: 92%.

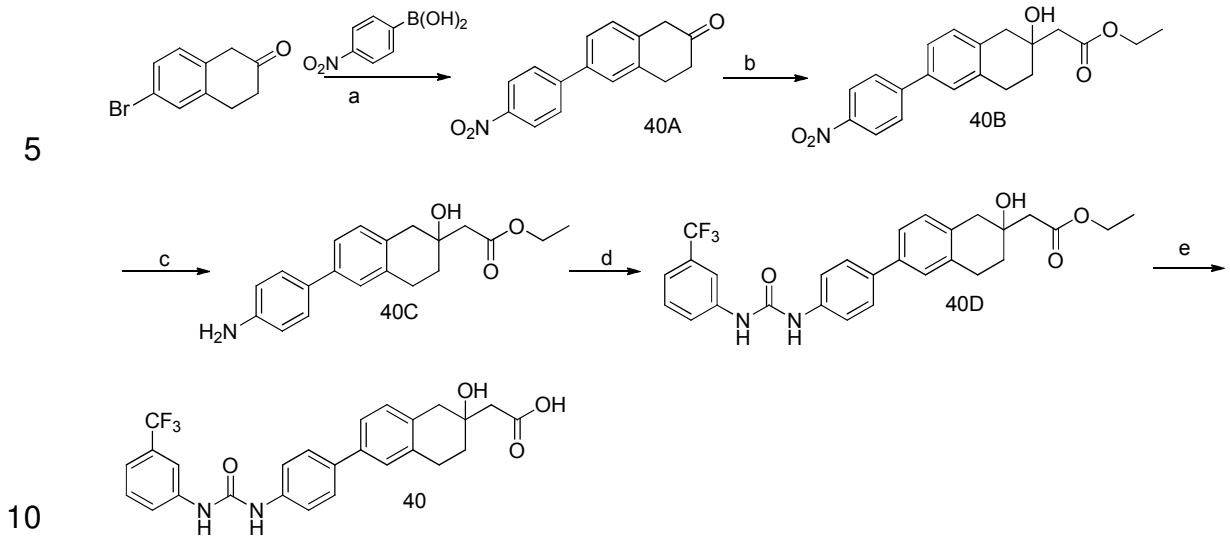
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
24		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 8.71 (bs, 4H), 8.58 (bs, 1H), 7.56- 7.49 (q, *J* = 8.7 Hz, 4H), 7.32 (m, 3H), 7.24-7.08 (m, 3H), 6.78 (d, *J* = 7.5 Hz, 1H), 2.88 (m, 3 H), 2.82 (m, 1H), 2.49 (m, 1H), 2.39 (m, 5H), 1.98 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 415 $(M+H)^+$; pureza HPLC: 92%.
25		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.6 (bs, 1H), 8.3 (bs, 1H), 8.0 (s, 1H), 7.5 (m, 4H), 7.3 (m, 2H), 7.1 (d, *J* = 8.8 Hz, 1H), 6.9 (d, *J* = 8.4 Hz, 1H), 6.7 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 3.85 (s, 3H), 2.8 (m, 2H), 2.4 (m, 1H), 2.35 (s, 3H), 2.2 (d, *J* = 8.8 Hz, 2H), 2.1 (s, 1H), 1.9 (m, 1H), 1.8 (s, 1H), 1.4 (m, 1H).	ESI-MS *m/z* = 445 $(M+H)^+$; pureza HPLC: 89%.
26		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.6 (bs, 1H), 12.2 (bs, 1H), 7.8 (d, *J* = 9.2 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.3 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 2.80 (m, 3H), 2.15 (m, 2H), 2.0 (m, 3H), 1.45 (m, 1H).	ESI-MS *m/z* = 469 $(M+H)^+$; pureza HPLC: 90%.
27		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.68 (bs, 1H), 8.55 (bs, 1H), 7.55-7.49 (q, *J* = 8.8 Hz, 4H), 7.32 (m, 4H), 7.07 (m, 3H), 2.88-2.73 (m, 3H), 2.45 (m, 1H), 2.29 (d, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 2.11 (m, 1H) 1.92 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 415 $(M+H)^+$; pureza HPLC: 92%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
28		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.0 (bs, 2H), 7.55 (m, 4H), 7.35 (m, 2H), 7.2 (m, 2H), 7.1 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.55 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 3.75 (s, 3H), 3.15 (d, *J* = 8.8 Hz, 1H), 2.85 (m, 3H), 2.30 (d, *J* = 7.2 Hz, 2H), 2.15 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 431 $(M+H)^+$; pureza HPLC: 92%.
29		^{1}H-RMN (400 MHz, DMSO-d_6): δ 10.9 (bs, 1H), 10.8 (bs, 1H), 7.86 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.47-7.41 (m, 3H), 7.29-7.24 (m, 3H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 2.90-2.83 (m, 3H), 2.45 (m, 1H), 2.20 (d, *J* = 6.0 Hz, 2H), 2.14 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 435 $(M+H)^+$; pureza HPLC: 89%.
30		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.99 (bs, 1H), 8.88 (bs, 1H), 7.57-7.48 (m, 5H), 7.40-7.02 (m, 6H), 6.77 (d, *J* = 7.2 Hz, 1H), 2.89-2.80 (m, 3H), 2.45 (m, 1H), 2.29 (m, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 467 $(M+H)^+$; pureza HPLC: 91%.
31	 Quiral: enantiómero 1	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.07 (bs, 1H), 8.88 (bs, 1H), 8.04 (s, 1H), 7.60-7.47 (m, 6H), 7.36-7.27 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 1H), 2.88-2.80 (m, 3H), 2.41 (m, 1H), 2.30 (d, *J* = 6.8 Hz, 2H), 2.16 (m, 1H), 1.92 (m, 1H), 1.43 (m, 1H).	ESI-MS *m/z* = 469 $(M+H)^+$. pureza HPLC: 97%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
32	 Quiral: enantiómero-2	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.07 (bs, 1H), 8.88 (bs, 1H), 8.02 (s, 1H), 7.60-7.47 (m, 6H), 7.36-7.27 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 1H), 2.88-2.80 (m, 3H), 2.41 (m, 1H), 2.30 (d, *J* = 6.8 Hz, 2H), 2.16 (m, 1H), 1.92 (m, 1H), 1.43 (m, 1H).	ESI-MS *m/z* = 469 $(M+H)^+$. pureza HPLC: 94%.
33		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 9.41 (s, 1H), 8.69 (s, 1H), 8.18 (t, *J* = 8.8 Hz, 1H), 8.04 (s, 1H), 7.58- 7.51 (m, 3H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.39 (m, 2H), 7.34 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 2.90-2.76 (m, 3H), 2.42 (m, 1H), 2.31 (d, *J* = 6.8 Hz, 2H), 2.11 (m, 1H), 1.92 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 485 $(M-H)^-$. pureza HPLC: 91%.
34		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.55 (bs, 1H), 8.80 (bs, 1H), 8.15 (m, 1H), 8.02 (dd, J_1 = 2.1 Hz, J_2 = 6.3 Hz, 1H), 7.75-7.30 (m, 6H), 7.15 (d, *J* = 8.4 Hz, 1H), 2.95-2.80 (m, 3H), 2.45 (m, 1H), 2.30 (d, *J* = 7.2 Hz, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.45 (m, 1H).	ESI-MS *m/z* = 503$(M-H)^-$. pureza HPLC: 97%.
35		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.03 (bs, 1H), 8.60 (s, 1H), 8.20 (t, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 12.0 Hz, 1H), 7.43 (m, 3H), 7.31 (s, 1H), 7.24-7.10 (m, 3H), 6.68 (d, *J* = 8.0 Hz, 1H), 2.89-2.80 (m, 3H), 2.45 (m, 1H), 2.30 (m, 5H), 2.11 (m, 1H), 1.92 (m, 1H), 1.43 (m,	ESI-MS *m/z* = 433 $(M+H)^+$. pureza HPLC: 97%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
36		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 9.05 (bs, 1H), 8.86 (bs, 1H), 7.52 (m, 4H), 7.31 (m, 2H), 7.08 (m, 3H), 6.60 (m, 1H), 2.87 (m, 3H), 2.45 (m, 1H), 2.26 (m, 2H), 2.23 (s, 6H), 2.11 (m, 1H), 1.90 (m, 1H), 1.42 (m, 1H).	ESI-MS *m/z* = 429 (M+1); pureza HPLC: 96%.
37		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H) 9.25 (bs, 1H), 9.1 (s, 1H), 8.7 (s, 1H), 8.0 (m, 2H), 7.85 (m, 1H), 7.75 (m, 2H), 7.65 (m, 1H), 7.5 (m, 1H), 7.35 (m, 1H), 7.15 (m, 1H), 2.8 (m, 3H), 2.5 (m, 1H), 2.3 (m, 2H), 2.1 (m, 1H), 2.0 (m, 1H), 1.5 (m, 1H).	ESI-LCMS *m/z*: 469; pureza: 97%.
38		^{1}H-RMN (300 MHz, DMSO-d_6): δ 10.67 (bs, 2H), 9.0 (s, 2H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 3.11-3.07 (m, 3H), 2.92-2.86 (m, 1H), 2.68-2.54 (m, 2H), 2.20-2.07 (m, 2H), 1.4 (m, 1H).	ESI-LCMS *m/z*: 470;pureza: 94%; pureza HPLC: 94 %
39		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.8 (s, 1H), 9.7 (s, 1H), 9.1 (s, 1H), 8.9 (d, *J* = 8.0 Hz, 1H), 7.8 (m, 3H), 7.4-7.3 (m, 2H), 7.2 (d, *J* = 8.0 Hz, 1H), 7.1 (m, 1H), 3-2.8 (m, 3H), 2.5-2.4 (m, 1H), 2.3 (d, *J* = 6.8 Hz, 2H), 2.1 (m, 1H), 2-1.9 (m, 1H), 1.5-1.4 (m, 1H).	ESI-LCMS *m/z*: 437 pureza: 96% pureza HPLC: 96 %

EJEMPLO 40

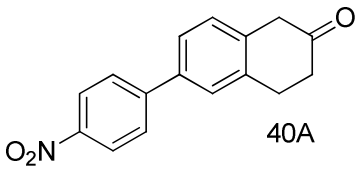


Reactivos y condiciones: a) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 ºC, 4h; b) EtOAc, LiHMDS, THF, -78 ºC a t.a., 4h; c) Pd/C, MeOH, H_2, t.a., 3h; d) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; e) NaOH, MeOH-THF-H_2O, t.a., 12h.

Procedimiento:

Acido 2-(2-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético:

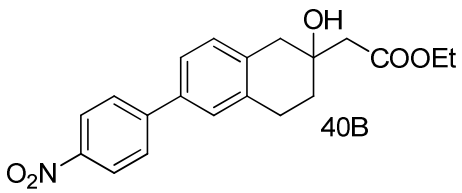
6-(4-Nitrofenil)-3,4-dihidronaftalen-2(1H)-ona (40A):



A una solución de 6-bromo-2-tetralona (1.5 g, 6.66 mmol) en 50 mL de una mezcla de 1,4-dioxano-H_2O (3:1),bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$(0.0736 g, 0.06 mmol), seguido por carbonato de cesio (6.49 g, 19.99 mmol) y ácido 4-nitrofenil-borónico (1.32 g, 7.99 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 4 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea usando acetato de etilo al 18% en hexano para producir el compuesto del título como un sólido (0.9 g, 50%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.31 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.5 (m, 2H), 7.27 (s, 1H), 3.66 (s, 2H), 3.16 (t, *J* = 6.9 Hz, 2H), 2.61 (t, *J* = 6.9 Hz, 2H).

2-(2-Hidroxi-6-(4-nitrofenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (40B):



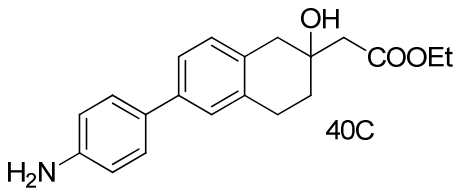
40B

A una solución de Li-HMDS (0.83 g, 5.05 mmol) en 20 mL de THF a -78 °C se le agregó acetato de etilo (0.44 g, 5.05 mmol). La mezcla se

agitó durante 15 min, seguido por la adición del producto del ejemplo 40A (0.4 g, 3.37 mmol). La mezcla de reacción se llevó entonces a temperatura ambiente y se agitó durante 4 h. La mezcla de reacción se apagó con HCl 1N. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea usando acetato de etilo al 30% en hexano para producir el compuesto del título como un sólido amarillo (0.35 g, 66%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.38 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.8 (bs, 1H), 3.16 (m, 1H), 3.0 (d, *J* = 16.8 Hz, 1H), 2.92-2.83 (m, 2H), 2.62 (s, 2H), 2.04 (m, 1H), 1.86 (m, 1H), 1.31 (t, *J* = 8.0 Hz, 3H). ESI-MS *m/z* = 356 $(M+H)^+$.

2-(6-(4-Aminofenil)-2-hidroxi-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (40C):



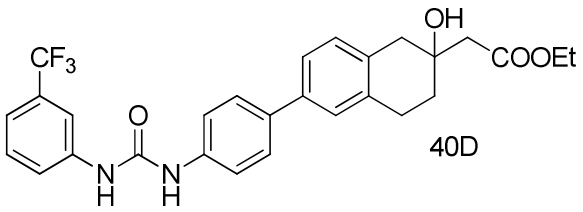
40C

A una solución del producto del ejemplo 40B (0.35 g, 0.98 mmol) en 10 mL de etanol se le agregó un exceso de Pd 10% /C (0.15 g). La mezcla de reacción se agitó bajo una atmósfera de H_2 a temperatura ambiente

durante 3 h. La mezcla de reacción se filtró sobre una almohadilla de celite, el filtrado se separó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó al vacío. El producto crudo se lavó con éter dietílico y pentano para producir el compuesto del título como un sólido (0.26 g, 81%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.28 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 4.24 (q, *J* = 6.8 Hz, 2H), 3.80 (bs, 2H), 3.10 (m, 1H), 2.99-2.79 (m, 3H), 2.62 (s, 2H), 2.01 (m, 1H), 1.83 (m, 1H), 1.29 (t, *J* = 6.4 Hz, 3H). ESI-MS *m/z* = 326 $(M+H)^+$.

2-(2-Hidroxi-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (40D)

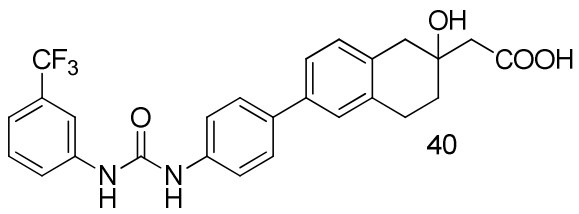


40D

A una solución del producto del ejemplo 40C (0.13 g, 0.40 mmol) y trietilamina (0.12 g, 1.20 mmol) en THF (10 mL)se le agregó isocianato de 3-(trifluorometil)fenilo (0.082 g, 0.44 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido amarillo pálido (0.1 g, 50%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ9.05 (s, 1H), 8.86 (s, 1H), 8.02 (s, 1H), 7.62-7.50 (m, 6H), 7.35-7.25 (m, 3H), 7.08 (m, 1H), 4.7 (s, 1H), 4.07 (q, J = 6.9 Hz, 2H), 2.90 (m, 2H), 2.75 (m, 2H), 2.5 (s, 2H), 1.86 (m, 2H), 1.20 (t, J = 7.8 Hz, 3H). ESI-MS m/z = 513 $(M+H)^+$.

Acido 2-(2-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (40):



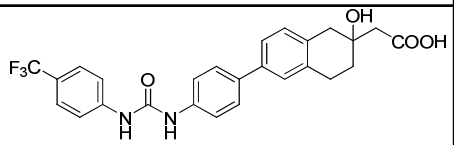
40

A una solución del producto del ejemplo 40D(0.1 g, 0.19 mmol) en 15 mL de una mezcla de THF-metanol-agua (2:1:1) se le agregó hidróxido de sodio (0.023 g, 0.58 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido pardo (0.06 g, 63%).

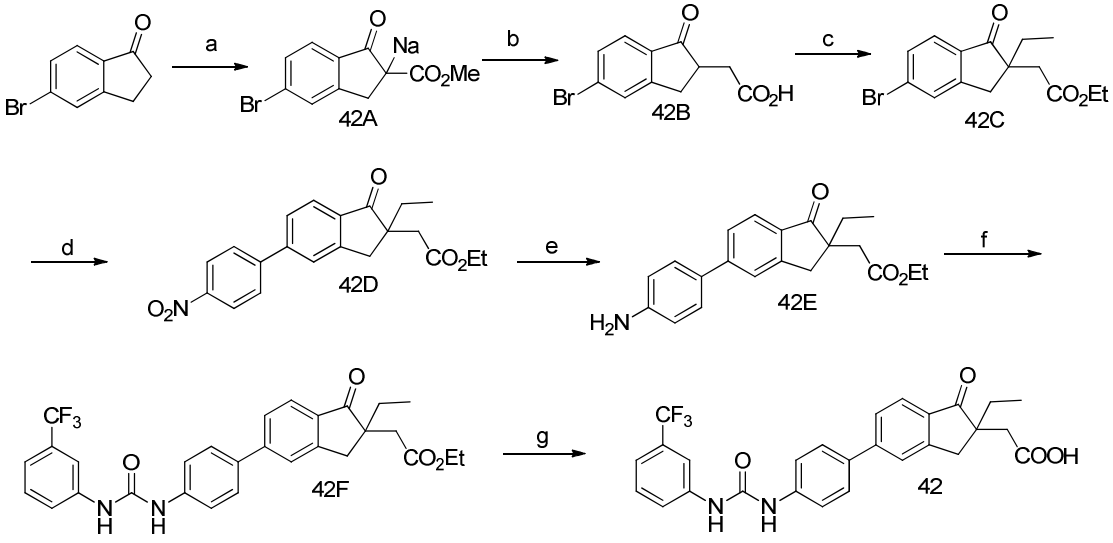
^{1}H-RMN (300 MHz, DMSO-d_6): δ12.2 (bs, 1H), 9.1 (s, 1H), 8.9 (s, 1H), 8.03 (s, 1H), 7.65-7.45 (m, 6H), 7.4-7.35 (m, 3H), 7.08 (d, J = 8.4 Hz, 1H), 4.8 (bs, 1H), 3.05-2.95 (m, 2H), 2.8 (m, 2H), 2.5 (s, 2H), 1.85 (m, 2H);

ESI-MS *m/z* = 485 $(M+H)^+$.

El ejemplo 41 se preparó mediante procedimientos análogos a los que se describen en el ejemplo 40, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos de ^{1}H-RMN	Masa/pureza
41		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H),9.24 (s, 1H), 9.0 (s, 1H), 7.64 (m, 4H), 7.55 (m, 4H), 7.3 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 4.7 (bs, 1H), 3.05-2.95 (m, 2H), 2.85-2.75 (m, 2H), 2.5 (s, 2H), 1.85 (m, 2H).	ESI-MS *m/z* = 485 $(M+H)^+$; LCMS pureza: 96%.

EJEMPLO 42



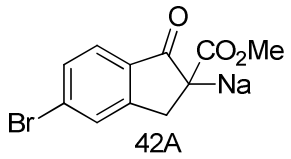
Reactivos y condiciones: a) $CO(OMe)_2$, NaH, THF, 75 °C, 16h;

b) $BrCH_2COOEt$, THF, 75 °C, 5h; c) NaH, EtI, DMF, t.a., 4h; d)$Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; e) Fe/NH_4Cl, EtOH-H_2O, 85 °C, 3h; f) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; g) LiOH, dioxano-H_2O, t.a., 12h.

Procedimiento

Acido 2-(2-etil-1-oxo-5-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-2,3-dihidro-1H-inden-2-il)acético

(5-Bromo-2-(metoxicarbonil)-1-oxo-2,3-dihidro-1H-inden-2-il) sodio (42A):

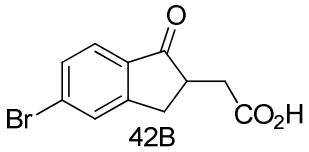


42A

A una solución enfriada en hielo de hidruro de sodio (2.72 g, 113.3 mmol) en THF (100 mL)se le agregó5-bromo-indanona (8 g, 37.9 mmol) y se agitó a temperatura ambiente durante 30 min. Después se le agregó carbonato de dimetilo (17.25 g, 189.56 mmol) y la mezcla se puso a reflujo por 16 h. La mezcla de reacción se enfrió a temperatura ambiente y se vació en agua de hielo. El pH de la solución se hizo básico usando una solución acuosa saturada de NaOH, y se extrajo dos veces con acetato de etilo y se concentró al vacío. El residuo obtenido se disolvió en éter dietílico y se enfrió a 0°C. Se le agregó una solución acuosa saturada de NaOH (10 mL) con agitación. La sal de sodio resultante se recogió por filtración y se secó al vacío para producir el compuesto del título crudo como un sólido (7 g).

^{1}H-RMN (400 MHz, DMSO-d_6): δ7.52 (s, 1H), 7.40 (m, 1H), 7.34 (m, 1H), 3.52 (s, 3H), 3.3 (s, 2H).

Acido 2-(5-bromo-1-oxo-2,3-dihidro-1H-inden-2-il)acético (42B):

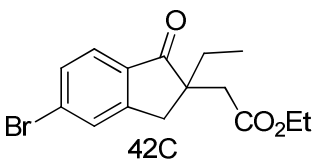


42B

A una solución del producto del ejemplo 42A(7 g, 24 mmol) en THF (50 mL)se le agregó bromoacetato de etilo (10.08 g, 60 mmol). La mezcla de reacción se puso a reflujo por 5 h. La mezcla de reacción se enfrió y se dividió entre acetato de etilo y agua. La capa orgánica separada se lavó con salmuera, se secó sobre sulfato de sodio, se filtró y se concentró al vacío. Al residuo se le agregó una mezcla de HCl–ácido acético 1:1 (40 mL) y se puso a reflujo por 16 h. La mezcla de reacción se enfrió a 0 ºC y el sólido se recogió por filtración, se lavó con agua y se secó al vacío para producir el compuesto del título como un sólido (6 g, 60%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ7.84 (s, 1H), 7.62-7.56 (m, 2H), 3.4-3.3 (m, 1H), 3.0-2.84 (m, 2H), 2.8-2.6 (m, 2H).

2-(5-Bromo-2-etil-1-oxo-2,3-dihidro-1H-inden-2-il)acetato de etilo (42C):

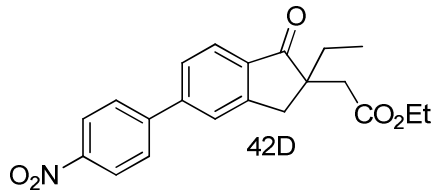


42C

A una solución enfriada en hielo de NaH (2 g, 50 mmol) en DMF (50 mL)se le agregó una solución del producto del ejemplo 42B (4.5 g, 16.8 mmol) en DMF (30 mL) durante un periodo de 30 min. La mezcla de reacción se agitó durante 10 min. Después se le agregó yoduro de etilo (13.1 g, 84.2 mmol) y la mezcla se agitó durante 4 h a temperatura ambiente. La reacción se llevó entonces a 0 ºC; el exceso de NaH se apagó con agua de hielo, y la capa acuosa se extrajo con acetato de etilo (2x100 mL). La capa orgánica combinada se secó sobre sulfato de sodio, se filtró y se separó al vacío para dar el compuesto del título crudo como un sólido (1 g, 18%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ7.64-7.6 (m, 2H), 7.5 (m, 1H), 4.0 (m, 2H), 3.18 (d, *J* = 17.2 Hz, 1H), 3.01 (d, *J* = 17.2 Hz, 1H), 2.86 (d, *J* = 16.4 Hz, 1H), 2.66 (d, *J* = 16.8 Hz, 1H), 1.6 (m, 2H), 1.1 (t, *J* = 7.3 Hz, 3H), 0.75 (t, *J* = 7.6 Hz, 3H).

2-(2-Etil-5-(4-nitrofenil)-1-oxo-2,3-dihidro-1H-inden-2-il)acetato de etilo (42D):



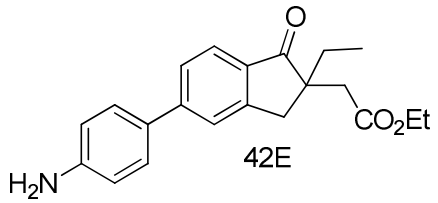
42D

A una solución del producto del ejemplo 42C (0.87 g, 2.7 mmol) en 20 mL de una mezcla de 1,4-dioxano-H_2O (3:1) bajo una atmósfera de

argón, se le agregó $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol), seguido por carbonato de cesio (2.6 g, 8.1 mmol) y ácido 4-nitrofenil-borónico (0.497 g, 2.9 mmol). La mezcla de reacción se desgasificó durante 10 min. La mezcla de reacción se puso a reflujo por 5 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, eluyendo con acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.8 g, 90%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.4-8.3 (m, 2H), 7.86 (m, 1H), 7.76 (m, 2H), 7.7-7.6 (m, 2H), 4.0 (q, *J* = 6.3 Hz, 2H), 3.28 (d, *J* = 17.7 Hz, 1H), 3.11 (d, *J* = 17.4 Hz, 1H), 2.92 (d, *J* = 16.2 Hz, 1H), 2.7 (d, *J* = 16.8 Hz, 1H), 1.8-1.6 (m, 2H), 1.1 (t, *J* = 7.2 Hz, 3H), 0.8 (t, *J* = 6.9 Hz, 3H).

2-(5-(4-Aminofenil)-2-etil-1-oxo-2,3-dihidro-1H-inden-2-il)acetato de etilo (42E):



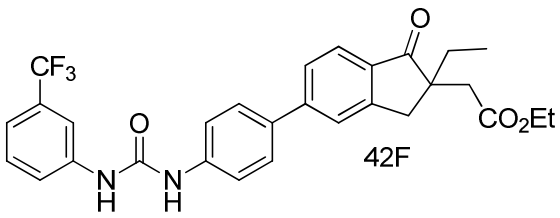
42E

A una solución del producto del ejemplo 42D (0.8 g, 2.17 mmol) en 15 mL de una mezcla de etanol-agua (2:1)se le agregó polvo de fierro (0.36 g, 6.5 mmol),seguido por NH_4Cl (0.058 g, 1.08 mmol). La mezcla de reacción

se puso a reflujo por 3 h. El disolvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó al vacío para dar el compuesto del título(0.65 g, 88%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.58-7.52 (m, 2H), 7.5-7.44 (m, 2H), 6.8-6.76 (m, 2H), 4.0 (m, 2H), 3.2 (d, *J* = 17.4 Hz, 1H), 3.05 (d, *J* = 16.8 Hz, 1H), 2.84 (d, *J* = 15.6 Hz, 1H), 2.66 (d, *J* = 16.8 Hz, 1H), 1.8-1.6 (m, 2H), 1.05(m, 3H), 0.8 (m, 3H).

2-(2-Etil-1-oxo-5-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-2,3-dihidro-1H-inden-2-il)acetato de etilo (42F):



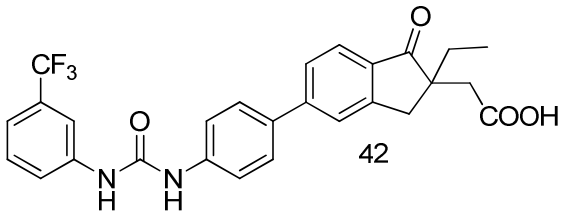
42F

A una solución del producto del ejemplo 42E(0.22 g, 0.65 mmol) y trietilamina (0.2 g, 1.95 mmol) en THF (10 mL)se le agregó isocianato de 3-(trifluorometil)fenilo (0.12 g, 0.65 mmol),y se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se trituró con éter dietílico y pentano para producir el compuesto del título como un sólido (0.21 g, 54%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.78-7.7 (m, 2H), 7.68-7.62 (m, 1H), 7.54 (m, 1H), 7.44-7.36 (m, 4H), 7.34 (m, 1H), 7.28 (m, 2H), 4.0 (q, *J* =

6.9 Hz, 2H), 3.2 (d, *J* = 17.4 Hz, 1H), 3.1 (d, *J* = 17.4 Hz, 1H), 3.0 (d, *J* = 16.5 Hz, 1H), 2.7 (d, *J* = 16.8 Hz, 1H), 1.7 (m, 2H), 1.1 (t, *J* = 6.9 Hz, 3H), 0.8 (t, *J* = 7.8 Hz, 3H).

Acido 2-(2-etil-1-oxo-5-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-2,3-dihidro-1H-inden-2-il)acético (42):

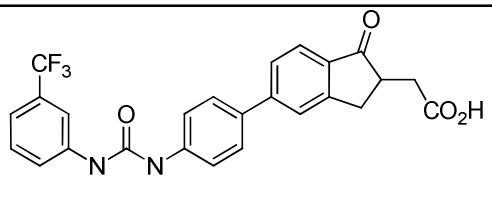
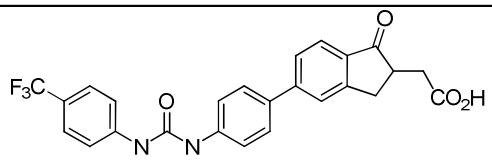
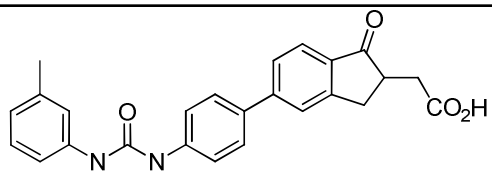
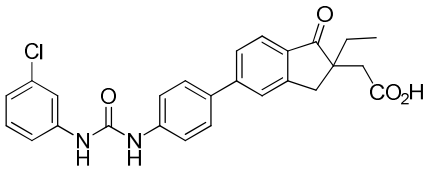


42

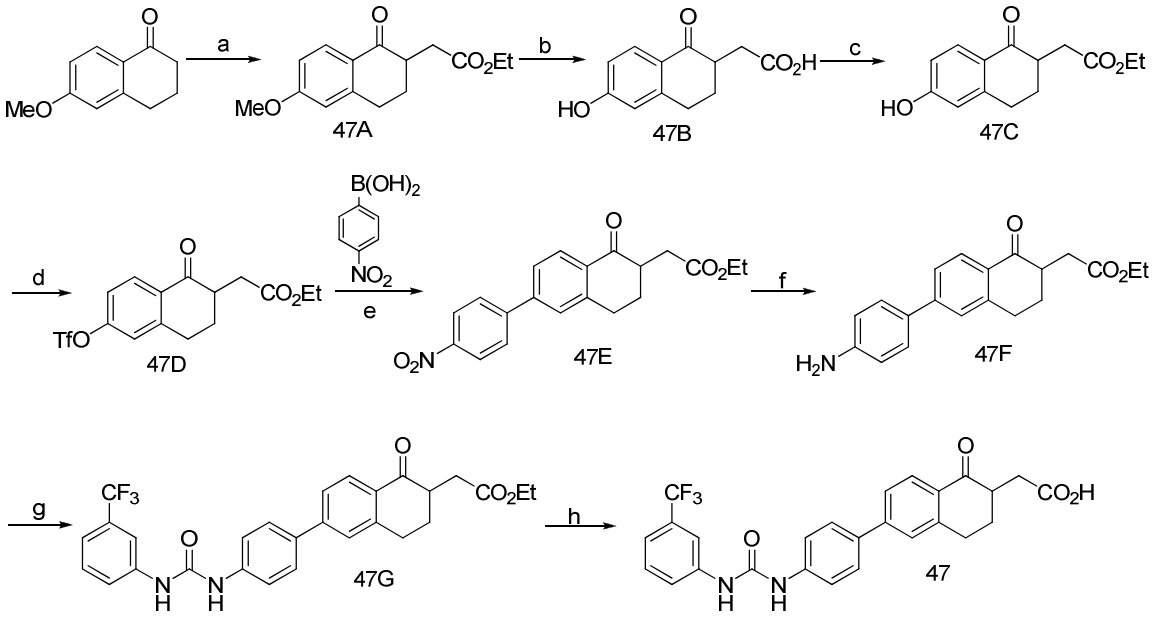
A una solución del producto del ejemplo 42F (0.2 g, 0.38 mmol) en 4 mL de una mezcla de 1,4-dioxano-agua (3:1) se le agregó hidróxido de litio (0.048 g, 1.1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido (0.15 g, 79%).

^{1}H-RMN (400 MHz, DMSO-*d*6): δ 8.1 (s, 1H), 7.8-7.6 (m, 4H), 7.46-7.4 (m, 3H), 7.3-7.2 (m, 3H), 3.2 (d, *J* = 17.2 Hz, 1H), 3.0 (d, *J* = 17.2 Hz, 1H), 2.7 (d, *J* = 16.4 Hz, 1H), 2.5 (d, *J* = 16.4 Hz, 1H), 1.5 (m, 2H), 0.7 (t, *J* = 7.2 Hz, 3H); ESI-MS m/z: 497 (M+H); pureza HPLC: 95.6%.

Los ejemplos 43-46 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 42, usando los materiales iniciales apropiados, excepto que en los ejemplos 43-45 no se hizo el paso de alquilación con yoduro de etilo en presencia de NaH como en el ejemplo 42.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/Pureza
43		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.15 (s, 1H), 9.05 (bs, 1H), 8.05 (bs, 1H), 7.85 (s, 1H), 7.75-7.66 (m, 4H), 7.65-7.5 (m, 5H), 3.4 (m, 1H), 3.0-2.9 (m, 2H), 2.8-2.6 (m, 2H).	ESI-MS *m/z* = 469 $(M+H)^+$; pureza HPLC: 91.8%.
44		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.3 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 7.86 (s, 1H), 7.8-7.9 (m, 10H), 3.4 (m, 1H), 3.0-2.6 (m, 4H).	ESI-MS *m/z* = 469 $(M+H)^+$; pureza HPLC: 93.7%.
45		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.3 (bs, 1H), 9.0 (bs, 1H), 8.8 (bs, 1H), 7.8 (s, 1H), 7.7 (m, 4H), 7.56 (m, 2H), 7.3 (s, 1H), 7.28-7.0 (m, 2H), 6.8 (m, 1H), 3.4 (m, 1H), 3.0-2.86 (m, 2H), 2.8-2.6 (m, 2H), 2.26 (s, 3H).	ESI-MS *m/z* = 415 $(M+H)^+$; LCMS pureza: 91%.
46		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.25 (bs, 1H), 7.8-7.5 (m, 8H), 7.3 (bs, 2H), 7.0 (s, 1H), 3.2 (d, *J* = 17.2 Hz, 1H), 3.05 (d, *J* = 17.2 Hz, 1H), 2.7 (d, *J* = 16.4 Hz, 1H), 2.5 (d, *J* = 16.4 Hz, 1H), 1.5 (m, 2H), 0.8 (t, *J* = 6.8 Hz, 3H).	ESI-MS m/z: 463 (M+H); pureza HPLC: 95%.

EJEMPLO 47

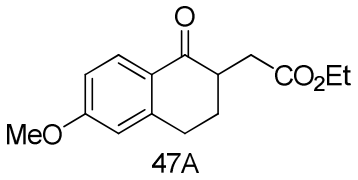


Reactivos y condiciones: a) n-BuLi, i-Pr_2NH_2,-60 ºC, 16 h; b) HBr acuoso, 100 ºC, 16 h; c) $MeSO_3H$, EtOH, t.a., 5h; d) Tf_2O, CH_2Cl_2, Et_3N, t.a., 2h; e) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 ºC, 2h; f) Pd/C, H_2, EtOH, t.a., 3h; g) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; h) LiOH, EtOH-H_2O, t.a., 12h.

Procedimientos

Acido 2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

Acido 2-(6-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (47A):

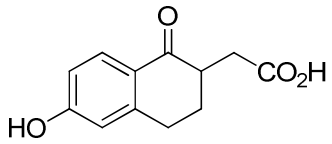


47A

A una solución de diisopropilamina (6.88 g, 68.11 mmol) en THF (50 mL) a -60 °C, se le agregó n-butil-litio (3.27 g, 51.04 mmol) y la mezclase agitó durante 0.5 h. A la mezcla de reacción se le agregó lentamente 6-metoxi-1-tetralona (6 g, 34.09 mmol) en THF (10 mL), la mezclase agitó durante 45 min y se le agregó bromoacetato de etilo (11.9 g, 71.25 mmol). Luego, la mezcla de reacción se agitó a temperatura ambiente durante 16 h y se apagó con solución saturada de NH_4Cl. La mezcla de reacción se extrajo con EtOAc (X2), la capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 anhidro, se filtró y se concentró, para dar 5.3 g del compuesto del título.

Alternativamente, el ejemplo 47A se puede obtener usando procedimientos similares a los que se describen en el ejemplo 79C.

Acido 2-(6-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (47B):

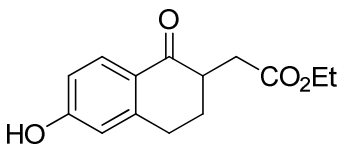


47B

Al producto del ejemplo 47A (5 g, 19.08 mmol)se le agregó HBr acuoso (75 mL) y la mezcla de reacción se puso a reflujo por 16 h. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo (2X100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El producto crudo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 25% en éter de petróleo, para producir el compuesto del título como un sólido (3 g, 71%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ12.07 (bs, 1H), 10.3 (bs, 1H), 7.73 (d, J = 8.4 Hz, 1H), 6.7 (m, 1H), 6.6 (m, 1H), 3.3-2.93 (m, 2H), 2.84-2.77 (m, 1H), 2.68 (m, 1H), 2.35 (m, 1H), 2.1 (m, 1H), 1.85 (m, 1H).

2-(6-Hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (47C):

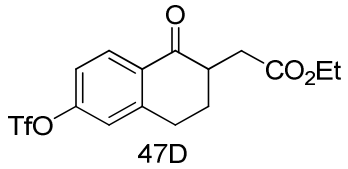


47C

A una solución del ejemplo 47B (2 g, 9.09 mmol) en etanol (30 mL)se le agregó ácido metanosulfónico (5 mL), y la mezcla se agitó a temperatura ambiente durante 6 h. El etanol se separó de la mezcla de reacción bajo presión reducida y el residuo se diluyó con acetato de etilo y se lavó con solución de salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó al vacío para producir el compuesto del título como un sólido (2.15 g, 97%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ7.94 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.26 (bs, 1H), 4.2 (q, *J* = 6.8 Hz, 2H), 3.1-2.85 (m, 4H), 2.4 (m, 1H), 2.2 (m, 1H), 1.95 (m, 1H), 0.8 (t, *J* = 6.8 Hz, 3H).

2-(1-Oxo-6-(trifluorometilsulfoniloxi)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (47D):



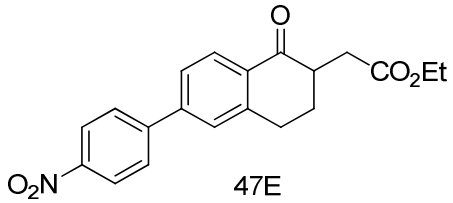
47D

A una solución enfriada en hielo del producto del ejemplo 47C (3 g, 12.09 mmol) y piridina (1.05 g, 13.29 mmol) en diclorometano (50 mL)se le agregó anhídrido tríflico (3.41 g, 12.09 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (50 mL) y se lavó con una solución acuosa saturada de NaCl (50 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de

vaporización instantánea, usando acetato de etilo al 5% en éter de petróleo, para dar el compuesto del título como un sólido (2.8 g, 62%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.12 (d, *J* = 8.8 Hz, 1H), 7.24-7.12 (m, 2H), 4.2 (q, *J* = 6.8 Hz, 2H), 3.2 (m, 1H), 3.1-2.9 (m, 3H), 2.5 (m, 1H), 2.3 (m, 1H), 2.0 (m, 1H), 1.2 (t, *J* = 6.8 Hz, 3H).

2-(6-(4-Nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (47E):



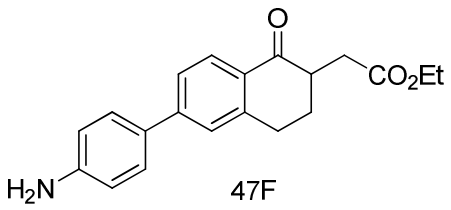
47E

A una solución del producto del ejemplo 47D (4.8 g, 12.6 mmol) en 26 mL de una mezcla de 1,4-dioxano-H_2O (4:1),bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$ (0.174 g, 0.15 mmol), seguido por carbonato de cesio (11.73 g, 36 mmol) y ácido 4-nitrofenil-borónico (2.3 g, 13.8 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 2 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida para dar un producto crudo, que se purificó por cromatografía de vaporización instantánea para producir el compuesto del título como un sólido (2.2 g, 59%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.4 (d, *J* = 7.6 Hz, 2H), 8.15 (d, *J* =

8.4 Hz, 1H), 7.78 (d, *J* = 7.2 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.5 (s, 1H), 4.2 (q, *J* = 6.8 Hz, 2H), 3.3-3.0 (m, 4H), 2.5 (m, 1H), 2.3 (m, 1H), 2.05 (m, 1H), 1.3 (t, *J* = 6.8 Hz, 3H).

2-(6-(4-Aminofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (47F):

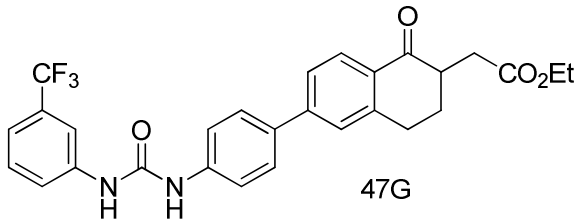


47F

A una solución del producto del ejemplo 47E (1.1 g, 3.11 mmol) en 30 mL de etanol, se le agregó un exceso de Pd 10% /C (0.2 g), y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se filtró sobre una almohadilla de celite, el filtrado se concentró bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El producto crudo se lavó con éter dietílico y pentano para producir el compuesto del título como un sólido (0.8 g, 80%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.04 (m, 1H), 7.46-7.39 (m, 4H), 6.75 (m, 2H), 4.19 (m, 2H), 3.8 (bs, 2H), 3.14-3.04 (m, 4H), 2.42 (m, 1H), 2.26 (m ,1H), 2.0 (m, 1H), 1.29 (m, 3H).

2-(1-Oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (47G):

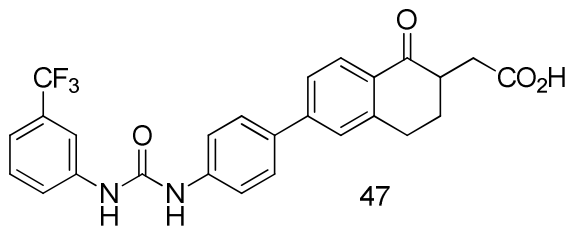


47G

A una solución del producto del ejemplo 47F(0.26 g, 0.18 mmol) y trietilamina (0.656 g, 0.55 mmol) en THF (5 mL)se le agregó isocianato de 3-(trifluorometil)fenilo(0.234 g, 0.18 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.1 g, 31%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ9.3 (bs, 1H), 9.0 (bs, 1H), 8.04 (s, 1H), 7.9 (m, 1H), 7.79-7.46 (m, 8H), 7.34 (m, 1H), 4.1 (q, J = 6.8 Hz, 2H), 3.2-2.9 (m, 3H), 2.75 (m, 2H), 2.2 (m, 1H), 1.2 (t, J = 6.8 Hz, 3H).

Acido 2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (47):

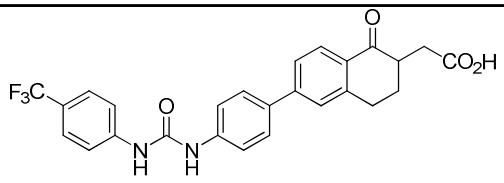
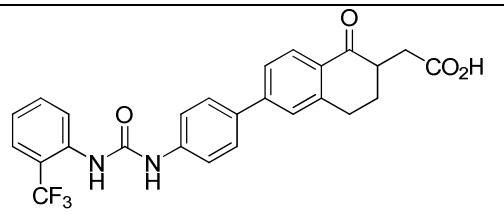
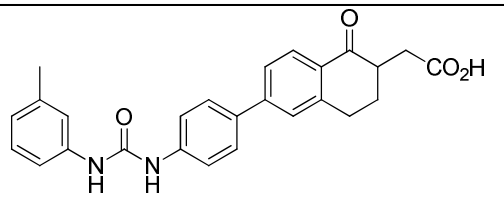
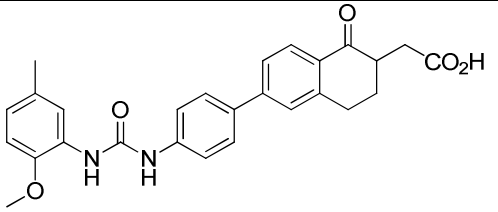
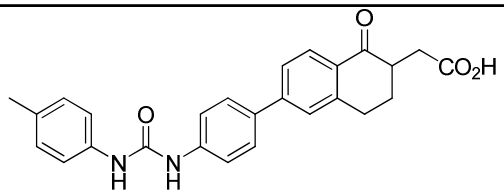


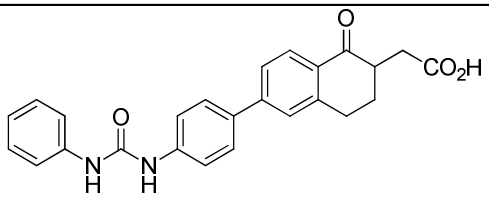
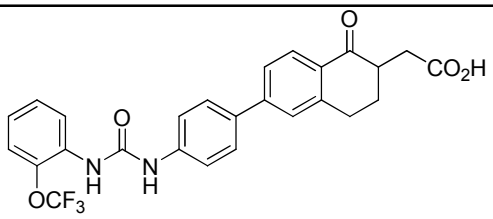
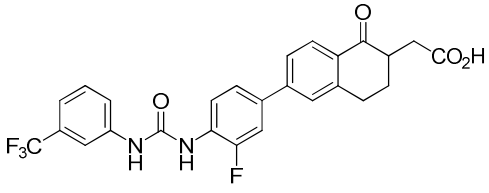
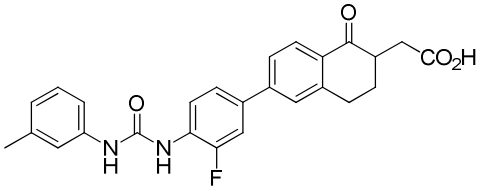
47

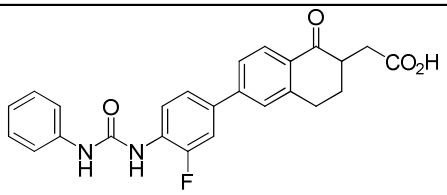
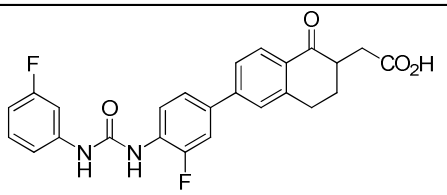
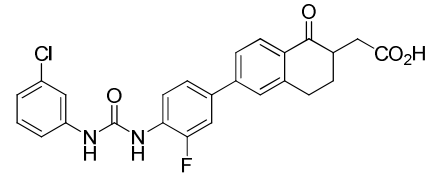
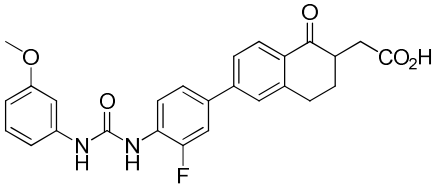
A una solución del producto del ejemplo 47H(0.06 g, 0.11 mmol) en 4 mL de una mezcla de etanol-agua (3:1) se le agregó hidróxido de litio (0.015 g, 0.35 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, y el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido blanco (0.042 g, 75%).

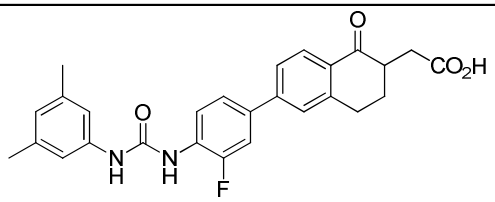
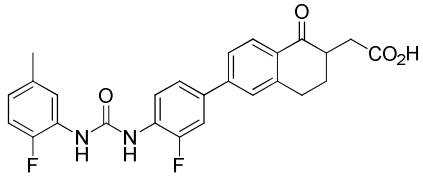
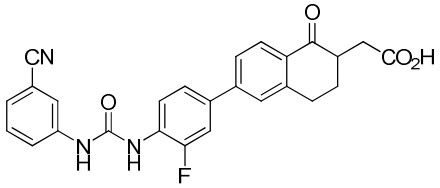
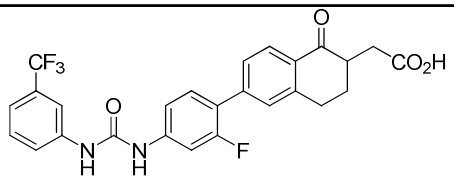
^{1}H-RMN (300 MHz, DMSO-d_6): δ12.0 (bs, 1H), 9.4 -9.0 (bs, 2H), 8.0 (m, 1H), 7.9 (m, 1H), 7.7 -7.54 (m, 7H), 7.46 (m, 1H), 7.3 (m, 1H), 3.2 -3.0 (m, 2H), 2.8 (m, 1H), 2.5 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H); ESI-MS *m/z* = 483 $(M+H)^+$; pureza HPLC: 92.5%.

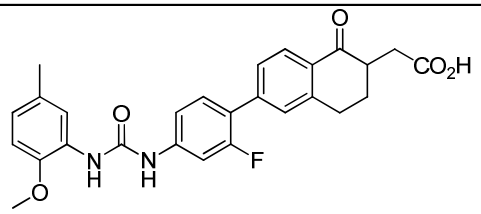
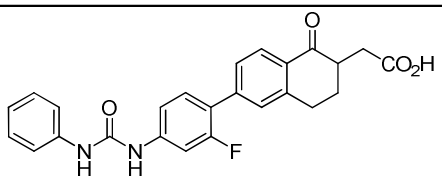
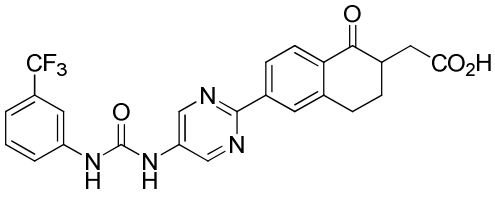
Los ejemplos 48-67 se prepararon mediante procedimientos análogos a los que se describen para el ejemplo 47, usando los materiales iniciales apropiados. Los ácidos borónicos requeridos (y las versiones con grupos funcionales adecuadamente protegidos de los mismos) aquí utilizados se compraron en caso de estar disponibles comercialmente, o se sintetizaron como se describe en la literatura o por medio de modificaciones rutinarias conocidas para los expertos en la materia, o se sintetizaron mediante procedimientos alternos conocidos por los expertos en la materia.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/Pureza
48		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.25 (bs, 1H), 9.05 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.75 -7.55 (m, 10H), 3.2-2.8 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 483 $(M+H)^+$; pureza HPLC: 90%.
49		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.6 (bs, 1H), 8.2 (bs, 1H), 8.0-7.9 (m, 2H), 7.8-7.5 (m, 8H), 7.3 (t, *J* = 8.0 Hz, 1H), 3.2-2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 483 $(M+H)^+$; pureza HPLC: 95%.
50		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.85 (bs, 1H), 8.65 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.74-7.54 (m, 6H), 7.3 (s, 1H), 7.24 (m, 1H), 7.16 (m, 1H), 6.8 (d, *J* = 6.8 Hz, 1H), 3.2-2.9 (m , 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.26 (s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 429 $(M+H)^+$; LCMS pureza: 95%.
51		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.5 (bs, 1H), 8.2 (bs, 1H), 8.0 (s, 1H), 7.9 (m, 1H), 7.7 -7. 5 (m, 6H), 6.9 (m, 1H), 6.8 (m, 1H), 3.8 (s, 3H), 3.2 -2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.26 (s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 459 $(M+H)^+$; LCMS pureza: 96.7%.
52		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.6 (bs, 1H), 9.3 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.7-7.5 (m, 6H), 7.4 (m, 2H), 7.06 (m, 2H), 3.2-2.8 (m, 3H), 2.7-2.6 (m, 2H), 2.26 (s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	pureza HPLC: 91%.

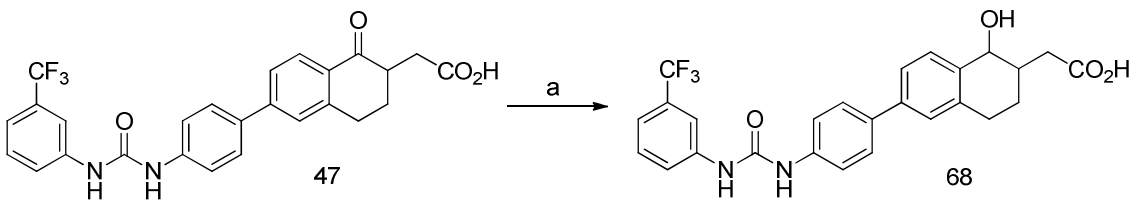
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
53		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 7.9 (d, *J* = 8.1 Hz, 1H), 7.7-7.45 (m, 8H), 7.25 (t, *J* = 7.5 Hz, 2H), 6.95 (t, *J* = 7.8 Hz, 1H), 3.2-2.85 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	pureza HPLC: 92%.
54		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.5 (bs, 1H), 8.6 (bs, 1H), 8.36 (m, 1H), 7.9 (m, 1H), 7.76 -7.56 (m, 6H), 7.38 (m, 2H),7.3 (m, 1H), 3.2-2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	pureza HPLC: 94.7%.
55		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 9.7 (bs, 1H), 8.9 (bs, 1H), 8.27 (t, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.9 (d, *J* = 8.7 Hz, 1H), 7.7 (m, 3H), 7.65-7.5 (m, 3H), 7.35 (d, *J* = 6.6 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	pureza HPLC: 96.75%.
56		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.15 (bs, 1H), 8.75 (bs, 1H), 8.3 (t, *J* = 8.8 Hz, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.7 (m, 3H), 7.6 (d, *J* = 8.8 Hz, 1H), 7.32 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.8 (d, *J* = 7.2 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.3(s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 447 $(M+H)^+$. pureza HPLC: 94.65%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
57		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (s, 1H), 8.7 (s, 1H), 8.3 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 9.0 Hz, 1H), 7.7 (m, 3H), 7.6 (d, *J* = 8.1 Hz, 1H), 7.5 (d, *J* = 8.4 Hz, 2H), 7.3 (t, *J* = 7.5 Hz, 2H), 7.0 (t, *J* = 7.8 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 433 $(M+H)^+$. pureza HPLC: 95.40%.
58		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.35 (s, 1H), 8.75 (s, 1H), 8.3 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 8.0 Hz, 1H) 7.7 (m, 3H), 7.6 (d, *J* = 8.8 Hz, 1H), 7.5 (d, *J* = 11.6 Hz, 1H), 7.3 (m, 1H), 7.1(d, *J* = 8.0 Hz, 1H), 6.82 (m, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 449 $(M-H)^-$. LCMS pureza: 90.46%.
59		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.3 (s, 1H), 8.8 (s, 1H), 8.3 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 8.4 Hz, 1H) 7.7 (m, 4H), 7.6 (d, *J* = 8.4 Hz, 1H), 7.35-7.2 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 467 $(M+H)^+$. pureza HPLC: 96.38%.
60		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.25 (s, 1H), 8.8 (s, 1H), 8.3 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 9.0 Hz, 1H) 7.7 (m, 3H), 7.6 (d, *J* = 9.0 Hz, 1H), 7.2 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.6 (d, *J* = 6.3 Hz, 1H), 3.75 (s, 3H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 463 $(M+H)^+$. pureza HPLC: 97.89%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
61		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.0 (s, 1H), 8.7 (s, 1H), 8.3 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 8.4 Hz, 1H) 7.7 (m, 3H), 7.6 (d, *J* = 8.4 Hz, 1H), 7.1 (s, 2H), 6.65 (s, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.25(s, 6H), 2.18 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 461 $(M+H)^+$. pureza HPLC: 93.13%.
62		1H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (s, 1H), 9.05 (s, 1H), 8.35 (t, *J* = 8.4 Hz, 1H), 8.0 (d, *J* = 6.9 Hz, 1H) 7.9 (d, *J* = 8.4 Hz, 1H), 7.75-7.65 (m, 3H), 7.6 (d, *J* = 8.1 Hz, 1H), 7.1 (m, 1H), 6.83 (m, 1H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.3(s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 465 $(M+H)^+$. pureza HPLC: 90.7%.
63		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.45 (s, 1H), 8.85 (s, 1H), 8.25 (t, *J* = 8.8 Hz, 1H), 8.0 (s, 1H), 7.9 (d, *J* = 8.0 Hz, 1H) 7.75-7.65 (m, 4H), 7.6 (d, *J* = 8.8 Hz, 1H), 7.55-7.45 (m, 2H), 3.2-2.9 (m, 3H), 2.75 (m, 1H), 2.45 (m, 1H), 2.18 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 458 $(M+H)^+$. pureza HPLC: 94.94%.
64		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.4 (bs, 1H), 9.0 (bs, 1H), 8.0 (s, 1H), 7.9 (m ,1H), 7.7-7.45 (m, 6H), 7.3 (m, 2H), 3.2-2.9 (m, 4H), 2.7 (m, 1H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 499 $(M-H)^-$; LCMS pureza: 90%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
65		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.7 (bs, 1H), 8.28 (bs, 1H), 7.98 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.66 (m, 1H), 7.56-7.46 (m, 3H), 7.2 (m, 1H), 6.9 (m, 1H), 6.76 (m, 1H), 3.8 (s, 3H), 3.2-2.9 (m, 2H), 2.7 (m, 1H), 2.4 (m ,2H), 2.26 (s, 3H), 2.2 (m, 1H), 2.0 (m, 1H).	ESI-MS *m/z* = 477 $(M+H)^+$; LCMS pureza: 93%.
66		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.05 (bs, 1H), 8.9 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.6 (m, 1H), 7.56-7.44 (m, 5H), 7.3 (m, 3H), 7.0 (m, 1H), 3.2-2.9 (m ,2H), 2.7 (m, 1H), 2.4 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	pureza HPLC: 91%.
67		^{1}H-RMN (300 MHz, DMSO-d_6): δ 10.7 (bs, 1H), 9.0 (2s, 2H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.25 (s, 1H), 8.1 (m, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.7 (d, *J* = 8.4 Hz, 1H), 7.5 (t, *J* = 7.5 Hz, 1H), 7.3 (d, *J* = 7.5 Hz, 1H), 3.1 (m, 2H), 2.8 (m, 1H), 2.6 (m, 2H), 2.4 (m, 2H).	ESI-LCMS *m/z*: 486 (pureza 89 %); pureza HPLC 96 %.

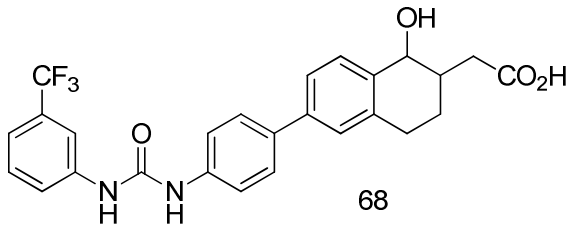
EJEMPLO 68



Reactivos y condiciones: a) $NaBH_4$, MeOH, t.a., 16h.

Procedimientos

Acido 2-(1-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (68)

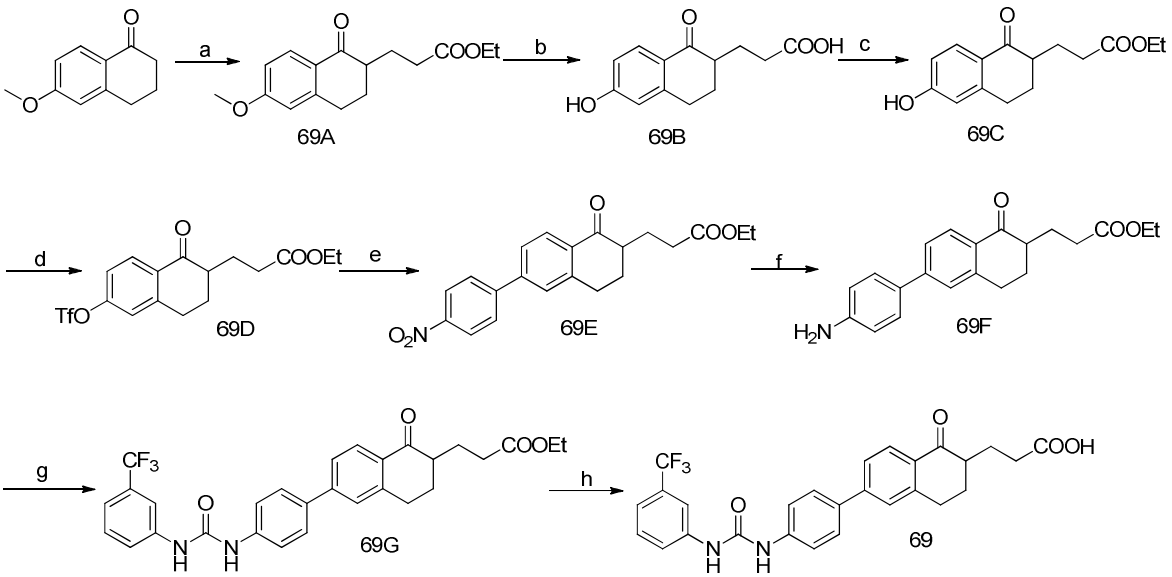


68

A una solución enfriada en hielo del producto del ejemplo 47 (0.08 g, 0.16 mmol) en metanol (5 mL)se le agregó en porciones borohidruro de sodio (0.025 g, 0.66 mmol), y la mezcla se agitó a temperatura ambiente durante 16 h. La mezcla de reacción se concentró bajo presión reducida y se diluyó agua. El sólido resultante se filtró y se trituró con éter dietílico y n-pentano para producir el compuesto del título como un sólido (0.068 g, 85%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ12.0 (bs, 1H), 9.4 (bs, 1H), 9.0 (bs, 1H), 8.1 (s, 1H), 7.7 (m, 1H), 7.6-7.44 (m, 6H), 7.4-7.2 (m, 4H), 4.6 (m, 1H), 4.3 (m, 1H), 2.8 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H), 1.7 (m, 1H), 1.2 (m, 1H).

EJEMPLO 69

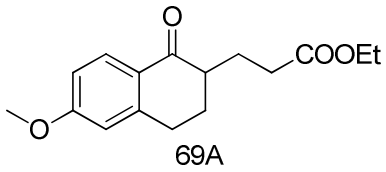


Reactivos y condiciones: a) LDA, bromopropionato de etilo, THF, -78 °C-t.a., 10 h; b) HBr acuoso, 100 °C, 12 h; c) $MeSO_3H$, EtOH, t.a., 18 h; d) Tf_2O, CH_2Cl_2, Py, t.a., 2 h; e) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 3 h; f) Pd/C, H_2, EtOH, t.a., 1 h; g) 3-CF_3PhNCO, Et_3N, THF, t.a., 12 h; h) LiOH, THF-H_2O, t.a., 12 h.

Procedimientos

Acido 3-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)propanoico

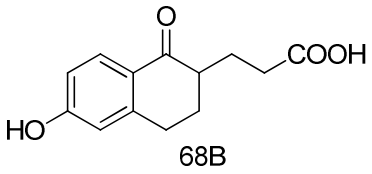
3-(6-Metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)propanoato de etilo (69A):



69A

A una solución enfriada previamente durante un periodo de 15 min a -78 °C de 6-metoxi-1-tetralona (4 g, 22.0 mmol) en THF (30 mL), se le agregó LDA 1.8M recién preparado (24.4 mL, 44.0 mmol). La mezcla de reacción se agitó durante 1 h a -78 °C. Se le agregó bromopropionato de etilo (4.4 mL, 39.37 mmol) durante un periodo de10 min a -78 °C, y la mezcla se agitó a temperatura ambiente durante 10 h. La mezcla de reacción se vació entonces en solución saturada de NH_4Cl (100 mL) y se extrajo con acetato de etilo (2x100 mL). La capa orgánica combinada se lavó con agua, seguido por solución de salmuera, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró bajo presión reducida para producir el compuesto del título crudo como un líquido (4.5 g, 69 %).

Acido 3-(6-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-propanoico (69B):

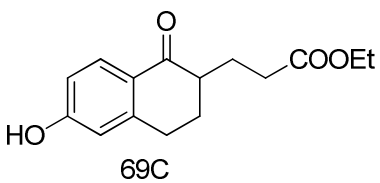


68B

Al producto del ejemplo 69A (4.5 g, 16.0 mmol)se le agregó HBr acuoso (50 mL), y la mezcla de reacción se puso a reflujo durante la noche. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo (2X100 mL). La capa orgánica se secó sobre Na_2SO_4 y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 40% en hexano, para producir el compuesto del título como un sólido (0.85 g, 24%).

^{1}H-RMN (300MHz, DMSO-d_6): δ 12.01 (bs, 1H), 10.27 (s, 1H), 7.74 (d, J = 9.0 Hz, 1H), 6.70 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 6.62 (s, 1H), 2.86 (m, 2H), 2.43 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H), 2.12-1.98 (m, 2H), 1.78-1.69 (m, 1H), 1.65-1.53 (m, 1H).

3-(6-Hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)propanoato de etilo (69C):

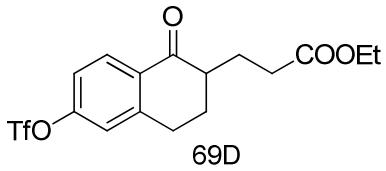


69C

A una solución del producto del ejemplo 69B (0.85 g, 3.63 mmol) en etanol (20 mL)se le agregó ácido metanosulfónico(0.3 mL) y la mezcla se agitó a temperatura ambiente durante 18 h. El etanol se separó de la mezcla de reacción bajo presión reducida y el residuo se diluyó con acetato de etilo y se lavó con una solución de salmuera. La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró bajo presión reducida y se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.9 g, 24%).

^{1}H-RMN (300MHz, DMSO-d_6): δ 10.27 (s, 1H), 7.73 (d, J = 8.1 Hz, 1H), 6.70 (dd, J_1 = 2.1 Hz, J_2 = 9.0 Hz, 1H), 6.62 (s, 1H), 4.05 (q, J = 6.9 Hz, 2H), 2.86 (m, 2H), 2.43 (m, 1H), 2.31 (t, J = 7.5 Hz, 2H) 2.13-1.98 (m, 2H), 1.77-1.57 (m, 2H), 1.17 (t, J = 6.9 Hz, 3H).

3-(1-Oxo-6-(trifluorometilsulfoniloxi)-1,2,3,4-tetrahidronaftalen-2-il)propanoato de etilo (69D):



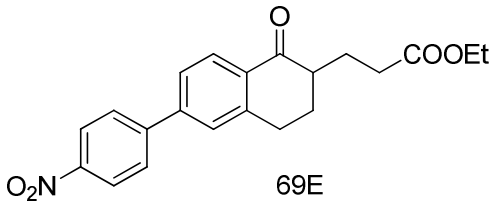
69D

A una solución enfriada en hielo del producto del ejemplo 69C (0.9 g, 3.43 mmol) y piridina (0.325 g, 4.12 mmol) en diclorometano (30 mL), se le agregó anhídrido tríflico (1.16 g, 4.12 mmol) y la mezcla se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (50 mL) y se lavó con una solución acuosa saturada de NaCl

(50 mL). La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró bajo presión reducida y se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 5% en hexano, para producir el compuesto del título como un sólido (0.95 g, 70%).

^{1}H-RMN (400MHz, DMSO-d_6): δ 8.02 (d, J = 8.8 Hz, 1H), 7.54 (s, 1H), 7.45 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 4.05 (q, J = 6.9 Hz, 2H), 3.04 (m, 2H), 2.68-2.61 (m, 1H), 2.42 (t, J = 7.6 Hz, 2H), 2.20-2.06 (m, 2H), 1.89-1.80 (m, 1H), 1.78-1.63 (m, 1H), 1.18 (t, J = 6.8 Hz, 3H).

<u>3-(6-(4-Nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)propanoato de etilo (69E):</u>



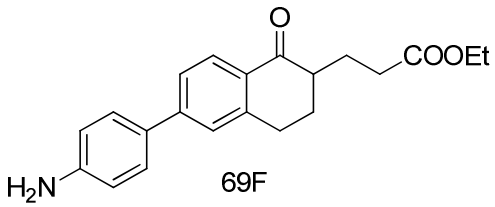
69E

A una solución del producto del ejemplo 69D (0.95 g, 2.41 mmol) en 30 mL de una mezcla de 1,4-dioxano-H_2O (4:1) bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$ (0.034 g, 0.028 mmol), seguido por carbonato de cesio (1.95 g, 6.02 mmol) y ácido 4-nitro-fenil-borónico (0.48 g, 2.89 mmol). La mezcla de reacción se desgasificó durante 15 min. Luego, la mezcla de reacción se puso a reflujo por 3 h, y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró y se

purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para dar el compuesto del título como un sólido (0.7 g, 79%).

^{1}H-RMN (400MHz, DMSO-d_6): δ 8.33 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.78-7.74 (m, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.08 (m, 2H), 2.66-2.59 (m, 1H), 2.43 (t, J = 8.0 Hz, 2H), 2.23-2.11 (m, 2H), 2.11-1.81 (m, 1H), 1.72-1.67 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H).

2-(6-(4-Aminofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-propanoato de etilo (69F):



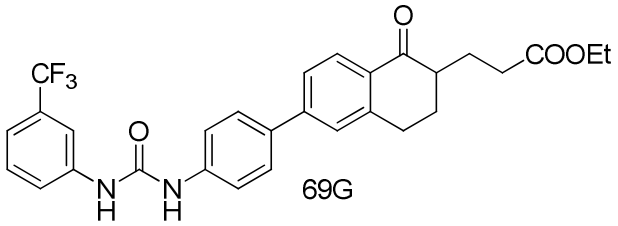
69F

A una solución del producto del ejemplo 69E (0.7 g, 1.90 mmol) en 20 mL de etanol se le agregó un exceso de Pd 10% /C (0.2 g), y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se filtró sobre una almohadilla de celite, el filtrado se separó bajo presión reducida, y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre Na_2SO_4, se filtró y se separó al vacío. El producto crudo se lavó con Et_2O y pentano para producir el compuesto del título como un sólido amarillo (0.61 g, 95%).

^{1}H-RMN (300MHz, DMSO-d_6): δ 7.83 (d, J = 8.4 Hz, 1H), 7.53-

7.44 (m, 4H), 6.64 (d, *J* = 7.5 Hz, 2H), 5.41 (bs, 2H), 4.06 (q, *J* = 6.9 Hz, 2H), 3.0 (m, 2H), 2.44 (m, 3H), 2.15-2.10 (m, 2H), 1.90-1.66 (m, 2H), 1.18 (t, *J* = 6.9 Hz, 3H).

3-(1-Oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il) propanoato de etilo (69G):

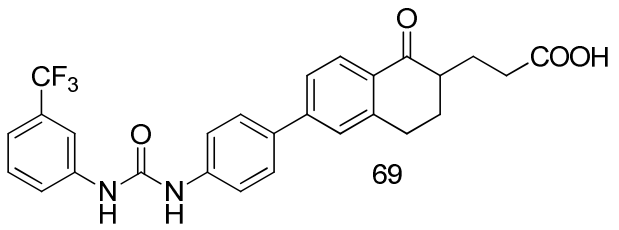


69G

A una solución del producto del ejemplo 69F (0.18 g, 0.534 mmol) y trietilamina (0.065 g, 0.64 mmol) en THF (5 mL)se le agregó isocianato de 3-(trifluorometil)fenilo(0.1 g, 0.534 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.1 g, 35%).

^{1}H-RMN (300MHz, DMSO-d_6): δ 9.10 (s, 1H), 8.98 (s, 1H), 8.03 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.72-7.69 (m, 2H), 7.62-7.49 (m, 6H), 7.31 (d, *J* = 7.2 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 2H), 3.05 (m, 2H), 2.43 (m, 3H), 2.19-2.11 (m, 2H), 1.82-1.65 (m, 2H), 1.18 (t, *J* = 7.8 Hz, 3H).

Acido 3-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)propanoico (69):



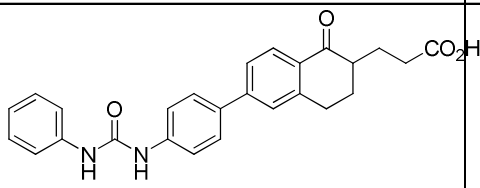
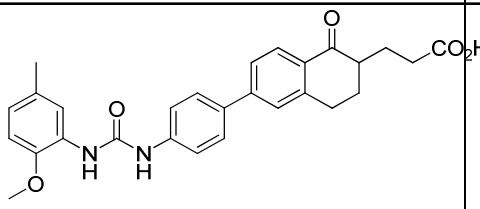
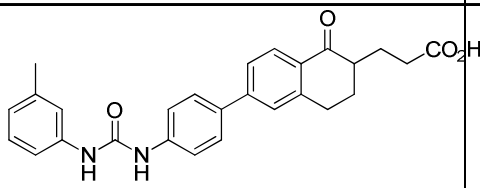
69

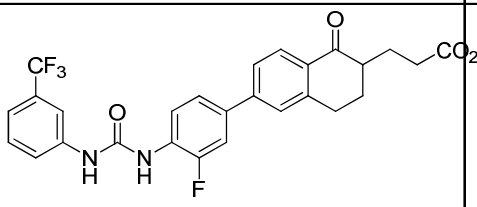
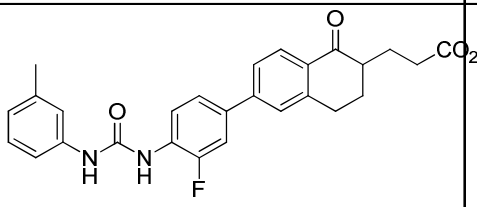
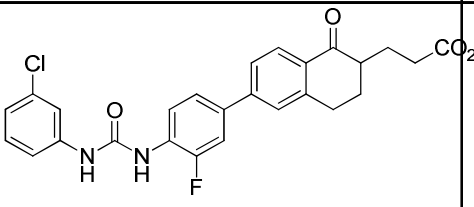
A una solución del producto del ejemplo 69G (0.1 g, 0.19 mmol) en 20 mL de una mezcla de THF-agua (2:1) se le agregó hidróxido de litio (0.024 g, 0.572 mmol), y la mezcla se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, y el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido blanco (0.060 g, 63%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ12.0 (bs, 1H), 9.20 (bs, 1H), 9.12 (bs, 1H), 8.02 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H) 7.72-7.68 (m, 2H),7.65-7.49 (m, 6H), 7.32 (d, *J* = 7.5 Hz, 1H), 3.06-3.02 (m, 2H), 2.56-2.50 (m, 1H), 2.35 (t, *J* = 7.5 Hz, 2H) 2.27-2.08 (m, 2H), 1.82-1.63 (m, 2H). ESI-MS *m/z* = 496 $(M+H)^+$; pureza HPLC: 99.22 %.

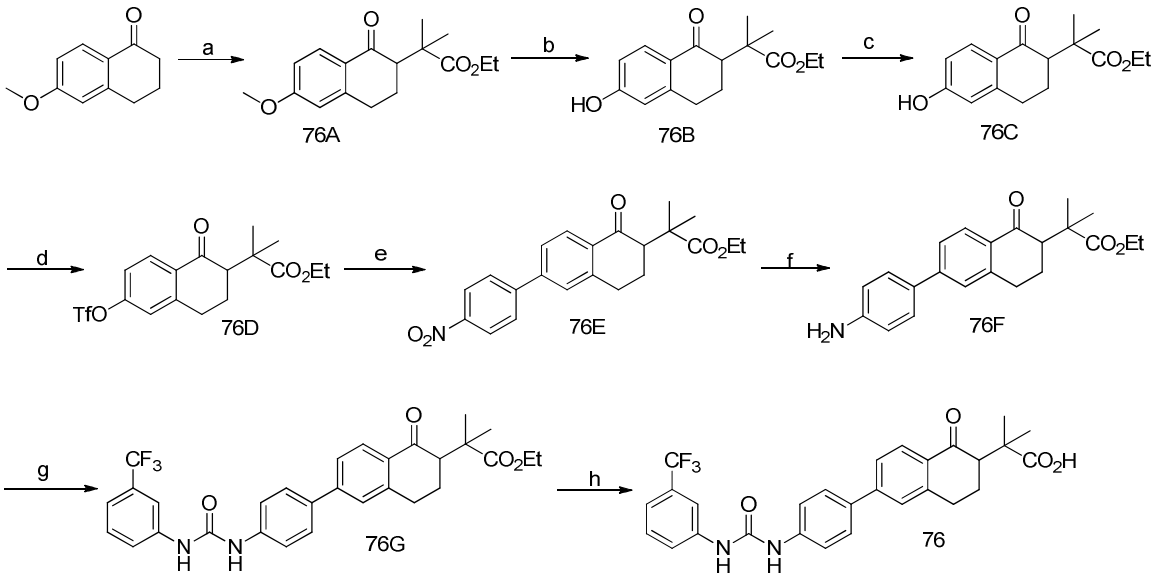
Los ejemplos 70-75 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 69, usando los materiales

iniciales apropiados. Los ácidos borónicos requeridos (y las versiones con grupos funcionales adecuadamente protegidos de los mismos) aquí utilizados se compraron en caso de estar disponibles comercialmente, o se sintetizaron como se describe en la literatura o por medio de modificaciones rutinarias conocidas para los expertos en la materia, o se sintetizaron mediante procedimientos alternos conocidos por los expertos en la materia.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
70		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 8.86 (s, 1H), 8.73 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 2H) 7.64-7.56 (m, 4H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H) 6.98 (t, *J* = 6.8 Hz, 1H), 3.05 (m, 2H), 2.68-2.53 (m, 1H), 2.35 (t, *J* = 7.6 Hz, 2H) 2.22-2.09 (m, 2H), 1.82 (m, 1H), 1.66 (m, 1H).	ESI-MS *m/z* = 429 $(M+H)^+$. LCMS pureza: 95.03%.
71		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.51 (s, 1H), 8.22 (s, 1H), 7.99 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H) 7.64-7.56 (m, 4H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.05 (m, 2H), 2.59-2.54 (m, 1H) 2.35 (t, *J* = 8.0 Hz, 2H), 2.24 (s, 3H), 2.22-2.07 (m, 2H), 1.83 (m, 1H), 1.65 (m, 1H).	ESI-MS *m/z* = 473 $(M+H)^+$. pureza HPLC: 94.49%.
72		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.03 (bs, 1H), 8.83 (bs, 1H), 7.93-7.88 (m, 1H), 7.68-7.60 (m, 6H), 7.33-7.14 (m, 3H) 6.80 (m, 1H), 3.05 (m, 2H), 2.56 (m, 1H), 2.40-2.05 (m, 7H), 1.83-1.65 (m, 2H).	pureza HPLC: 94.84%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
73		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.51 (bs, 1H), 8.82 (bs, 1H), 8.27 (t, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H) 7.79-7.65 (m, 3H),7.62-7.50 (m, 3H), 7.35 (m, 1H), 3.06 (m, 2H), 2.59-2.55 (m, 1H), 2.35 (t, *J* = 7.8 Hz, 2H) 2.28-2.04 (m, 2H), 1.85 (m, 1H), 1.66 (m, 1H).	pureza HPLC: 90.44%.
74		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.06 (s, 1H), 8.70 (s, 1H), 8.30 (t, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H) 7.72-7.56 (m, 4H),7.32-7.14 (m, 3H), 6.82 (d, *J* = 7.5 Hz, 1H), 3.05 (m, 2H), 2.55 (m, 1H), 2.39-2.21 (m, 5H), 2.19-2.06 (m, 2H), 1.82 (m, 1H), 1.64 (m, 1H).	ESI-MS *m/z* = 459 $(M-H)^-$. pureza HPLC: 96.45%.
75		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.30 (s, 1H), 8.77 (s, 1H), 8.26 (t, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H) 7.76-7.66 (m, 4H),7.60 (d, *J* = 8.8 Hz, 1H), 7.33 (m, 1H), 7.25 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 1H) 3.05 (m, 2H), 2.59-2.56 (m, 1H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.23-2.07 (m, 2H), 1.82 (m, 1H), 1.66 (m, 1H).	ESI-MS *m/z* = 480 $(M-H)^-$. LCMS pureza: 98.96%.

EJEMPLO 76

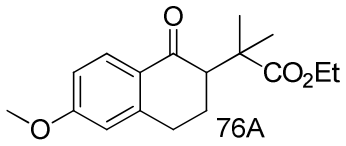


Reactivos y condiciones: a) α-bromo-isobutirato de etilo, NaH, THF, t.a.; b) HBr acuoso, 100 °C; c) $MeSO_3H$, EtOH, t.a.; d) Tf_2O, CH_2Cl_2, Et_3N, t.a.; e) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C; f) Pd/C, H_2, EtOH, t.a.; g) 3-CF_3PhNCO, Et_3N, THF, t.a.; h) LiOH, THF-H_2O, t.a.

Procedimientos

Acido 2-metil-2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)propanoico (76)

2-(6-Metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-2-metilpropanoato de etilo (76A):

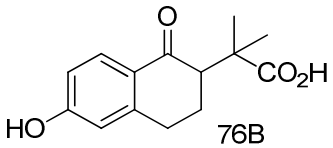


76A

A una solución enfriada en hielo de 6-metoxi-1-tetralona (8 g, 136 mmol) en THF (90 mL)se le agregó hidruro de sodio (2.18 g, 90.9 mmol), y la mezclase agitó durante 10 min. Se le agregó α-bromo-isobutiratode etilo (17.7 g, 90.9 mmol) y la mezclase agitó durante 3 h. La mezcla de reacción se apagó con agua enfriada en hielo y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró al vacío para producir el compuesto del título como un sólido(13 g).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 9.2 Hz, 1H), 6.8 (m, 1H), 6.68 (m, 1H), 4.2 (m, 2H), 3.8 (s, 3H), 3.15-3.0 (m, 3H), 2.2 (m, 1H), 1.9 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

Acido 2-(6-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-2-metilpropanoico (76B):

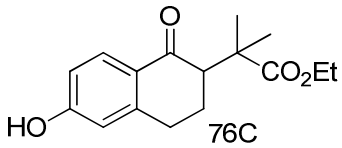


76B

Al producto del ejemplo 76A (13 g, 44.8 mmol)se le agregó HBr acuoso (190 mL) y la mezcla de reacción se puso a reflujo durante la noche. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo (2X100 mL). La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró bajo presión reducida para producir el compuesto del título como un sólido (11 g).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 10.2 (bs, 1H), 7.7 (m, 1H), 6.7 (m, 1H), 6.6 (s, 1H), 3.1-2.8 (m, 3H), 2.15 (m, 1H), 1.7 (m, 1H), 1.15 (s, 3H), 1.0 (s, 3H).

2-(6-Hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-2-metil-propanoato de etilo (76C):

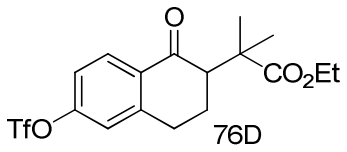


76C

A una solución del producto del ejemplo 76B (11 g, 44.3 mmol) en etanol (150 mL) se le agregó ácido metanosulfónico(20 mL), y la mezcla se

agitó a temperatura ambiente durante 5 h. El etanol se separó de la mezcla de reacción bajo presión reducida y el residuo se diluyó con acetato de etilo y agua. La capa orgánica se separó, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró al vacío para producir el compuesto del título como un sólido (6.4 g, 51%) . ^{1}H-RMN (300 MHz, $CDCl_3$): δ 7.84 (m, 1H), 6.74 (m, 1H), 6.66 (bs, 1H), 4.2 (m, 2H), 3.1-2.8 (m, 3H), 2.1 (m, 1H), 1.95 (m, 1H), 1.3 (m, 6H), 1.15 (s, 3H).

2-Metil-2-(1-oxo-6-(trifluorometilsulfoniloxi)-1,2,3,4-tetrahidronaftalen-2-il)propanoato de etilo (76D):



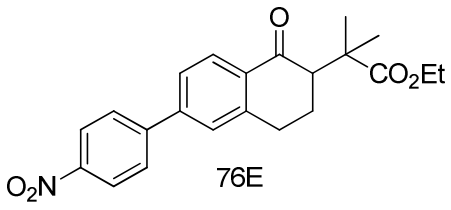
76D

A una solución enfriada en hielo del producto del ejemplo 76C (6.4 g, 23.1 mmol) y piridina (2.01 g, 25.44 mmol) en diclorometano (75 mL)se le agregó anhídrido tríflico (6.53 g, 23.15 mmol), y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano (100 mL) y se lavó con una solución acuosa saturada de NaCl (75 mL). La capa orgánica se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró bajo presión reducida y se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 5% en hexano, para producir el compuesto del título como un sólido (3.8 g, 40%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.08 (m, 1H), 7.18 (m, 2H), 4.2 (m,

2H), 3.2-3.0 (m, 3H), 2.3 (m, 1H), 2.0 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

2-Metil-2-(6-(4-nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-propanoato de etilo (76E):

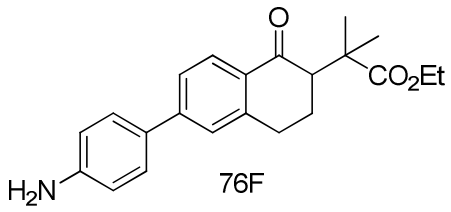


76E

A una solución del producto del ejemplo 76D (3.8 g, 9.3 mmol) en 35 mL de una mezcla de 1,4-dioxano-H_2O (3:1) bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$(0.129 g, 0.11 mmol),seguido por carbonato de cesio (9.1 g, 27.9 mmol) y ácido 4-nitrofenil-borónico (1.71 g, 10.23 mmol). La mezcla de reacción se desgasificó durante 5 min. Luego, la mezcla de reacción se puso a reflujo por 5 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró bajo presión reducida y se purificó por cromatografía de vaporización instantánea para producir el compuesto del título como un sólido (2.5 g, 71%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.0 (m, 1H), 7.5-7.3 (m, 4H), 6.75 (m, 2H), 4.2 (m, 2H), 3.2-3.0 (m, 3H), 2.2 (m, 1H), 2.0 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

2-(6-(4-Aminofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-2-metilpropanoato de etilo (76F):

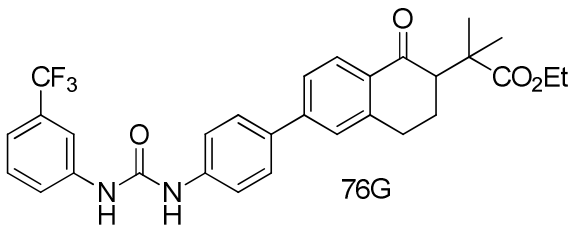


76F

A una solución del producto del ejemplo 76E (1.5 g, 3.93 mmol) en 15 mL de una mezcla de etanol-agua (2:1)se le agregó polvo de fierro (0.66 g, 11.81 mmol),seguido por NH_4Cl (0.106 g, 1.96 mmol). La mezcla se puso a reflujo por 3 h. El disolvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre Na_2SO4, se filtró y se separó al vacío para producir el compuesto del título(1.3 g, 95%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.6 (m, 2H), 8.2 (m, 1H), 7.55 (m, 2H), 7.51 (m, 1H), 7.5 (s, 1H), 4.2 (m, 2H), 3.2-3.0 (m, 3H), 2.3 (m, 1H), 2.0 (m, 1H), 1.25 (m, 6H), 1.2 (s, 3H).

2-Metil-2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)propanoato de etilo (76G):

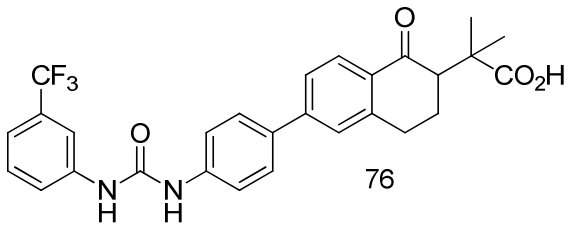


76G

A una solución del producto del ejemplo 76F(0.25 g, 0.71 mmol) y trietilamina (0.28 g, 2.85 mmol) en THF (10 mL)se le agregó isocianato de 3-(trifluorometil)fenilo (0.18 g, 0.997 mmol), y la mezcla se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se trituró con éter dietílico y pentano para producir el compuesto del título como un sólido (0.2 g, 59%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.86 (m, 1H), 7.74-7.6 (m, 4H), 7.44-7.28 (m, 8H), 4.2 (m, 2H), 3.15-3.0 (m, 3H), 2.26 (m, 1H), 1.9 (m, 1H), 1.3 (m, 6H), 1.2 (s, 3H).

Acido 2-metil-2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)propanoico (76):



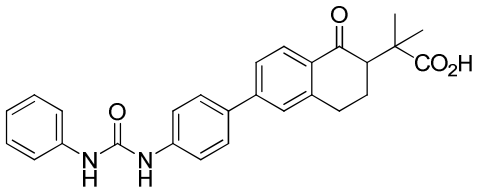
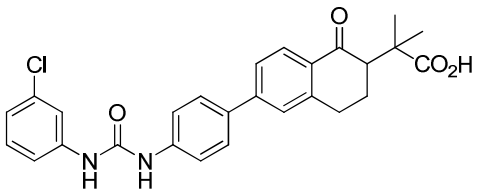
76

A una solución del producto del ejemplo 76G (0.2 g, 0.37 mmol) en 4 mL de una mezcla de dioxano-agua (3:1)se le agregó hidróxido de litio (0.062 g, 1.48 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La

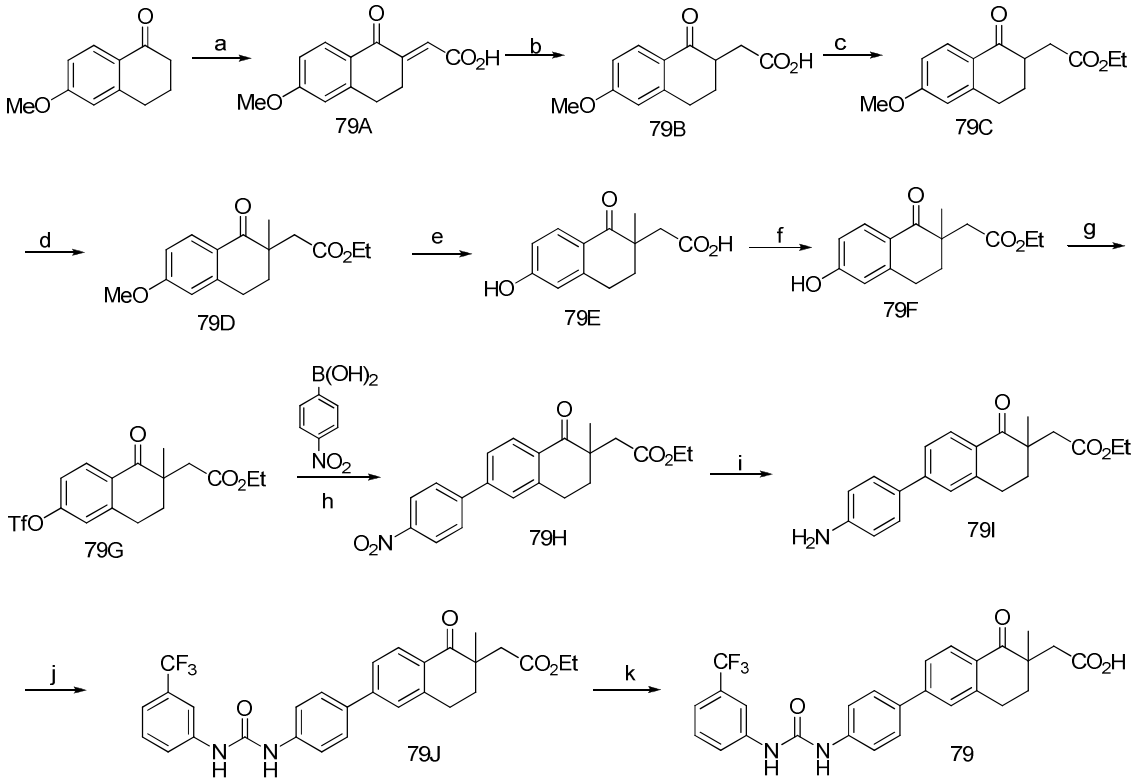
solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido (0.075 g, 40%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.1 (bs, 1H), 9.0 (bs, 1H), 8.04 (s, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.7 (d, J = 8.8 Hz, 2H), 7.68-7.58 (m, 5H), 7.52 (t, J = 8 Hz, 1H), 7.3 (d, J = 7.6 Hz, 1H), 3.2-3.0 (m, 3H), 2.25 (m, 1H), 1.8 (m, 1H), 1.2 (s, 3H), 1.05 (s, 3H). ESI-MS m/z = 511 $(M+H)^+$; pureza HPLC: 90%.

Los ejemplos 77-78 se prepararon mediante procedimientos análogos a los que se describen arriba para el ejemplo 76, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/Pureza
77		^{1}H-RMN (400 MHz, DMSO-d_6): δ11.9 (bs, 1H), 8.85 (bs, 1H), 8.72 (bs, 1H), 7.87 (d, J = 8 Hz, 1H), 7.7 (d, J = 8.8, 1H), 7.64-7.56 (m, 5H), 7.46 (d, J = 8 Hz, 2H), 7.3 (t, J = 7.6 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.2-3.02 (m, 3H), 2.28-2.2 (m, 1H), 1.9-1.8 (m, 1H), 1.2 (s, 3H), 1.06 (s, 3H).	ESI-MS m/z = 443 $(M+H)^+$; pureza HPLC: 97%.
78		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.0 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.75-7.65 (m, 3H), 7.64-7.55 (m, 4H), 7.3 (m, 2H), 7.0 (m, 1H), 3.1 (m, 3H), 2.3 (m, 1H), 1.8 (m, 1H), 1.2 (s, 3H), 1.06 (s, 3H).	ESI-MS m/z = 477 $(M+H)^+$; pureza HPLC: 95%.

EJEMPLO 79

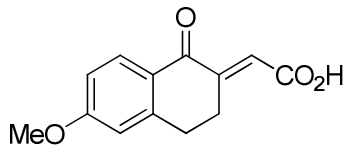


Reactivos y condiciones: a) Acido glioxálico, H_2SO_4, diglima, 85 °C, 12h; b) Zn, AcOH, 80 °C, 2h; c) $MeSO_3H$, EtOH, t.a., 5h; d) MeI, NaH, DMF, t.a., 4h; e) HBr acuoso, 100 °C, 12h; f) $MeSO_3H$, EtOH, t.a., 5h; g) Tf_2O, CH_2Cl_2, Et_3N, t.a., 1h; h) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; i) Fe-NH_4Cl, EtOH-H_2O, 85 °C, 3h; j) 3-CF_3PhNCO, Et_3N, THF, t.a.,12h; k) LiOH, EtOH-H_2O, t.a., 12h.

Procedimiento

Acido 2-(2-metil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

Acido 2-(6-metoxi-1-oxo-3,4-dihidronaftalen-2(1H)-iliden)acético (79A):

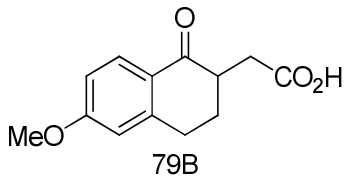


79A

A una solución agitada de 6-metoxi-tetralona (25 g, 141 mmol) en diglima (50 mL)se le agregó ácido glioxálico (30 mL, 303 mmol) y agua (14 mL),seguidos por ácido sulfúrico (6.5 mL, 35 mmol). La mezcla de reacción se calentó a 85 °C durante la noche. La mezcla de reacción se enfrió a 0 °C y el sólido resultante se filtró y se lavó con agua (3x25 mL), y se secó bajo presión reducida para producir el compuesto del título como un sólido (28 g, 85%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ12.9 (bs, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.0 (m, 2H), 6.6 (s, 1H), 3.8 (s, 3H), 3.3 (m, 2H), 3.0 (m, 2H). ESI-MS *m/z*: 233 $(M+H)^+$.

Acido 2-(6-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (79B):

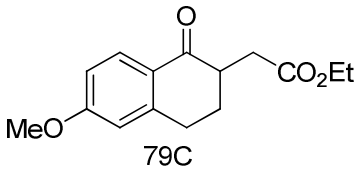


79B

A una solución del producto del ejemplo 79A (28 g, 120 mmol) en una mezcla de ácido acético–agua (224 mL+84 mL), se le agregó zinc (19.6 g, 300 mmol) y la mezcla se agitó a 80 °C durante 2 h. Luego, la mezcla de reacción se filtró sobre una almohadilla de celite y la capa orgánica se eliminó bajo presión reducida. Al residuo se le agregó agua (50 mL). El sólido resultante se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido (27 g, 95%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ12.2 (bs, 1H), 7.8 (d, J = 8.4 Hz, 1H), 6.9 (m, 2H), 3.8 (s, 3H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.7 (m, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 1.9 (m, 1H).

2-(6-Metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (79C):



79C

A una solución del producto del ejemplo 79B (20 g, 47 mmol) en

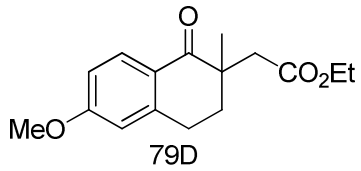
etanol (150 mL)se le agregó ácido metanosulfónico (20 mL), y la mezcla se agitó a temperatura ambiente durante 5 h. El etanol se separó de la mezcla de reacción bajo presión reducida y el residuo se diluyó con acetato de etilo y se extrajo con solución de salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó al vacío para producir el compuesto del título como un sólido (10 g, 71%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.8 Hz, 1H), 6.82 (dd, J_1= 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.67 (s, 1H), 4.2 (m, 2H), 3.8 (s, 3H), 3.12-2.89 (m, 4H), 2.4 (m, 1H), 2.26 (m, 1H), 1.98 (m, 1H), 1.28 (t, *J* = 7.6 Hz, 3H).

Ruta alterna:

A una solución de LDA (4.5g, 42.6 mmol) en THF (45 mL) a -60 ℃, se le agregó lentamente 6-metoxi-1-tetralona (5g, 28.4 mmol). La mezcla de reacción se agitó durante 40 min. Después se le agregó bromoacetato de etilo (5.69 g, 34.09 mmol) y la mezcla de reacción se agitó a t.a. durante 5 h. La mezcla de reacción se apagó entonces con una solución saturada de NH_4Cl y se extrajo con EtOAc varias veces. La capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 anhidro, se filtró y se concentró para dar 7g del compuesto del título.

2-(6-Metoxi-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (79D):

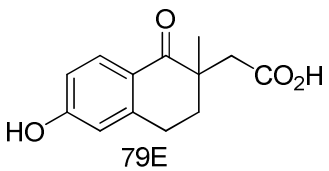


79D

A una solución enfriada en hielo de NaH (4.58 g, 114 mmol) en DMF (100 mL)se le agregó una solución del producto del ejemplo 79C (10 g, 38 mmol) en DMF (50 mL) durante un periodo de 30 min. La mezcla de reacción se agitó durante 10 min. Después se le agregó yoduro de metilo (27.08 g, 191 mmol) y la mezclase agitó durante 4 h a temperatura ambiente. La reacción se llevó entonces a 0 °C, el exceso de NaH se apagó con agua de hielo y la capa acuosa se extrajo con acetato de etilo (2X100 mL). La capa orgánica combinada se secó sobre sulfato de sodio, se filtró y se separó al vacío para dar el compuesto del título crudo como un sólido (12 g).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 7.75 (d, J = 8.4 Hz, 2H), 6.7 (dd, J_1= 1.6 Hz, J_2= 8.4 Hz, 1H), 6.62 (m, 1H), 4.0 (m, 2H), 3.0-2.7 (m, 3H), 2.4 (d, J = 16.0 Hz, 1H), 2.25 (m, 1H), 1.8 (m, 1H), 1.15 (m, 3H), 1.1 (s, 3H).

Acido 2-(6-hidroxi-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (79E):

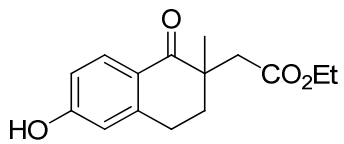


79E

Al producto del ejemplo 79D (12 g, 43.47 mmol) se le agregó HBr acuoso (180 mL) y la mezcla de reacción se puso a reflujo durante la noche. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo (2X100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida para dar producto crudo, que se purificó usando cromatografía de vaporización instantánea con acetato de etilo al 40% en hexano para producir el compuesto del título como un sólido (8.2 g, 80.6%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.08 (bs, 1H), 10.29 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 6.7 (m, 1H), 6.62 (m, 1H), 3.0-2.71 (m, 3H), 2.49-2.33 (m, 2H), 1.8 (m, 1H), 1.1 (s, 3H).

2-(6-Hidroxi-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (79F):



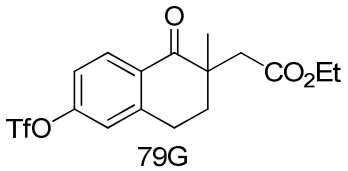
79F

A una solución del producto del ejemplo 79E (8.2 g, 35 mmol) en etanol (100 mL)se le agregó ácido metanosulfónico (15 mL) y la mezcla se agitó a temperatura ambiente durante 5 h. El etanol se separó de la mezcla de reacción bajo presión reducida, y el residuo se diluyó con acetato de etilo y se extrajo con solución de salmuera. La capa orgánica se secó sobre sulfato

de sodio, se filtró y se separó al vacío para producir el compuesto del título como un sólido (7.1 g, 77%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ7.92 (d, J = 9.0 Hz, 1H), 6.72 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 6.63 (s, 1H), 4.1 (q, J = 6.9 Hz, 2H), 3.06-2.8 (m, 3H), 2.5-2.33 (m, 2H), 1.9 (m, 1H), 1.3-1.18 (m, 6H).

2-(2-Metil-1-oxo-6-(trifluorometilsulfoniloxi)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (79G):

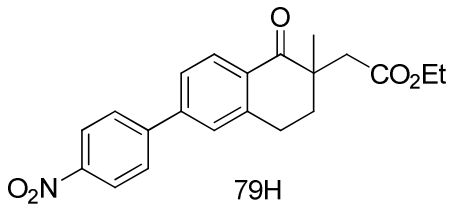


79G

A una solución enfriada en hielo del producto del ejemplo 79F (5 g, 19.08 mmol) y piridina (1.65 g, 20.88 mmol) en diclorometano (40 mL)se le agregó anhídrido tríflico (5.38 g, 19.08 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó con diclorometano (100 mL) y se lavó con una solución acuosa saturada de NaCl (75 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 5% en hexano, para dar el compuesto del título como un jarabe (4 g, 53%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.16 (d, J = 8.4 Hz, 1H), 7.2 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 7.16 (s, 1H), 4.1 (q, J = 7.8 Hz, 2H), 3.2 -2.9 (m, 3H), 2.52-2.4 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, J = 7.2 Hz, 3H).

2-(2-Metil-6-(4-nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (79H):

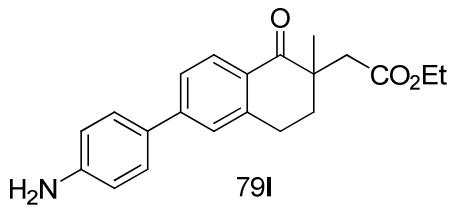


79H

A una solución del producto del ejemplo 79G (2.6 g, 6.59 mmol) en 20 mL de una mezcla de 1,4-dioxano-H_2O (3:1) bajo una atmósfera de argón se le agregó $Pd(PPh_3)_4$(0.09 g, 0.077 mmol), seguido por carbonato de cesio (6.45 g, 19.78 mmol) y ácido 4-nitro-fenil-borónico (1.21 g, 7.24 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 5 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea para producir el compuesto del título como un sólido (1.6 g, 69%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.32 (d, *J* = 8.4 Hz, 2H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.76 (m, 2H), 7.58 (m, 1H), 7.46 (s, 1H), 4.1 (m, 2H), 3.2-2.95 (m, 3H), 2.5 (m, 2H), 2.0 (m, 1H), 1.3 (s, 3H), 1.25 (m, 3H).

2-(6-(4-Aminofenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (79I):

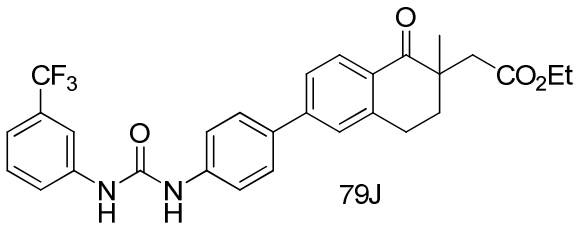


79I

A una solución del producto del ejemplo 79H (1.6 g, 4.35 mmol) en 45 mL de una mezcla de etanol-agua (2:1)se le agregó polvo de fierro (0.73 g, 13 mmol),seguido por NH_4Cl (0.117 g, 2.16 mmol). La mezcla se puso a reflujo por 3 h. El disolvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó al vacío para dar el compuesto del título(1.3 g, 88%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.07 (d, *J* = 8.4 Hz, 1H), 7.49-7.46 (m, 3H), 7.37 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.11 (m, 2H), 3.8 (bs, 2H), 3.11-2.9 (m, 3H), 2.5-2.39 (m, 2H), 1.96 (m, 1H), 1.29 (s, 3H), 1.2 (m, 3H).

2-(2-Metil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (79J):

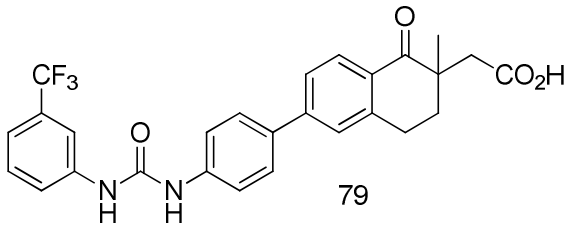


79J

A una solución del producto del ejemplo 79I(0.55 g, 1.63 mmol) y trietilamina (0.49 g, 4.89 mmol) en THF (20 mL)se le agregó isocianato de 3-(trifluorometil)fenilo (0.45 g, 2.44 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.45 g, 53%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.7 (s, 1H), 7.62 (m, 1H), 7.5-7.42 (m, 2H), 7.4-7.3 (m, 6H), 7.1 (m, 1H), 4.1 (q, *J* = 7.2 Hz, 2H), 3.2-2.9 (m, 3H), 2.56-2.44 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, *J* = 7.2 Hz, 3H).

Acido 2-(2-metil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (79):



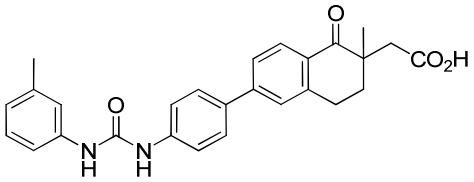
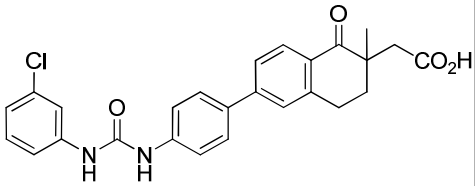
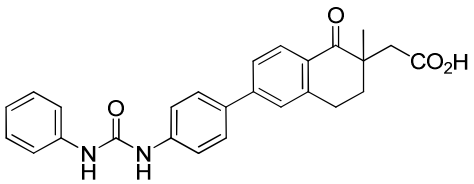
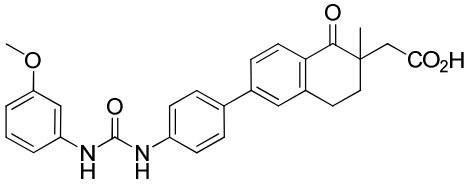
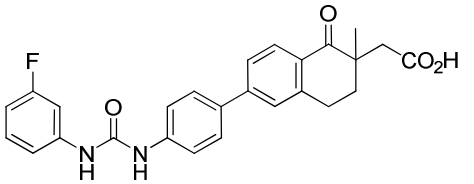
79

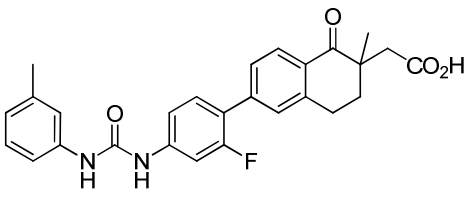
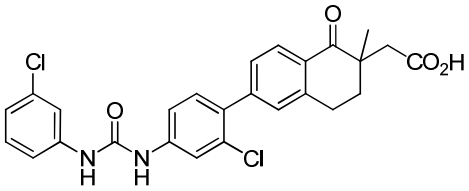
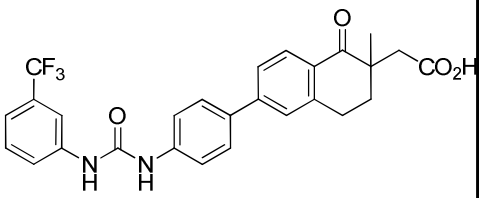
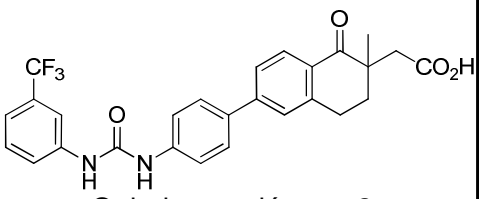
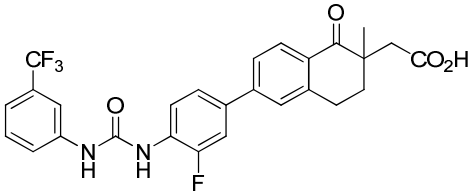
A una solución del producto del ejemplo 79J (0.12 g, 0.22 mmol) en 10 mL de una mezcla de etanol-agua (4:1)se le agregó hidróxido de litio(0.026 g, 0.66 mmol). La mezcla se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se

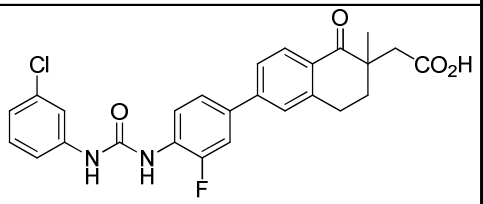
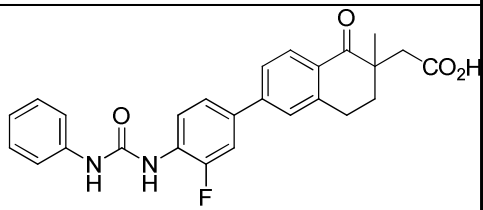
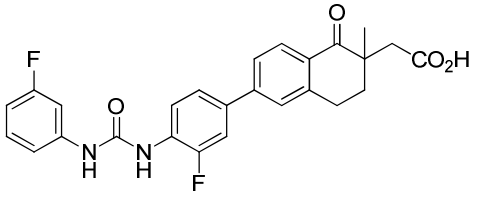
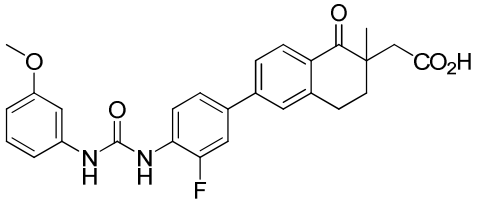
disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, y el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido blanco (0.06 g, 54%).

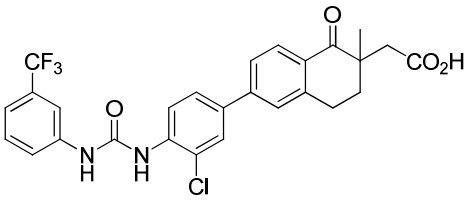
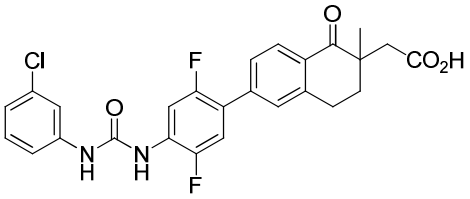
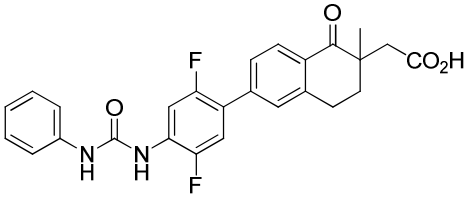
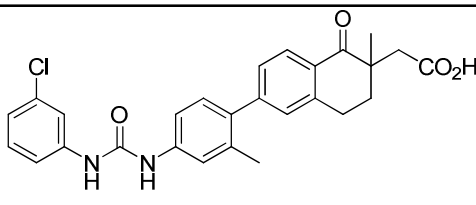
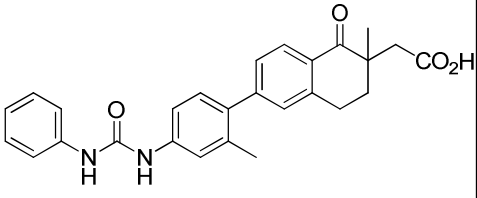
^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.16 (bs, 1H), 9.04 (bs, 1H), 8.04 (m, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.7 (d, *J* = 8Hz, 2H), 7.66-7.56 (m, 5H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 3.2-2.9 (m, 2H), 2.6 (d, *J* = 15.6 Hz, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H); ESI-MS *m/z* = 497 $(M+H)^+$; pureza LCMS: 98%.

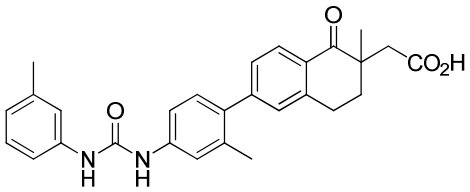
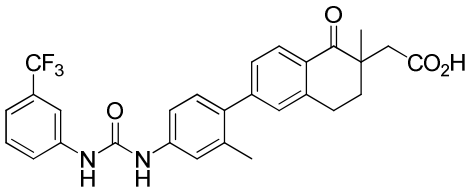
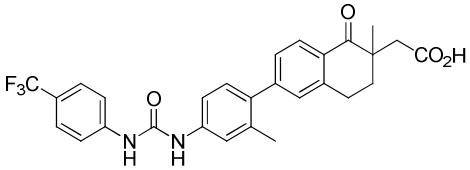
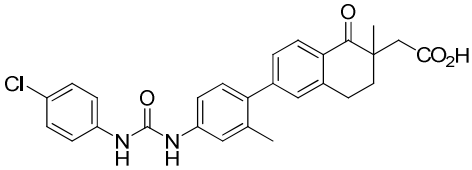
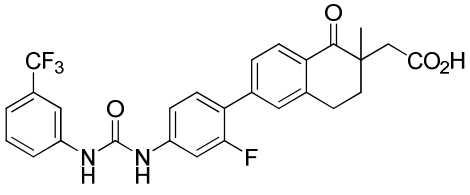
Los ejemplos 80-114 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 79, usando los materiales iniciales apropiados. Los ácidos borónicos requeridos (y las versiones con grupos funcionales adecuadamente protegidos de los mismos) aquí utilizados se compraron en caso de estar disponibles comercialmente, o se sintetizaron como se describe en la literatura o por medio de modificaciones rutinarias conocidas para los expertos en la materia, o se sintetizaron mediante procedimientos alternos conocidos por los expertos en la materia. Los compuestos quirales se obtuvieron usando procedimientos similares a los que se describen en el ejemplo 129.

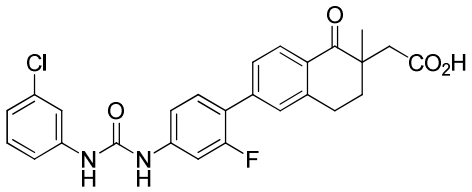
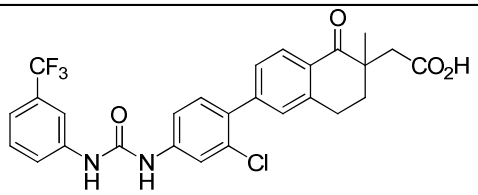
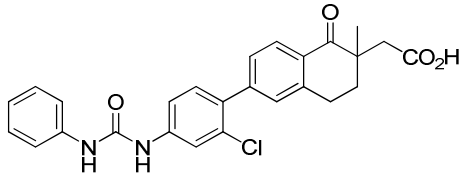
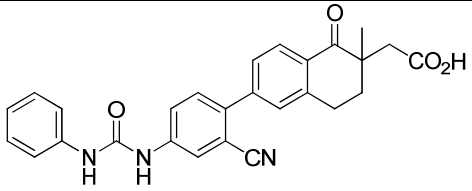
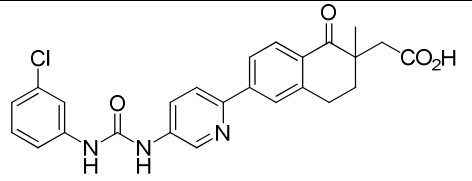
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
80		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (bs, 1H), 8.9 (bs, 1H), 7.9 (d, *J* = 7.5 Hz, 1H), 7.7-7.5 (m, 6H), 7.32 (s, 1H), 7.25 (m, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.8 (d, *J* = 7.8 Hz, 1H), 3.3-2.9 (m, 2H), 2.85 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 441 $(M-H)^-$; LCMS pureza: 92%.
81		^{1}H-RMN (400 MHz, DMSO-d_6): δ 7.96 (d, *J* = 8 Hz, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.5 (s, 1H), 7.48-7.36 (m, 5H), 7.25 (t, *J* = 12 Hz, 1H), 6.95 (d, *J* = 8 Hz, 1H), 3.2-2.8 (m, 2H), 2.7-2.5 (m, 2H), 2.2 (d, *J* = 15 Hz, 1H), 1.75 (d, *J* = 12 Hz, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 463 $(M+H)^+$; pureza HPLC: 96%
82		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.85 (bs, 1H), 8.75 (bs, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.74-7.54 (m, 6H), 7.46 (d, *J* = 7.8 Hz, 2H), 7.3 (t, *J* = 7.5 Hz, 2H), 6.98 (t, *J* = 7.8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16 Hz, 1H), 2.4 (d, *J* = 16.2 Hz, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 429 $(M+H)^+$; pureza HPLC: 97%.
83		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.15 (bs, 1H), 9.05 (bs, 1H), 7.8 (d, *J* = 8 Hz, 2H), 7.75-7.55 (m, 5H), 7.2 (m, 2H), 6.95 (d, *J* = 6 Hz, 1H), 6.55 (m, 1H), 3.75 (s, 3H), 3.3-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 459 $(M+H)^+$; pureza HPLC: 97%.
84		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 7.8 (d, *J* = 8 Hz, 2H), 7.7 (d, *J* = 8.8 Hz, 2H), 7.65-7.55 (m, 3H), 7.5 (d, *J* = 12.4 Hz, 1H), 7.3 (q, *J* = 8 Hz, 1H), 7.15 (d, *J*	ESI-MS *m/z* = 447 $(M+H)^+$; pureza HPLC: 98%.

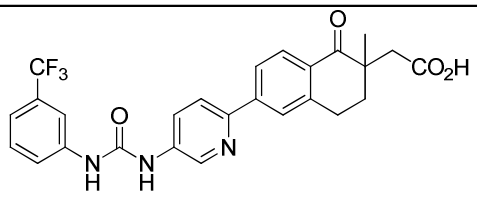
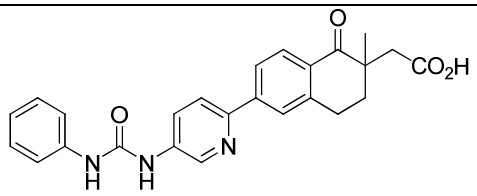
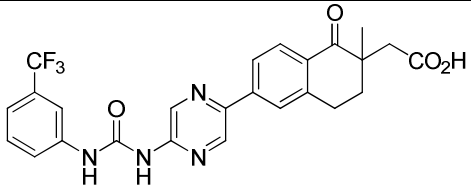
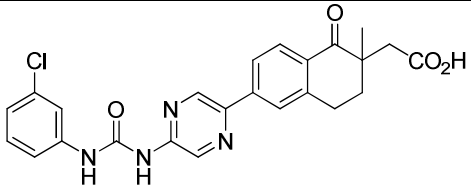
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
85		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.8-7.7 (d, *J* = 14.4 Hz, 1H), 7.58-7.3 (m, 6H), 7.18-7.08 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 6.9 Hz, 1H), 3.2-2.8 (m, 3H), 2.6 (m, 2H), 2.3 (s, 3H), 1.8 (m, 1H), 1.2 (s, 3H).	pureza HPLC: 98%
86		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.2 (2s, 2H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.8 (m, 1H), 7.7 (bs, 1H), 7.48-7.26 (m, 6H), 7.05 (m, 1H), 3.2-2.8 (m, 3H), 2.35 (m, 2H), 1.9 (m, 1H), 1.25 (s, 3H).	pureza HPLC: 95%
87	 Quiral: enantiómero 1	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.12 (bs, 1H), 9.0 (bs, 1H), 8.02 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.75-7.5 (m, 8H), 7.3 (d, *J* = 7.8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.2 Hz, 1H), 2.4 (d, *J* = 15.9 Hz, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	pureza HPLC: 98%; pureza HPLC quiral: 99%
88	 Quiral: enantiómero 2	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.12 (bs, 1H), 9.0 (bs, 1H), 8.02 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.75-7.5 (m, 8H), 7.3 (d, *J* = 7.8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.2 Hz, 1H), 2.4 (d, *J* = 15.9 Hz, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	pureza HPLC: 98.7%; pureza HPLC quiral: 97.5%
89		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.54 (s, 1H), 8.85 (s, 1H), 8.25 (t, *J* = 8.4 Hz, 1H), 8.05 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H) 7.75-7.65 (m, 3H), 7.62-7.5 (m, 3H), 7.35 (m, 1H), 3.2-2.9 (m, 2H), 2.84 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 513 $(M-H)^-$. pureza HPLC: 97.11%.

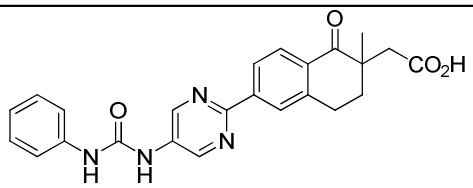
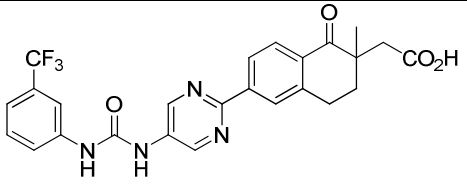
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
90		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.33 (s, 1H), 9.0 (s, 1H), 8.25 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 9.0 Hz, 1H) 7.75-7.65 (m, 4H), 7.6 (d, *J* = 8.4 Hz, 1H), 7.35-7.25 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 3.2-2.9 (m, 2H), 2.83 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 481 $(M+H)^+$. pureza HPLC: 97.55%.
91		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.24 (s, 1H), 8.8 (s, 1H), 8.27 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 8.8 Hz, 1H) 7.75-7.65 (m, 3H), 7.6 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.3 (t, *J* = 7.6 Hz, 2H), 7.0 (t, *J* = 7.2 Hz, 1H), 3.2-2.9 (m, 2H), 2.82 (m, 1H), 2.35 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 445 $(M-H)^-$. pureza HPLC: 95.51%.
92		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.35 (s, 1H), 8.76 (s, 1H), 8.3 (t, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H) 7.7 (m, 3H), 7.6-7.5 (m, 1H), 7.35 (m, 1H), 7.1 (d, *J* = 7.6 Hz, 1H), 6.83 (m, 2H), 3.2-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 465 $(M+H)^+$. pureza HPLC: 92.08%.
93		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.25 (s, 1H), 8.8 (s, 1H), 8.3 (t, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 8.8 Hz, 1H) 7.7 (m, 3H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.2 (m, 2H), 6.95 (d, *J* = 9.2 Hz, 1H), 6.6 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 3.75 (s, 3H), 3.2-2.9 (m, 2H), 2.81 (d, *J* = 16.4 Hz, 1H), 2.36 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 477 $(M+H)^+$. LCMS pureza: 99.34%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
94		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.95 (bs,1), 8.65 (s, 1H), 8.3 (m, 1H), 8.1 (s, 1H), 7.95 -7.85 (m, 2H), 7.75-7.65 (m, 3H), 7.6-7.5 (m, 2H), 7.35 (d, *J* = 7.2 Hz, 1H), 3.2-2.8 (m, 2H), 2.6 (m, 1H), 2.3 (m, 2H), 1.9 (m, 1H), 1.3 (s, 3H).	pureza HPLC: 95%.
95		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.5 (s, 1H), 9.0 (s, 1H), 8.2 (m, 1H), 7.9 (d, *J* = 8.8 Hz, 1H), 7.75 (s, 1H), 7.6-7.5 (m, 3H), 7.4-7.2 (m, 2H), 7.1 (d, *J* = 8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16 Hz, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 499 $(M+H)^+$; pureza HPLC: 95.4%
96		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.42 (bs, 1H), 9.1 (bs, 1H), 8.16 (m, 1H), 7.95 (d, *J* = 8.4 Hz,, 1H), 7.6-7.4 (m, 5H), 7.3 (t, *J* = 7.6 Hz, 2H), 7.0 (t, *J* = 7.2 Hz, 1H), 3.3-2.9 (m, 2H), 2.8 (d, *J* = 16 Hz, 1H), 2.4 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	pureza HPLC: 93.4%
97		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.95 (bs, 1H), 8.85 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.45-7.3 (m, 6H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.0 (m, 1H), 3.2-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 477 $(M+H)^+$; pureza HPLC: 98.7%.
98		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.9 (2s, 2H), 7.9 (d, *J* = 7.6 Hz, 1H), 7.5-7.28 (m, 8H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.0 (t, *J* = 7.2 Hz, 1H), 3.2-2.8 (m, 2H), 2.78 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 445 $(M+H)^+$; pureza HPLC: 95%.

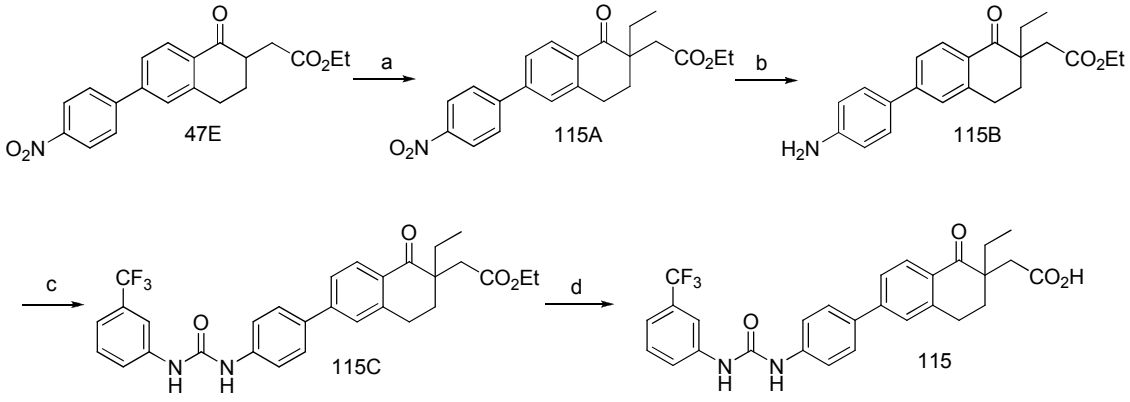
Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
99		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.6-9.0 (bs, 2H), 7.9 (d, *J* = 7.5 Hz, 1H), 7.56 (s, 1H), 7.4-7.25 (m, 4H), 7.12 (m, 2H), 7.0 (bs, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 3.2-2.95 (m, 2H), 2.85 (d, *J*=16.2 Hz, 1H), 2.56 (m, 2H), 2.3 (s, 3H), 2.26 (s, 3H), 1.8 (m, 1H), 1.2 (s, 3H);	ESI-MS *m/z* = 456 (M+H); pureza HPLC: 95%.
110		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.6-9.0 (bs, 2H), 8.08 (s, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.6 (m, 1H), 7.5 (m, 2H), 7.36-7.24 (m, 4H), 7.18 (m, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 (d, *J* = 16.2 Hz, 2H), 2.3 (s, 3H), 1.85 (m, 1H), 1.2 (s, 3H);	ESI-MS *m/z* = 510 $(M+H)^+$; pureza HPLC: 96%.
101		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.6 (d, *J* = 8.1 Hz, 3H), 7.3 (m, 2H), 6.9 (m, 2H), 3.2-2.8 (m, 3H), 2.6 (m, 2H), 2.2 (s, 3H), 1.8 (m, 1H), 1.2(s, 3H);	ESI-MS *m/z* = 510 $(M+H)^+$; pureza HPLC: 96.5%.
102		^{1}H-RMN (400 MHz, DMSO-d_6): δ 7.9 (d, *J* = 8.4 Hz, 1H), 7.6 (m, 3H), 7.32-7.2 (m, 5H), 7.0 (bs, 1H), 3.2-2.9 (m, 3H), 2.4 (m, 2H), 2.2 (m, 3H), 1.8 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 477 $(M+H)^+$; pureza HPLC: 92%.
103		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.2 (bs, 2H), 8.03 (s, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.64-7.48 (m, 6H), 7.38-7.24 (m, 2H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 1.9 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 515 $(M+H)^+$; pureza HPLC: 97%

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
104		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.2 (bs, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.7 (s, 1H), 7.6 (d, *J* = 14 Hz, 1H), 7.54-7.44 (m, 3H), 7.35-7.25 (m, 3H), 7.0 (m, 1H), 3.2-2.9 (m, 2H), 2.85 (d, *J* = 15.3 Hz, 1H), 2.4 (d, *J* = 16.2 Hz, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 481 $(M+H)^+$; pureza HPLC: 99%
105		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.4 (s, 1H), 8.04 (s, 1H), 7.94 (d, *J* = 8 Hz, 1H), 7.88 (bs, 1H), 7.62 (m, 1H), 7.5 (t, *J* = 7.6 Hz, 1H), 7.4-7.3 (m, 6H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	pureza HPLC: 94%.
106		^{1}H-RMN (300 MHz, DMSO-d_6): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.7 (s, 1H), 7.4-7.3 (m, 6H), 7.2 (m, 1H), 7.0 (m, 1H), 3.2-2.8 (m, 3H), 2.3 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	pureza HPLC: 95%.
107		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (s, 1H), 9.15 (bs, 1H), 8.9 (bs, 1H), 8.1 (s, 1H), 8.0 (d, *J* = 7.5 Hz, 1H), 7.8 (m, 1H), 7.65-7.45 (m, 6H), 7.3 (t, *J* = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.2 (s, 3H).	ESI-MS *m/z* = 453 $(M+H)^+$; pureza HPLC: 92%.
108		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.56 (s, 1H), 9.48 (s, 1H), 8.75 (s, 1H), 8.15-7.95 (m, 5H), 7.72 (s, 1H), 7.32 (m, 2H), 7.05 (s, 1H), 3.2-2.95 (m, 2H), 2.84 (m, 1H), 2.5-2.3 (m, 2H), 1.9 (m, 1H), 1.17 (s, 3H).	ESI-MS *m/z* = 464 $(M+H)^+$; pureza HPLC: 96.3%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
109		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.48-9.45 (2bs, 2H), 8.76 (s, 1H), 8.2-7.95 (m, 6H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 3.2-2.95 (m, 2H), 2.84 (d, *J* = 16 Hz, 1H), 2.5-2.3 (m, 2H), 1.92 (m, 1H), 1.18 (s, 3H).	ESI-MS *m/z* = 498 $(M+H)^+$; pureza HPLC: 93.9%.
110		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.6 (s, 1H), 9.22 (s, 1H), 8.79 (s, 1H), 8.2-7.95 (m, 5H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.3 (t, *J* = 8.4 Hz, 2H), 7.0 (t, *J* = 7.2 Hz, 1H), 3.18-2.95 (m, 2H), 2.83 (d, *J* = 16.4 Hz, 1H), 2.5-2.3 (m, 2H), 1.9 (m, 1H), 1.18 (s, 3H).	ESI-MS *m/z* = 430 $(M+H)^+$; pureza HPLC: 97.4%.
111		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H),10.06 (s, 1H), 9.91 (s, 1H), 9.19 (s, 1H), 9.02 (s, 1H), 8.1-7.95 (m, 4H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.4 (d, *J* = 7.2Hz, 1H), 3.2-2.95 (m, 2H), 2.85 (d, *J* = 16.0 Hz, 1H), 2.5-2.35 (m, 2H), 1.9 (m, 1H), 1.18 (s, 3H).	ESI-MS *m/z* = 497 $(M-H)^-$; pureza HPLC: 95.7%.
112		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H),10.24 (bs, 1H), 9.98 (bs, 1H), 9.22 (s, 1H), 9.01 (s, 1H), 8.1-7.95 (m, 3H), 7.76 (s, 1H), 7.35 (m, 2H), 7.09 (m, 1H), 3.15-2.95 (m, 2H), 2.84 (d, *J* = 15.9 Hz, 1H), 2.5-2.35 (m, 2H), 1.9 (m, 1H), 1.18 (s, 3H).	ESI-MS *m/z* = 465 $(M+H)^+$; pureza HPLC: 97.5%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
113		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 9.0 (s, 2H), 8.3 (m, 2H), 8.0 (d, *J* = 8.4 Hz, 1H), 7.5 (d, *J* = 7.8 Hz, 2H), 7.3 (t, *J* = 7.8 Hz, 2H), 7.0 (t, *J* = 7.2 Hz, 1H), 3.3 (m, 2H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.4 (m, 2H), 1.8 (m, 1H), 1.2 (s, 3H).	ESI-LCMS *m/z*: 431 (pureza 91.3 %); pureza HPLC 98 %.
114		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 10.0 (bs, 2H), 9.0 (s, 2H), 8.4 (m, 2H), 8.0 (m, 2H), 7.7 (d, *J* = 7.5 Hz, 1H), 7.5 (t, *J* = 7.8 Hz, 1H), 7.3 (d, *J* = 6.9 Hz, 1H), 3.1 (m, 3H), 2.8 (m, 1H), 2.4 (m, 1H), 1.9 (d, *J* = 12.6 Hz, 1H), 1.2 (s, 3H).	ESI-LCMS *m/z*: 498 (pureza 98%). pureza HPLC 98%.

EJEMPLO 115



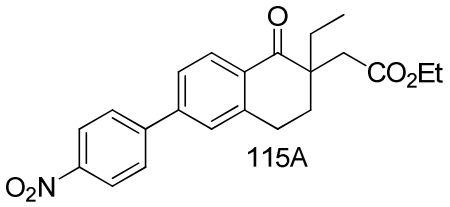
Reactivos y condiciones: a) EtI, KOH, acetona, t.a., 12 h; b)Fe-NH_4Cl, EtOH-H_2O, 85 °C, 2h; c) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; d) LiOH,

THF-H_2O, t.a., 12h.

Procedimiento

Acido 2-(2-etil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

2-(2-Etil-6-(4-nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (115A):



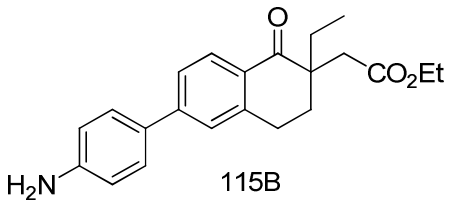
115A

A una solución del producto del ejemplo 47E (1.2 g, 3.39 mmol) en acetona (20 mL) se le agregó hidróxido de potasio (0.57 g, 10.17 mmol), seguido por yoduro de etilo (2.57 g, 16.5 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. La acetona se eliminó bajo presión reducida, el residuo se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 15% en éter de petróleo, para producir el compuesto del título como un sólido (0.43 g, 33%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.4 (d, *J* = 9.0 Hz, 2H), 8.2 (d, *J* = 8.4 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 2H), 7.6 (d, *J* = 7.6 Hz, 1H), 7.5 (s, 1H), 4.1 (m,

2H), 3.2-2.9 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, *J* = 7.2 Hz, 3H), 0.9 (t, *J* = 7.6 Hz, 3H).

2-(6-(4-Aminofenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (115B):

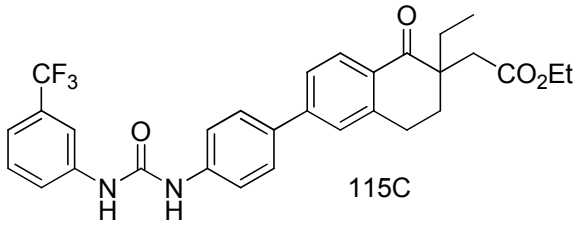


115B

A una solución del producto del ejemplo 115A (0.43 g, 1.12 mmol) en 22 mL de una mezcla de etanol-agua (2:1) se le agregó polvo de fierro (0.189 g, 3.37 mmol), seguido por NH_4Cl (0.030 g, 0.55 mmol), y la mezclase puso a reflujo por 2 h. El disolvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró, se concentró al vacío y se trituró con n-pentano, para dar el compuesto del título (0.35 g, 89%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.1 (d, *J* = 8.4 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 2H), 7.6-7.3 (m, 4H), 4.1 (m, 2H), 3.8 (bs, 2H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.6-2.4 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.3 (t, *J* = 7.6 Hz, 3H), 0.9 (t, *J* = 7.2 Hz, 3H).

2-(2-Etil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (115C):

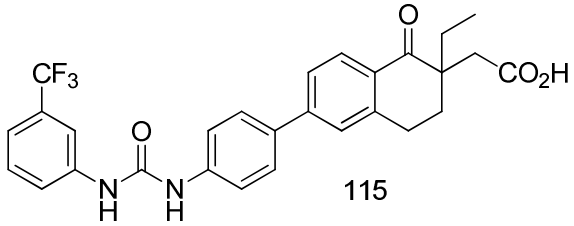


115C

A una solución del producto del ejemplo 115B(0.2 g, 0.56 mmol) y trietilamina (0.234 mL, 1.70 mmol) en THF (4 mL) se le agregó isocianato de 3-(trifluorometil)fenilo (0.084 mL, 0.56 mmol). La mezcla se agitó a temperatura ambiente durante 12 h. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo 25-30% en éter de petróleo, para producir el compuesto del título como un sólido (0.25 g, 81%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.1 (d, 8.4 Hz, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.5-7.3 (m, 9H), 7.1 (s, 1H), 4.1 (q, *J* = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.4-1.2 (m, 5H), 0.9 (t, *J* = 7.2 Hz, 3H).

Acido 2-(2-etil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (115):

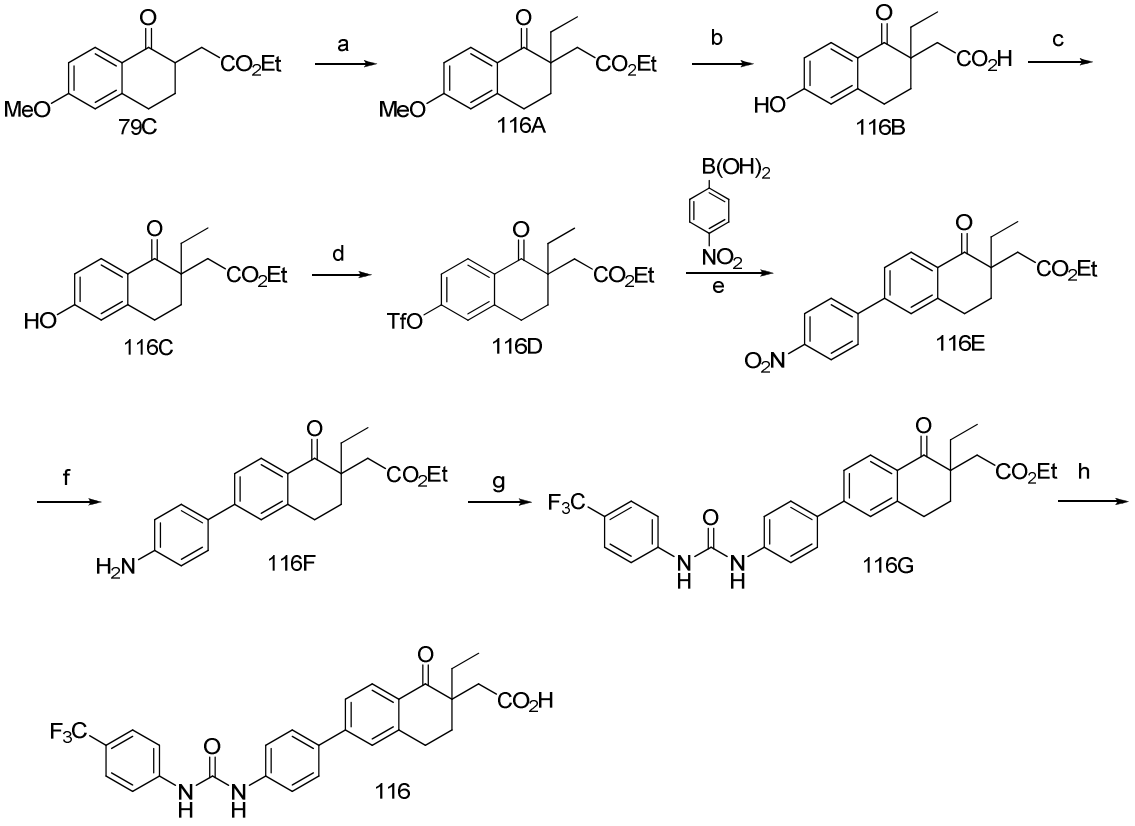


115

A una solución del producto del ejemplo 115C (0.25 g, 0.46 mmol) en 3 mL de una mezcla de etanol-agua (2:1) se le agregó hidróxido de litio (0.054 g, 1.38 mmol). La mezcla se agitó a temperatura ambiente durante 12 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. El sólido resultante se recogió por filtración, se trituró con n-pentano y éter dietílico y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.15 g, 63%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ12.1 (bs, 1H), 9.3 (bs, 1H), 9.1 (bs, 1H), 8.1 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.7 -7.5 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (t, J = 7.8 Hz, 3H); ESI-MS *m/z*: 511 $(M+H)^+$; pureza HPLC: 95%.

EJEMPLO 116



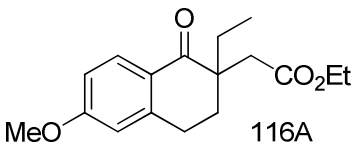
Reactivos y condiciones: a) EtI, NaH, DMF, t.a., 5h; b) HBr acuoso, 100 °C, 3h; c) $MeSO_3H$, EtOH, t.a., 16h; d) Tf_2O, CH_2Cl_2, Et_3N, t.a., 2h; e) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 4h; f) Fe-NH_4Cl, EtOH-H_2O, 85 °C, 4h; g) 4-CF_3PhNCO, Et_3N, THF, t.a., 12h; h) LiOH, THF-H_2O, t.a., 12h.

Procedimiento

Acido 2-(2-etil-1-oxo-6-(4-(3-(4-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

2-(2-Etil-6-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de

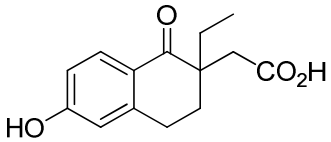
etilo (116A):



116A

A una solución enfriada en hielo del producto del ejemplo 79C (7 g, 26.8 mmol) en DMF (80 mL) se le agregó NaH (1.93 g, 80.4 mmol) en porciones, y la mezcla de reacción se agitó durante 10 min. Después se le agregó yoduro de etilo (20.91 g, 134.03 mmol) y la mezcla se agitó durante 5 h a temperatura ambiente. La mezcla de reacción se vació en agua de hielo y la capa acuosa se extrajo con acetato de etilo. La capa orgánica combinada se secó sobre sulfato de sodio, se filtró y se separó al vacío para dar el compuesto del título como un sólido (7.8 g).

Acido 2-(2-etil-6-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (116B):



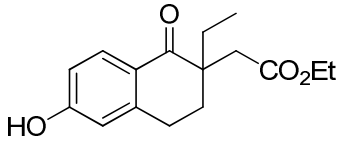
116B

Al producto del ejemplo 116A (7.8 g, 26.9 mmol) se le agregó HBr acuoso (120 mL) y la mezcla de reacción se puso a reflujo por 3 h. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida, para dar un producto crudo que se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 30%

en éter de petróleo, para producir el compuesto del título como un sólido (3.5 g, 53%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ12.0 (s, 1H), 10.3 (s, 1H), 7.8 (d, J = 8.4 Hz, 1H), 6.7 (d, J = 7.4 Hz, 1H), 6.6 (s, 1H), 3.0 (m, 1H), 2.7 (m, 2H), 2.4 (m, 2H), 1.9 (m, 1H), 1.7-1.5 (m, 2H), 0.9 (t, J = 7.6 Hz, 3H).

2-(2-Etil-6-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (116C):

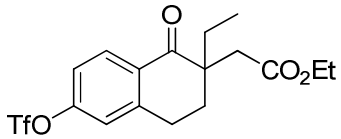


116C

A una solución del producto del ejemplo 116B (3.5 g, 14.17 mmol) en etanol (50 mL) se le agregó ácido metano sulfónico (6 mL) y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. El etanol se separó de la mezcla de reacción bajo presión reducida y el residuo se diluyó con acetato de etilo y se lavó con solución de salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida para dar un producto crudo que se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en éter de petróleo, para producir el compuesto del título como un sólido (3.2 g, 82%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ10.2 (s, 1H), 8.0 (d, J = 8.4 Hz, 1H), 6.7 (d, J = 7.4 Hz, 1H), 6.6 (s, 1H), 4.0 (m, 2H), 3.2-2.7 (m, 3H), 2.5-2.3 (m, 2H), 2.2-1.9 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, J = 7.2 Hz, 3H), 0.8 (t, J = 7.6 Hz, 3H).

2-(2-Etil-1-oxo-6-(trifluorometilsulfoniloxi)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (116D):

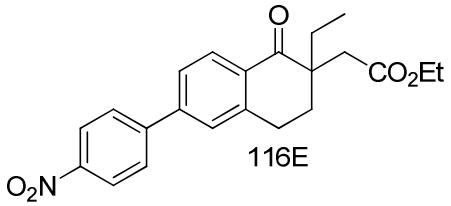


116D

A una solución enfriada en hielo del producto del ejemplo 116C (3.2 g, 11.6 mmol) y piridina (1.01 g, 12.7 mmol) en diclorometano (40 mL) se le agregó anhídrido tríflico (3.28 g, 11.6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano y se extrajo con solución acuosa saturada de NaCl. La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 5% en éter de petróleo, para dar el compuesto del título como un jarabe (3 g, 63%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.2 (d, *J* = 8.4 Hz, 1H), 7.3-7.2 (m, 2H), 4.2 (m, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, *J* = 7.2 Hz, 3H), 1.0 (t, *J* = 7.6 Hz, 3H).

2-(2-Etil-6-(4-nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (116E):

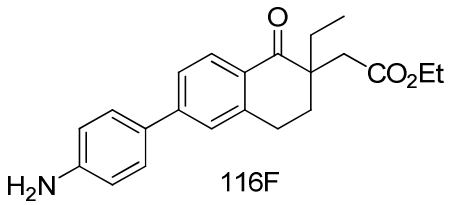


116E

A una solución del producto del ejemplo 116D (0.6 g, 1.47 mmol) en 14 mL de una mezcla de 1,4-dioxano-H_2O (2:1), bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$(0.02 g, 0.017 mmol), seguido por carbonato de cesio (1.44 g, 4.41 mmol) y ácido 4-nitrofenil-borónico (0.246 g, 1.47 mmol). La mezcla de reacción se desgasificó durante 5 min y se puso a reflujo por 4 h. Después el disolvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 15% en éter de petróleo, para producir el compuesto del título como un sólido (0.5 g, 89%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.4 (d, *J* = 9.0 Hz, 2H), 8.2 (d, *J* = 8.4 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 2H), 7.6 (d, *J* = 7.6 Hz, 1H), 7.5 (s, 1H), 4.1 (m, 2H), 3.2-2.9 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.2 (t, *J* = 7.2 Hz, 3H), 0.9 (t, *J* = 7.6 Hz, 3H).

<u>2-(6-(4-Aminofenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (116F):</u>



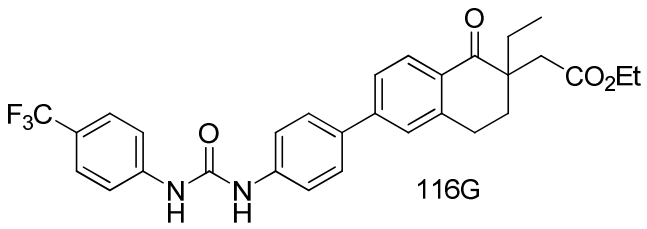
116F

A una solución del producto del ejemplo 116E (0.55 g, 1.44

mmol) en 30 mL de una mezcla de etanol-agua (2:1) se le agregó polvo de fierro (0.24 g, 4.3 mmol), seguido por NH_4Cl (0.039 g, 0.72 mmol). La mezcla de reacción se agitó y se puso a reflujo por 4 h. El disolvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y el filtrado se concentró bajo presión reducida, se trituró con n-pentano para producir el compuesto del título (0.3 g, 60%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.1 (d, *J* = 8.4 Hz, 1H), 7.8 (d, *J* = 8.4 Hz, 2H), 7.6-7.3 (m, 4H), 4.1 (m, 2H), 3.8 (bs, 2H), 3.1 (m, 1H), 3.0-2.8 (m, 2H), 2.6-2.4 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.3 (t, *J* = 7.6 Hz, 3H), 0.9 (t, *J* = 7.2 Hz, 3H).

2-(2-Etil-1-oxo-6-(4-(3-(4-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (116G):



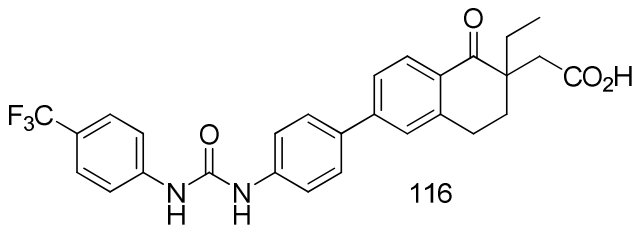
116G

A una solución del producto del ejemplo 116F(0.2 g, 0.56 mmol) y trietilamina (0.17 g, 1.68 mmol) en THF (5 mL)se le agregó isocianato de 4-(trifluorometil)fenilo(0.106 g, 0.57 mmol). La mezcla se agitó a temperatura ambiente durante 12 h. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando

acetato de etilo al 25% en éter de petróleo, para producir el compuesto del título como un sólido (0.18 g, 58%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.0 (d, 8.4 Hz, 1H), 7.7 (bs, 1H), 7.52-7.42 (m, 5H), 7.38-7.32 (m, 2H), 7.28-7.20 (m, 4H), 4.1 (q, *J* = 7.2 Hz, 2H), 3.14-2.8 (m, 3H), 2.55-2.4 (m, 2H), 2.05 (m, 1H), 1.8-1.64 (m, 2H), 1.2 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H).

Acido 2-(2-etil-1-oxo-6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (116):



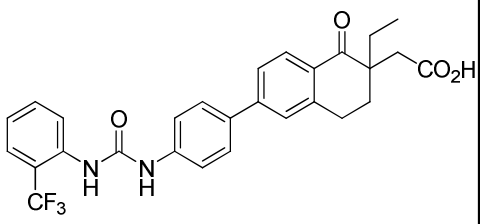
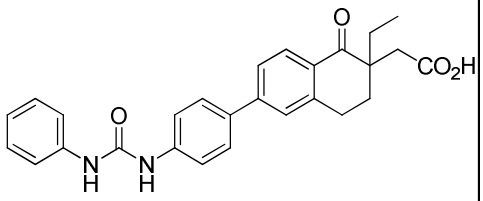
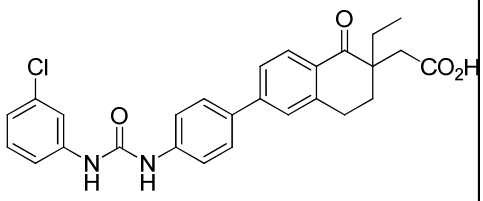
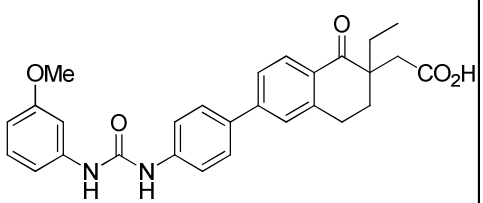
116

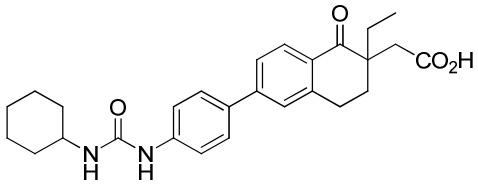
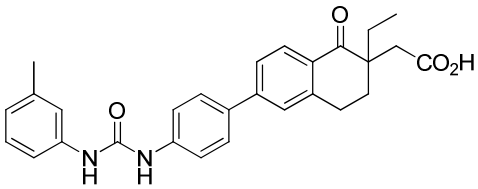
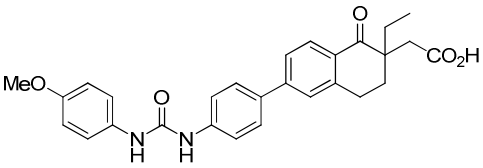
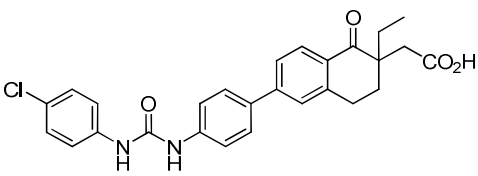
A una solución del producto del ejemplo 116G(0.18 g, 0.76 mmol) en 6 mL de una mezcla de etanol-agua (2:1) se le agregó hidróxido de litio (0.128 g, 2.28 mmol). La mezcla se agitó a temperatura ambiente durante 12 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. El sólido resultante se recogió por filtración, se trituró con n-pentano y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.1 g, 59%).

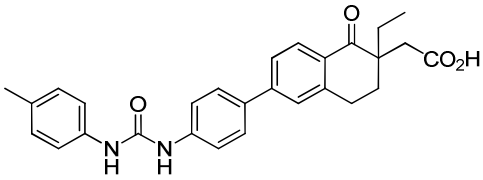
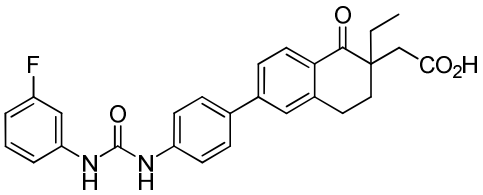
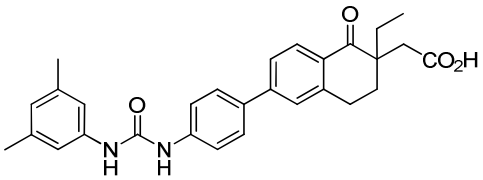
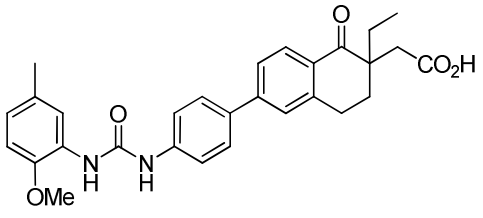
^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 9.2 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.8-7.5 (m, 10H), 3.2-2.9 (m, 2H), 2.85-2.7 (d,

J = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1,8-1.45 (m, 2H), 0.95 (m, 3H); ESI-MS *m/z*: 511 $(M+H)^+$; pureza HPLC: 94%.

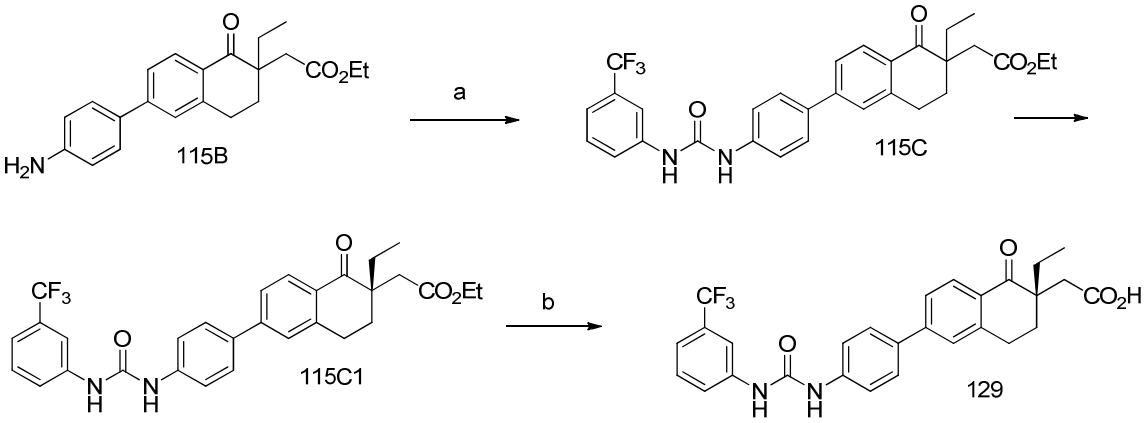
Los ejemplos 117-128 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 116, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
117		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.7 (bs, 1H), 8.35 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 2H), 7.7-7.5 (m, 8H), 7.3 (t, *J* = 6.3 Hz, 1H), 3.3-2.9 (m, 2H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (m , 3H).	pureza HPLC: 92%
118		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.2-8.8 (m, 2H), 7.8 (d, *J* = 8.4 Hz, 1H), 7.7-7.55 (m, 6H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.3 (t, *J* = 7.5 Hz, 2H), 6.95 (t, *J* = 7.5 Hz, 1H), 3.2-2.6 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, *J* = 7.8 Hz, 3H).	pureza HPLC: 91%
119		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.0 (bs, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.73-7.56 (m, 6H), 7.3 (m, 3H), 7.02 (m, 1H), 3.2-2.7 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.75-1.45 (m, 2H), 0.9 (t, *J* = 7.5 Hz, 3H).	pureza HPLC: 92%
120		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.6-9.0 (bs, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.66-7.48 (m, 6H), 7.26 (s, 1H), 7.16 (t, *J* = 8.4 Hz, 1H), 7.0 (d, *J* = 8.4 Hz, 1H), 6.56 (m, 1H), 3.8 (s, 3H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.4 Hz, 1H), 2.4 (m, 1H), 2.3 (d, *J* = 16.2 Hz, 1H), 2.0 (m, 1H), 1.78-1.5 (m, 2H), 0.85 (t, *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 473 $(M+H)^+$; pureza HPLC: 90%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
121		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.8 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.65-7.52 (m, 4H), 7.45 (d, *J* = 8.4 Hz, 2H), 6.4 (bs, 1H), 3.5 (s, 1H), 3.2-2.8 (m, 2H), 2.6 (d, *J* = 16 Hz, 1H), 2.35 (d, *J* = 16 Hz, 1H), 2.0 (m, 1H), 1.9-1.5 (m, 8H), 1.4-1.0 (m, 5H), 0.85 (t, *J* = 7.6 Hz, 3H).	pureza HPLC: 90%.
122		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.0 (bs, 1H), 8.8 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.7-7.5 (m, 6H), 7.31 (s, 1H), 7.28-7.1 (m, 2H), 6.8 (d, *J* = 7.5 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 3H), 2.0 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t , *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 457 $(M+H)^+$; pureza HPLC: 98%.
123		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 8.8 (bs, 1H), 8.58 (bs, 1H), 7.9 (d, *J* = 7.8Hz, 1H), 7.7-7.66 (d, *J* = 8.4 Hz, 2H), 7.64-7.52 (m, 4H), 7.38 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.8 (s, 3H), 3.2-2.8 (m, 2H), 2.6 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (m, 3H).	ESI-MS *m/z* = 473 $(M+H)^+$; pureza HPLC: 99%.
124		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 8.95 (2s, 2H), 7.9 (d, *J* = 7.8 Hz, 1H) , 7.7 (d, *J* = 8.4 Hz, 2H), 7.6 (m, 4H), 7.5 (d, *J* = 8.4 Hz, 2H), 7.3 (d, *J* = 8.4 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.5 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, *J* =	ESI-MS *m/z* = 477 $(M+H)^+$; pureza HPLC: 98%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
125		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.0-8.6 (bs, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.62-7.54 (m, 5H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.1 (d, *J* = 8.4 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.4 Hz, 1H), 2.4 (m, 2H), 2.25 (s, 3H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H).	pureza HPLC: 98%
126		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.7-7.4 (m, 7H), 7.3 (m, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.8 (t, *J* = 6.8 Hz, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 1.9 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t, *J* = 7.6 Hz, 3H).	pureza HPLC: 91%.
127		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 8.92 (bs, 1H), 8.62 (bs, 1H), 7.9 (d, *J* = 8.0 Hz, 1H), 7.7-7.5 (m, 6H), 7.1 (m, 2H), 6.6 (m, 1H), 3.2-2.8 (m, 2H), 2.6 (d, *J* = 16.4 Hz, 1H), 2.4 (m, 2H), 2.2 (s, 6H), 2.0 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (t, *J* = 7.6 Hz, 3H).	ESI-MS *m/z* = 470 $(M+H)^+$; pureza HPLC: 90%.
128		^{1}H-RMN (400 MHz, DMSO-d_6): δ 10.6 (bs, 1H), 8.8 (bs, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.8 (m, 2H), 7.6 -7.4 (m, 5H), 6.9 (d, *J* = 7.8 Hz, 1H), 6.8 (d, *J* = 7.5 Hz, 1H), 3.8 (s, 3H), 3.0-2.6 (m, 3H), 2.4 (m, 1H), 2.3 (s, 3H), 2.1 (m, 1H), 1.9 (m, 1H), 1.8-1.6 (m, 2H), 0.9 (m, 3H).	pureza HPLC: 90%.

EJEMPLO 129

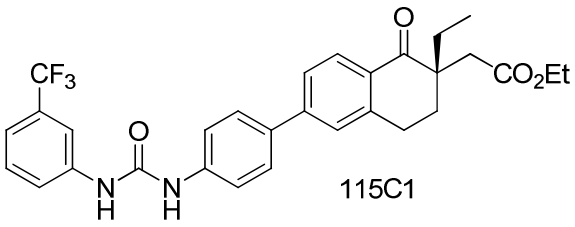


Reactivos y condiciones: a) 3-CF_3PhNCO, Et_3N, THF, t.a., 6h; b) LiOH, dioxano-H_2O, t.a., 12h.

Procedimientos

Acido (S)-2-(2-etil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

(S)-2-(2-Etil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (115C1):



A una solución del producto del ejemplo 115B(0.29 g, 0.82 mmol) y trietilamina (0.25 g, 2.47 mmol) en THF (10 mL) se le agregó isocianato de 3-(trifluorometil)fenilo (0.185 g, 0.98 mmol). La mezcla se agitó a temperatura

ambiente durante 6 h. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en éter de petróleo, para producir el ejemplo 115C como un sólido (0.34 g, 77%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.1 (d, 8.4 Hz, 1H), 7.7 (m, 1H), 7.6 (m, 1H), 7.5-7.3 (m, 9H), 7.1 (s, 1H), 4.1 (q, *J* = 6.9 Hz, 2H), 3.2-2.8 (m, 3H), 2.5 (m, 2H), 2.1 (m, 1H), 1.8-1.6 (m, 2H), 1.4-1.2 (m, 5H), 0.9 (t, *J* = 7.2 Hz, 3H).

El ejemplo 115C (0.5 g, que se derivan de 0.32g obtenidos arriba y otro lote de 180 mg usando procedimientos similares a los que se describen para el ejemplo 115C),era una mezcla racémica 1:1, y se separó en una columna quiral para obtener los enantiómeros individuales de 115C1 (t_R= 15.67 min) y 115C2 (t_R= 20.16 min) usando las siguientes condiciones.

Columna: CHIRAL PAK ODH (4.6x250 mm) 5 µ

Fase móvil: A: hexano, B: etanol

A:B(Iso) 85:15; velocidad de flujo: 0.8 mL/min

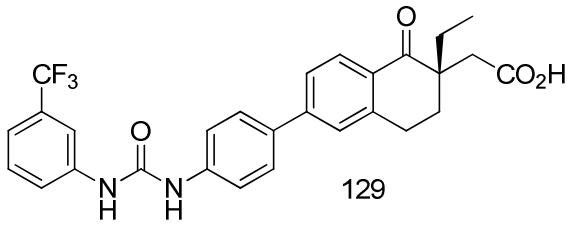
115C1: 0.17 g, t_R 15.67 min, rotación óptica +22 (c1 $CHCl_3$)

115C2: 0.168 g, t_R 20.16 min, rotación óptica -22 (c1 $CHCl_3$)

Configuraciones absolutas confirmadas por estudios deVCD:

La configuración absoluta de 115G1 es *S,* y la de 115G2 es *R*.

<u>Acido (S)-2-(2-etil-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (129):</u>

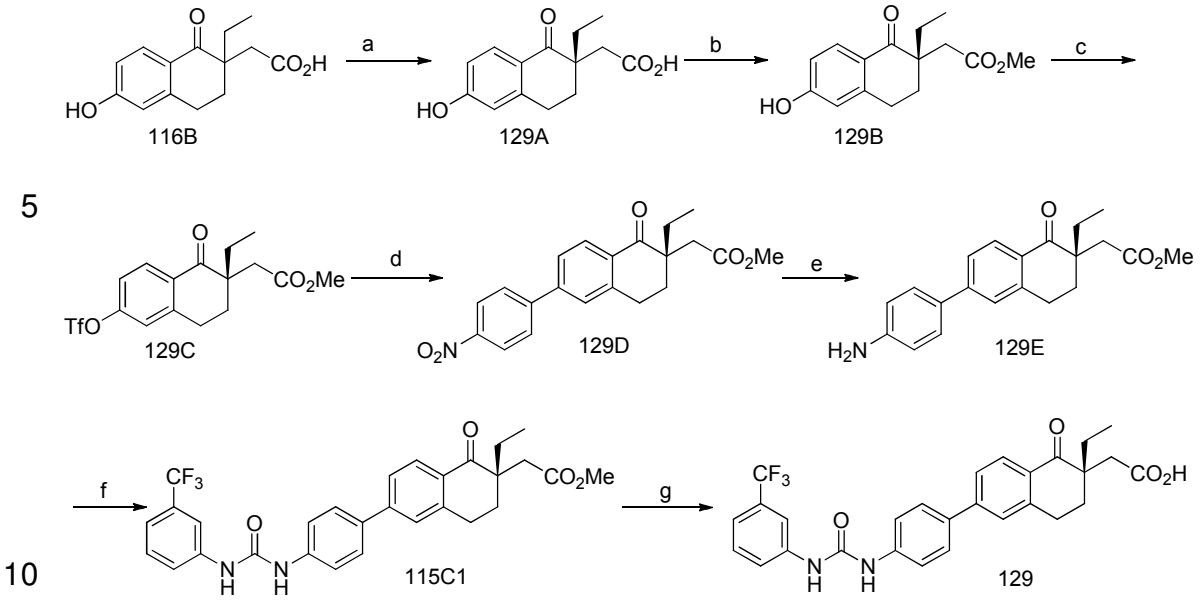


129

A una solución del producto del ejemplo 115C1(0.12 g, 0.22 mmol) en 4 mL de una mezcla etanol-agua (3:1)se le agregó hidróxido de litio (0.028 g, 0.67 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración, se trituró con n-pentano y se secó al vacío, para producir el compuesto del título como un sólido (0.08 g, 72%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.22 (bs, 1H), 9.09 (bs, 1H), 8.05 (s, 1H), 7.9 (d, J = 8.4 Hz, 1H), 7.6-7.4 (m, 8H), 7.3 (d, J = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (t, J = 5.7 Hz, 3H); ESI-MS *m/z*: 511 $(M+H)^+$.

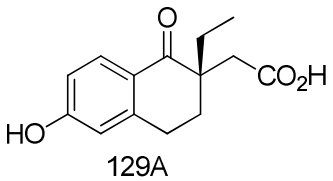
Síntesis alterna del ejemplo 129



Reactivos y condiciones: a) Cinconidina, IPA-H_2O, 80 °C – t.a., 24h, luego HCl 6N, t.a.; b) H_2SO_4, MeOH, 70 °C, 12h; c) Tf_2O, CH_2Cl_2, Et_3N, t.a., 1h; d) ácido 4-nitrofenil-borónico, $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; e) Fe-NH_4Cl, EtOH-H_2O, 85 °C, 3h; f) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; g) LiOH, THF-H_2O, t.a., 12h.

Procedimientos

Acido (S)-2-(2-etil-6-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (129A):



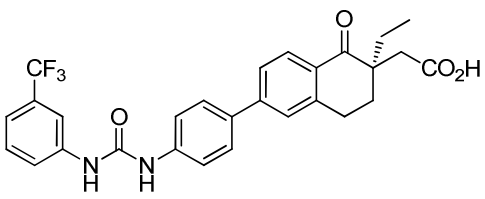
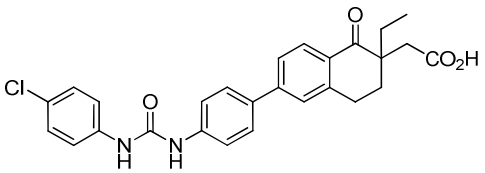
A una solución del producto del ejemplo 116B (10 g, 40.3 mmol) en alcohol isopropílico (64 mL) y agua (16 mL) se le agregó cinconidina (11.85 g, 40.3 mmol) y la mezclase calentó 4 ha 80 °C. La solución resultante se agitó a temperatura ambiente durante 16 h y la sal se filtró y se lavó con una mezcla de alcohol isopropílico(10 mL) y agua (10 mL).La sal se disolvió en HCl 6N (40 mL) y se extrajo con acetato de etilo (2x50 mL). La capa orgánica se lavó con agua, solución de salmuera, se secó y se concentró para producir el compuesto del título como un sólido blanco (1.3 g, 26%).

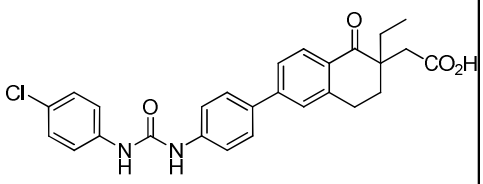
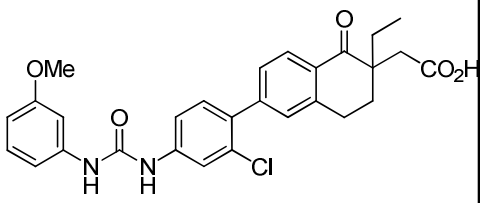
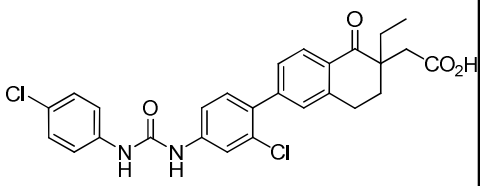
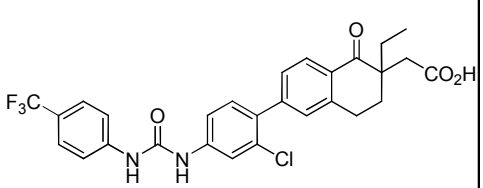
^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 10.2 (s, 1H), 7.74 (d, J = 8.4 Hz, 1H), 6.70 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 6.60 (d, J = 1.2 Hz, 1H), 3.0-2.88 (m, 1H), 2.77 (m, 1H), 2.7 (d, J = 16.8 Hz, 1H), 2.38 (m, 1H), 2.31 (d, J = 16.4 Hz, 1H), 1-95-1.85 (m, 1H), 1.62 (m, 1H), 1.48 (m, 1H), 0.8 (t, J = 7.2 Hz, 3H).

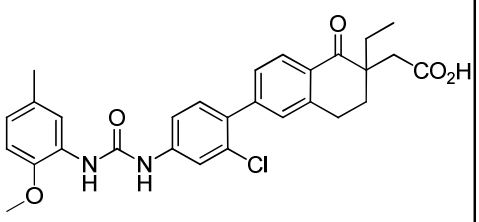
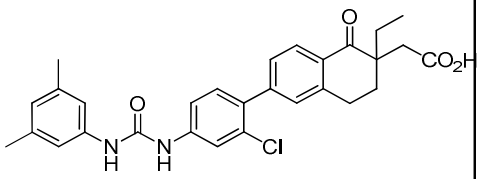
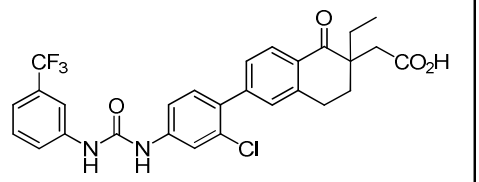
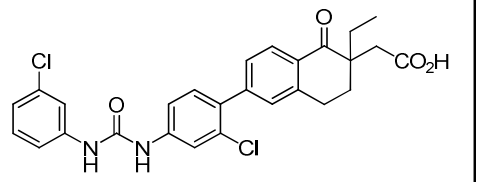
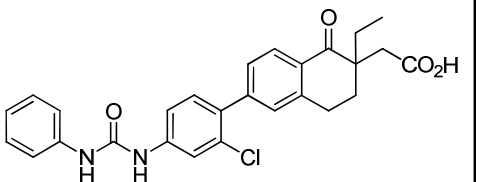
Los ejemplos 129B, 129C, 129D, 129E y 115C1 se sintetizaron a partir del compuesto 129A quiral usando procedimientos similares a los que se describen para elejemplo116.

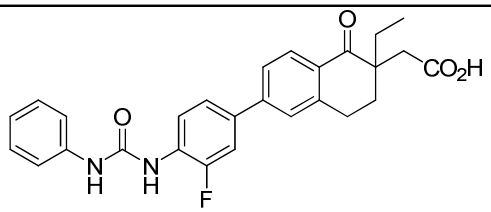
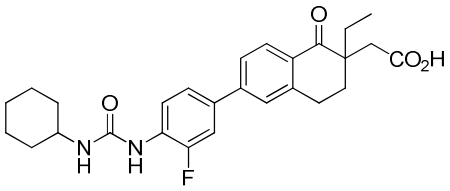
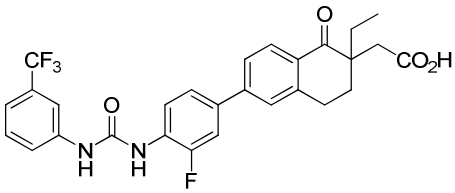
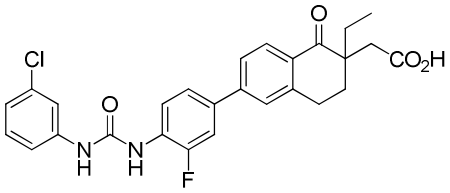
Los ejemplos 130-172 se prepararon mediante procedimientos análogos a los que se describen en los ejemplos 116 y 129, usando los materiales iniciales apropiados. Los ácidos borónicos requeridos (y las versiones con grupos funcionales adecuadamente protegidos de los mismos) aquí utilizados se compraron en caso de estar disponibles comercialmente, o se sintetizaron como se describe en la literatura o por medio de modificaciones rutinarias conocidas para los expertos en la materia, o se

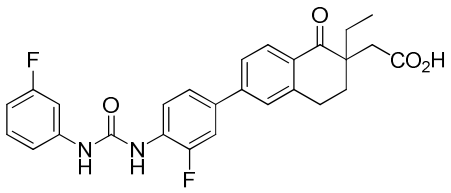
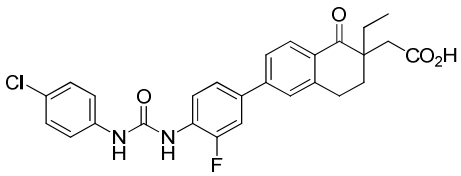
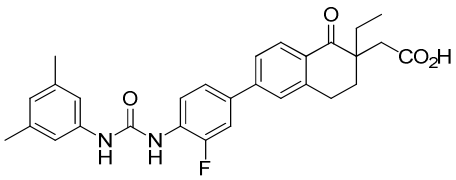
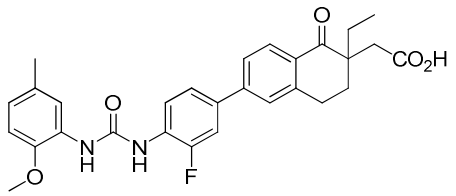
sintetizaron mediante procedimientos alternos conocidos por los expertos en la materia.

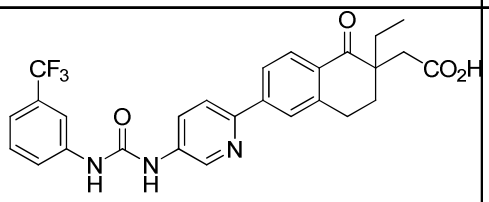
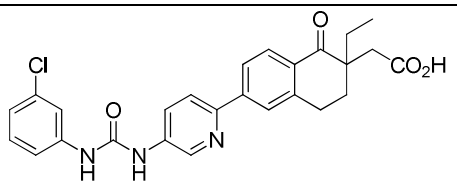
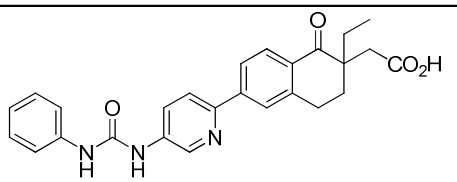
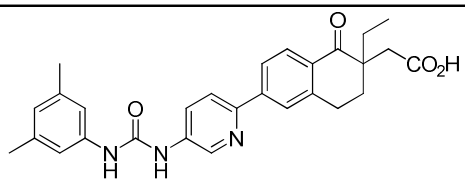
Ej.	Estructura	Datos analíticos	$(M+H)^+$
130	 Quiral	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.22 (bs, 1H), 9.09 (bs, 1H), 8.05 (s, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.6-7.4 (m, 8H), 7.3 (d, *J* = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (t, *J* = 5.7 Hz, 3H).	pureza HPLC: 97%
131	 Quiral: enantiómero 1	^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.1 (bs, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.7-7.54 (m, 6H), 7.5 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 3.2-2.9 (m, 2H), 2.79 (d, *J* = 16.8 Hz, 1H), 2.45 (m, 1H), 2.41 (d, *J* =16.4 Hz, 1H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, *J* = 7.2 Hz, 3H).	pureza HPLC: 99%

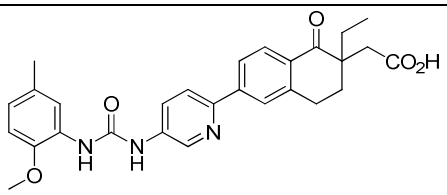
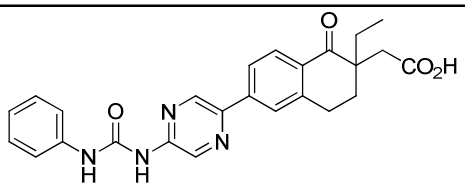
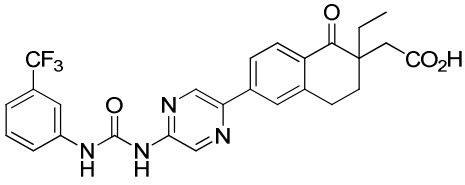
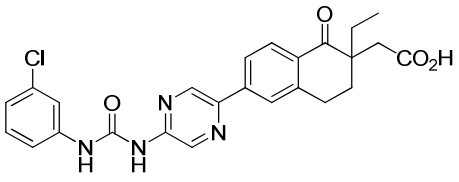
Ej.	Estructura	Datos analíticos	$(M+H)^+$
132	 Quiral: enantiómero 2	^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (s, 1H), 9.1 (bs, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.7-7.54 (m, 6H), 7.5 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 3.2-2.9 (m, 2H), 2.79 (d, *J* = 16.8 Hz, 1H), 2.45 (m, 1H), 2.41 (d, *J* = 16.4 Hz, 1H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, *J* = 7.2 Hz, 3H).	pureza HPLC: 97%
133		^{1}H-RMN (300 MHz, DMSO-d_6): δ δ 12.1 (bs, 1H), 9.1 (bs, 1H), 8.9 (bs, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.45-7.3 (m, 4H), 7.2 (m, 2H), 6.95 (d, *J* = 9.0 Hz, 1H), 6.6 (m, 1H), 3.78 (s, 3H), 3.3-2.9 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 507 $(M+H)^+$; pureza HPLC: 96%
134		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 8.24 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.64 (d, *J* = 9.3 Hz, 2H), 7.36-7.25 (m, 4H), 6.66 (m, 1H), 6.49 (m, 1H), 3.29-2.73 (m, 4H), 2.22 (m, 1H), 1.84 (m, 1H), 1.7-1.45 (m, 2H), 0.9 (t, *J* = 6.9 Hz, 3H).	pureza HPLC: 98.89%.
135		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 8.02 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.7 (m, 3H), 7.6 (m 3H), 7.4 (m, 2H), 7.1 (m, 1H), 3.2-2.96 (m, 2H), 2.85 (d, *J* = 15.9 Hz, 1H), 2.6 (m, 1H), 2.3 (d, *J* = 16.8 Hz, 1H), 1.9 (m, 1H), 1.7-1.45 (m, 2H), 0.9 (t, *J* = 7.5 Hz, 3H).	ESI-MS *m/z* = 545 $(M+H)^+$; pureza HPLC: 97.6%.

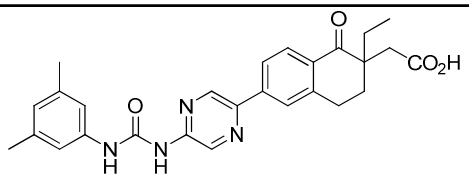
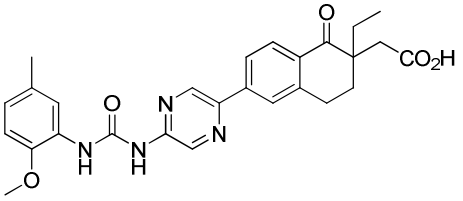
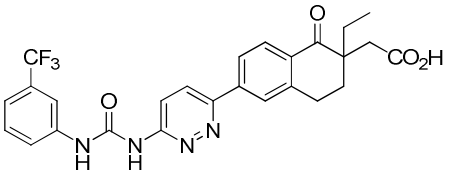
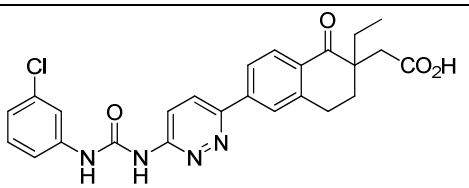
Ej.	Estructura	Datos analíticos	$(M+H)^+$
136		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.7 (bs, 1H), 8.8 (bs, 1H), 8.0-7.85 (m, 3H), 7.42-7.3 (m, 4H), 6.9 (m, 1H), 6.78 (m, 1H), 3.8 (s, 3H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.26 (s, 3H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (m, 3H).	ESI-MS *m/z* = 521 $(M+H)^+$; pureza HPLC: 95.8%.
137		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.0 (bs, 1), 8.7 (bs, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.86 (s, 1H), 7.45-7.3 (m, 3H), 7.0 (m, 3H), 6.65 (s, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.4 (m, 2H), 2.26 (s, 6H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.85 (t, *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 505 $(M+H)^+$; pureza HPLC: 97%.
138		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.3 (bs, 2H), 8.1 (s, 1H), 7.9 (m, 2H), 7.6-7.0 (m, 7H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.4 (m, 2H), 0.85 (m, 3H).	pureza HPLC: 90%.
139		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs,1), 9.15 (bs, 1H), 9.1 (bs, 1H), 7.95 (m, 1H), 7.85 (bs, 1H), 7.7 (s, 1H), 7.5-7.2 (m, 6H), 7.0 (s, 1H), 3.2-2.8 (m, 3H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.4 (m, 2H), 0.9 (t, *J* = 6.9 Hz, 3H).	ESI-MS *m/z* = 510 $(M+H)^+$; pureza HPLC: 90%.
140		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.05 (bs, 1H), 8.95 (bs, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.6-7.2 (m, 8H), 7.0 (d, *J* = 7.8 Hz, 1H), 3.2-2.8 (m, 2H), 2.6 (d, *J* = 15.9 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.9-1.6 (m, 2H), 0.9 (t, *J* = 6.9 Hz, 3H).	pureza HPLC: 97%.

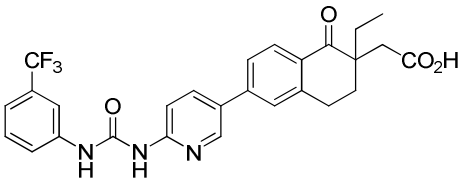
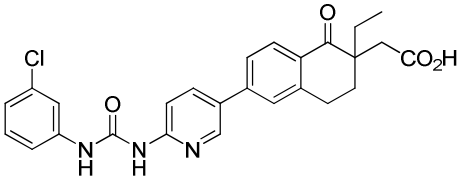
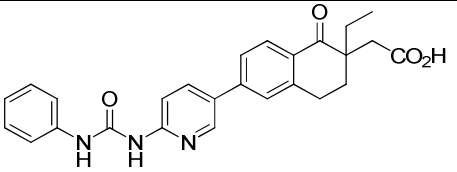
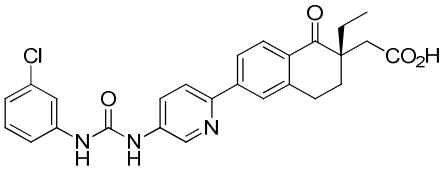
Ej.	Estructura	Datos analíticos	$(M+H)^+$
141		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.6 (bs, 1H), 9.0 (bs, 1H), 8.2 (m, 1H), 7.9 (d, *J* = 8.1 Hz, 1H), 7.7-7.4 (m, 6H), 7.3 (t, *J* = 7.5 Hz, 2H), 7.0 (t, *J* = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (m, 1H), 2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.9 (m, 3H).	ESI-MS *m/z* = 461 $(M+H)^+$; pureza HPLC: 90%.
142		^{1}H-RMN (300 MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.28 (t, *J* = 9 Hz, 1H), 7.9 (d, *J* = 8.1 Hz, 1H), 7.7-7.6 (m, 3H), 7.5 (d, *J* = 9.9 Hz, 1H), 6.7 (d, *J* = 6.9 Hz, 1H), 3.6-3.4 (m, 1H), 3.2-2.8 (m, 3H), 2.57 (d, *J* = 16.2 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 4H), 1.4-1.2 (m, 7H), 0.85 (t, *J* = 6.9 Hz, 3H).	pureza HPLC: 97%.
143		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.6 (bs, 1H), 8.9 (bs, 1H), 8.25 (m, 1H), 8.05 (s, 1H), 7.9 (m, 1H), 7.72-7.5 (m, 6H), 7.36 (m, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 15.9Hz, 1H), 2.3 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 3H).	ESI-MS *m/z* = 528 $(M+H)^+$; pureza HPLC: 95%.
144		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (s, 1H), 8.85 (s, 1H), 8.25 (m, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.8 - 7.55 (m, 5H), 7.35-7.2 (m, 2H), 7.1 (t, *J* = 8 Hz, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.2 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.85 (t, *J* = 7.6 Hz, 3H).	ESI-MS *m/z* = 494 $(M+H)^+$; pureza HPLC: 90%

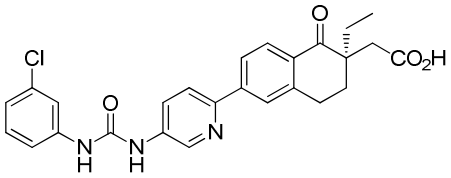
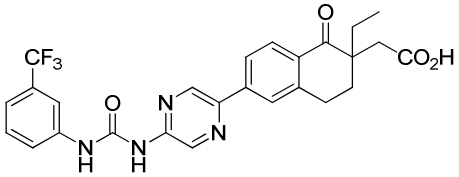
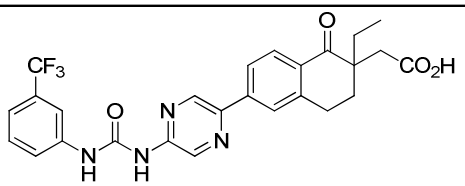
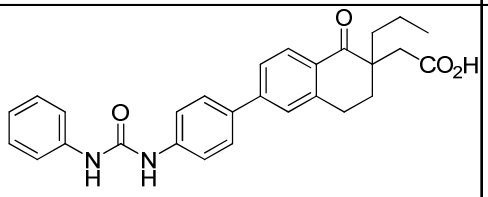
Ej.	Estructura	Datos analíticos	$(M+H)^+$
145		^{1}H-RMN (300 MHz, DMSO-d_6): δ 10.8 (bs, 1H), 10.4 (bs, 1H), 7.87 (d, *J* = 8.0 Hz, 2H), 7.56-7.40 (m, 5H), 7.29-7.13 (m, 2H), 6.74 (m, 1H), 3.2-2.7 (m, 3H), 2.6 (d, *J* = 16.2 Hz, 1H), 2.2 (m, 2H), 1.7-1.5 (m, 2H), 0.9 (t, *J* = 6.9 Hz, 3H).	pureza HPLC: 92%.
146		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.26 (m, 1H), 8.76 (m, 1H), 8.27 (t, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 9.3 Hz, 1H), 7.74 -7.56 (m, 4H), 7.54 (d, *J* = 6.4 Hz, 2H), 7.3 (d, *J* = 6.3 Hz, 2H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16.1 Hz, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.75-1.5 (m, 2H), 0.8 (t, *J* = 7.8 Hz , 3H).	pureza HPLC: 96%.
147		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.05 (bs, 1H), 8.75 (s, 1H), 8.3 (m, 1H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.72-7.62 (m, 3H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.2 (s, 2H), 6.6 (s, 1H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16 Hz, 1H), 2.4 (m, 2H), 2.3 (s, 6H), 2.0 (m, 1H), 1.8-1.5 (m, 2H), 0.8 (t, *J* = 7.8 Hz, 3H).	pureza HPLC: 91%.
148		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.4 (bs, 1H), 8.8 (bs, 1H), 8.3 (t, *J* = 8.4 Hz , 1H), 8.0 (s, 1H), 7.9 (d, *J* = 9 Hz, 1H), 7.7-7.65 (m, 3H), 7.54 (m, 1H), 6.9 (d, *J* = 8.4 Hz, 1H), 6.8 (d, *J* = 8.4 Hz, 1H), 3.8 (s, 3H), 3.2-2.9 (m, 2H), 2.8 (d, *J* = 16 Hz, 1H), 2.35 (m, 2H), 2.25 (s, 3H), 2.0 (m, 1H), 1.7-1.5 (m, 2H), 0.8 (t, *J* = 7.8 Hz , 3H).	pureza HPLC: 92%.

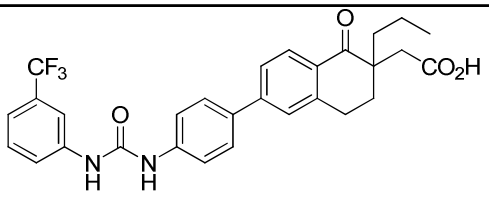
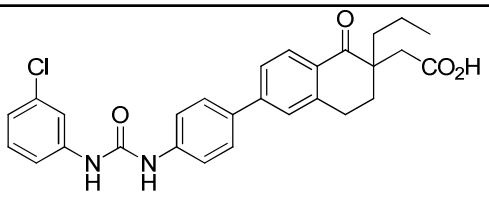
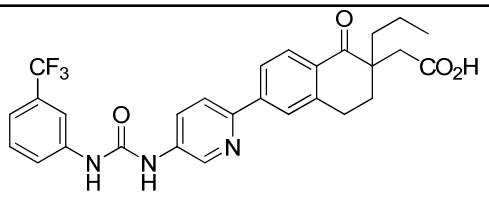
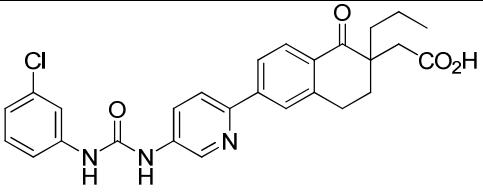
Ej.	Estructura	Datos analíticos	$(M+H)^+$
149		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.50 (bs, 1H), 8.76 (s, 1H), 8.20-7.90 (m, 6H), 7.70-7.50 (m, 2H), 7.36-7.33 (m, 1H), 3.16-2.76 (m, 3H), 2.50-2.20 (m, 2H), 2.0-1.98 (m, 1H), 1.68-1.54 (m, 2H), 0.84 (m, 3H).	ESI-MS *m/z* = 512 $(M+H)^+$. pureza HPLC: 95.3%.
150		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.78 (bs, 1H), 9.64 (bs, 1H), 8.80 (s, 1H), 8.15-8.06 (m, 2H), 8.0-7.95 (m, 3H), 7.72 (s, 1H), 7.3 (t, *J* = 8.4 Hz, 2H), 7.06-7.03 (m, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.8 Hz, 3H).	ESI-MS *m/z* = 478 $(M+H)^+$. pureza HPLC: 95.66 %.
151		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.2 (bs, 1H), 8.9 (bs, 1H), 8.73 (s, 1H), 8.12-7.96 (m, 5H), 7.4 (d, *J* = 7.8 Hz, 2H), 7.3 (t, *J* = 8.4 Hz, 2H), 7.0 (m, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H).	ESI-MS *m/z* = 444 $(M+H)^+$. pureza HPLC: 91.6 %.
152		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.4 (bs, 1H), 9.0 (bs, 1H), 8.74 (s, 1H), 8.15-7.95 (m, 5H), 7.1 (s, 2H), 6.64 (s, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.24 (s, 6H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.8 Hz, 3H).	pureza HPLC: 94.4 %.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
153		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.78 (bs, 1H), 8.7 (s, 1H), 8.35 (s, 1H), 8.15-7.95 (m, 6H), 6.9 (d, J = 8.1 Hz, 1H), 6.78 (dd, J_2 = 8.4 Hz, J_1 = 1.5 Hz, 1H), 3.85 (s, 3H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.24 (s, 3H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H).	pureza HPLC: 98.67 %.
154		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.83 (bs, 1H), 9.81 (bs, 1H), 9.21 (s, 1H), 9.0 (s, 1H), 8.04-7.96 (m, 3H), 7.52 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 2H), 7.0 (t, J = 7.6 Hz, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.0 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.8 Hz, 3H).	ESI-MS m/z = 445 $(M+H)^+$; pureza HPLC: 90%.
155		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.95 (bs, 1H), 9.87 (bs, 1H), 9.17 (s, 1H), 9.03 (s, 1H), 8.05-7.9 (m, 4H), 7.67 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.4 (d, J = 7.8 Hz, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.2 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 7.8 Hz, 3H).	ESI-MS m/z = 513 $(M+H)^+$; pureza HPLC: 91.59%.
156		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.8 (bs, 1H), 9.7 (bs, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 8.04-7.89 (m, 3H), 7.76 (m, 1H), 7.36-7.28 (m, 2H), 7.11 (m, 1H), 3.2-2.95 (m, 2H), 2.8 (d, J = 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, J = 6.9	ESI-MS m/z = 479 $(M+H)^+$; pureza HPLC: 91.12 %.

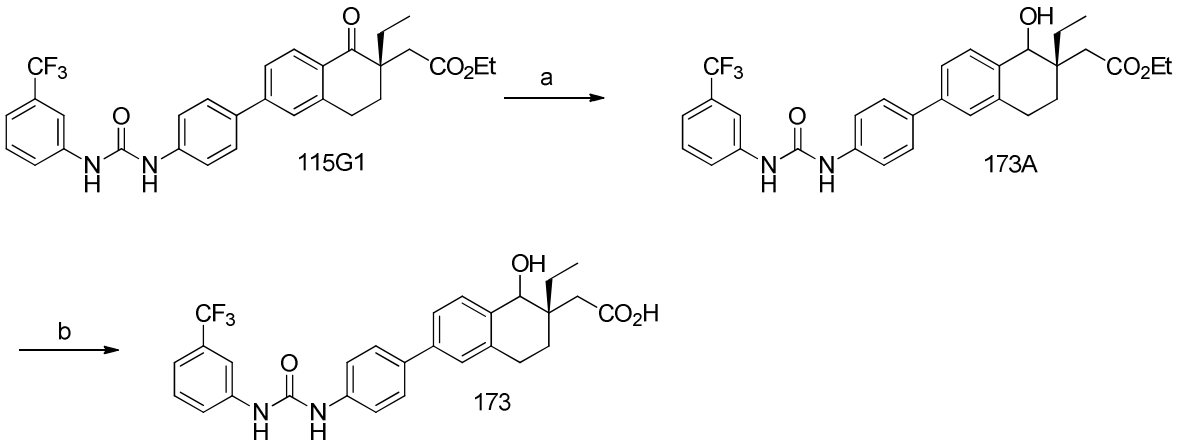
Ej.	Estructura	Datos analíticos	$(M+H)^+$
157		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.05 (s, 1), 9.79 (bs, 1H), 9.62 (bs, 1H), 9.16 (s, 1H), 9.0 (s, 1H), 8.04-7.98 (m, 3H), 7.15 (s, 2H), 6.69 (s, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J*= 16.8 Hz, 1H), 2.5-2.3 (m, 2H), 2.26 (s, 6H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (m, 3H).	pureza HPLC: 91.88%.
158		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.05 (s, 1H), 10.29 (bs, 1H), 9.94 (bs, 1H), 9.0 (s, 2H), 8.04-7.98 (m, 4H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.89 (s, 3H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 16.2 Hz, 1H), 2.5-2.3 (m, 2H), 2.24 (s, 3H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 3H).	pureza HPLC: 95.39%.
159		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 10.29 (m, 2H), 8.32 (d, *J* = 7.2 Hz, 1H), 8.25 (m, 1H), 8.07-7.98 (m, 4H), 7.64-7.57 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.8 Hz, 3H).	ESI-MS *m/z* =513 $(M+H)^+$; pureza HPLC: 98.83%.
160		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs,1H), 10.29 (s, 1H), 9.95 (bs, 1H), 8.38-8.20 (m, 2H), 8.18-8.0 (m, 3H), 7.78 (s, 1H), 7.38 (m, 2H), 7.15 (s, 1H), 3.2-2.95 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.0 (m, 1H), 1.70-1.52 (m, 2H), 0.84 (t, *J* = 7.8 Hz, 3H).	ESI-MS *m/z* =479$(M+H)^+$; pureza HPLC: 93.4%

Ej.	Estructura	Datos analíticos	$(M+H)^+$
161		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 10.7 (s, 1H), 9.73 (s, 1H), 8.73 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H) 7.68-7.53 (m, 4H), 7.56 (t, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 6.9 Hz, 1H), 3.1-2.9 (m, 2H), 2.8 (d, *J* = 16.2 Hz, 1H), 2.50-2.36 (m, 2H), 2.0 (m, 1H), 1.75-1.45 (m, 2H), 0.84 (m, 3H).	ESI-MS *m/z* = 512 $(M+H)^+$. pureza HPLC: 95.8%.
162		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 11.45 (s, 1H), 8.35 (s, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.88-7.8 (m, 2H), 7.65-7.5 (m, 4H), 7.25 (t, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 3.15-2.75 (m, 4H), 2.1 (d, *J* = 15.6 Hz, 1H), 1.84 (m, 1H), 1.7-1.45 (m, 2H), 0.88 (t, *J* = 7.8 Hz, 3H).	ESI-MS *m/z* = 478 $(M+H)^+$. pureza HPLC: 96.3%.
163		^{1}H-RMN (300 MHz, DMSO-d_6): δ 10.4 (s, 1H), 9.9 (s, 1H), 8.7 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.8-7.65 (m, 3H), 7.5 (d, *J* =7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.03 (t, *J* = 6.9 Hz, 1H), 3.2-2.9 (m, 2H), 2.76 (d, *J* = 16.8 Hz, 1H), 2.50-2.35 (m, 2H), 2.0 (m, 1H), 1.75-1.45 (m, 2H), 0.84 (t, *J* = 7.8 Hz, 3H).	ESI-MS *m/z* = 444 $(M+H)^+$. pureza HPLC: 92.7%.
164	 Quiral	^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.26 (bs, 1H), 9.20 (bs, 1H), 8.75 (s, 1H), 8.15 (m, 1H), 8.03 (m, 4H), 7.74 (s, 1H), 7.34 (m, 2H), 7.07 (m, 1H), 3.13-3.02 (m, 2H), 2.8 (d, *J* = 16.4 Hz, 1H), 2.5-2.35 (m, 2H), 2.03 (m, 1H), 1.71-1.58 (m, 2H), 0.86 (t, *J* = 6.8	ESI-MS *m/z* = 478 $(M+H)^+$. pureza HPLC: 96.32 %.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
165	 Quiral	^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.26 (bs, 1H), 9.20 (bs, 1H), 8.75 (s, 1H), 8.15 (m, 1H), 8.03 (m, 4H), 7.74 (s, 1H), 7.34 (m, 2H), 7.07 (m, 1H), 3.13-3.02 (m, 2H), 2.8 (d, *J* = 16.4 Hz, 1H), 2.5-2.35 (m, 2H), 2.03 (m, 1H), 1.71-1.58 (m, 2H), 0.86 (t, *J* = 6.8 Hz, 3H).	ESI-MS *m/z* = 478 $(M+H)^+$. pureza HPLC: 99.17%.
166	 Quiral: enantiómero 1	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.08 (s, 1H), 10.0 (bs, 1H), 9.93 (bs, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.1-7.9 (m, 4H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.4 (d, *J* = 6.3 Hz, 1H), 3.2-3.0 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.68-1.55 (m, 2H), 0.84 (m, 3H).	ESI-MS *m/z* = 513 $(M+H)^+$; pureza HPLC: 98%.
167	 Quiral: enantiómero 2	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.08 (s, 1H), 10.0 (bs, 1H), 9.93 (bs, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.1-7.9 (m, 4H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.4 (d, *J* = 6.3 Hz, 1H), 3.2-3.0 (m, 2H), 2.8 (d, *J* = 15.9 Hz, 1H), 2.5-2.3 (m, 2H), 2.02-1.98 (m, 1H), 1.68-1.55 (m, 2H), 0.84 (m, 3H).	ESI-MS *m/z* = 513 $(M+H)^+$; pureza HPLC: 97.5%.
168		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.07 (bs, 1H), 9.1-8.9 (s, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.68-7.56 (m, 6H), 7.48-7.46 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 3.08-2.92 (m, 2H), 2.80 (d, *J* = 16.4 Hz, 1H), 2.40 (m, 1H), 1.96 (m, 1H), 1.61 (m, 1H), 1.45-1.15 (m, 4H), 0.84 (m, 3H).	ESI-LCMS *m/z*: 457 (98%); pureza HPLC: 98%.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
169		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.8 (bs, 2H), 8.05 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.6 (m, 8H), 7.3 (d, *J* = 7.5 Hz, 1H), 3.1 (m, 1H), 2.8 (m, 2H), 2.35 (d, *J* = 15.9 Hz, 1H), 2.0 (d, *J* = 12.6 Hz, 1H), 1.6 (m, 1H), 1.4 (m, 4H), 0.8 (t, *J* = 6.9 Hz, 3H).	ESI-LCMS *m/z*: 523 (pureza 96%); pureza HPLC: 94%.
170		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (s, 1H), 9.35 (bs, 2H), 7.9 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.6 (m, 6H), 7.3 (m, 2H), 7.0 (d, *J* = 5.7 Hz, 1H), 3.0 (m, 2H), 2.8 (m, 1H), 2.4 (d, *J* = 16.2 , 1H), 2.0 (d, *J* = 13.2 Hz, 1H), 1.6 (m, 1H), 1.5-1.2 (m, 4H), 0.8 (m, 3H).	ESI-LCMS *m/z*: 491 (pureza 95%); pureza HPLC: 96%.
171		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.5 (bs, 2H), 8.8 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8 (m, 5H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.5 (t, *J* = 7.2 Hz, 1H), 7.35 (d, *J* = 6.9 Hz, 1H), 3.1-3.0 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 2.0 (m, 1H), 1.6 (m, 1H), 1.4 (m, 3H), 0.8 (m, 3H).	ESI-LCMS *m/z*: 526 (pureza 92%); pureza HPLC: 92.5%.
172		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.4 (s, 2H), 8.75 (s, 1H), 8.1 (d, *J* = 6.8 Hz, 1H), 8.0 (m, 4H), 7.7 (s, 1H), 7.3 (m, 2H), 7.0 (m, 1H), 3.1-2.9 (m, 3H), 2.8 (d, *J* = 16.4 Hz, 1H), 2.4 (m, 2H), 2.0 (d, *J* = 13.2 Hz, 1H), 1.6 (m, 1H), 1.4 (m, 2H), 0.8 (t, *J* = 7.2 Hz, 3H).	ESI-LCMS *m/z*: 492 (pureza 97%); pureza HPLC: 98%.

EJEMPLO 173

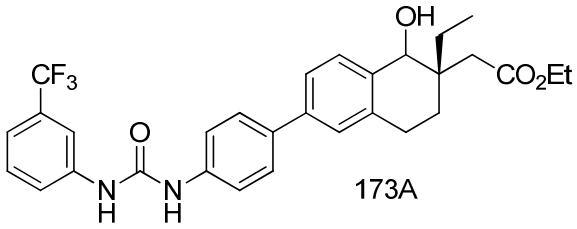


Reactivos y condiciones: a) $NaBH_4$, EtOH, t.a., 5h; b) LiOH, dioxano-H_2O, t.a., 8h.

Procedimientos

Acido 2-((2S)-2-etil-1-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

2-((2S)-2-Etil-1-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (173A):

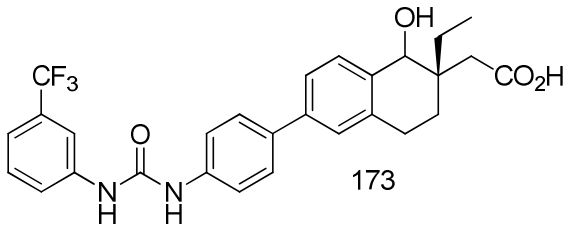


A una solución enfriada en hielo del producto del ejemplo 115G1 (0.4 g, 0.74 mmol) en etanol (10 mL) se le agregó en porciones borohidruro de

sodio (0.197 g, 5.18 mmol), y la mezcla se agitó a temperatura ambiente durante 5 h. El etanol se separó bajo presión reducida y el residuo se diluyó en agua. El sólido resultante se filtró y el producto crudo se purificó por cromatografía de vaporización instantánea para producir el compuesto del título como un sólido (0.22 g, 55%).

^{1}H-RMN (300 MHz,$CDCl_3$): δ 7.68 (bs, 1H), 7.57 (m, 1H), 7.5 (d, *J* = 6.0 Hz, 1H), 7.4 (s, 1H), 7.32-7.27 (m, 2H), 7.23 (m, 2H), 7.09-7.02 (m, 3H), 4.67 (s, 1H), 4.15 (q, *J* = 6.9 Hz, 2H), 3.8 (bs, 1H), 2.78 (t, *J* = 6.3 Hz, 2H), 2.36 (q, *J* = 14.4 Hz, 2H), 1.8 (m, 1H), 1.67-1.6 (m, 2H), 1.45 (m, 1H), 1.29 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H).

Acido 2-((2S)-2-etil-1-hidroxi-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (173):



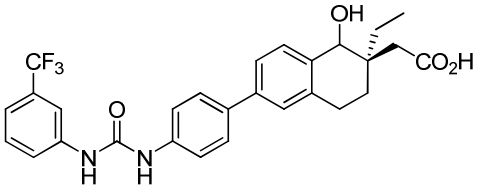
173

A una solución del producto del ejemplo 173A(0.15 g, 0.27 mmol) en 4 mL de una mezcla de dioxano-agua (3:1)se le agregó hidróxido de litio (0.046 g, 1.09 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 8 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se

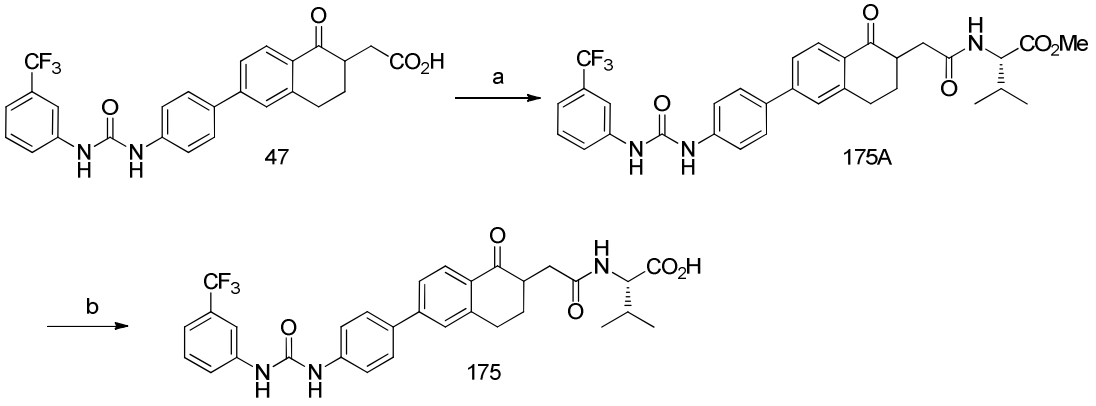
secó al vacío, para producir el compuesto del título como un sólido blanco (0.05 g, 36%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.7 (bs, 1H), 9.46 (bs, 1H), 8.05 (s, 1H), 7.63 (m, 3H), 7.54-7.4 (m, 4H), 7.36-7.26 (m, 3H), 4.5 (s, 1H), 2.6 (m, 2H), 2.2 (m, 2H), 1.8-1.55 (m, 3H), 1.3 (m, 1H), 1.0-0.8 (m, 3H); pureza HPLC: 98%.

El ejemplo 174 se preparó mediante procedimientos análogos a los que se describen en el ejemplo 173, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos Analíticos	$(M+H)^+$
174		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.7 (bs, 1H), 9.46 (bs, 1H), 8.05 (s, 1H), 7.63 (m, 3H), 7.54-7.4 (m, 4H), 7.36-7.26 (m, 3H), 4.5 (s, 1H), 2.6 (m, 2H), 2.2 (m, 2H), 1.8-1.55 (m, 3H), 1.3 (m, 1H), 1.0-0.8 (m, 3H).	pureza HPLC: 99.8%

EJEMPLO 175

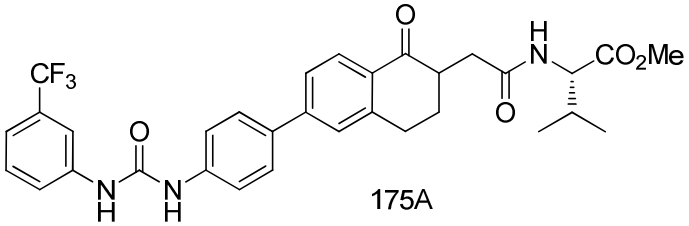


Reactivos y condiciones: a) HATU, THF, éster metílico de valina, t.a., 8h; b) LiOH, THF-H_2O, t.a., 12h.

Procedimientos

Acido (2S)-3-metil-2-(2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetamido)butanoico

(2S)-3-Metil-2-(2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetamido)butanoato de metilo (175A):



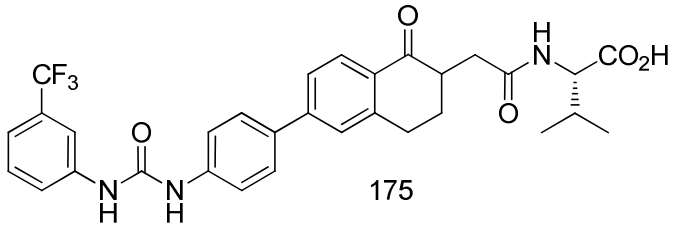
175A

A una solución del producto del ejemplo 47A (0.2 g, 0.414 mmol) y N-etil-diisopropilamina (0.16 g, 1.24 mmol) en THF (10 mL)se le agregó HATU (0.19 g, 0.497 mmol), seguido por éster metílico de valina (0.07 g, 0.413 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 8 h. La mezcla de reacción se dividió entonces entre acetato de etilo y agua. La capa orgánica se separó, se lavó con solución saturada de NaCl, se secó sobre sulfato de sodio, se filtró y se concentró. El residuo obtenido se purificó por cromatografía en columna, usando como eluente acetato de etilo al 25% en hexano, para producir el compuesto del título como un sólido (0.12 g, 49%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ9.09 (bs, 1H), 8.97 (bs, 1H),

8.22 (m, 1H), 8.03 (bs, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.65-7.58 (m, 5H), 7.5 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 4.21 (m, 1H), 3.63 (s, 3H), 3.05-2.8 (m, 2H), 2.4-2.3 (m, 2H), 2.2-1.8 (m, 4H), 0.9 (s, 6H).

Acido (2S)-3-metil-2-(2-(1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetamido)butanoico (175):

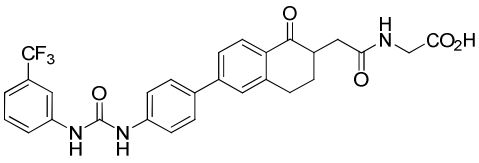
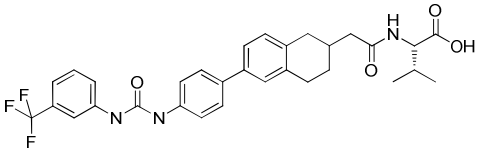
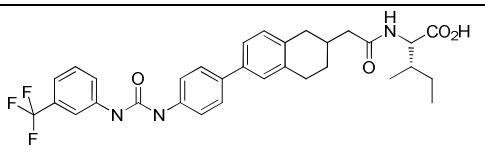


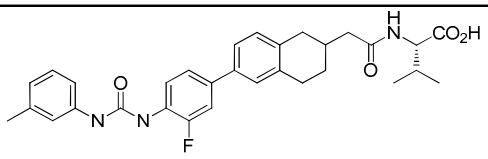
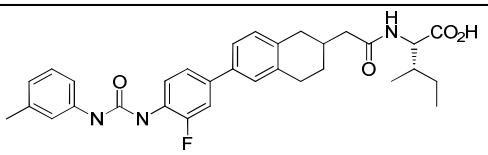
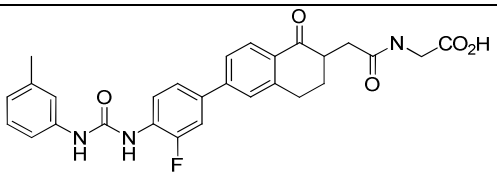
175

A una solución del producto del ejemplo 175A(0.1 g, 0.16 mmol) en 4 mL de una mezcla THF-agua (3:1)se le agregó hidróxido de litio (0.02 g, 0.5 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido (0.05 g, 51%).

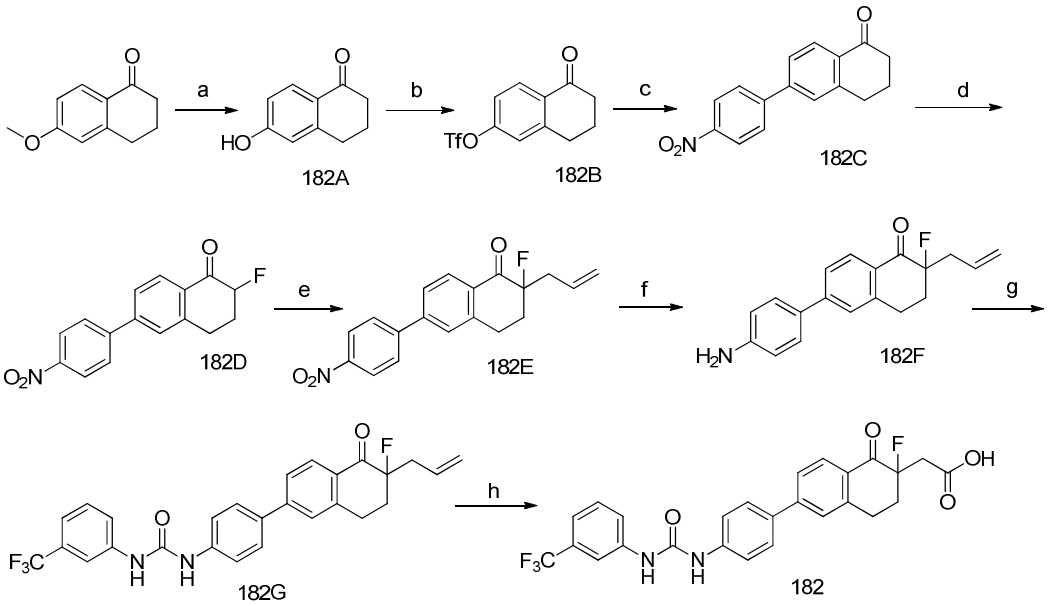
^{1}H-RMN (400 MHz, DMSO-d_6): δ12.5 (bs, 1H), 9.18 (bs, 1H), 9.04 (bs, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.9 (d, *J* = 7.6 Hz, 1H), 7.7 (d, *J* = 8.4 Hz, 2H), 7.66-7.5 (m, 6H), 7.32 (d, *J* = 8.4 Hz, 1H), 4.2 (m, 1H), 3.1-2.9 (m, 2H), 2.8 (m, 1H), 2.4 (m, 2H), 2.2-2.0 (m, 2H), 1.9 (m, 1H), 0.9 (m, 6H); pureza HPLC: 94.8%.

Los ejemplos 176-181 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 175, o variaciones rutinarias de los mismos, empezando del ácido tetralon-2-acético (por ejemplo, el ejemplo 47) y aminoácido requeridos, o versiones con grupos funcionales adecuadamente protegidos de los mismos, seguido por desprotección mediante los procedimientos bien conocidos de los expertos en la materia.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
176		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.5 (bs, 1H), 8.17 (s, 1H), 8.11 (m, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.86-7.76 (m, 4H), 7.74-7.64 (m, 3H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 3.85 (m, 2H), 3.4 (m, 1H), 3.1-2.8 (m, 2H), 2.65 (m, 2H), 2.2 (m, 1H), 2.0 (m, 1H).	pureza HPLC: 96.06%.
177		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.51 (bs, 1H), 9.31 (bs, 1H), 9.10 (bs, 1H), 8.04 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.62-7.47 (m, 6H), 7.30 (m, 3H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.18 (t, *J* = 6.3 Hz, 1H), 2.85-2.71 (m, 3H), 2.43 (m, 1H), 2.26 (d, *J* = 7.2 Hz, 2H), 2.08 (m, 2H), 1.90 (m, 1H), 1.45 (m, 1H), 0.9 (m, 6H).	ESI-MS *m/z* = 567 $(M+H)^+$; pureza HPLC: 92%.
178		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.40 (bs, 1H), 9.06 (bs, 1H), 8.87 (bs, 1H), 8.02 (m, 2H), 7.59-7.49 (m, 6H), 7.33 (t, *J* = 7.6 Hz, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 4.22 (m, 1H), 2.88-2.79 (m, 3H), 2.45 (m, 1H), 2.25 (d, *J* = 6.4 Hz, 2H), 2.15 (m, 1H), 1.90-1.79 (m, 2H), 1.41 (m, 2H), 1.23 (m, 1H), 0.89 (m, 6H).	ESI-MS *m/z* = 582 $(M+H)^+$; pureza HPLC: 90%.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
179		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.40 (bs, 1H), 9.07 (bs, 1H), 8.64 (bs, 1H), 8.20 (t, *J* = 8.4 Hz, 1H), 7.96 (m, 1H), 7.52 (d, *J* = 12.8 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.37 (m, 2H), 7.31 (s, 1H), 7.25-7.15 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.2 Hz, 1H), 4.16 (t, *J* = 6.4 Hz, 1H), 2.89-2.77 (m, 3 H), 2.32 (s, 3H), 2.28 (d, *J* = 7.2 Hz 2H), 2.14-2.05 (m, 3H), 1.89 (m, 1H), 1.40 (m, 1H), 0.85 (m, 6H).	ESI-MS *m/z* = 532 $(M+H)^+$; pureza HPLC: 95%.
180		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.40 (bs, 1H), 9.06 (bs, 1H), 8.63 (bs, 1H), 8.20 (t, *J* = 8.4 Hz, 1H), 7.98 (bs, 1H), 7.52 (d, *J*=13.2 Hz, 1H), 7.43 (m, 3H), 7.31-7.15 (m, 3H) 7.08 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 4.20 (m, 1H), 2.98-2.79 (m, 3H), 2.28 (s, 3H), 2.24 (d, *J* = 6.8 Hz, 2H), 2.14 (m, 2H), 1.99-1.79 (m, 2H), 1.41 (m, 1H), 1.16 (m, 2H), 0.86 (m, 6H).	ESI-MS *m/z* = 546$(M+H)^+$; pureza HPLC: 91%.
181		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.03 (bs, 1H), 8.70 (bs, 1H), 8.34-8.24 (m, 2H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.73-7.66 (m, 3H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.31 (bs, 1H), 7.26-7.15 (m, 2H), 6.82 (d, *J* = 7.2 Hz, 1H), 3.77 (m, 2H), 3.1-2.9 (m, 3H), 2.84-2.71 (m, 1H), 2.4 (m, 1H), 2.29 (s, 3H), 2.0 (m, 1H), 1.87 (m, 1H).	pureza HPLC: 94%

EJEMPLO 182

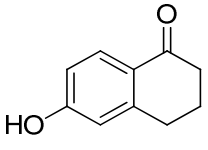


Reactivos y condiciones: a) HBr acuoso, reflujo, 12h; b) Tf_2O, DMAP, Py, t.a., 1h; c) ácido 4-NO_2fenil-borónico, $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; d) SelectFluor, MeOH, 80 °C, 4h; e) bromuro de alilo, TBAI, KOH, t.a., 18h; f) Fe/NH_4Cl, EtOH, H_2O, reflujo, 2h; g) 3-CF_3-PhNCO, Et_3N, THF, t.a., 12h; h) LiOH, THF-H_2O, t.a., 12h.

Procedimientos

Acido 2-(2-fluoro-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

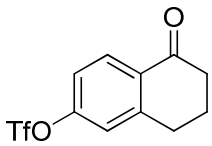
6-Hidroxi-3,4-dihidronaftalen-1(2H)-ona (182A):



Se agregó HBr acuoso (100 mL) a 6-metoxi-1-tetralona (10.0 g, 56.8 mmol), y la mezcla de reacción se puso a reflujo durante la noche. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo (2X100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto crudo se purificó usando cromatografía de vaporización instantánea, usando acetato de etilo al 40% en hexano, para producir el compuesto del título como un sólido (8.0 g, 86%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ7.99 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 6.23 (bs, 1H), 2.9 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.11 (m, 2H); ESI-MS *m/z* = 163 $(M+H)^+$.

Trifluorometanosulfonato de 5-oxo-5,6,7,8-tetrahidronaftalen-2-ilo (182B):



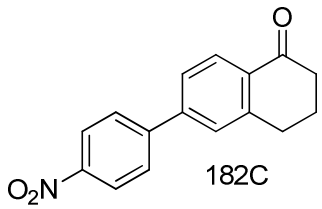
182B

A una solución enfriada en hielo del producto del ejemplo 182A (8.0 g, 49.3 mmol), DMAP (1.20 g, 9.83 mmol) y 2,6-lutidina (5.20 g, 49.3 mmol) en diclorometano (15 mL) se le agregó anhídrido tríflico (16.7 g, 59.2 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h. Luego, la mezcla de reacción se diluyó con diclorometano (50 mL) y se lavó con solución acuosa saturada de NaCl (50 mL). La capa orgánica se secó

sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 5% en hexano, para dar el compuesto del título como un sólido (12 g, 85%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.14 (d, *J* = 8.4 Hz, 1H), 7.2 (m, 2H), 3.01 (t, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H), 2.18 (m, 2H); ESI-MS *m/z* = 295 $(M+H)^+$.

6-(4-Nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (182C):

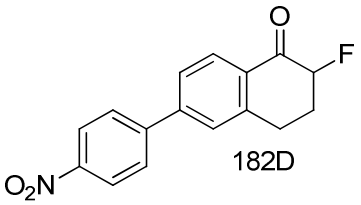


182C

A una solución del producto del ejemplo 182B (5.0 g, 16.8 mmol) en 60 mL de una mezcla de 1,4-dioxano-H_2O (3:1), bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$ (0.023 g, 0.19 mmol), seguido por carbonato de cesio (13.7g, 42.0 mmol) y ácido 4-nitro-fenil-borónico (2.81 g, 16.8 mmol). La mezcla de reacción se desgasificó durante 5 min. Después, la mezcla de reacción se puso a reflujo por 5 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea para producir el compuesto del título como un sólido (3.5 g, 77%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.34-8.30 (m, 2H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.78-7.75 (m, 2H), 7.57-7.51 (m, 2H), 3.06 (t, *J* = 6.0 Hz, 2H), 2.71 (t, *J* = 6.0 Hz, 2H), 2.23-2.17 (m, 2H); ESI-MS *m/z* = 268 $(M+H)^+$.

2-Fluoro-6-(4-nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (182D):

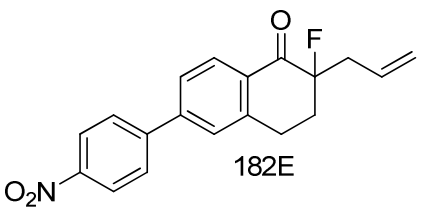


182D

Al producto del ejemplo 182C (0.8 g, 2.99 mmol) en 20 mL de metanol se le agregó Select fluor (1.27 g, 3.58 mmol). La mezcla de reacción se puso a reflujo por 4 h y entonces el disolvente se separó al vacío para obtener un residuo. El residuo se disolvió en diclorometano. El material insoluble se filtró y el filtrado se lavó con agua, seguida por solución de salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró, para producir el compuesto del título como un sólido (0.6 g, 70%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.35 (m, 2H), 8.20 (d, *J* = Hz, 1H), 7.75(m, 2H), 7.65 (m, 1H), 7.52 (s, 1H), 5.30-5.10 (m, 1H), 3.30 (m, 2H), 2.65 (m, 1H), 2.40 (m, 1H); ESI-MS *m/z* = 286 $(M+H)^+$.

2-Alil-2-fluoro-6-(4-nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (182E):

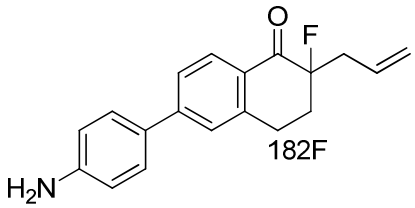


182E

A una solución del producto del ejemplo 182D (3.0 g, 10.5 mmol), KOH (1.17 g, 21.0 mmol) y TBAI (0.77 g, 2.00 mmol) en tolueno (120 mL) a 0 °C se le agregó bromuro de alilo (1.89 g, 15.7 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Después, la mezcla de reacción se diluyó con agua y acetato de etilo. La capa orgánica separada se lavó con agua, solución de salmuera, se secó sobre sulfato de sodio, se filtró y se concentró bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para producir el compuesto del título como un sólido (2.5 g, 73%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.38-8.32 (m, 2H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.80-7.75 (m, 2H), 7.61 (m, 1H), 7.50 (s, 1H), 5.86 (m, 1H), 5.23 (d, *J* =8.4 Hz, 2H), 3.25-3.09 (m, 2H), 2.77-2.25 (m, 4H); ESI-MS *m/z* = 326 $(M+H)^+$.

<u>2-Alil-6-(4-aminofenil)-2-fluoro-3,4-dihidronaftalen-1(2H)-ona (182F):</u>



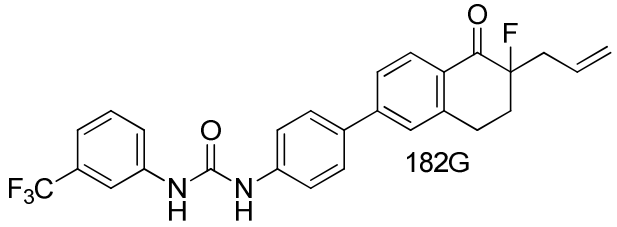
182F

A una solución del producto del ejemplo 182E (0.51g, 1.53 mmol) en 25 mL de una mezcla de etanol-agua (2:1) se le agregó polvo de fierro (0.214 g, 3.86 mmol) y NH_4Cl (0.040g, 0.74 mmol). La mezcla de reacción se puso a reflujo por 2 h y el disolvente se eliminó bajo presión reducida. El producto crudo se purificó por cromatografía de vaporización instantánea,

usando metanol al 2% en cloroformo, para producir el compuesto del título como un sólido (0.3 g, 66%).

^{1}H-RMN (300MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.5 Hz, 1H), 7.53 (dd, J_1 = 1.2 Hz, J_2 = 8.1 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.39 (s, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.98-5.84 (m, 1H), 5.29-5.20 (m, 2H), 3.84 (bs, 2H), 3.16-2.97 (m, 2H), 2.80-2.54 (m, 2H), 2.46-2.33 (m, 2H); ESI-MS *m/z* = 296 $(M+H)^+$.

1-(4-(6-Alil-6-fluoro-5-oxo-5,6,7,8-tetrahidronaftalen-2-il)fenil)-3-((trifluorometil)fenil)urea (182G):

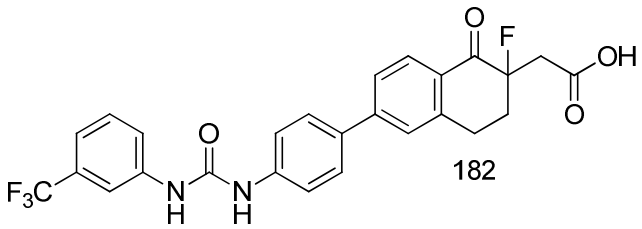


182G

A una solución del producto del ejemplo 182F (0.25 g, 0.84 mmol) y trietilamina (0.128 g, 1.26 mmol) en THF (15 mL)se le agregó isocianato de 3-(trifluorometil)fenilo(0.158 g, 0.84 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después, el disolvente se eliminó bajo presión reducida y el producto crudo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.2 g, 50%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.5 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 7.54- 7.44 (m, 5H), 7.40-7.28 (m, 4H), 5.90-5.80 (m, 1H), 5.29-5.20 (m, 2H), 3.40-2.98 (m, 2H), 2.60-2.50 (m, 2H), 2.48-2.30 (m, 2H); ESI-MS *m/z* = 483 $(M+H)^+$.

Acido 2-(2-fluoro-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (182):

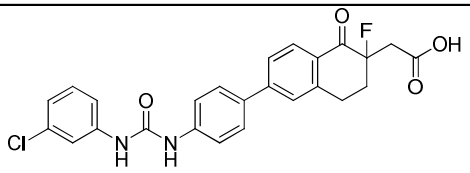
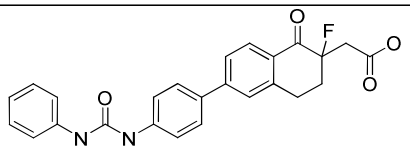


182

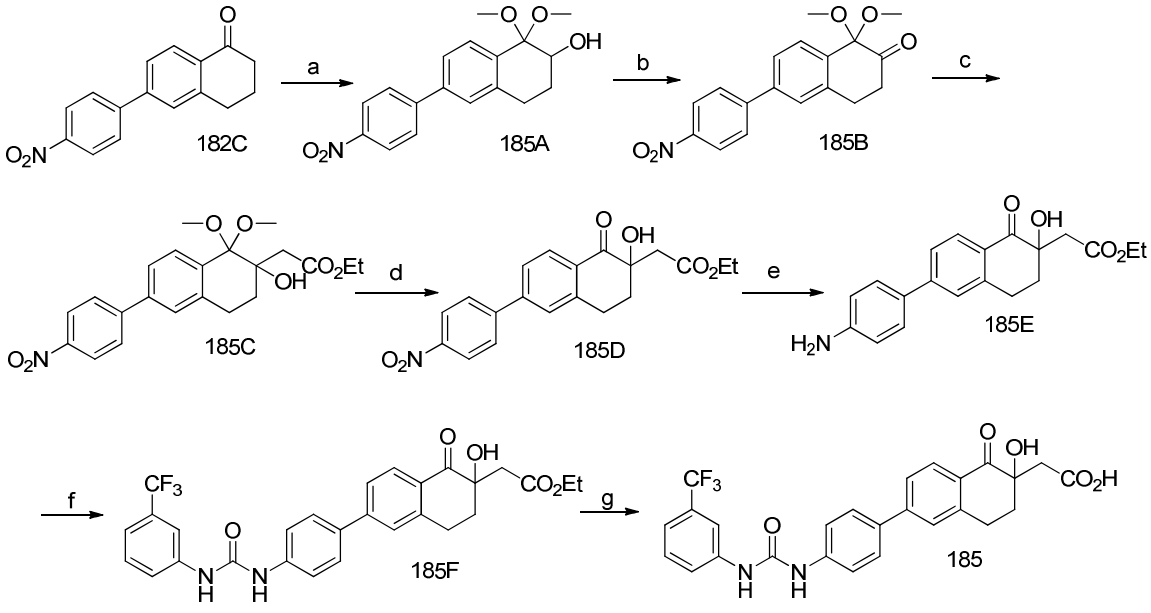
A una solución del producto del ejemplo 182G(0.30 g, 0.62 mmol) y $NaIO_4$ (1.33 g, 6.2 mmol) en 30 mL de una mezcla de acetona-agua (2:1)se le agregó $KMnO_4$ (0.196 g, 1.24 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida para obtener el producto crudo, que se purificó por HPLC preparativa, para producir el compuesto del título como un sólido (0.075 g, 25%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.5 (bs, 1H), 9.11 (bs, 1H), 9.01 (bs, 1H), 7.96 (m, 2H), 7.72 (t, J = 8.4 Hz, 4H), 7.62-7.50 (m, 4H), 7.32 (d, J = 7.6 Hz, 1H), 3.20-3.05 (m, 4H), 2.90 (m, 1H), 2.66 (m, 1H); ESI-MS *m/z* = 501 $(M+H)^+$; pureza HPLC: 96%.

Los ejemplos 183 y 184 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 182, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos ^{1}H-RMN	Masa /Pureza
183		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.50 (bs, 1H), 8.96 (2s, 2H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 8.8 Hz, 5H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.33-7.27 (m, 2H), 7.03 (m, 1H), 3.20-3.02 (m, 4H), 2.90 (m, 1H), 2.67 (m, 1H).	MS *m/z* = 467 $(M+H)^+$; pureza HPLC: 98%.
184		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.60 (bs, 1H), 8.88 (bs, 1H), 8.73 (bs, 1H), 7.95 (d, *J* = 8.4Hz, 1H), 7.71 (t, *J* = 8.8 Hz, 4H), 7.59 (d, *J* =8.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 3.17 (m, 2H), 3.16-3.04 (m, 2H), 2.93 (m, 1H), 2.89 (m, 1H).	ESI-MS *m/z* = 432 $(M+H)^+$; pureza HPLC: 93%.

EJEMPLO 185



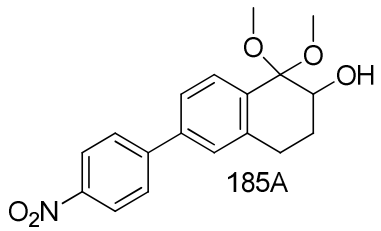
Reactivos y condiciones: a) $PhI(OAc)_2$, AcOH, t.a., 16h; b)

dicromato de piridinio, acetona, t.a., 18h ; c) LiHMDS, EtOAc, THF, 0 ºCat.a.,4h; d) HCl 3N, MeOH, t.a., 18h; e) Pd/C, H_2, EtOH, t.a., 3h; f) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; g) NaOH, MeOH-THF-H_2O, t.a., 18h.

Procedimiento

Acido 2-(2-hidroxi-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

1,1-Dimetoxi-6-(4-nitrofenil)-1,2,3,4-tetrahidronaftalen-2-ol (185A):



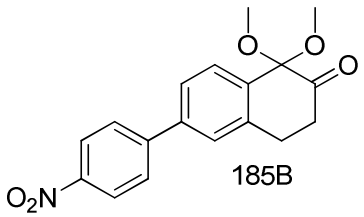
185A

A una solución enfriada en hielo del producto del ejemplo 182C (7.0 g, 26.2 mmol) y $PhI(OAc)_2$ (8.44 g,26.2 mmol) en metanol (180 ml)se le agregó KOH (4.40 g, 78.6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. El disolvente de la reacción se separó al vacío y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró. El producto se lavó con pentano para dar el compuesto del título como un sólido (7.0 g, 81%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.28 (m, 2H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.75-7.71 (m, 2H), 7.45 (dd, J_1= 2.0 Hz, J_2= 8.4 Hz, 1H), 7.41 (s, 1H),

4.29 (t, *J* = 4.0 Hz, 1H), 3.45 (s, 3H), 3.12 (s, 3H), 3.0 (m,1H), 2.83 (m, 1H), 2.27-2.22 (m, 1H), 2.16-2.10 (m, 1H), 1.56 (m, 1H); ESI-MS *m/z* = 330 $(M+H)^+$.

1,1-Dimetoxi-6-(4-nitrofenil)-3,4-dihidronaftalen-2(1H)-ona (185B):

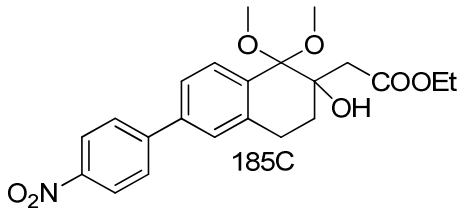


185B

A una solución del producto del ejemplo 185A (0.2 g, 0.6 mmol) y tamices moleculares (3A, 0.5 g) en 10 mL de diclorometano, bajo una atmósfera de argón, se le agregó dicromato de piridinio (0.36 g, 0.97 mmol), seguido por anhídrido acético (0.1 mL). La mezcla de reacción se agitó durante 18 h a temperatura ambiente. Después, la mezcla de reacción se filtró y el filtrado se lavó con agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.12 g, 63%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.31 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 9.0 Hz, 2H), 7.54 (dd, J_1 = 1.5 Hz, J_2 = 8.4 Hz, 1H), 7.46 (s, 1H), 3.38 (s, 6H), 3.25 (t, *J* = 6.0 Hz, 2H), 2.75 (t, *J* = 6.9 Hz, 2H). ESI-MS *m/z* = 328 $(M+H)^+$.

2-(2-Hidroxi-1,1-dimetoxi-6-(4-nitrofenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (185C):

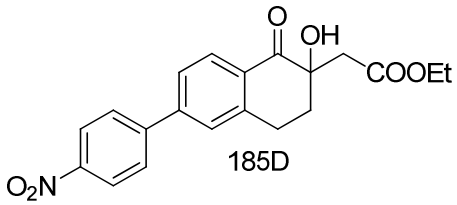


185C

A una solución de LiHMDS (0.63 g, 3.82 mmol) en 10 mL de THF a -78 °C, se le agregó acetato de etilo (0.2 g, 2.29 mmol) y la mezclase agitó durante 15 min. Después se le agregó el producto del ejemplo 185B (0.25 g, 0.76 mmol). La mezcla de reacción se llevó de -78 °C a temperatura ambiente durante 4 h y luego se apagó con HCl 1N. La mezcla de reacción se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido blanquecino (0.15 g, 48%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 9.0 Hz, 2H), 7.82-7.72 (m, 3H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.4 (s, 1H), 4.2 (q, *J* = 6.9 Hz, 2H), 3.6 (s, 3H), 3.2 (s,3H), 3.0 (m, 2H), 2.75 (d, *J* = 14.7 Hz, 1H), 2.4 (d, *J* = 14.7 Hz, 1H), 2.3-2.1 (m, 2H), 1.3 (m, 3H). ESI-MS *m/z* = 416 $(M+H)^+$.

2-(2-Hidroxi-6-(4-nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)-acetato de etilo (185D):

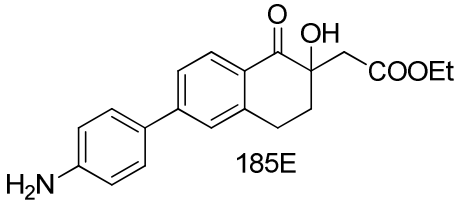


185D

A una solución del producto del ejemplo 185C (0.15 g, 0.36 mmol) en 5 mL de etanol a 0 °C, se le agregó HCl3N (2 mL) y se agitó durante 18 h a t.a. La mezcla de reacción se apagó con agua y el sólido se recogió por filtración para producir el compuesto del título como un sólido blanco (0.08 g, 61%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.34 (d, *J* = 9.3 Hz, 2H), 8.04 (d, *J* = 9.3 Hz, 2H), 7.98 (s, 1H), 7.78 (m, 2H), 5.76 (bs, 1H), 4.02 (q, *J* = 7.8 Hz, 2H), 3.2 (m, 1H), 3.0-2.95 (m, 2H), 2.65 (d, *J* = 15.3 Hz, 1H), 2.39 (m, 1H), 2.16 (m, 1H), 1.15 (t, *J* = 6.9 Hz, 3H); ESI-MS *m/z* = 370 $(M+H)^+$.

<u>2-(6-(4-Aminofenil)-2-hidroxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (185E):</u>



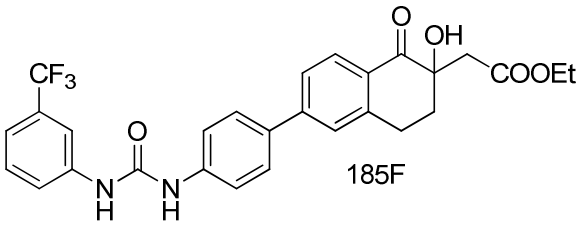
185E

A una solución del producto del ejemplo 185D (0.08 g, 0.21 mmol) en 5 mL de etanol se le agregó un exceso de Pd 10% /C (0.04 g), y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. La mezcla

de reacción se filtró sobre una almohadilla de celite y el filtrado se separó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó al vacío. El producto crudo se lavó con Et_2O y pentano para producir el compuesto del título como un sólido blanquecino (0.05 g, 68%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.55-7.35 (m, 4H), 6.75 (m, 1H), 4.53 (bs, 1H), 4.2 (m, 2H), 3.83 (bs, 2H), 3.18 (m, 2H), 2.67 (m, 2H), 2.40 (m, 1H), 2.25 (m, 1H), 1.28 (t, *J* = 6.9 Hz, 3H); ESI-MS *m/z* = 340 $(M+H)^+$.

2-(2-Hidroxi-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (185F):

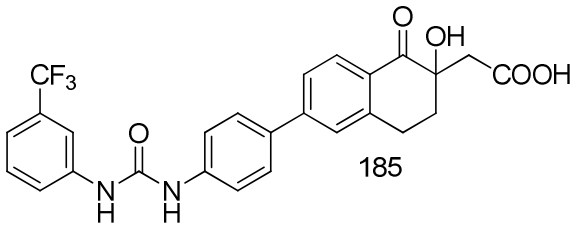


185F

A una solución del producto del ejemplo 185E(0.2 g, 0.58 mmol) y trietilamina (0.17 g, 1.76 mmol) en THF (10 mL), se le agregó isocianato de 3-(trifluorometil)fenilo (0.12 g, 0.64 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando metanol al 1% en cloroformo, para producir el compuesto del título como un sólido blanco (0.14 g, 45%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.2 (bs, 1H), 9.0 (bs, 1H), 8.05 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.75-7.45 (m, 8H), 7.35 (d, *J* = 7.8 Hz, 1H), 5.7 (s, 1H), 4.0 (q, *J* = 7.2 Hz, 2H), 3.2 (m, 1H), 2.95 (m, 2H), 2.7 (d, *J* = 15.3 Hz, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 1.2 (t, *J* = 7.2 Hz, 3H); ESI-MS *m/z* =527 $(M+H)^+$.

Acido 2-(2-hidroxi-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)ureido)-fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (185):



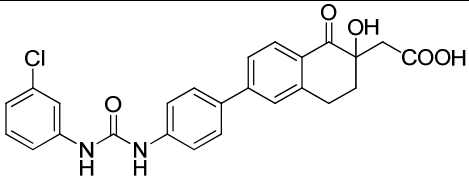
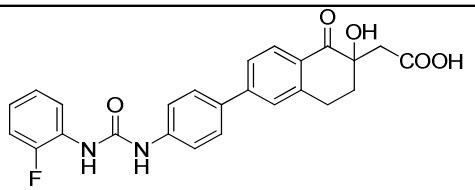
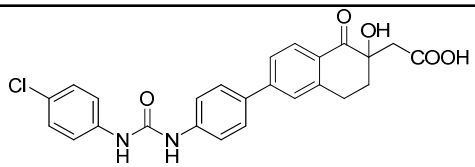
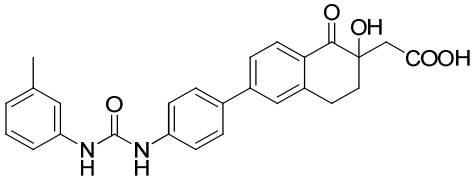
185

A una solución del producto del ejemplo 185F (0.14 g, 0.26 mmol) en 15 mL de una mezcla de THF-metanol (2:1) se le agregó NaOH 2N (0.031 g, 0.79 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se neutralizó con HCl ac. 2N. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.09 g, 69%).

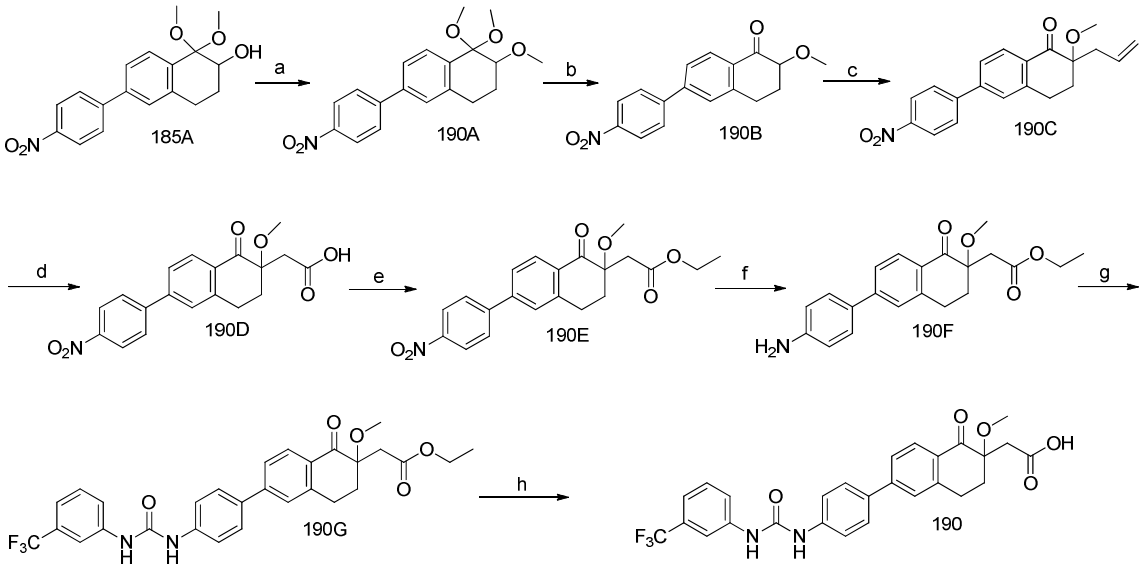
^{1}H-RMN (400 MHz, DMSO-d_6): δ 11.4 (bs, 2H), 8.13 (s, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 6.0 Hz, 1H), 7.62 (d, *J* = 6.4 Hz, 1H), 7.5-7.35 (m, 6H), 7.22 (d, *J* = 7.2 Hz, 1H), 6.0 (bs, 1H), 3.15 (m, 1H), 3.03 (d, *J* = 15.6

Hz, 1H), 2.85 (m, 1H), 2.5 (m, 1H), 2.35 (d, *J* = 15.6 Hz, 1H), 2.0 (m, 1H); ESI-MS *m/z* = 449 $(M+H)^+$;pureza HPLC: 96.49%.

Los ejemplos 186-189 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 185, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
186		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.04 (s, 2H),7.92 (d, *J* = 8.0 Hz, 1H), 7.75-7.55 (m, 7H), 7.31 (m, 2H), 7.03 (d, *J* = 6.8 Hz, 1H), 5.63 (bs, 1H), 3.2 (m, 1H), 2.93 (m, 2H), 2.6-2.4 (m, 2H), 2.1 (m, 1H).	ESI-MS *m/z* = 465 $(M+H)^+$. pureza HPLC: 97.5%.
187		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.36 (bs, 1H), 8.68 (bs, 1H),8.15 (t, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.75-7.55 (m, 6H), 7.25 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.03 (m, 1H), 3.2 (m, 1H), 2.95-2.8 (m, 2H), 2.5-2.35 (m, 2H), 2.1 (m, 1H).	ESI-MS *m/z* = 449 $(M+H)^+$; pureza HPLC: 93.3%.
188		^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.49 (bs, 2H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.7-7.45 (m, 8H), 7.32 (d, *J* = 8.4 Hz, 2H), 3.2 (m, 1H), 2.95-2.8 (m, 2H), 2.5-2.4 (m, 2H), 2.1 (m, 1H).	ESI-MS *m/z* = 465 $(M+H)^+$. LCMS pureza: 92%.
189		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.16 (bs,1H), 8.94 (bs, 1H),7.92 (d, *J* = 7.8 Hz, 1H), 7.75-7.55 (m, 6H), 7.35-7.25 (m, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.8 (d, *J* = 6.9 Hz, 1H), 3.39 (m, 1H), 3.21 (m, 1H), 2.92 (d, *J* = 15.3 Hz, 2H), 2.55 (m, 1H), 2.28 (s, 3H), 2.12 (m, 1H).	ESI-MS *m/z* = 445 $(M+H)^+$. LCMS pureza: 91.88%.

EJEMPLO 190

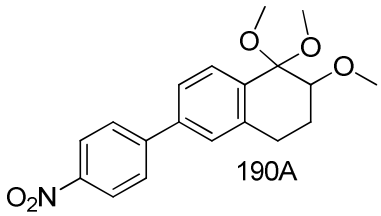


Reactivos y condiciones: a) NaH, MeI, THF, t.a., 16h; b) HCl 3N, EtOH, t.a., 3h; c) bromuro de alilo, TBAI, KOH, tolueno, t.a., 16h; d) $KMnO_4$, $NaIO_4$, t.a., 16h; e) $MeSO_3H$, EtOH, t.a., 12h; f) Fe-NH_4Cl, EtOH-H_2O, 90 °C, 2h; g) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; h) LiOH, THF-H_2O, t.a., 12h.

Procedimientos

Acido 2-(2-metoxi-1-oxo-6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

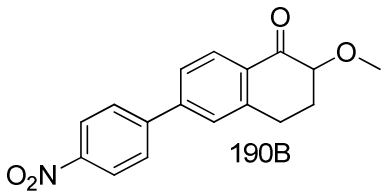
1,1,2-Trimetoxi-6-(4-nitrofenil)-1,2,3,4-tetrahidronaftaleno (190A):



A una solución enfriada en hielo del producto del ejemplo 185A (2.0 g, 6.1 mmol) y NaH (0.76 g, 31.91 mmol) en THF (120 mL), se le agregó yoduro de metilo (15.1 g, 106.1 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. Después, la mezcla de reacción se apagó con agua enfriada en hielo y se extrajo con acetato de etilo. La capa orgánica separada se secó sobre Na_2SO_4, se filtró y se separó bajo presión reducida, para dar el compuesto del título como un sólido (6.0 g, 83%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.29-8.25 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.73-7.69 (m, 2H), 7.45 (dd, J_1= 2.0 Hz, J_2= 8.4 Hz, 1H), 7.37 (s, 1H), 3.87 (m, 1H), 3.42 (s, 6H), 3.07 (s, 3H), 2.95 (m, 1H), 2.83-2.77 (m, 1H), 2.28-2.19 (m, 2H)); ESI-MS *m/z* = 344 $(M+H)^+$.

2-Metoxi-6-(4-nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (190B):



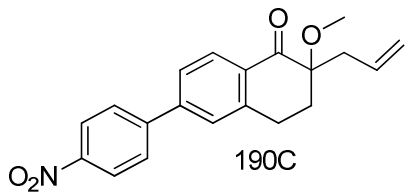
190B

Se agregó HCl 3N (60 mL) a una solución enfriada en hielo del producto del ejemplo 190A (6.0 g, 17.4mmol) en etanol (150 mL), y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. El residuo se dividió entre acetato de etilo y agua. El disolvente se eliminó bajo presión reducida y se le agregó agua hasta que el compuesto precipitó. El sólido se recogió por

filtración y se secó. El producto se lavó con pentano para dar el compuesto del título como un sólido (5.0 g, 96%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.35 (m, 2H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.75 (m, 2H), 7.55 (m, 1H), 7.50 (s, 1H), 4.00 (m, 1H), 3.60 (s, 3H), 3.25 (s, 1H), 3.10 (m, 1H), 2.40 (m, 1H), 2.30 (m, 1H); ESI-MS *m/z* = 298 $(M+H)^+$

2-Alil-2-metoxi-6-(4-nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (190C):



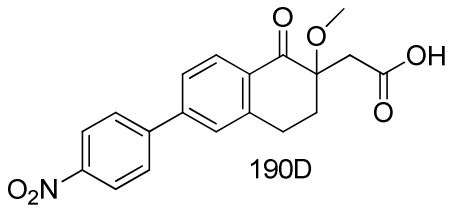
190C

A una solución enfriada en hielo del producto del ejemplo 190B (6.0 g, 20.2 mmol), KOH (2.82 g, 50.5 mmol) y TBAI (2.98 g, 8.0 mmol) en tolueno (120 mL), se le agregó bromuro de alilo (3.63 g, 30.6 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 16 h. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre Na_2SO_4, se filtró y se eliminó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para producir el compuesto del título como un sólido (4.46g , 64%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.35 (m, 2H), 8.16 (d, *J* =8.4 Hz, 1H), 7.75 (m, 2H), 7.55 (dd, J_1= 2.0 Hz, J_2= 8.4 Hz, 1H), 7.5 (s, 1H), 5.83 (m,

1H), 5.16 (d, *J* = 12.0 Hz, 2H), 3.32 (m, 1H), 3.24 (s, 3H), 2.95-2.79 (m, 1H), 2.75 (m, 1H), 2.52-2.42 (m, 2H), 2.35-2.06 (m, 1H); ESI-MS *m/z* = 338 $(M+H)^+$

Acido 2-(2-metoxi-6-(4-nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (190D):

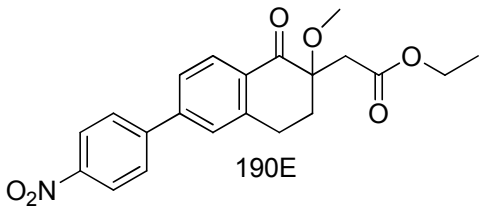


190D

A una solución enfriada en hielo del producto del ejemplo 190C (0.20 g, 0.59 mmol) y $NaIO_4$ (1.26 g, 5.90 mmol) en una mezcla de acetona-agua (2:1) se le agregó $KMnO_4$ (0.187 g, 1.18 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre Na_2SO_4, se filtró y se separó bajo presión reducida, para producir el compuesto del título como un sólido (0.14 g, 69%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ12.10 (bs, 1H), 8.35-8.31 (m, 3H), 8-16-7.99 (m, 3H), 7.77 (d, *J* = 7.2 Hz, 1H), 3.35 (m, 1H), 3.25 (m, 1H), 3.19 (s, 3H), 2.92 (m, 1H), 2.73 (d, *J* = 16.8 Hz, 1H), 2.45 (m, 2H); ESI-MS *m/z* = 356 $(M+H)^+$.

2-(2-Metoxi-6-(4-nitrofenil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il) acetato de etilo (190E):

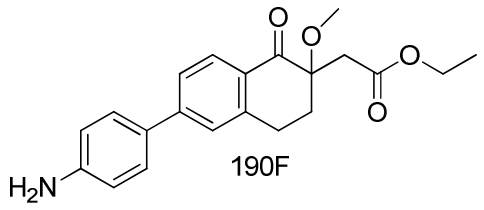


190E

A una solución del producto del ejemplo 190D (0.26 g, 0.18 mmol) en etanol (15 mL) se le agregó ácido metanosulfónico (0.5ml) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para producir el compuesto del título como un sólido (0.07 g, 46%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ8.38-8.31 (m, 2H) , 8.16 (d, J = 8.4 Hz, 1H), 7.80-7.75 (m, 2H), 7.56 (m, 1H), 7.48 (s, 1H), 4.2 (q, J = 7.5 Hz, 2H), 3.45 (m, 1H), 3.25 (s, 3H), 2.95-2.73 (m, 3H), 2.5 (m, 2H), 1.25 (t, J = 6.9 Hz, 3H); ESI-MS m/z = 384 $(M+H)^+$.

2-(6-(4-Aminofenil)-2-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il) acetato de etilo (190F):

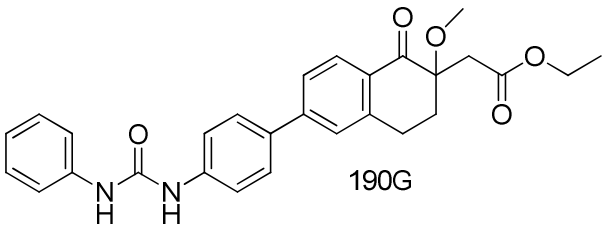


190F

A una solución del producto del ejemplo 190E (0.5 g, 1.30 mmol) en 30 mL de una mezcla de etanol-agua (2:1), se le agregó polvo de fierro (0.182 g, 3.26 mmol) y NH_4Cl (0.034g, 0.65 mmol). La mezcla de reacción se puso a reflujo por 2 h. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando metanol al 2% en cloroformo, para producir el compuesto del título como un sólido (0.4 g, 86%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.06 (d, *J* = 8.1 Hz, 1H), 7.47-7.43 (m, 3H), 7.38 (s, 1H), 6.73 (m, 2H), 4.15 (q, *J* = 7.5 Hz, 2H), 3.80 (bs, 2H), 3.42-3.35 (m, 1H), 3.3 (s, 3H), 2.94-2.79 (m, 3H), 2.53-2.36 (m, 2H), 1.2 (t, *J* = 6.9 Hz, 3H); ESI-MS *m/z* = 354 $(M+H)^+$.

2-(2-Metoxi-1-oxo-6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (190G):



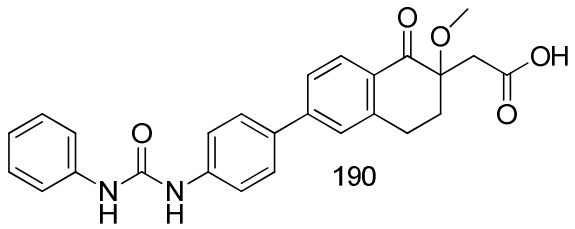
190G

A una solución del producto del ejemplo 190F (0.200 g, 0.56 mmol) y trietilamina (0.178 g, 1.68 mmol) en THF (10 mL)se le agregó isocianato de fenilo (0.067 g, 0.56 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización

instantánea, usando 10% en hexano para producir el compuesto del título como un sólido (0.2g, 76%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ8.86 (bs, 1H), 8.72 (bs, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.69 (m, 2H), 7.64-7.57 (m, 4H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.29 (t, *J* = 6.9 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 4.07 (q, *J* = 6.9 Hz, 2H), 3.23 (m, 1H), 3.13 (s, 3H), 2.93 (m, 1H), 2.86 (d, *J* = 15.3 Hz, 2H), 2.43 (m,2H), 1.18 (t, *J* = 7.8 Hz,3H); ESI-MS *m/z* = 473 $(M+H)^+$.

Acido 2-(2-metoxi-1-oxo-6-(4-(3-fenilureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (190):

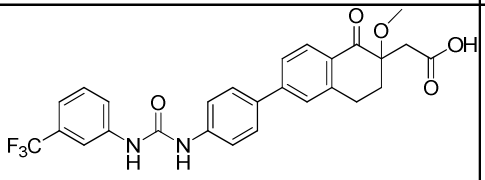
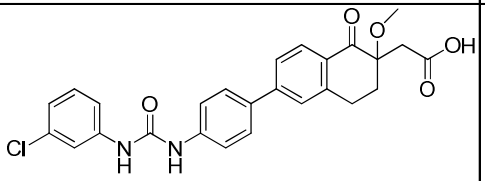
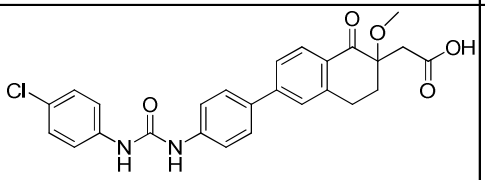
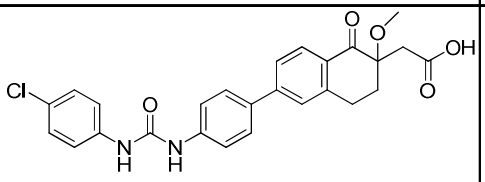


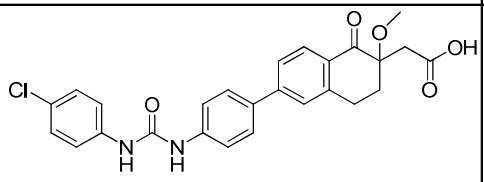
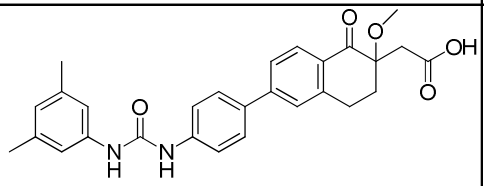
190

A una solución del producto del ejemplo 190G(0.2 g, 0.42 mmol) en 12 mL de una mezcla de THF-agua (3:1)se le agregó hidróxido de litio (0.088 g, 2.11 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 ℃ y el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.05 g, 26%).

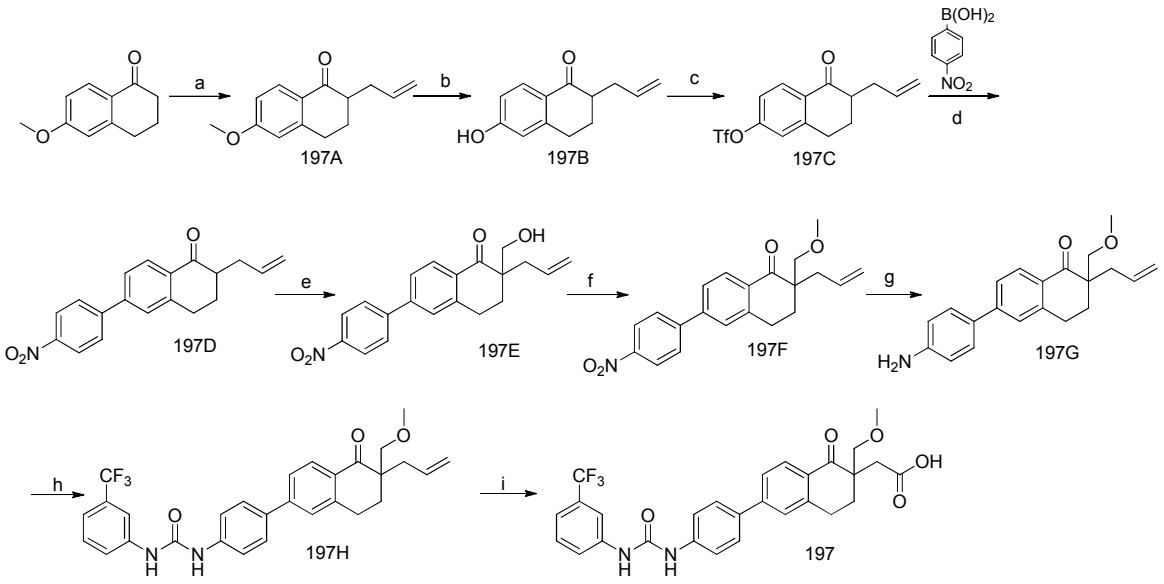
^{1}H-RMN (400 MHz, $CDCl_3$): δ12.0 (bs, 1H), 8.87 (bs, 1H), 8.74 (bs, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.59 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 3.23-3.15 (m, 1H), 3.12 (s, 3H), 2.90 (d, *J* = 15.2 Hz, 2H), 2.68 (m,1H), 2.46 (m, 2H); ESI-MS *m/z* = 445 $(M+H)^+$; pureza HPLC: 90%.

Los ejemplos 191-196 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 190, usando los materiales iniciales apropiados. Los enantiómeros se separaron de las mezclas racémicas usando procedimientos similares a los que se describen en el ejemplo 129.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
191		^{1}H-RMN (400MHz, DMSO-d_6): δ 12.20 (bs, 1H), 9.10 (bs, 1H), 8.99 (bs, 1H), 8.03 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.71(d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.60 (m, 4H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 3.24-3.15 (m, 1H), 3.13 (s, 3H), 2.91 (m, 2H), 2.69 (m, 1H), 2.50-2.39 (m, 2H).	ESI-MS *m/z* = 513 $(M+H)^+$; pureza HPLC:98%.
192		^{1}H-RMN (400MHz, DMSO-d_6): δ 12.20 (bs, 1H), 8.94 (bs, 2H), 7.94 (d, *J* = 11.2 Hz, 1H), 7.70 (d, *J* = 11.3 Hz, 3H), 7.66-7.57 (m, 4H), 7.34-7.26 (m, 2H), 7.05-7.01 (m, 1H), 3.23 (m, 1H), 3.12 (s, 3H), 2.90 (m, 2H), 2.72 (m, 1H), 2.44 (m, 2H).	ESI-MS *m/z* = 479$(M+H)^+$; pureza HPLC: 98%.
193		^{1}H-RMN (400MHz, DMSO-d_6): δ 12.20 (bs, 1H), 8.92 (2s, 2H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.72-7.66 (m, 2H), 7.63-7.57 (m, 4H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 3.23 (m, 1H), 3.13 (s, 3H), 2.90 (d, *J* = 15.3 Hz, 2H), 2.74 (m, 1H), 2.43 (m, 2H).	ESI-MS *m/z* = 479$(M+H)^+$; pureza HPLC: 90%.
194 Quiral: enantiómero 2		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.90 (2s, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.72-7.56 (m, 6H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 2H), 3.23 (m, 1H), 3.12 (s, 3H), 2.90 (d, *J* = 10.5 Hz, 2H), 2.70 (s, 1H), 2.44 (m, 2H).	ESI-MS *m/z* = 479 $(M+H)^+$; pureza HPLC: 96%.

Ej.	Estructura	Datos ^{1}H-RMN	Masa/pureza
195	 Quiral: enantiómero 1	^{1}H-RMN (300MHz, DMSO-d_6): δ 12.20 (bs, 1H), 8.90 (2s, 2H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.72-7.56 (m, 6H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 2H), 3.23 (m, 1H), 3.12 (s, 3H), 2.90 (d, *J* = 10.5 Hz, 2H), 2.70 (m, 1H), 2.44 (m, 2H).	ESI-MS *m/z* = 479 $(M+H)^+$; pureza HPLC: 96%
196		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.10 (bs, 1H), 8.68 (bs, 1H), 8.60 (bs, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.70-7.56 (m, 6H), 7.09 (s, 2H), 6.62 (s, 1H), 3.18 (m, 1H), 3.12 (s, 3H), 2.90 (d, *J* = 15.6 Hz, 2H), 2.73 (m, 1H), 2.43 (m, 2H), 2.24 (s, 6H).	ESI-MS *m/z* = 473 $(M+H)^+$; pureza HPLC:96%

EJEMPLO 197

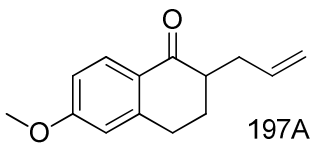


Reactivos y condiciones: a) bromuro de alilo, KOtBu, THF, t.a., 18h; b) BBr_3, CH_2Cl_2, t.a., 12h; c) Tf_2O, Py, CH_2Cl_2, t.a., 3h; d) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 3h; e) HCHO, NaOH 2N, THF, t.a., 3h; f) NaH, MeI, THF, t.a., 18h; g) Fe-NH_4Cl, EtOH-H_2O, 90 °C, 2h; h) 3-CF_3PhNCO, Et_3N, THF, t.a., 12h; i) $KMnO_4$, $NaIO_4$, acetona-H_2O, t.a., 18h.

Procedimientos

Acido 2-(2-(metoximetil)-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético

2-Alil-6-metoxi-3,4-dihidronaftalen-1(2H)-ona (197A) :

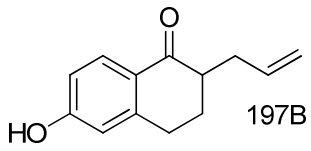


197A

A una solución de 6-metoxi-1-tetralona (10.0 g, 56.0 mmol) y ter-butóxido de potasio en THF (50 mL) se le agregó bromuro de alilo (5.4 g, 45.0 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18 h. Después, la mezcla de reacción se diluyó con acetato de etilo. La capa orgánica separada se lavó con agua, solución de salmuera, se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 4% en hexano, para producir el compuesto del título como un sólido (2.0 g, 15%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.01 (d, J = 8.4 Hz, 1H), 6.80 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 1H), 6.68 (m, 1H), 5.89-5.79 (m, 1H), 5.12 (t, J = 17.2 Hz, 2H) 3.85 (s, 3H), 2.95 (m, 2H), 2.93-2.72 (m, 1H), 2.53-2.46 (m, 1H), 2.29-2.17 (m, 2H), 1.89-1.79 (m, 1H).

2-Alil-6-hidroxi-3,4-dihidronaftalen-1(2H)-ona (197B):



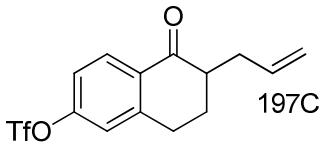
197B

Al producto del ejemplo 197A (2.0 g, 9.00 mmol) a -78 ℃ en diclorometano (75 mL) se le agregó lentamente, gota a gota, BBr_3, y la mezcla de reacción se agitó durante la noche. Después, la mezcla de reacción se apagó con agua enfriada en hielo y se extrajo con diclorometano (2X100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó al vacío.

El residuo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 15% en hexano, para producir el compuesto del título como un líquido (0.9 g, 60%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ7.98 (d, *J* = 8.4 Hz, 1H), 6.76 (dd, J_1 = 2.1 Hz, J_2 = 8.4 Hz, 1H), 6.66 (m, 1H), 5.90-5.77 (m, 1H), 5.12-5.04 (m, 2H), 2.92 (m, 2H), 2.78-2.70 (m, 1H), 2.56-2.46 (m, 1H), 2.31-2.15 (m, 2H), 1.91-1.78 (m, 1H).

Trifluorometanosulfonato de 6-alil-5-oxo-5,6,7,8-tetrahidronaftalen-2-ilo (197C):

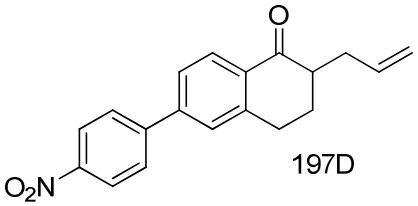


A una solución enfriada en hielo del producto del ejemplo 197B (0.9 g, 4.45 mmol) y piridina (0.421 g, 5.34 mmol) en diclorometano (20 mL)se le agregó anhídrido tríflico (1.5 g, 5.34 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 3 h. Después, la mezcla de reacción se diluyó con diclorometano (50 mL) y se lavó con solución acuosa saturada de NaCl (50 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó al vacío. El residuo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para dar el compuesto del título como un sólido (1.1 g, 61%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.12 (d, *J* = 8.1 Hz, 1H), 7.21-7.16

(m, 2H), 5.90-5.75 (m, 1H), 5.14-5.07 (m, 2H), 3.04 (m, 2H), 2.79-2.70 (m, 1H), 2.62-2.52 (m, 1H), 2.32-2.22 (m, 2H), 1.96-1.82 (m, 1H).

2-Alil-6-(4-nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (197D):

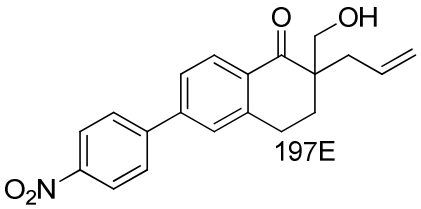


197D

A una solución del producto del ejemplo 197C (1.0 g, 2.99 mmol) en 20 mL de una mezcla 1,4-dioxano-H_2O (4:1), bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$ (0.04 g, 0.035 mmol), seguido por carbonato de cesio (2.42 g, 7.48 mmol) y ácido 4-nitrofenil-borónico (0.6 g, 3.59 mmol). La mezcla de reacción se desgasificó durante 5 min. Después, la mezcla de reacción se puso a reflujo por 3 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para dar el compuesto del título como un sólido (0.9 g, 61%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.32 (m, 2H), 8.14 (d, J = 8.0 Hz, 1H), 7.77 (m, 2H), 7.55 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.49 (s, 1H), 5.91-5.80 (m, 1H), 5.10 (t, J = 16.0 Hz, 2H), 3.07 (m, 2H), 2.80-2.75 (m, 1H), 2.63-2.56 (m, 1H), 2.34-2.26 (m, 2H), 1.97-1.86 (m, 1H).

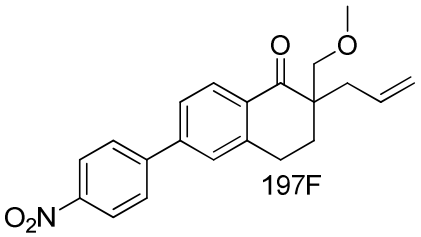
2-Alil-2-(hidroximetil)-6-(4-nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (197E):



A una solución del producto del ejemplo 197D (0.9 g, 2.92 mmol) en 7 mL de THF, bajo una atmósfera de argón, se le agregó una solución de formaldehído al 37% (5 mL), seguido por solución de NaOH 2N (2 mL) a t.a. La mezcla de reacción se agitó durante 3 h y el disolvente se eliminó bajo presión reducida. El residuo se acidificó con HCl 2N y se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó al vacío para dar un producto crudo que se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 15% en hexano, para dar el compuesto del título como un sólido (0.62 g, 61%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ8.33 (d, J = 8.4 Hz, 2H), 8.06-7.93 (m, 3H), 7.76-7.73 (m, 2H), 5.79-5.65 (m, 1H), 5.05 (m, 2H), 3.77 (d, J = 5.7 Hz, 1H), 3.50 (d, J = 9.6 Hz, 1H), 3.11-3.01 (m, 2H), 2.44 (m, 1H), 2.30-2.14 (m, 2H), 2.03-1.94 (m, 1H).

2-Alil-2-(metoximetil)-6-(4-nitrofenil)-3,4-dihidronaftalen-1(2H)-ona (197F):

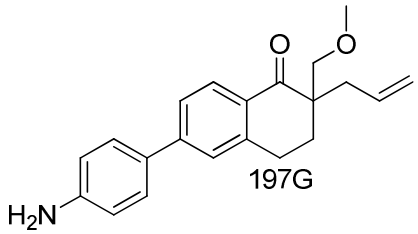


197F

A una solución enfriada en hielo del producto del ejemplo 197E (0.6 g, 1.83 mmol) y NaH (0.146 g, 3.67 mmol) en THF (20 mL), se le agregó yoduro de metilo (1.29 g, 9.15 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 18 h. Después, la mezcla de reacción se diluyó con agua y se extrajo con acetato de etilo (60 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para dar el compuesto del título como un sólido blanco (0.3 g, %).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.32 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 5.2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.55 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.47 (s, 1H), 5.80-5.71 (m, 1H), 5.13-5.07 (m, 2H), 3.74 (d, J = 9.2 Hz, 1H), 3.42 (d, J = 9.6 Hz, 1H), 3.33 (s, 3H), 3.11-3.05 (m, 2H), 2.53-2.48 (m, 1H), 2.38 (m, 2H), 2.16-2.10 (m, 1H).

2-Alil-6-(4-aminofenil)-2-(metoximetil)-3,4-dihidronaftalen-1(2H)-ona (197G):

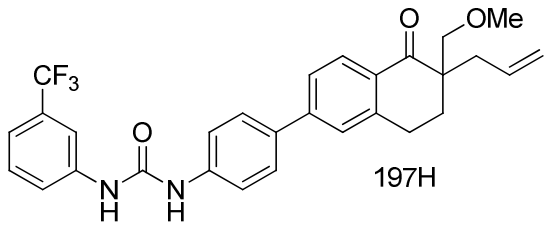


197G

A una solución de 197F (0.3 g, 0.847 mmol) en 25 mL de una mezcla de etanol-agua (2:1) se le agregó polvo de fierro (0.09g, 1.7 mmol) y NH_4Cl (0.023 g, 0.427 mmol). La mezcla de reacción se puso a reflujo por 2 h y el disolvente se eliminó bajo presión reducida y se extrajo con acetato de etilo (40 mL). La capa orgánica se lavó con agua, se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida, para dar el compuesto del título como un sólido amarillo (0.22 g, %).

^{1}H-RMN (300 MHz, DMSO-d_6): δ7.83 (d, J = 8.4 Hz, 1H), 7.53-7.44 (m, 4H), 6.64 (d, J = 9.0 Hz, 2H), 5.75-5.65 (m, 1H), 5.42 (s, 2H), 5.09-5.03 (m, 2H), 3.62 (d, J = 9.0 Hz, 1H), 3.21 (s, 3H), 2.99-2.5 (m, 2H), 2.44-2.27 (m, 1H), 2.25-2.12 (m, 2H), 2.00-1.94 (m, 2H).

1-(4-(6-Alil-6-(metoximetil)-5-oxo-5,6,7,8-tetrahidronaftalen-2-il)fenil)-3-(3-(trifluorometil)fenil)urea (197H):

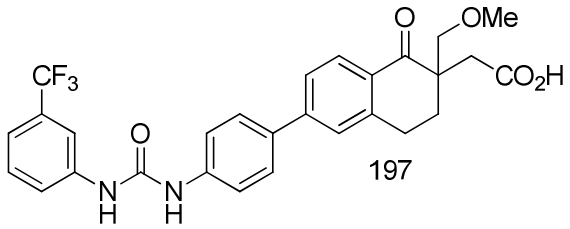


197H

A una solución del producto del ejemplo 197G (0.26 g, 1.21 mmol) y trietilamina (0.138 g, 1.37 mmol) en THF (5 mL)se le agregó isocianato de 3-(trifluorometil)fenilo (0.256 g, 1.37 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando metanol al 1% en cloroformo, para dar el compuesto del título como un sólido (0.46 g, 31%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ9.10 (s, 1H), 8.98 (s, 1H), 8.03 (s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.72-7.69 (m, 2H), 7.64-7.43 (m ,6H), 7.32 (d, J = 7.8 Hz, 1H), 5.77-5.68 (m, 1H), 5.09-5.04 (m, 2H), 3.63 (d, J = 9.0 Hz, 1H), 3.33 (m, 1H), 3.21 (s, 3H), 2.5 (m, 2H), 2.45 -2.38 (m, 1H), 2.3-2.15 (m, 2H), 2.04-1.95 (m, 1H).

Acido 2-(2-(metoximetil)-1-oxo-6-(4-(3-(3-(trifluorometil)fenil)-ureido)fenil)-1,2,3,4-tetrahidronaftalen-2-il)acético (197):

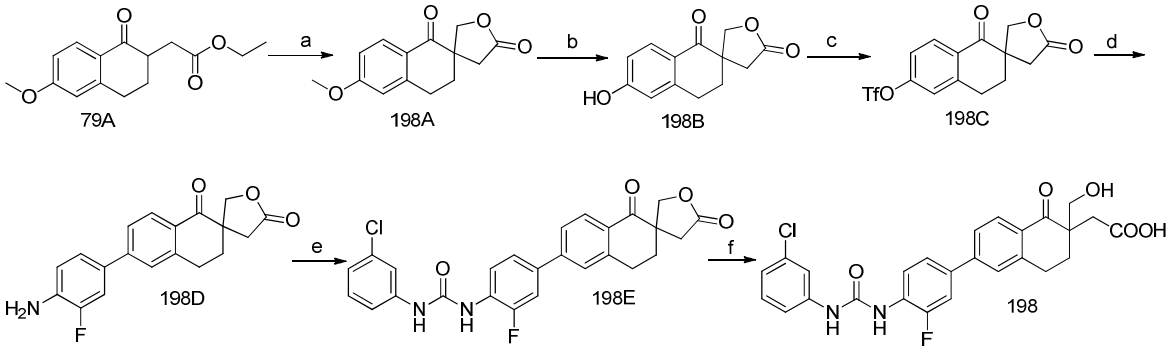


197

A una solución del producto del ejemplo 197H(0.45 g, 0.11 mmol) y $NaIO_4$ en 15 mL de una mezcla de acetona-agua (3:1)se le agregó $KMnO_4$ (0.015 g, 0.35 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se extrajo con acetato de etilo. La capa orgánica se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida. El residuo se purificó por HPLC preparativa para producir el compuesto del título (30 mg).

^{1}H-RMN (300 MHz, DMSO-d_6): δ12.0 (bs, 1H), 9.12 (s, 1H), 9.00 (s, 1H), 8.03 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.72-7.68 (m, 2H), 7.61-7.49 (m, 6H), 7.32 (d, J = 7.8 Hz, 1H), 3.61 (d, J = 9.0 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 3.22 (s, 3H), 3.11 (m, 1H), 2.99 (m, 1H), 2.88-2.82 (m, 1H), 2.44 (m, 2H), 2.27-2.18 (m, 1H); ESI-MS m/z = 527 $(M+H)^+$; pureza HPLC: 98.63 %.

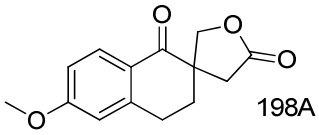
EJEMPLO 198



Reactivos y condiciones: a) HCHO, NaOH 2N, THF, t.a., 3h; b) HBr acuoso, 100 °C, 1h; c) Tf_2O, Py, CH_2Cl_2, t.a., 3h; d) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 3h; e) 3-ClPhNCO, Et_3N, THF, t.a., 4h; f) LiOH, THF-H_2O, t.a., 4h.

Acido 2-(6-(4-(3-(3-clorofenil)ureido)-3-fluorofenil)-2-(hidroximetil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético

6'-Metoxi-3',4'-dihidro-1'H,2H-espiro[furan-3,2'-naftalen]-1',5(4H)-diona (198A):

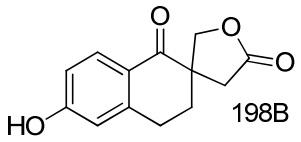


A una solución del producto del ejemplo 79A (2.0 g, 7.0 mmol) en 20 mL de THF, bajo una atmósfera de argón, se le agregó una solución de formaldehído al 37% (15 mL), seguida por solución acuosa de NaOH 2N (0.06 g, 15.0 mmol) a temperatura ambiente. La mezcla de reacción se agitó

durante 3 h, el disolvente se separó al vacío y el residuo se acidificó con HCl 2N. La capa acuosa se extrajo con acetato de etilo y la capa orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró, para producir el compuesto del título crudo como un material gomoso (0.6 g, 31%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ7.87 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.89 (s, 1H), 4.45 (d, J = 8.8 Hz, 1H), 4.25 (d, J = 8.8 Hz, 1H), 3.83 (s, 3H), 2.98-2.91 (m, 2H), 2.70 (m, 2H), 2.22 (m, 2H).

6'-Hidroxi-3',4'-dihidro-1'H,2H-espiro[furan-3,2'-naftalen]-1',5(4H)-diona (198B):

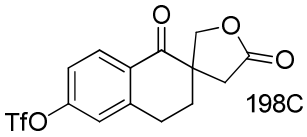


198B

Al producto del ejemplo 198A (0.6 g, 2.43 mmol) se le agregó HBr acuoso (20 mL) y la mezcla de reacción se puso a reflujo por 1 h. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo (2X100 mL). La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se eliminó bajo presión reducida, para producir el compuesto del título como un sólido (0.37 g, 65%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.01 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.67 (s, 1H), 5.51 (s, 1H), 4.58 (d, J = 8.8 Hz, 1H), 4.22 (d, J = 8.0 Hz, 1H), 3.1-2.98 (m, 3H), 2.50-2.46 (m, 1H), 2.26 (t, J = 6.4 Hz, 2H).

Trifluorometanosulfonato de1',5-dioxo-3',4,4',5-tetrahidro-1'H,2H-espiro[furan-3,2'-naftalen]-6'-ilo (198C):

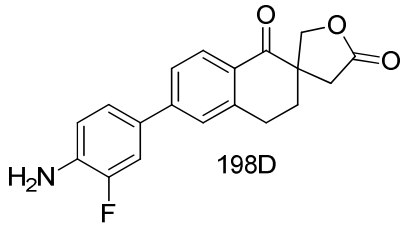


198C

A una solución enfriada en hielo del producto del ejemplo 198B (0.37 g, 1.59 mmol) y piridina (0.138 g, 1.75 mmol) en diclorometano (15 mL) se le agregó anhídrido tríflico (0.493 g, 1.75 mmol) y la mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se diluyó con diclorometano (50 mL) y se extrajo con solución acuosa saturada de NaCl (50 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para dar el compuesto del título como un sólido (0.46 g, 79%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ8.08 (d, J = 9.6 Hz, 1H), 7.59 (s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 4.53 (d, J = 8.8 Hz, 1H), 4.25 (d, J = 9.2 Hz, 1H), 3.05 (t, J = 6.0 Hz, 2H), 2.75 (d, J = 7.6 Hz, 2H), 2.29 (m, 2H).

6'-(4-Amino-3-fluorofenil)-3',4'-dihidro-1'H,2H-espiro[furan-3,2'-naftalen]-1',5(4H)-diona (198D):

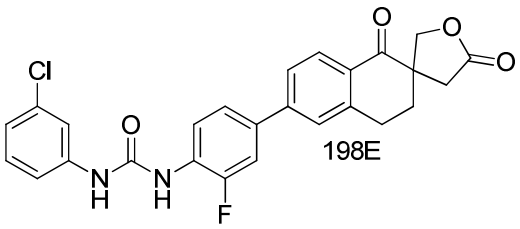


198D

A una solución del producto del ejemplo 198C (0.3 g, 0.824 mmol) en 12 mL de una mezcla de 1,4-dioxano-H_2O (4:1), bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$(0.011 g, 0.009 mmol), seguido por carbonato de cesio (0.67 g, 2.06 mmol) y ácido 4-amino-2-fluoro-fenil-borónico (0.234 g, 0.989 mmol). La mezcla de reacción se desgasificó durante 15 min. Después, la mezcla de reacción se puso a reflujo por 3 h y el disolvente se eliminó al vacío. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto crudo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (1.3 g, 72%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ7.92 (d, J = 8.4 Hz, 1H), 7.48-7.43 (m, 2H), 7.27 (t, J = 8.8 Hz, 1H), 6.48 (dd, J_1 = 2.4 Hz, J_2= 8.4 Hz, 1H), 6.42 (dd, J_1= 2.4 Hz, J_2= 16.4 Hz, 1H), 5.74 (s, 2H), 4.50 (d, J = 9.2 Hz, 1H), 4.28 (d, J = 9.2 Hz, 1H), 3.05 (m, 2H), 2.73 (d, J = 9.6 Hz, 2H), 2.26 (m, 2H).

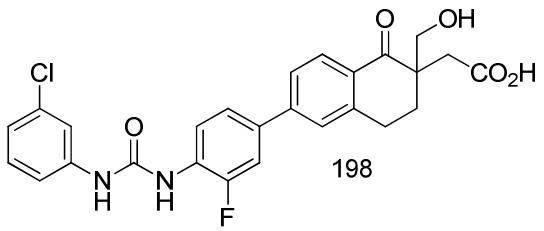
3-Cloro-N-(4-(1',5-dioxo-3',4,4',5-tetrahidro-1'H,2H-espiro[furan-3,2'-naftalen]-6'-il)-2-fluorofenil)benzamida (198E):



A una solución del producto del ejemplo 198D (0.1 g, 0.307 mmol) y trietilamina (0.034 g, 0.338 mmol) en THF (5 mL)se le agregó isocianato de 3-clorofenilo (0.052 g, 0.338 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 4 h. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 40% en hexano, para producir el compuesto del título como un sólido (0.09 g, 31%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ9.31 (s, 1H), 8.78 (m, 1H), 8.28 (t, J = 8.4 Hz, 1H), 7.98 (d, J = 5.7 Hz, 1H), 7.75-7.71 (m, 4H), 7.63-7.60 (m, 1H), 7.36-7.23 (m, 2H), 7.07-7.04 (m, 1H), 4.51 (d, J = 9.0 Hz, 1H), 4.3 (d, J = 9.3 Hz, 1H), 3.16 (d, J = 4.8 Hz, 1H), 3.06 (m, 1H), 2.75 (d, J = 4.2 Hz, 2H), 2.28 (t, J = 5.7 Hz, 2H).

Acido 2-(6-(4-(3-(3-clorofenil)ureido)-3-fluorofenil)-2-(hidroximetil)-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (198):

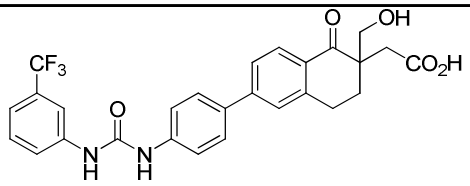
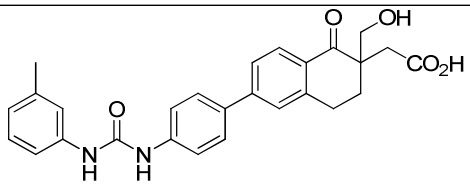


198

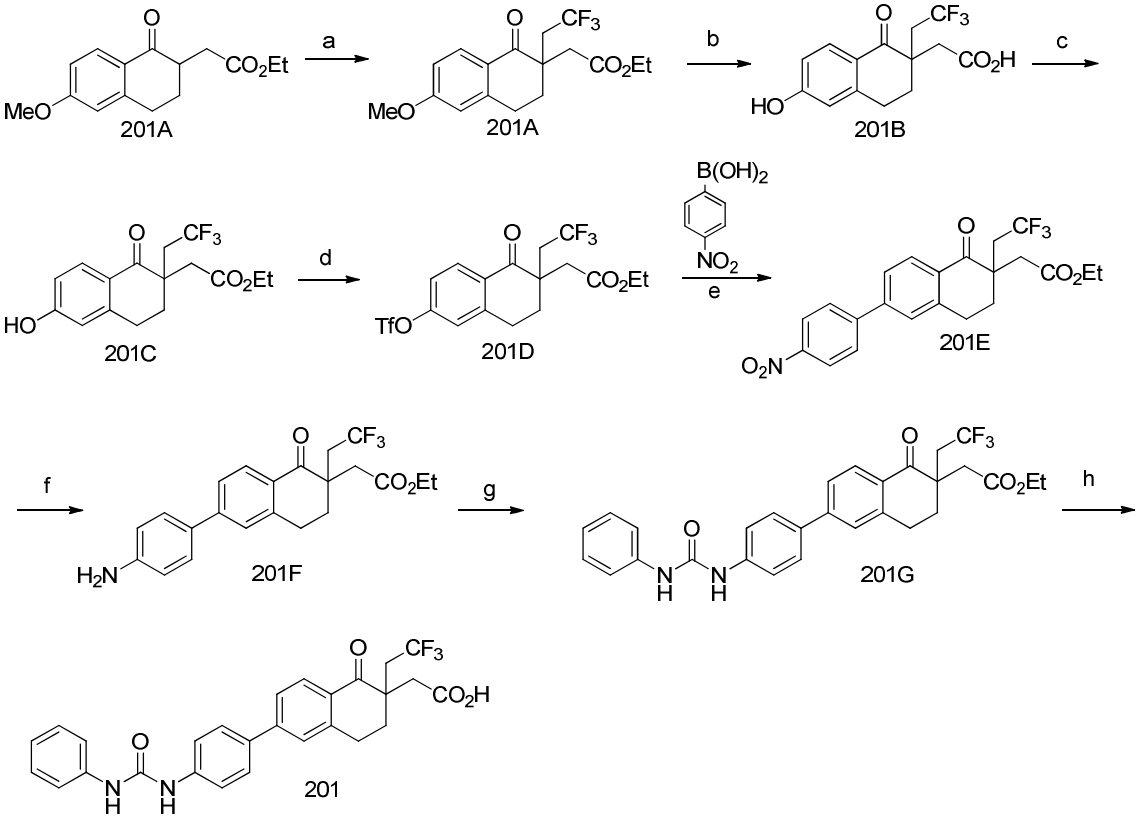
A una solución del producto del ejemplo 198E (0.09 g, 0.188 mmol) en 15 mL de una mezcla de THF-agua (2:1)se le agregó hidróxido de litio (0.023 g, 0.564 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 4h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.05 g, 53%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ12.0 (bs, 1H), 9.70 (bs, 1H), 9.11 (bs, 1H), 8.20 (t, J = 8.1 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H) 7.76 (s, 1H),7.68-7.64 (m, 3H), 7.57 (d, J = 9.0 Hz, 1H) 7.32-7.28 (m, 2H), 7.03 (m, 1H), 3.15-2.90 (m, 4H), 2.74-2.67 (m, 1H), 2.44-2.34 (m, 1H), 2.28-2.16 (m, 1H), 2.00 (m, 1H); ESI-MS m/z = 466 (M-CH_2OH).

Los ejemplos 199 y 200 se prepararon mediante procedimientos análogos a los que se describen en el ejemplo 198, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos ^{1}H-RMN	Masa /Pureza
199		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 2H), 8.14 (s, 1H), 7.96 (m, 1H), 7.80 (m, 1H), 7.66 (m, 1H) 7.47-7.40 (m, 2H),7.33 (m, 4H), 7.20 (d, *J* = 7.6 Hz, 1H), 3.09 (m, 1H), 2.94 (m, 3H), 2.33 (m, 2H), 2.02 (m, 2H).	ESI-MS *m/z* = 481 (M-CH_2OH); pureza HPLC: 95.09 %.
200		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 9.12 (bs, 2H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.70-7.55 (m, 6H), 7.35 (s, 1H), 7.25 (m, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 6.9 Hz, 1H), 3.20-3.02 (m, 2H), 2.97-2.86 (m, 2H), 2.70 (m, 2H) 2.30 (s, 3H), 2.20-2.12 (m, 1H), 2.08-1.90 (m, 1H).	ESI-MS *m/z* = 429 (M-CH_2OH); pureza HPLC: 95.33 %.

EJEMPLO 201

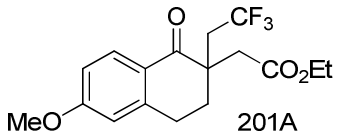


Reactivos y condiciones: a) CF_3CH_2I, NaH, DMF, t.a., 4h; b) HBr acuoso, 100 °C, 12h; c) $MeSO_3H$, EtOH, t.a., 5h; d) Tf_2O, CH_2Cl_2, Et_3N, t.a., 1h; e) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; f) Fe-NH_4Cl, EtOH-H_2O, 80 °C, 3h; g) PhNCO, Et_3N, THF, t.a., 12h; h) LiOH, THF-H_2O, t.a., 12h.

Procedimiento

Acido 2-(1-oxo-6-(4-(3-fenilureido)fenil)-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético

2-(6-Metoxi-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (201A):

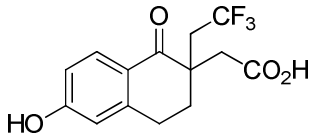


201A

Una solución de 2-(6-metoxi-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (3 g, 11.4 mmol) en DMF (10 mL) se agregó durante un periodo de 30 min a una solución enfriada en hielo de NaH (1.14 g, 28.5 mmol) en DMF (20 mL), y la mezcla de reacción se agitó durante 10 min. Después se agregó yoduro de trifluoroetilo (5.9 g, 28.22 mmol) y la mezcla se agitó durante 2 h a temperatura ambiente. La reacción se llevó entonces a 0 °C, el exceso de NaH se apagó con agua de hielo y se extrajo con acetato de etilo (2X50 mL). La capa orgánica combinada se secó sobre sulfato de sodio, se filtró y se separó al vacío, para dar el compuesto del título como un sólido (1.5 g, 38%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.02 (d, *J* = 9.3 Hz, 1H), 6.85 (dd, J_1 = 2.7 Hz, J_2 = 9.0 Hz, 1H), 6.68 (d, *J* = 2.7 Hz, 1H), 4.1 (q, *J* = 6.9 Hz, 2H), 3.86 (s, 3H), 3.05-2.9 (m, 4H), 2.6-2.4 (m, 4H), 1.23 (t, *J* = 6.9 Hz, 3H); ESI-MS *m/z*: 345 $(M+H)^+$

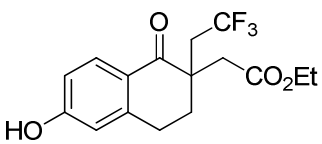
Acido 2-(6-hidroxi-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético (201B):



201B

Al producto del ejemplo 201A (1.5 g, 4.36 mmol) se le agregó HBr acuoso (15 mL) y la mezcla de reacción se puso a reflujo durante la noche. La mezcla de reacción se llevó entonces a temperatura ambiente y se extrajo con acetato de etilo (2X100 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida, para producir un compuesto crudo como un sólido (1.2 g)que se llevó al siguiente paso sin más purificación

2-(6-Hidroxi-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (201C):

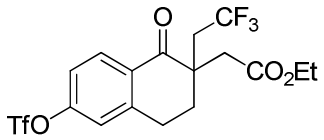


201C

A una solución del producto del ejemplo 201B (1.2 g, 3.97 mmol) en etanol (15 mL) se le agregó ácido metanosulfónico (2 mL) y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. El etanol se separó de la mezcla de reacción bajo presión reducida y el residuo se diluyó con acetato de etilo y se lavó con solución de salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y el disolvente se eliminó bajo presión reducida. El producto crudo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para dar el compuesto del título como un jarabe (0.9 g, 62%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ7.97 (d, *J* = 9.2 Hz, 1H), 6.75 (dd, J_1 = 2.4 Hz, J_2 = 8.8 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 4.1 (q, *J* = 6.8 Hz, 2H), 3.0-2.8 (m, 4H), 2.62-2.5 (m, 2H), 2.4 (m, 1H), 2.3 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ESI-MS *m/z*: 329 $(M-H)^-$

2-(1-Oxo-2-(2,2,2-trifluoroetil)-6-(trifluorometilsulfoniloxi)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (201D):



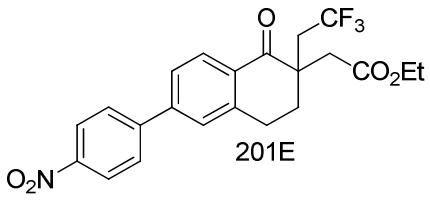
201D

A una solución enfriada en hielo del producto del ejemplo 201C (1.3 g, 3.93 mmol) y piridina (0.34 g, 4.72 mmol) en diclorometano (15 mL) se le agregó anhídrido tríflico (1.33 g, 4.71 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se diluyó con diclorometano (100 mL) y se lavó con una solución acuosa saturada de

NaCl (25 mL). La capa orgánica se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 5% en hexano, para dar el compuesto del título como un jarabe (1.1 g, 61%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ8.16 (d, *J* = 9.0 Hz, 1H), 7.28-7.18 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.09 (t, *J* = 6.3 Hz, 2H), 2.95-2.8 (m, 2H), 2.66-2.45 (m, 3H), 2.34 (m, 1H), 1.24 (t, *J* = 6.9 Hz, 3H).

2-(6-(4-Nitrofenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (201E):



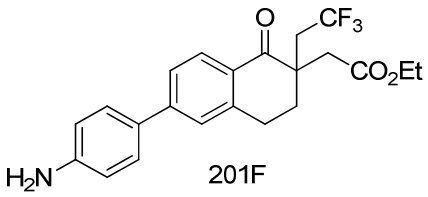
201E

A una solución del producto del ejemplo 201D (0.9 g, 1.94 mmol) en 13 mL de una mezcla de 1,4-dioxano-H_2O (3:1)se le agregó $Pd(PPh_3)_4$ (0.022 g, 0.02 mmol) bajo una atmósfera de argón, seguido por carbonato de cesio (1.9 g, 5.8 mmol) y ácido 4-nitro-fenil-borónico (0.35 g, 2.09 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 4 h y luego el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea para

producir el compuesto del título como un sólido (0.4 g, 47%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.33 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.6 (m, 1H), 7.5 (s, 1H), 4.14 (q, *J* = 6.8 Hz, 2H), 3.13 (t, *J* = 6.0 Hz, 2H), 2.95-2.85 (m, 2H), 2.7-2.58 (m, 2H), 2.5 (m, 1H), 2.4 (m, 1H), 1.25 (t, *J* = 6.8 Hz, 3H). ESI-MS *m/z*: 436 $(M+H)^+$

2-(6-(4-Aminofenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (201F):

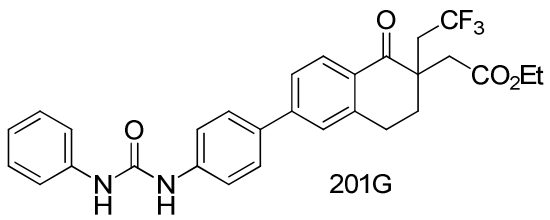


201F

A una solución del producto del ejemplo 201E (0.4 g, 0.9 mmol) en 15 mL de una mezcla de etanol-agua (2:1) se le agregó polvo de fierro (0.12 g, 2.3 mmol), seguido por NH_4Cl (0.024 g, 0.45 mmol), y la mezcla de reacción se puso a reflujo por 4 h. El disolvente se eliminó bajo presión reducida y el residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó al vacío para dar el compuesto del título (0.2 g, 50%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ7.86 (d, *J* = 8.4 Hz, 1H), 7.6-7.45 (m, 4H), 6.65 (d, *J* = 9.0 Hz, 2H), 5.44 (bs, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.1-2.8 (m, 4H), 2.75-2.6 (m, 2H), 2.38 (m, 1H), 2.15 (m, 1H), 1.14 (t, *J* = 7.2 Hz, 3H). ESI-MS *m/z*: 406 $(M+H)^+$

2-(1-Oxo-6-(4-(3-fenilureido)fenil)-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (201G):

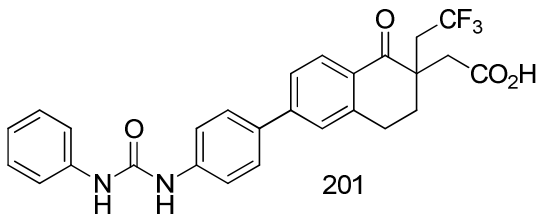


201G

A una solución del producto del ejemplo 201F (0.12 g, 0.3 mmol) y trietilamina (0.06 g, 0.6 mmol) en THF (5 mL) se le agregó isocianato de fenilo (0.035 g, 0.3 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.08 g, 66%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ8.1 (d, 8.4 Hz, 1H), 7.6-7.45 (m, 5H), 7.42-7.35 (m, 5H), 7.19 (m, 1H), 6.6 (s, 1H), 6.5 (s, 1H), 4.1 (q, *J* = 7.2 Hz, 2H), 3.1 (m, 2H), 2.9 (m, 2H), 2.63 (m, 2H), 2.5-2.3 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ESI-MS *m/z*: 526 $(M+H)^+$

Acido 2-(1-oxo-6-(4-(3-fenilureido)fenil)-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético (201):

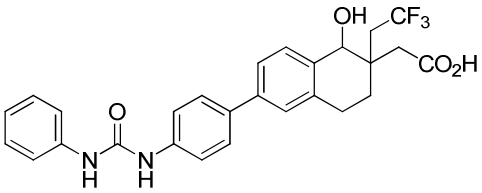
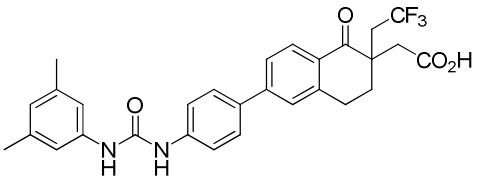
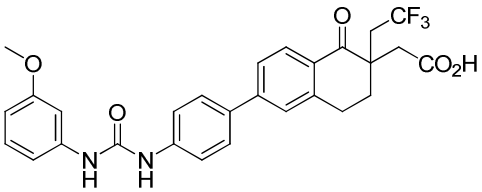
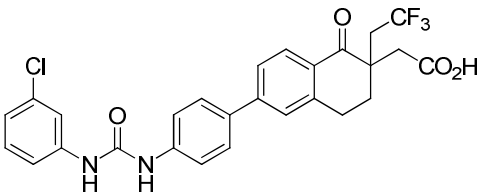


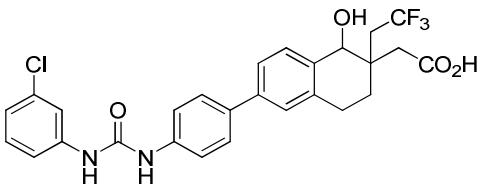
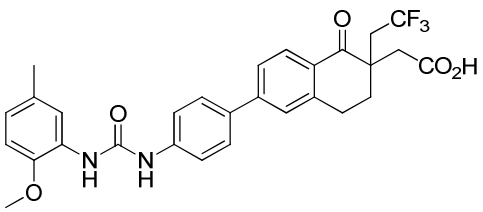
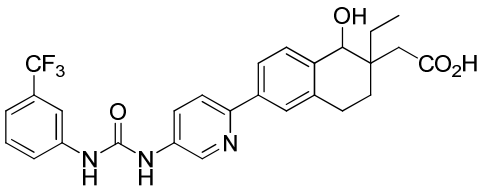
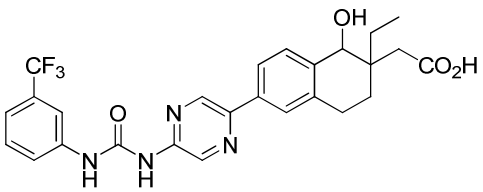
201

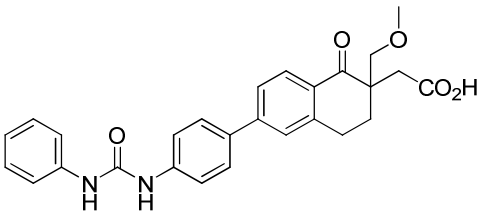
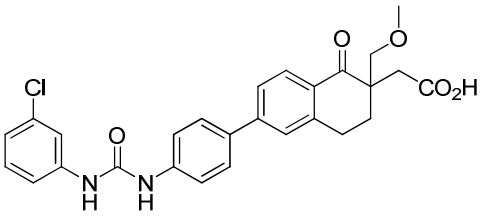
A una solución del producto del ejemplo 201G (0.08 g, 0.15 mmol) en 4 mL de una mezcla de THF-agua (3:1)se le agregó hidróxido de litio (0.025 g, 0.61 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido blanco (0.05 g, 66%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ12.4 (bs, 1H), 9.15 (bs, 1H), 8.95 (bs, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.7 -7.62 (m, 4H), 7.57 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 3.2-2.9 (m, 3H), 2.83-2.67 (m, 2H), 2.6-2.45 (m, 2H), 2.15 (m, 1H); ESI-MS *m/z*: 495 $(M-H)^-$; pureza HPLC: 95%.

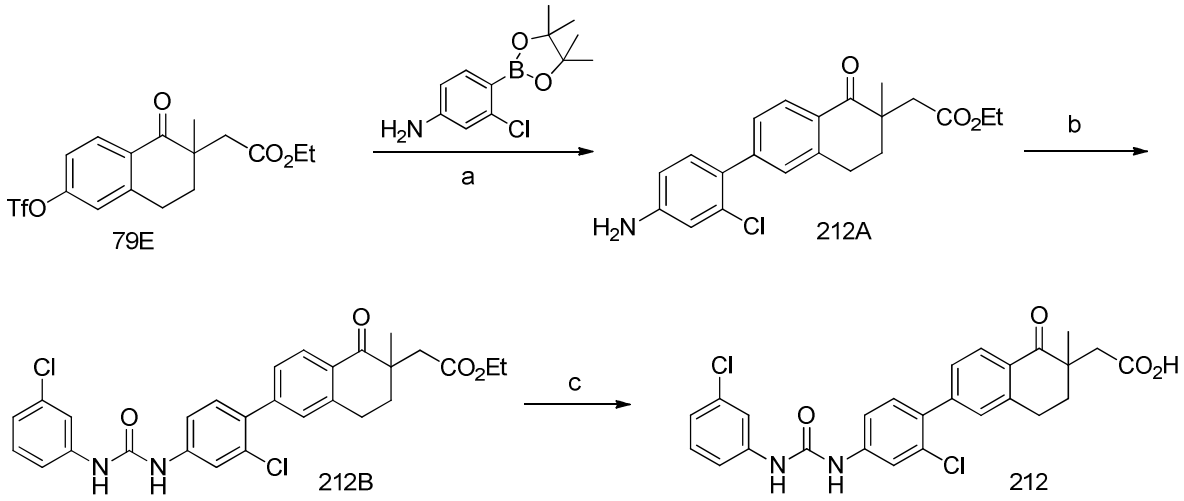
Los ejemplos 202-211 se prepararon mediante procedimientos análogos a los que se describen en el ejemplos 173, 197 y 201, usando los materiales iniciales apropiados.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
202		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.78 (s, 1H), 8.7 (s, 1H), 7.6-7.52 (m, 4H), 7.5-7.4 (m, 3H), 7.38-7.26 (m, 4H), 6.97 (t, *J* = 7.5 Hz, 1H), 5.5 (d, *J* = 6.3 Hz, 1H), 4.5 (d, *J* = 5.4 Hz, 1H), 2.9-2.55 (m, 4H), 2.4-2.2 (m, 2H), 1.94 (m, 2H).	ESI-MS *m/z*: 499 $(M+H)^+$; pureza HPLC: 99%.
203		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.16 (bs, 1H), 8.9 (bs, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.7-7.55 (m, 6H), 7.1 (s, 2H), 6.6 (s, 1H), 3.2-2.9 (m 3H), 2.84-2.7 (m, 2H), 2.55 (m, 1H), 2.45 (m, 1H), 2.24 (s, 6H), 2.16 (m, 1H).	ESI-MS *m/z*: 525 $(M+H)^+$; pureza HPLC: 97%.
204		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.9 (bs, 1H), 8.8 (bs, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.72-7.55 (m, 6H), 7.24-7.16 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 6.3 Hz, 1H), 3.74 (s, 3H), 3.2-2.9 (m, 3H), 2.85-2.65 (m, 3H), 2.55 (m, 1H), 2.17 (m, 1H).	ESI-MS *m/z*: 525 $(M-H)^-$; pureza HPLC: 98%.
205		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.2 (bs, 2H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.74 - 7.64 (m, 5H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.32-7.28 (m, 2H), 7.02 (m, 1H), 3.2-2.9 (m, 3H), 2.82 (d, J = 16.4 Hz, 1H), 2.7 (m, 1H), 2.56 (m, 1H), 2.45 (m, 1H), 2.18 (m, 1H).	ESI-MS *m/z*: 529 $(M-H)^-$; LCMS pureza: 98%.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
206		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.32 (bs, 1H), 9.24 (bs, 1H), 7.74 (s, 1H), 7.65 -7.52 (m, 4H), 7.5-7.35 (m, 3H), 7.3 (m, 2H), 7.0 (m, 1H), 4.54 (s, 1H), 2.95-2.8 (m, 4H), 2.5-2.2 (m, 2H), 1.9 (m, 2H).	ESI-MS *m/z*: 531 $(M-H)^-$; LCMS pureza: 93%.
207		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.51 (s, 1H), 8.23 (s, 1H), 8.0 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.75-7.55 (m, 6H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 7.6 Hz, 1H), 3.85 (s, 3H), 3.2-2.9 (m 3H), 2.84-2.65 (m, 2H), 2.55 (m, 1H), 2.45 (m, 1H), 2.24 (s, 3H), 2.18 (m, 1H).	ESI-MS *m/z*: 541 $(M+H)^+$; LCMS pureza: 93%.
208		^{1}H-RMN (400 MHz, DMSO-d_6): δ 9.39 (bs, 1H), 9.31 (bs, 1H), 8.73 (bs, 1H), 8.1 (d, *J* = 8.4 Hz, 1H), 8.0 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.76 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 4.42 (s, 1H), 2.81 (m, 2H), 2.13 (m, 2H), 1.84 (m, 1H), 1.7 (m, 1H), 1.56 (m, 1H), 1.4 (m, 1H), 0.9 (t, *J* = 6.8 Hz, 3H).	ESI-MS *m/z*: 512 $(M+H)^+$; LCMS pureza: 96%.
209		^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.0 (bs, 1H), 10.0 (bs, 1H), 9.8 (bs, 1H), 9.1 (s, 1H), 8.9 (s, 1H), 8.05 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.8 (s, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.2 Hz,	ESI-MS *m/z*: 513 $(M+H)^+$; LCMS pureza: 90%.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
210		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 8.85 (s, 1H), 8.7 (s, 1H), 7.9 (d, *J* = 7.5 Hz, 1H), 7.7 (d, *J* = 8.4 Hz, 2H), 7.65-7.55 (m, 4H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.3 (t, *J* = 7.5 Hz, 2H), 7.0 (m, 1H), 3.6 (d, *J* = 9.3 Hz, 1H), 3.36 (d, *J* = 9.9 Hz, 1H), 3.22 (s, 3H), 3.12-2.89 (m, 2H), 2.85 (m, 1H), 2.42 (m, 2H), 2.18 (m, 1H).	pureza HPLC: 92%.
211		^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.05 (bs, 1H), 8.95 (s, 2H), 7.9 (d, *J* = 7.5 Hz, 1H), 7.7 (d, *J* = 9.0 Hz, 2H), 7.63-7.57 (m, 4H), 7.34-7.29 (m, 2H), 7.03 (m, 1H), 3.6 (d, *J* = 9.3 Hz, 1H), 3.36 (d, *J* = 9.9 Hz, 1H), 3.22 (s, 3H), 3.18-2.9 (m, 2H), 2.85 (m, 1H), 2.42 (m, 2H), 2.15 (m, 1H).	ESI-MS *m/z*: 491 $(M-H)^-$; pureza HPLC: 91%.

EJEMPLO 212

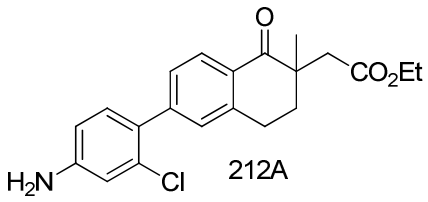


Reactivos y condiciones: a) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; b) 3-ClPhNCO, Et_3N, THF, t.a., 12h; c) LiOH, THF-H_2O, t.a., 12h.

Procedimientos

Acido 2-(6-(2-cloro-4-(3-(3-clorofenil)ureido)fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético

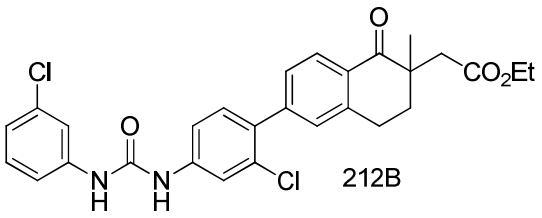
2-(6-(4-Amino-2-clorofenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (212A):



A una solución del producto del ejemplo 79E (2.5 g, 6.34 mmol) en 35 mL de una mezcla de 1,4-dioxano-H_2O (5:1) bajo una atmósfera de

argón, se le agregó $Pd(PPh_3)_4$(0.088 g, 0.076 mmol), seguido por carbonato de cesio (6.2 g, 19.02 mmol) y ácido 4-amino-2-clorofenil borónico, éster de pinacol (1.607 g, 6.34 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 5 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se filtró y se separó bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea para producir el compuesto del título como un sólido (2 g, 85%). ^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 1H), 7.38-7.36 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.28 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 6.64-6.61 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H), 4.1 (q, J = 6.8 Hz, 2H), 3.8 (bs, 2H), 3.1 (m, 1H), 2.95 (m, 2H), 2.5 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.25 (m, 3H).

2-(6-(2-Cloro-4-(3-(3-clorofenil)ureido)fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (212B):



212B

A una solución del producto del ejemplo 212A(1.8 g, 4.84 mmol) y trietilamina (2.024 g, 14.52 mmol) en THF (25 mL) se le agregó1-cloro-3-isocianato benceno (0.892 g, 5.81 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión

reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 12% en hexano, para producir el compuesto del título como un sólido (1.2 g, 47.2%).

^{1}H-RMN (300 MHz, $CDCl_3$): δ 8.05 (s, 1H), 8.02 (s, 1H), 7.48 (m, 2H), 7.36 (m, 1H), 7.29 (m, 1H), 7.21 (m, 1H), 7.11-7.03 (m, 5H), 4.11 (q, *J* = 7.5 Hz, 2H), 3.12-2.89 (m, 3H), 2.44 (m, 2H), 1.95 (m, 1H), 1.3 (s, 3H), 1.2 (t, *J* = 7.2 Hz, 3H).

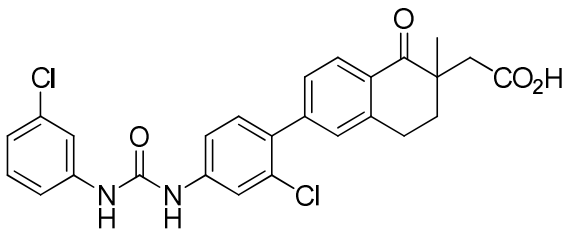
El compuesto 212B (0.88g) era una mezcla racémica con una relación enantiomérica 1:1, y se separó en una columna quiral para obtener los enantiómeros individuales 212B1 (t_R= 17.32 min) y 212B2 (t_R= 19.06 min) usando las siguientes condiciones:

Columna: CHIRAL PAK IA 4.6 X 250mm, 5 µ

ID columna: ANL_CHIRAL IA_141

Fase móvil: A= n-hexano, C= etanol; isocrática: 90:10; velocidad de flujo: 1.0 mL/min

<u>Acido 2-(6-(2-cloro-4-(3-(3-clorofenil)ureido)fenil)-2-metil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (212):</u>

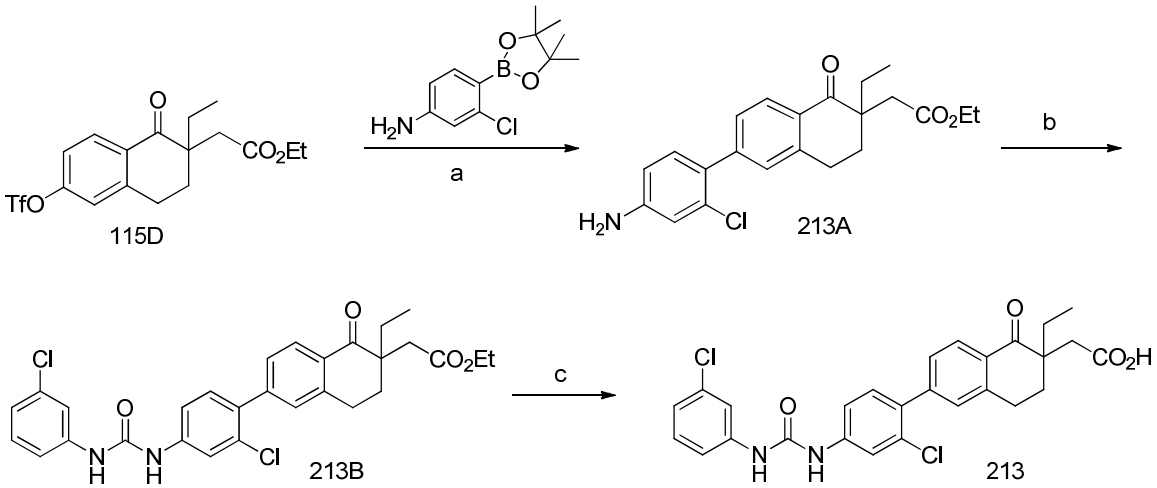


Quiral: enantiómero1

A una solución del producto del ejemplo 212B1 (0.25 g, 0.476 mmol) en 10 mL de una mezcla dioxano-agua (4:1) se le agregó hidróxido de litio (0.08 g, 1.903 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.19 g, 80%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.1 (bs, 1H), 9.03 (bs, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.8 (d, *J* = 1.8 Hz, 1H), 7.7 (m, 1H), 7.43-7.39 (m, 4H), 7.32-7.3 (m, 2H), 7.06-7.03 (m, 1H), 3.11-2.98 (m, 2H), 2.87 (d, *J* = 15.6 Hz, 1H), 2.5 (m, 1H), 2.4 (d, J = 16.5 Hz, 1H), 1.87 (m, 1H), 1.2 (s, 3H); ESI-MS *m/z* = 495 $(M-H)^-$; pureza HPLC: 95%.

EJEMPLO 213

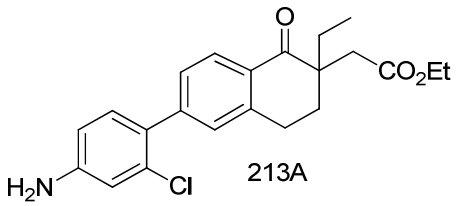


Reactivos y condiciones: a) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; b) 3-ClPhNCO, Et_3N, THF, t.a., 12h; c) LiOH, THF-H_2O, t.a., 12h.

Procedimientos

Acido 2-(6-(2-cloro-4-(3-(3-clorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético

2-(6-(4-Amino-2-clorofenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (213A):



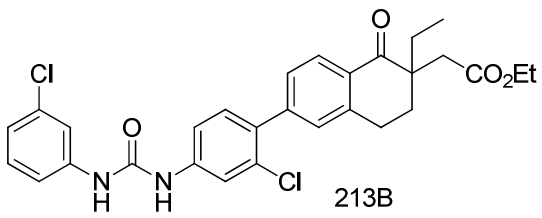
213A

A una solución del producto del ejemplo 115D (3 g, 7.35 mmol) en 40 mL de una mezcla de 1,4-dioxano-H_2O (3:1), bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$(0.085 g, 0.073 mmol), seguido por carbonato de cesio (7.18 g, 22.04 mmol) y 3-cloro-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)anilina (1.862 g, 7.35 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 3 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica separada se secó sobre sulfato de sodio, se

filtró y se concentró bajo presión reducida, para dar un producto crudo que se purificó por cromatografía de vaporización instantánea para producir el compuesto del título como un sólido (3 g, 58%).

^{1}H-RMN (400MHz, DMSO- d_6): δ 8.07 (d, J = 7.6 Hz, 1H), 7.36 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.26 (m, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 2 Hz, 1H), 6.62 (dd, J_1 = 2 Hz, J_2 = 8.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.13-3.07 (m, 1H), 3.00-2.88 (m, 2H), 2.52-2.38 (m, 2H), 2.09-2.03 (m, 1H), 1.82-1.6 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.8 Hz, 3H).

2-(6-(2-Cloro-4-(3-(3-clorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (213B):



213B

A una solución del producto del ejemplo 213A (3 g, 7.77 mmol) y trietilamina (2.18 mL, 15.55 mmol) en THF (10 mL) se le agregó3-cloro-3-isocianato benceno (0.944 mL, 7.77 mmol), y la mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido amarillo (1 g, 14%).

^{1}H -RMN (300 MHz , DMSO-d_6): δ 9.13 (s, 1H), 9.06 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 2.1 Hz, 1H), 7.72 (s, 1H), 7.46-7.28 (m, 6H), 7.06-7.02 (m, 1H), 4.02 (q, J = 7.2 Hz, 2H), 3.31-2.8 (m, 3H), 2.5-2.34 (m, 2H), 2.03-1.99 (m, 1H), 1.73-1.53 (m, 2H), 1.14 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H).

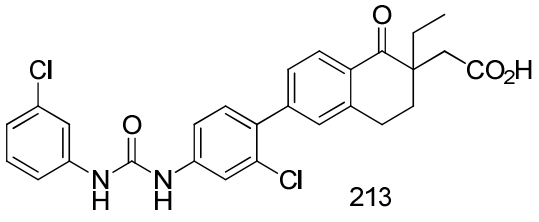
El compuesto 213B (1 g) era una mezcla racémica con una relación enantiomérica 1:1, y se separó en una columna quiral para obtener los enantiómeros individuales 213B1 (t_R = 15.15 min) y 213B2 (t_R= 16.97 min) usando las siguientes condiciones:

Columna: CHIRAL PAK IA 4.6 X 250mm, 5 µ

ID columna: ANL_CHIRAL IA_141

Fase móvil: D= n-hexano (0.1% DEA), C=etanol; Isocrática: 90:10; Velocidad de flujo: 1.0 mL/min.

Acido 2-(6-(2-cloro-4-(3-(3-clorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (213):



213

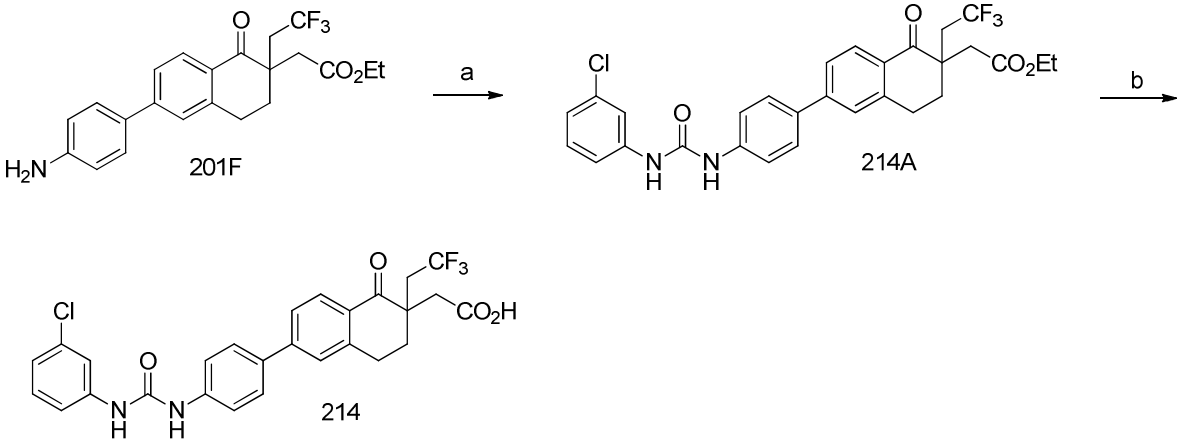
Quiral: enantiómero 1

A una solución del producto del ejemplo 213B1 (0.35 g, 0.649 mmol) en 12 mL de una mezcla de THF-agua (5:1) se le agregó hidróxido de

litio (0.136 g, 3.24 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido blanco (0.24 g, 71%).

^{1}H-RMN (300 MHz , DMSO-d_6): δ 12.16 (bs, 1H) , 9.21 (bs, 2H), 7.93 (d, J = 8.1 Hz, 1H), 7.87 (s, 1H), 7.72 (s, 1H), 7.41-7.27 (m, 6H), 7.08-7.0 (m, 1H), 3.07-3.03 (m, 1H), 2.94-2.79 (m, 2H), 2.50-2.34 (m, 2H), 2.00-1.95 (m, 1H), 1.72-1.49 (m, 2H), 0.85 (t, J = 7.5 Hz, 3H); LCMS : 98.6% m/z = 511 $(M+H)^+$; pureza HPLC: 94%.

EJEMPLO 214

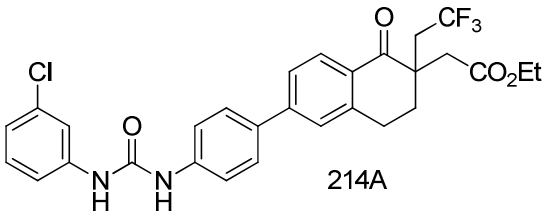


Reactivos y condiciones: a) 3-ClPhNCO, Et_3N, THF, t.a., 12h; b) LiOH, THF-H_2O, t.a., 12h.

Procedimientos

Acido 2-(6-(4-(3-(3-clorofenil)ureido)fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético

2-(6-(4-(3-(3-Clorofenil)ureido)fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (214A):



214A

A una solución del producto del ejemplo 201F (1.6 g, 3.95 mmol) y trietilamina (0.79 g, 7.89 mmol) en THF (10 mL) se le agregó isocianato de 3-clorofenilo (0.604 g, 3.95 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. El disolvente se eliminó bajo presión reducida y el producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (1.6 g, 64.5%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ 8.95 (bs, 2H), 7.93 (d, J = 8.1 Hz, 1H), 7.73-7.57 (m, 7H), 7.31-7.29 (m, 2H), 7.05-7.02 (m, 1H), 4.04 (q, J = 7.3 Hz, 2H), 2.91-2.85 (m, 4H), 2.72-2.64 (m, 2H), 2.39 (m, 2H), 1.15 (t, J =

7.2 Hz, 3H). Rendimiento = 64.5%.

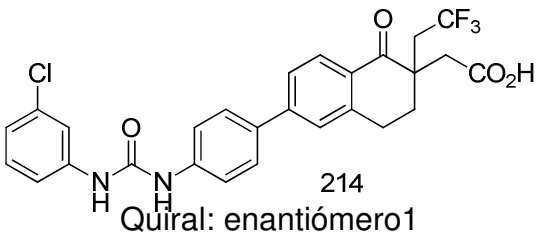
El compuesto 214A era una mezcla racémica con una relación enantiomérica 1:1, y se separó en una columna quiral para obtener los enantiómeros individuales 214A1 (t_R 5.832 min) y 214A2 (t_R 6.469 min) usando las siguientes condiciones de preparación:

Columna: CHIRAL PAK IA 4.6 X 250mm, 5 µ

ID columna: ANL_CHIRAL IA_110

Fase móvil: A= n-hexano, C= etanol; isocrática: 60:40; Velocidad de flujo: 1.0 mL/min.

Acido 2-(6-(4-(3-(3-clorofenil)ureido)fenil)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético (214):



214

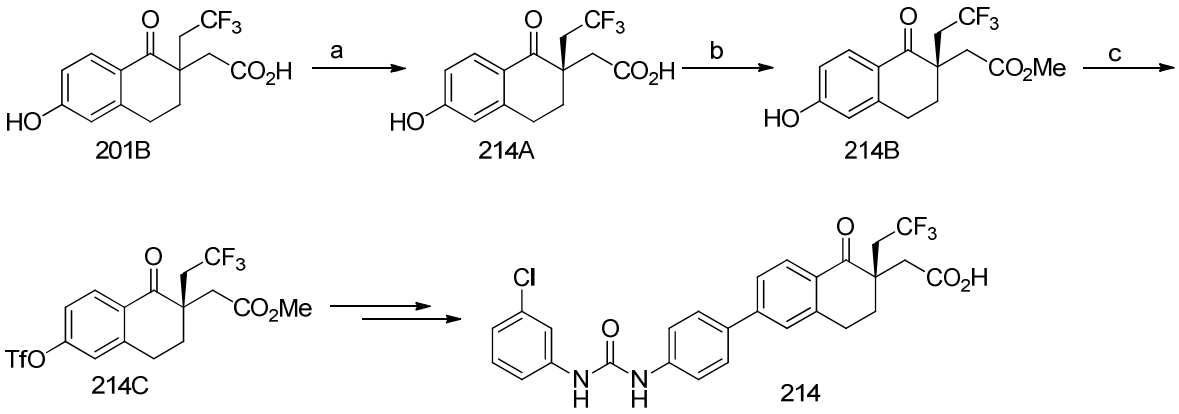
Quiral: enantiómero1

A una solución del producto del ejemplo 214A1 (0.35 g, 0.626 mmol) en 10 mL de una mezcla de THF-agua (4:1)se le agregó hidróxido de litio (0.131 g, 3.13 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, el sólido se recogió por filtración

y se secó al vacío para producir el compuesto del título como un sólido blanco (0.22 g, 65%).

^{1}H-RMN (400 MHz, DMSO-d_6): δ 11.8 (bs, 1H), 9.8 (bs, 2H), 7.95 (d, J = 8 Hz, 1H), 7.75 (m, 1H), 7.7 -7.5 (m, 6H), 7.36-7.26 (m, *2*H), 7.0 (d, *J* = 7.2 Hz, 1H), 3.16-2.96 (m, 3H), 2.95-2.78 (m, 2H), 2.54 (m, 1H), 2.46 (m, 1H), 2.16-2.12 (m, 1H); ESI-MS *m/z*: 495 $(M-H)^-$; pureza HPLC: 95%.

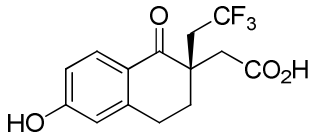
Síntesis alterna del ejemplo 214:



Reactivos y condiciones: a) cinconidina, IPA-H_2O, 80 °C – t.a., 24h,luegoHCl 5N, t.a.; b) H_2SO_4, MeOH, 70 °C, 12h; c) Tf_2O, CH_2Cl_2, Et_3N, t.a., 1h.

Procedimientos

Acido (S)-2-(6-hidroxi-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético



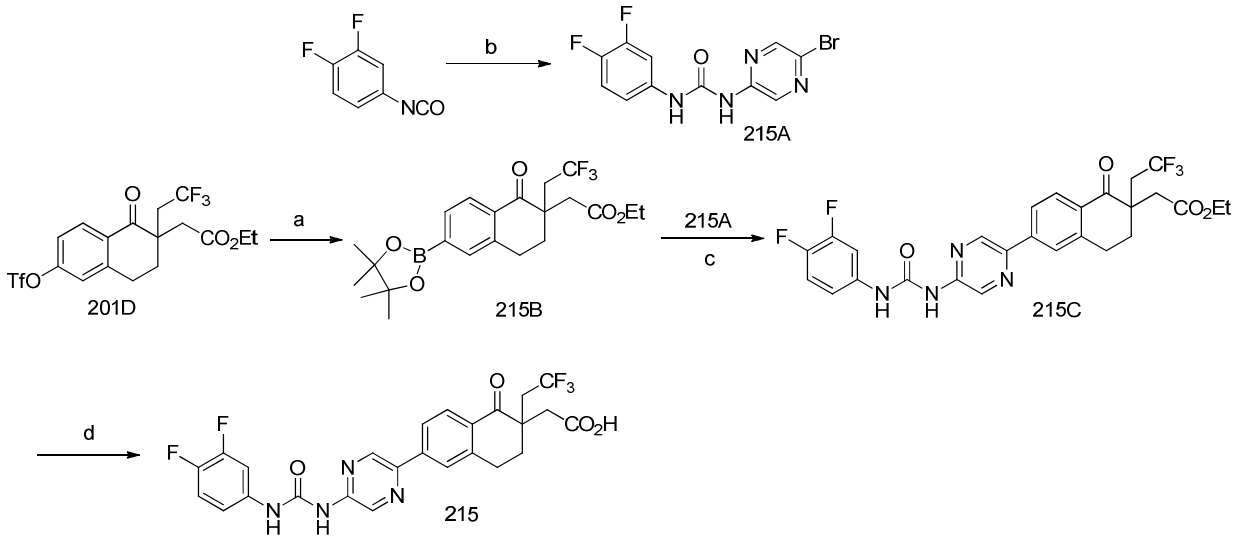
214A

A una solución del producto del ejemplo 201B (1 g, 3.31 mmol) en alcohol isopropílico (9 mL) y agua (3 mL) se le agregó cinconidina (0.97 g, 3.31 mmol) y la mezcla de reacción se calentó a 80 °C por 4 h. La solución resultante se agitó a temperatura ambiente durante 16 h y la sal se filtró y se lavó con una mezcla de alcohol isopropílico (2 mL) y agua (2 mL). La sal se disolvió en HCl 5N (5 mL), se extrajo con acetato de etilo (25 mL), se secó y se concentró, para producir el compuesto del título como un sólido blanco (0.18 g, 18%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.2 (bs, 1H), 10.4 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 6.74 (dd, J_1 = 2.1 Hz, J_2 = 8.1 Hz, 1H), 6.64 (s, 1H), 3.05-2.80 (m, 3H), 2.75-2.60 (m, 2H), 2.45 (m, 1H), 2.35 (m, 1H), 2.15-2.0 (m, 1H).

Los compuestos 214B, 214C y 214 se pueden sintetizar a partir del compuesto quiral 214A usando procedimientos análogos a los que se describen para los ejemplos 201 y 214.

EJEMPLO 215

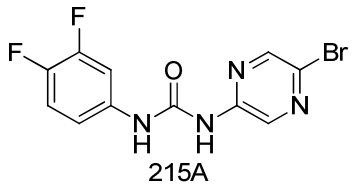


Reactivos y condiciones: e) $PdCl_2(dppf)$, KOAc, dioxano, 100 °C, 5h; b) 2-amino-4-bromo-pirazina, Et_3N, tolueno, 120 °C, 12h; c) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; d) LiOH, EtOH-H_2O, t.a., 12h.

Procedimientos

Acido 2-(6-(5-(3-(3,4-difluorofenil)ureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético

1-(5-Bromopirazin-2-il)-3-(3,4-difluorofenil)urea (215A):

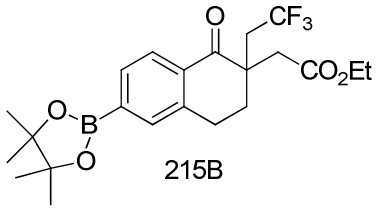


A una solución de 2-amino-4-bromo-pirazina (9 g, 51.72 mmol) y

trietilamina (3.98 mL, 28.4 mmol) en tolueno (100 mL) se le agregó isocianato de 3,4-difluorofenilo (8.8 g, 56.9 mmol) y la mezcla de reacción se agitó a 120 °C durante 12 h. El disolvente se eliminó bajo presión reducida y el residuo se purificó por cromatografía de vaporización instantánea, eluyendo con acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (10 g, 59%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.69 (s, 1H), 9.46 (s, 1H), 8.93 (d, J = 1.2 Hz, 1H), 8.52 (d, J = 1.8 Hz, 1H), 7.74-7.64 (m, 1H), 7.46-7.32 (m, 1H), 7.22-7.14 (m, 1H).

2-(1-Oxo-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (215B):



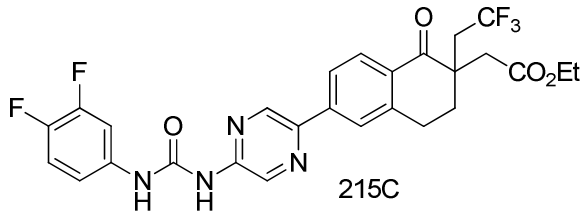
215B

A una solución del ejemplo 201D (6.6 g, 14.27 mmol) en 50 mL de 1,4-dioxano en una atmósfera de argón, se le agregó aducto de $PdCl_2$(dppf)-CH_2Cl_2 (0.58 g, 0.71 mmol), seguido por acetato de potasio(4.19 g, 42.85 mmol) y 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (3.62 g, 14.27 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 5 h, se enfrió a temperatura ambiente y se filtró sobre una almohadilla de celite.El filtrado se concentró bajo presión

reducida y el residuo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 10% en hexano, para producir el compuesto del título como un líquido viscoso (5.6 g, 89%).

^{1}H-RMN (400MHz, $CDCl_3$):δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.70 (s, 1H), 4.14-4.09 (q, *J* = 7.2 Hz, 2H), 3.06-3.03 (m, 2H), 2.89-2.82 (m, 2H), 2.63-2.56 (m, 2H), 2.42-2.29 (m, 2H), 1.35-1.31 (m, 3H), 1.24-1.19 (m, 12H).

2-(6-(5-(3-(3,4-Difluorofenil)ureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (215C):



215C

A una solución del ejemplo 215B (2.3 g, 3.22 mmol) en 60 mL de una mezcla de 1,4-dioxano-H_2O (5:1) bajo una atmósfera de argón, se le agregó $Pd(PPh_3)_4$ (0.3 g, 0.26 mmol), seguido por carbonato de cesio (5.11 g, 15.67 mmol) y el compuesto 215A (2.063 g, 6.27 mmol). La mezcla de reacción se desgasificó durante 30 min. La mezcla de reacción se puso a reflujo por 16 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua, la capa orgánica se separó, se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de

etilo al 18% en hexano, para producir el compuesto del título como un sólido (1 g, 32%).

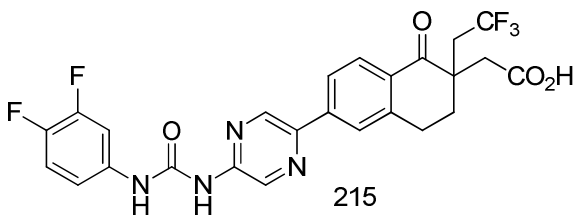
^{1}H-RMN (300 MHz, DMSO-d_6): δ 9.82 (s, 1H), 9.75 (s, 1H), 9.16 (d, J = 1.5 Hz, 1H), 9.03 (d, J = 1.5 Hz, 1H), 8.10-7.95 (m, 3H), 7.78-7.68 (m, 1H), 7.48-7.35 (m, 1H), 7.26-7.18 (m, 1H), 4.08-3.98 (q, J = 7.2 Hz, 2H), 3.26-3.10 (m, 2H), 3.08-2.85 (m, 2H), 2.80-2.64 (m, 2H), 2.48-2.36 (m, 1H), 2.28-2.15 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H). ESI-MS m/z = 563 (M+1).

El compuesto 215Cera una mezcla racémica con una relación enantiomérica 1:1, y se separó en una columna quiral para obtener los enantiómeros individuales 215C1 (t_R 9.394 min) y 215C2 (t_R 12.342 min) usando las siguientes condiciones de preparación:

Columna: CHIRAL PAK IA 4.6 X 250mm, 5 µ

Fase móvil: A= n-hexano, C=isopropanol; isocrática: 70:30; Velocidad de flujo: 1.0 mL/min

<u>Acido 2-(6-(5-(3-(3,4-difluorofenil)ureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético (215):</u>



215

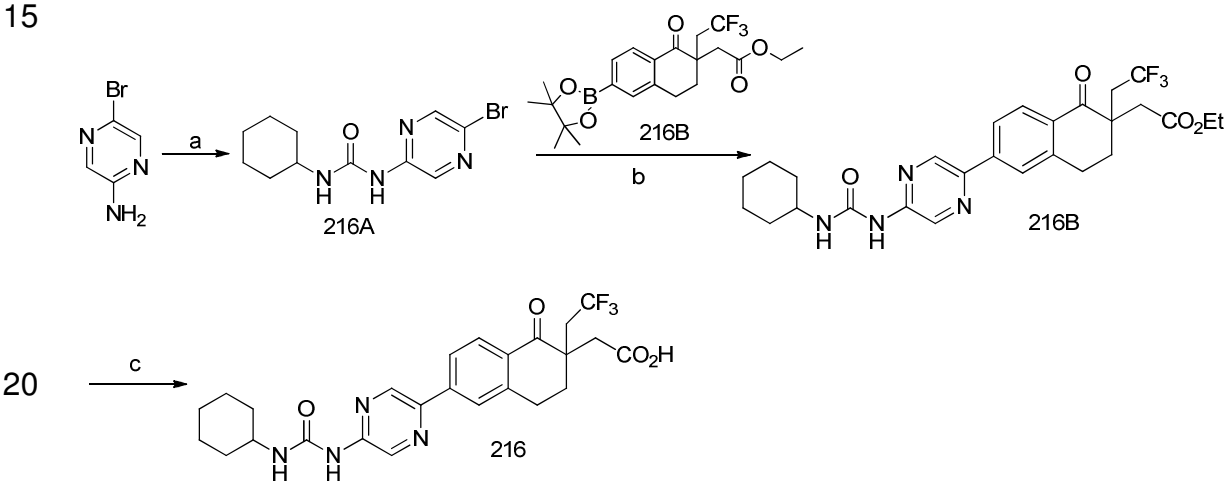
Quiral: enantiómero1

A una solución del producto del ejemplo 215C (0.35 g, 0.62 mmol) en 30 mL de una mezcla de etanol-agua (5:1)se le agregó hidróxido de

litio (0.075 g, 3.11 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución acuosa de HCl 2N hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido blanco (0.255 g, 76%).

^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.42 (bs, 1H), 9.83 (s, 1H), 9.77 (s, 1H), 9.16 (d, J = 1.2 Hz, 1H), 9.02 (d, J = 1.5 Hz, 1H), 8.1-7.94 (m, 3H), 7.78-7.68 (m, 1H), 7.46-7.35 (m, 1H), 7.24 (m, 1H), 3.41-3.35 (m, 1H), 3.20-2.95 (m, 2H), 2.88-2.80 (m, 2H), 2.65-2.55 (m, 1H), 2.50-2.42 (m, 1H), 2.24-2.14 (m, 1H). ESI-MS m/z = 535 {(M+H)$^+$}. pureza HPLC: 98.87%.

EJEMPLO 216



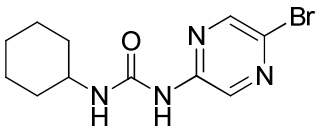
Reactivos y condiciones: a) isocianato de ciclohexilo, Et_3N,

tolueno, 120 °C, 12h ; b) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 5h; c) LiOH, dioxano-H_2O, t.a., 12h.

Procedimientos

Acido 2-(6-(5-(3-ciclohexilureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético

1-(5-Bromopirazin-2-il)-3-ciclohexilurea (216A):

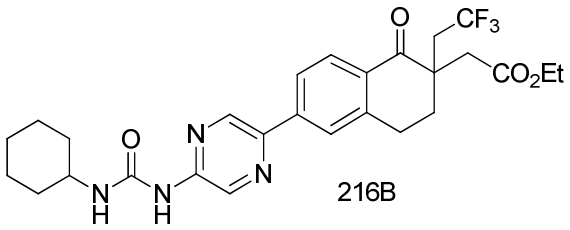


216A

A una solución de 2-amino-4-bromo-pirazina (3 g, 17.24 mmol) y trietilamina (1 mL, 7.17 mmol) en 20 mL de tolueno se le agregó isocianato ciclohexano (2.158 g, 17.24 mmol)y se agitó a 120 °C durante 5 h. El disolvente se evaporó bajo presión reducida y el residuo se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 15% en hexano, para producir el compuesto del título como un sólido (1.60 g, 31%).

^{1}H-RMN (300MHz, $CDCl_3$):δ 9.6 (bs, 1H), 8.38 (bs, 1H), 8.2 (m, 2H), 3.8 (m, 1H), 2.04-1.95 (m, 2H), 1.75-1.58 (m, 3H), 1.49-1.13 (m, 5H).

2-(6-(5-(3-Ciclohexilureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (216B):



216B

A una solución del ejemplo 216A (1.50 g, 5.01 mmol) en 15 mL de una mezcla de 1,4-dioxano-H_2O (3:1) bajo una atmósfera de argón se le agregó$Pd(Ph_3P)_4$ (0.07 g, 0.06 mmol), seguido por carbonato de cesio(4.90 g, 15.04 mmol) y el ejemplo216B(2.2 g, 5.01 mmol). La mezcla de reacción se desgasificó durante 5 min. La mezcla de reacción se puso a reflujo por 5 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua, la capa orgánica se separó, se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 30% en hexano, para producir el compuesto del título como un sólido (0.88 g, 33%).

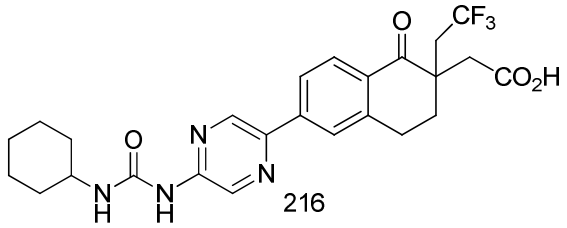
^{1}H-RMN (300MHz, $CDCl_3$):δ 8.8 (bs, 2H), 8.6 (s, 1H), 8.39 (bs, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 7.9-7.85 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.85 (m, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.9-2.85 (m, 2H), 2.67-2.60 (m, 2H), 2.4-2.3 (m, 2H), 2.0 (m, 2H), 1.7-1.6 (m, 3H), 1.4-1.2 (m, 8H).

El compuesto 216B (0.88g) era una mezcla racémica con una relación enantiomérica 1:1, y se separó en una columna quiral para obtener los enantiómeros individuales 216B1 (t_R 11.1 min) y 216B2 (t_R 15.1 min) usando las siguientes condiciones:

Columna: Chiralpak IA (4.6X250mm) 5µ

Fase móvil D= n-hexano (0.1%TFA) B= IPA; isocrática: D:B = 80:20; Velocidad de flujo: 1.0 mL/min.

Acido 2-(6-(5-(3-ciclohexilureido)pirazin-2-il)-1-oxo-2-(2,2,2-trifluoroetil)-1,2,3,4-tetrahidronaftalen-2-il)acético (216):



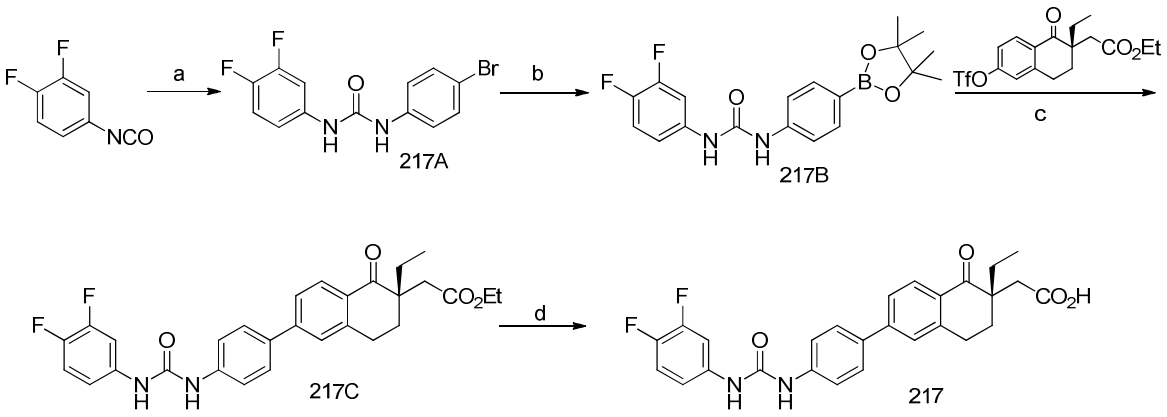
216

Quiral: enantiómero1

A una solución del ejemplo 216B1 (300 mg, 0.563 mmol) en 7 mL de una mezcla de 1,4-dioxano-H_2O (3:1)se le agregó LiOH (40.5 mg, 1.69 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución saturada de ácido cítrico hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C, el sólido se recogió por filtración y se secó al vacío para producir el compuesto del título como un sólido blanco (0.220 g, 77%).

^{1}H-RMN (400MHz, DMSO-d_6):δ 12.4 (bs, 1H), 9.56 (bs, 1H), 9.04 (s, 1H), 8.9 (s, 1H), 8.06-7.95 (m, 3H), 7.4 (d, J = 7.2 Hz, 1H), 3.56 (m, 1H), 3.16-2.69 (m, 5H), 2.5-2.37 (m, 2H), 2.13 (m, 1H), 1.8 (m, 2H), 1.65-1.5 (m, 3H), 1.39-1.2 (m, 5H); LCMS m/z =505$(M+H)^+$; pureza HPLC = 97.8%.

EJEMPLO 217

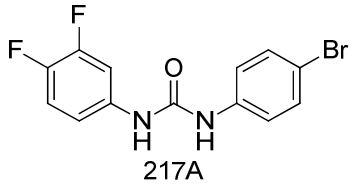


Reactivos y condiciones: a) 4-bromo anilina, THF, t.a., 12h; b) $PdCl_2(dppf)$, bis-pinacolatodiborano, KOAc, DMF, 85 °C, 6h; c) $Pd(PPh_3)_4$, Cs_2CO_3, dioxano-H_2O, 80 °C, 12h; d) LiOH, dioxano-H_2O, t.a., 12h.

Procedimientos

Acido (S)-2-(6-(4-(3-(3,4-difluorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético

1-(4-Bromofenil)-3-(3,4-difluorofenil)urea (217A):

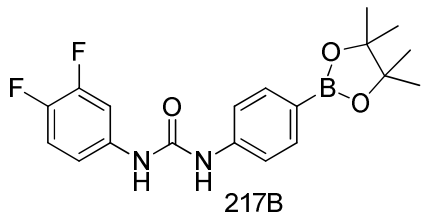


A una solución de 4-bromo-anilina (0.75 g, 4.36 mmol) en THF (20 mL) se le agregó isocianato de 3,4-difluorofenilo (0.74 g, 4.8 mmol) y se

agitó a temperatura ambiente durante 2 h. El disolvente se eliminó bajo presión reducida y el residuo se trituró con cloroformo (60 mL) para producir el compuesto del título como un sólido (0.6 g, 42%).

^{1}H-RMN (300 MHz, DMSO-d_6):δ 8.9 (s, 1H), 8.87 (s, 1H), 7.64 (m, 1H), 7.47-7.41 (m, 4H), 7.39 (m, 1H), 7.2 (m, 1H).

1-(3,4-Difluorofenil)-3-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)fenil)urea (217B):



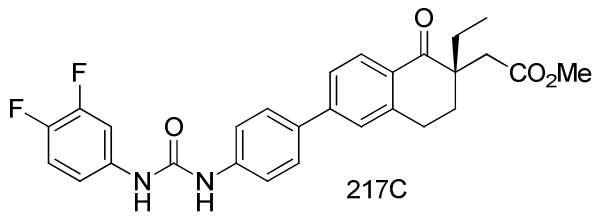
217B

A una solución del ejemplo 217A (1.0 g, 3.06 mmol) en 15 mL de DMF se le agregó $PdCl_2(dppf)CH_2Cl_2$ (0.125 g, 0.153 mmol), seguido por acetato de potasio (0.6 g, 6.11 mmol) y 4,4,4',4',5,5,5',5'-octametil-2,2'-bi(1,3,2-dioxaborolano) (0.932 g, 3.67 mmol), y la solución se desgasificó durante 30 min usando argón. La mezcla de reacción se agitó a 85 °C durante 6 h y luego se concentró bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se secó sobre Na_2SO_4 y se concentró bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 15% en DCM, para producir el compuesto del título como un sólido (0.6 g, 52%).

^{1}H-RMN (400 MHz, DMSO-d_6):δ 8.9 (m, 2H), 7.7 (m, 1H), 7.63-

7.59 (m, 2H), 7.5-7.42 (m, 2H), 7.4-7.3 (m, 1H), 7.1 (m, 1H), 1.3 (s, 12H). ESI-MS *m/z* = 375 $(M+H)^+$.

(S)-2-(6-(4-(3-(3,4-Difluorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acetato de metilo (217C):



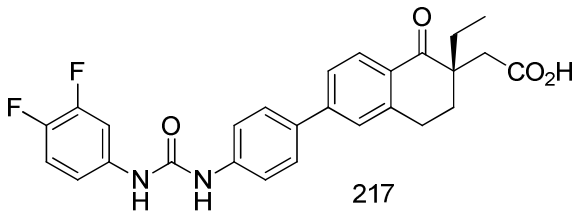
217C

A una solución de (*S*)-2-(2-etil-1-oxo-6-(trifluorometilsulfoniloxi)-1,2,3,4-tetrahidronaftalen-2-il)acetato de etilo (129C, 0.3 g, 0.761 mmol) en 10 mL de una mezcla de 1,4-dioxano-H_2O (4:1), bajo una atmósfera de argón, se le agregó$Pd(PPh_3)_4$ (0.018 g, 0.015 mmol), seguido por carbonato de cesio (0.74 g, 2.28 mmol) y el ejemplo 217B (0.313 g, 0.837 mmol). La mezcla de reacción se desgasificó durante 30 min. La mezcla de reacción se puso a reflujo por 12 h y el disolvente se eliminó bajo presión reducida. El residuo se dividió entre acetato de etilo y agua. La capa orgánica se separó, se secó sobre Na_2SO_4, se filtró y se concentró bajo presión reducida. El producto se purificó por cromatografía de vaporización instantánea, usando acetato de etilo al 20% en hexano, para producir el compuesto del título como un sólido (0.15 g, 40%).

^{1}H-RMN (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 8.03 (s, 1H), 7.44-7.37 (m, 3H), 7.35-7.31 (m, 4H), 7.18 (m, 1H), 7.08-6.97 (m, 2H), 3.67 (s, 3H),

3.14 (m, 1H), 3.04 (d, *J* = 16 Hz, 1H), 2.90 (m, 1H), 2.5 (d, *J* = 16 Hz, 1H), 2.45 (m, 1H), 2.05 (m, 1H), 1.79-1.6 (m, 2H), 0.94 (t, *J* = 7.6 Hz, 3H); ESI-MS *m/z* = 493 $(M+H)^+$.

Acido (S)-2-(6-(4-(3-(3,4-difluorofenil)ureido)fenil)-2-etil-1-oxo-1,2,3,4-tetrahidronaftalen-2-il)acético (217):



217

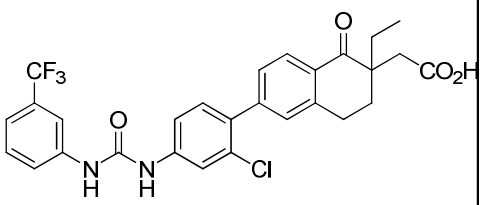
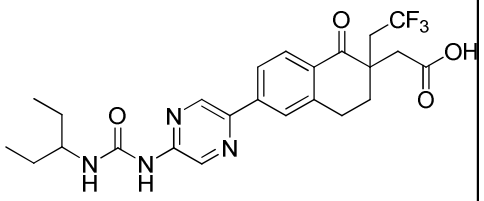
Quiral

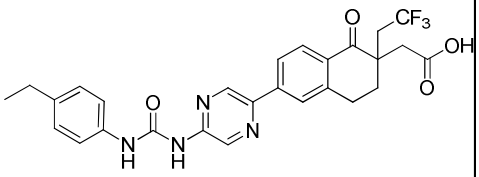
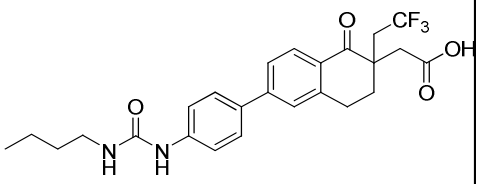
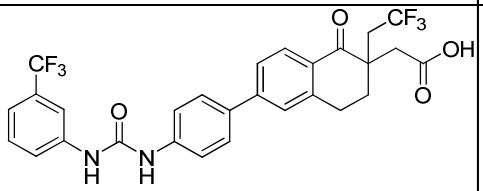
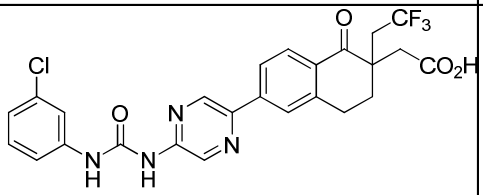
A una solución del ejemplo 217C (70 mg, 0.142 mmol) en 5 mL de una mezcla de 1,4-dioxano-H_2O (4:1) se le agregó LiOH (17.9 mg, 0.426 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 12 h. Después de que el disolvente se separó al vacío, el residuo se disolvió en agua y se lavó con acetato de etilo. La capa acuosa se acidificó agregando una solución saturada de ácido cítrico hasta obtener un pH de 2. La solución resultante se enfrió a 0 °C y el sólido se recogió por filtración y se secó al vacío, para producir el compuesto del título como un sólido amarillo pálido (0.035 g, 51%).

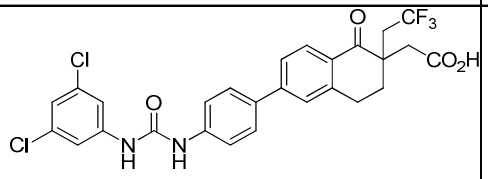
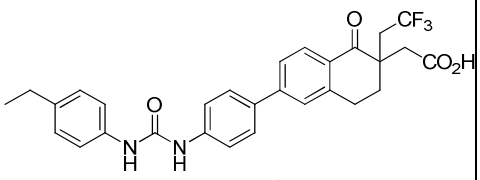
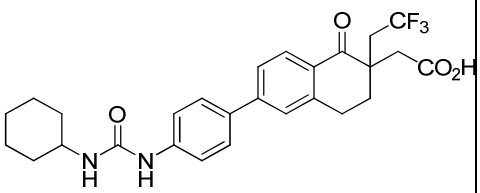
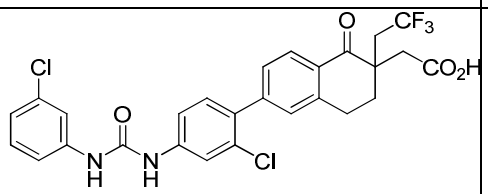
^{1}H-RMN (400MHz, DMSO-d_6):δ 12.05 (bs, 1H), 8.95 (s, 1H), 8.9 (s, 1H), 7.92 (d, *J* = 8 Hz, 1H), 7.7-7.65 (m, 3H), 7.63-7.56 (m, 4H), 7.35 (q, *J* = 8 Hz, 1H), 7.15 (m, 1H), 3.07 (m, 1H), 2.96 (m, 1H), 2.8 (d, *J* = 16.8 Hz, 1H),

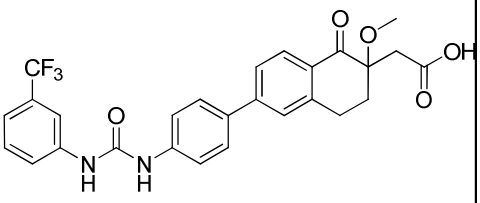
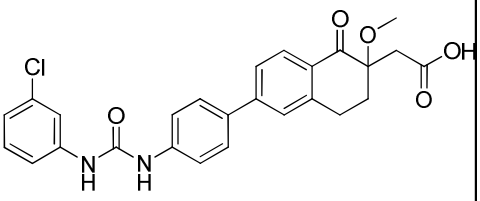
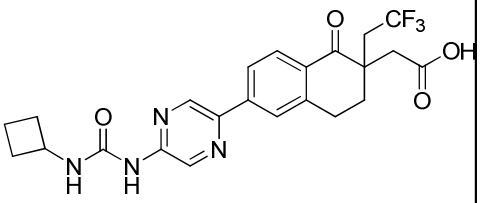
2.44 (m, 1H), 2.4 (d, *J* = 16 Hz, 1H), 1.9 (m, 1H), 1.68 (m, 1H), 1.54 (m, 1H), 0.84 (t, *J* = 7.2 Hz, 3H); LCMS *m/z* =479$(M+H)^+$; pureza = 95%.

Los ejemplos 218-230 se prepararon mediante procedimientos análogos a los que se describen en los ejemplos 190 y 212-217, usando los materiales iniciales apropiados. Los ácidos borónicos requeridos (y las versiones con grupos funcionales adecuadamente protegidos de los mismos) aquí utilizados se compraron en caso de estar disponibles comercialmente, o se sintetizaron como se describe en la literatura o por medio de modificaciones rutinarias conocidas para los expertos en la materia, o se sintetizaron mediante procedimientos alternos conocidos por los expertos en la materia.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
218	 Quiral: enantiómero 1	^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.1 (bs, 1H), 9.23 (s, 1H), 9.18 (s, 1H), 8.02 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H), 7.63-7.58 (m, 1H), 7.56-7.51 (m, 1H), 7.46-7.32 (m, 5H), 3.14-3.04 (m, 1H), 2.97-2.89 (m, 1H), 2.84-2.77 (m, 1H), 2.48-2.36 (m, 2H), 2.02-1.96 (m, 1H), 1.74-1.62 (m, 1H), 1.58-1.50 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H).	ESI-MS *m/z*: 545 $(M+H)^+$; pureza HPLC: 99%.
219	 Quiral: enantiómero 1	^{1}H-RMN (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.52 (bs, 1H), 9.04 (s, 1H), 8.92 (s, 1H), 8.04-7.95 (m, 3H), 7.23 (d, J = 8.4 Hz, 1H), 3.55 (m, 1H), 3.15-2.96 (m, 3H), 2.75 (m, 2H), 2.50-2.40 (m, 2H), 2.15 (m, 1H), 1.6-1.35 (m, 4H), 0.9 (t, J = 7.6 Hz, 6H).	ESI-MS *m/z*: 493 $(M+H)^+$; pureza HPLC: 99%.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
220	 Quiral: enantiómero 1	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.9 (bs , 1H), 9.7 (bs, 1H), 9.18 (d, J = 1.5 Hz, 1H), 8.99 (d, J = 1.2 Hz, 1H), 8.07-7.97 (m, 3H) 7.43 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 3.2-2.7 (m, 6H), 2.6-2.50 (m, 2H), 2.46 (m, 1H), 2.18 (m, 1H), 1.15 (t, J = 7.5 Hz, 3H).	ESI-MS m/z: 525 $(M-H)^-$; pureza HPLC: 98%.
221	 Quiral: enantiómero 1	^{1}H-RMN (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 8.85 (bs, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.66-7.58 (m, 4H), 7.5 (d, J = 8.8 Hz, 2H), 6.44 (bs, 1H), 3.12–2.9 (m, 5H), 2.85-2.65 (m, 2H), 2.5-2.4 (m, 2H), 2.12 (m, 1H), 1.45 -1.25 (m, 4H), 0.9 (t, J = 7.2 Hz, 3H).	ESI-MS m/z: 477 $(M+H)^+$; pureza HPLC: 95%.
222	 Quiral: enantiómero 1	^{1}HNMR (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.22 (bs, 1H), 9.1 (bs, 1H), 8.03 (s, 1H) ,7.93 (d, J = 7.6 Hz, 1H), 7.72-7.58 (m, 7H), 7.53 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.2 Hz, 1H), 3.2-2.65 (m, 5H), 2.6-2.44 (m, 2H), 2.18 (m, 1H).	ESI-MS m/z: 565 $(M+H)^+$; pureza HPLC: 98%.
223	 Quiral: enantiómero 1	^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.87 (s, 1H), 9.83 (s, 1H), 9.17 (s, 1H), 9.02 (s, 1H), 8.12-7.96 (m, 3H), 7.77 (s, 1H), 7.36 (d, J = 4.8 Hz, 2H), 7.1 (m, 1H), 3.24-2.92 (m, 3H), 2.83 (d, J = 16.4 Hz, 1H), 2.8-2.65 (m, 1H), 2.57 (d, J = 16.0 Hz, 1H), 2.50-2.42 (m,	ESI-MS m/z: 531 $(M-H)^-$; pureza HPLC: 99%

Ej.	Estructura	Datos analíticos	$(M+H)^+$
224	 Quiral: enantiómero 1	^{1}H-RMN (300 MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.32 (bs, 1H), 9.26 (bs, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.75-7.5 (m, 8H), 7.16 (s, 1H), 3.20-2.90 (m, 3H), 2.85-2.64 (m, 2H), 2.6-2.4 (m, 2H), 2.19-2.08 (m, 1H).	ESI-MS *m/z*: 565 $(M+H)^+$; pureza HPLC: 99%.
225	 Quiral: enantiómero 1	^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.3 (bs, 1H), 8.85 (s, 1H), 8.65 (s, 1H), 7.93 (d, J = 8 Hz, 1H), 7.71-7.57 (m, 6H), 7.37 (d, J = 8 Hz, 2H), 7.12 (d, J = 7.6 Hz, 2H), 3.2-2.92 (m, 3H), 2.84-2.65 (m, 2H), 2.60-2.40 (m, 4H), 2.21-2.10 (m, 1H), 1.16 (t, J = 7.2 Hz, 3H).	ESI-MS *m/z*: 525 $(M+H)^+$; pureza HPLC: 99%.
226	 Quiral: enantiómero 1	^{1}H-RMN (400 MHz, DMSO–d_6): δ 12.4 (bs, 1H), 8.5 (bs, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.63 (m, 4H), 7.49 (d, J = 8.4 Hz, 2H), 6.14 (d, J = 7.2 Hz, 1H), 3.46 (m, 1H), 3.15-2.9 (m, 3H), 2.85-2.6 (m, 2H), 2.55-2.40 (m, 2H), 2.17-2.10 (m, 1H), 1.88-1.60 (m, 4H), 1.53 (m, 1H), 1.40-1.12 (m, 5H).	ESI-MS *m/z*: 503 $(M+H)^+$; pureza HPLC: 99%.
227	 Quiral: enantiómero 1	^{1}H-RMN (400 MHz, DMSO-d_6): δ 12.4 (bs , 1H), 9.12 (bs, 1H), 9.05 (bs, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.46-7.37 (m, 4H), 7.34-7.30 (m, 2H), 7.05 (m, 1H), 3.2-2.9 (m,	ESI-MS *m/z*: 565 $(M+H)^+$; pureza HPLC: 99%.

Ej.	Estructura	Datos analíticos	$(M+H)^+$
228	 Quiral: enantiómero 1	1H-RMN (300MHz, DMSO-d_6): δ 12.2 (bs, 1H), 9.13 (s, 1H), 9.01 (s, 1H), 8.03 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.75-7.48 (m, 8H), 7.32 (d, J = 7.8 Hz, 1H), 3.28-3.15 (m, 1H), 3.13 (s, 3H), 2.90 (d, J = 15.6 Hz, 2H), 2.72 (d, J = 15.3 Hz, 1H), 2.42-2.38 (m, 2H).	ESI-MS *m/z*: 512 $(M+H)^+$; pureza HPLC: 98%.
229	 Quiral: enantiómero 1	1H-RMN (400MHz, DMSO-d_6): δ 12.2 (bs, 1H), 8.95 (s, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.73-7.56 (m, 7H), 7.32-7.28 (m, 2H), 7.05-7.01 (m , 1H), 3.28-3.15 (m, 1H), 3.13 (s, 3H), 2.94-2.86 (m, 2H), 2.71 (d, J = 16 Hz, 1H), 2.48-2.38 (m, 2H).	ESI-MS *m/z*: 479 $(M+H)^+$; pureza HPLC: 99%.
230	 Quiral: enantiómero 1	^{1}H-RMN (400MHz, DMSO-d_6): δ 12.4 (bs, 1H), 9.51 (bs, 1H), 9.04 (d, J = 1.6 Hz, 1H), 8.92 (d, J = 1.2 Hz, 1H), 8.05-7.95 (m, 3H), 7.23 (d, J = 7.6 Hz, 1H), 4.19 (m, 1H), 3.18-2.90 (m, 3H), 2.85-2.6 (m, 2H), 2.50-2.40 (m, 2H), 2.3-2.1 (m, 3H), 1.9 (m, 2H), 1.65 (m, 2H).	ESI-MS *m/z*: 477 $(M+H)^+$; LCMS pureza: 98%.

Ensayo biológico

Inhibición de la actividad de DGAT1 humana *in vitro*

La DGAT1 humana se expresó en células de insecto Sf9 usando un sistema de expresión de baculovirus. Se prepararon microsomas y se usaron como enzima para el análisis de inhibición *in vitro* en cualquiera de dos formatos que miden la producción de producto de coenzima A o tridecanoil glicerol, respectivamente. Todos los pasos se hicieron a 21-23 °C. Todos los datos de la inhibición de DGAT1 con los compuestos de prueba se recopilaron bajo condiciones en donde la formación de producto fue lineal con el tiempo de reacción.

Para la inhibición de la formación del producto CoA, los compuestos de prueba se prepararon en 100% DMSO, se diluyeron 100 veces en amortiguador de ensayo, y se agregaron 10 uL a placas de media área de 96 pocillos (Greiner 675076). Se agregó un volumen igual (10 uL) de enzima 3X en amortiguador y los componentes se incubaron 30 minutos de incubación previa a la reacción, para dejar que la enzima y el compuesto de prueba lleguen al equilibrio de unión. La mezcla de enzima 3X contenía ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}-acético 30 uM para los pocillos de control totalmente inhibidos. Algunos ensayos se hicieron con la inclusión de didecanoil glicerol en la incubación previa a la reacción de compuesto de prueba y enzima. Las reacciones de DGAT (30 uL) se iniciaron después de la adición de 10 uL de solución de substrato 3X. Las condiciones de reacción finales consistieron en HEPES 20

mM, pH 7.5, $MgCl_2$ 2mM, CHAPS 1 mM, didecanoil glicerol 50 uM, decanoil-CoA 3 uM, proteína microsomal 1 ug/mL, y 1% de DMSO. Después de una incubación de reacción de 60 minutos, las reacciones se detuvieron y el producto CoA se derivatizó con 30 µL de amortiguador que contenía ácido{4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético 10 uM y 7-dietilamino-3-(4'-maleimidilfenil)-4-metilcumarina50 uM (CPM). La fluorescencia se leyó usando una lectora Envision a exc 405 nm / em 480 nm, aproximadamente 30 minutos después de la adición de la solución final. La inhibición se normalizó a los controles que contenían DMSO o ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético 10 uM. Las CI_{50}se ajustaron usando GraphPad Prism para una dosis-respuesta sigmoidal.

Para la inhibición de la formación del producto triacil glicerol, se corrieron reacciones de 11 uL en placas Polyplate-384 (PerkinElmer6007300), empezando con una incubación previa a la reacción de 30 minutos de 5 uL de enzima 2.2X y 1 uL de DMSO 100%, que contenía compuesto de prueba o compuesto de control, ácido {4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético. Algunos ensayos se hicieron con la inclusión de didecanoil glicerol en la incubación previa a la reacción de compuestos de prueba y enzima. Las reacciones se iniciaron después de 30 minutos de incubación previa a la reacción mediante la adición de 5 uL de substrato 2.2X. Las condiciones de reacción finales consistieron en HEPES 50 mM, pH 7.5, $MgCl_2$ 2mM, CHAPS 1mM, didecanoil glicerol 25 uM,

decanoil-CoA0.5 uM, [^{14}C]-decanoil-CoA 0.3 nCi/uL o [^{3}H]-decanoil-CoA 0.5 nCi/uL, proteína microsomal 0.05-4 ug/mL, y 1% DMSO. Después de 60 minutos de incubación de reacción, las reacciones se detuvieron con 40 uL de isopropanol al 45% y carbonato de sodio 50 mM en agua, y se mezclaron. El producto tridecanoil glicerol se extrajo agregando 30 uL de Microscint-E (Perkin Elmer) y 2 horas de incubación (sellado). Las placas se leyeron en una lectora Microbeta Microplate. La inhibición se normalizó a los controles que contenían DMSO o ácido{4-[4-(4-amino-7,7-dimetil-7*H*-pirimido[4,5-*b*][1,4]oxazin-6-il)fenil]ciclohexil}acético 10 uM. Las CI_{50} se ajustaron usando GraphPad Prism a una dosis-respuesta sigmoidal.

Datos biológicos

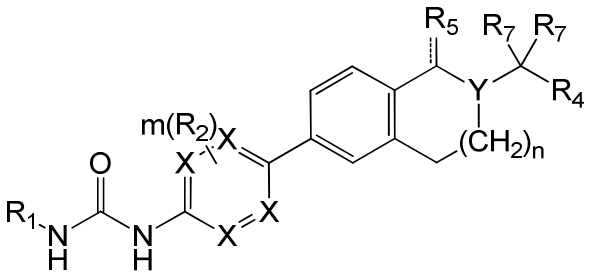
Los compuestos ejemplificados de la presente invención se probaron en uno o más de los ensayos de DGAT anteriormente descritos y se encontró que eran inhibidores de DGAT1, con una CI_{50}< 10 uM o % inhibición >50 a 10 uM. A continuación se indican los datos de algunos compuestos específicos probados en el ensayo de fluorescencia (CPM) de DGAT1 humana.

Ejemplo #	CI_{50} hDGAT (nM)	Ejemplo #	CI_{50} hDGAT (nM)	Ejemplo #	CI_{50} hDGAT (nM)
1	1880.0	143	11.2	219	5955.0
20	586.0	144	5.8	220	0.3
40	357.0	154	47.8	223	0.7
42	60.0	164	4.5	224	2.8
47	180.5	173	10.8	225	1.2
68	503.0	182	48.0	226	6.1
69	113.6	185	32.0	228	6.9
76	112.0	190	67.6	229	5.2
79	35.4	192	10.6	230	27.5
81	18.8	197	2.3		
90	12.0	198	55.0		
109	14.2	201	2.6		
115	2.9	202	6.5		
116	18	205	3.5		
129	3.1	212	32.8		
130	138.3	213	5.9		
131	2.5	214	0.6		
139	10.8	215	1.8		
140	31.8	216	2.7		
141	9.4	218	7.4		

NOVEDAD DE LA INVENCIÓN

REIVINDICACIONES

1.- Un compuesto de fórmula (I):

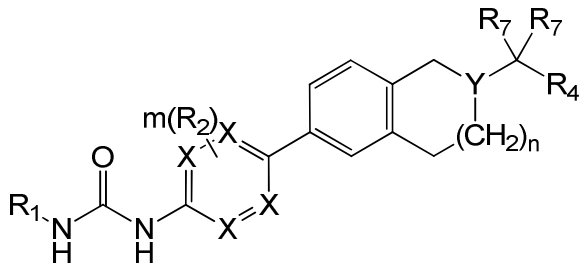


(I)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo y heteroarilo pueden estar sustituidos con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno urea, amida, hidroxilo, SF_5, oxo y nitro; R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno urea, amida, hidroxilo, oxo y nitro; R_4 es CH_2COOH, COOH, éster, o amida; R_5 es hidrógeno, hidroxilo, u oxo; cada R_7 es independientemente H o alquilo de C_1-C_3; cada X es independientemente C o N, siempre que por lo menos dos X sean C; Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno,

hidroxilo, alcoxi, COOH y éster; m es 0-3;n es 0-1, con la condición de que cuando n es 0, Y es CR_3; o una sal farmacéuticamente aceptable del mismo.

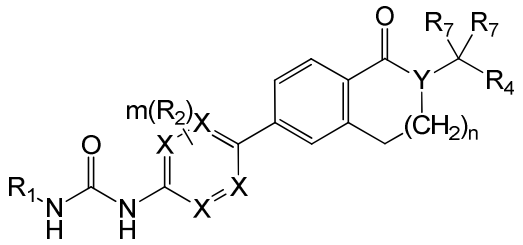
2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula (I)(A):



(I)(A)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro; R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro; R_4 es CH_2COOH, COOH, éster, o amida; cada R_7 es independientemente H o alquilo de C_1-C_3; cada X es independientemente C o N, siempre que por lo menos dos X sean C; Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster; m es 0-3; n es 0-1, con la condición de que cuando n es 0, Y es CR_3; o una sal farmacéuticamente aceptable del mismo.

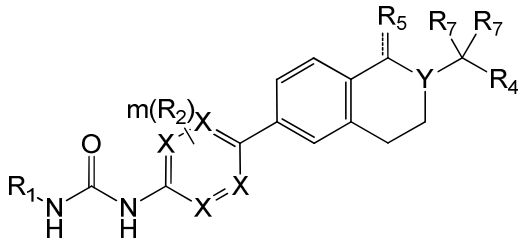
3.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula (I)(B):



(I)(B)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro; R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro; R_4 es CH_2COOH, COOH, éster, o amida; cada R_7 es independientemente H o alquilo de C_1-C_3;cada X es independientemente C o N, siempre que por lo menos dos X sean C; Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster; m es 0-3; n es 0-1, con la condición de que cuando n es 0, Y es CR_3;o una sal farmacéuticamente aceptable del mismo.

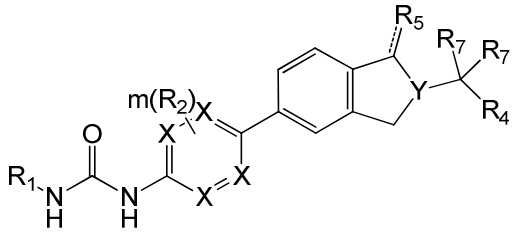
4.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula (I)(C):



(I)(C)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro; R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro; R_4 es CH_2COOH, COOH, éster, o amida; R_5 es hidrógeno, hidroxilo, u oxo; cada R_7 es independientemente H o alquilo de C_1-C_3;cada X es independientemente C o N, siempre que por lo menos dos X sean C; Y es N o CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster; m es 0-3;o una sal farmacéuticamente aceptable del mismo.

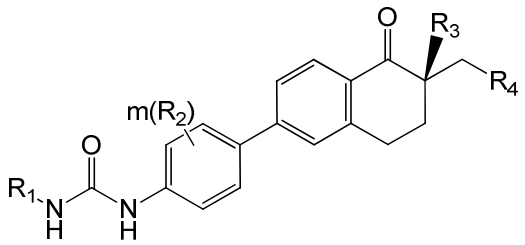
5.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula (I)(D):



(I)(D)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro; R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro; R_4 es CH_2COOH, COOH, éster, o amida; R_5 es hidrógeno, hidroxilo, u oxo; cada R_7 es independientemente H o alquilo de C_1-C_3;cada X es independientemente C o N, siempre que por lo menos dos X sean C; Y es CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster; m es 0-3;o una sal farmacéuticamente aceptable del mismo.

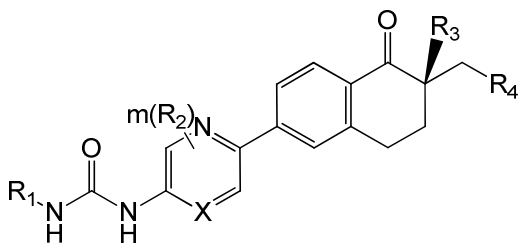
6.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula (I)(F):



(I)(F)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro; R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro; R_4 es CH_2COOH, COOH, éster, o amida; R_3 es alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster; m es 0-3;o una sal farmacéuticamente aceptable del mismo.

7.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque está representado por la fórmula (I)(H):



(I)(H)

en donde R_1 es alquilo de C_1-C_6, cicloalquilo de C_3-C_7, arilo o heteroarilo, en donde dicho arilo o heteroarilo puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en acilo, alquilo de C_1-C_6, alquilsulfonilo, alcoxi, alcoxicarbonilo, ciano, halógeno, urea, amida, hidroxilo, SF_5, oxo y nitro; R_2 se selecciona del grupo que consiste en H, alquilo de C_1-C_6, alcoxi, ciano, halógeno, urea, amida, hidroxilo, oxo y nitro; R_4 es CH_2COOH, COOH, éster, o amida; X es independientemente C o N; R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, en donde dicho alquilo de C_1-C_6 puede estar sustituido adicionalmente con uno a tres grupos seleccionados de halógeno, hidroxilo, alcoxi, COOH y éster; m es 0-2;o una sal farmacéuticamente aceptable del mismo.

8.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque R_5 es hidroxilo, o una sal farmacéuticamente aceptable del mismo.

9.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5 y 7, caracterizado además porque las X son C, o una sal farmacéuticamente aceptable del mismo.

10.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizado además porque R_1 es fenilo que puede estar sustituido con uno a tres grupos seleccionados del grupo que consiste en metilo, etilo, OCF_3, $-OCF_2H$, trifluorometilo, metoxi, etoxi, ciano, Cl, o F, o una sal farmacéuticamente aceptable del mismo.

11.- El compuesto de conformidad con cualquiera de las

reivindicaciones 1 a 7, caracterizado además porque R_1 es alquilo de C_1-C_6, o una sal farmacéuticamente aceptable del mismo.

12.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizado además porque R_2 es alquilo de C_1-C_3, F, Cl, o CN, o una sal farmacéuticamente aceptable del mismo.

13.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque Y es CR_3, en donde R_3 es H, alquilo de C_1-C_6, hidroxilo, halógeno, o alcoxi, o una sal farmacéuticamente aceptable del mismo.

14.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque Y es CR_3, en donde R_3 es metilo, CH_2CF_3, CH_2OCH_3 o etilo; o una sal farmacéuticamente aceptable del mismo.

15.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque Y es N, o una sal farmacéuticamente aceptable del mismo.

16.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizado además porque m es 0.

17.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizado además porque R_4 es $–CH_2COOH$ o COOH, o una sal farmacéuticamente aceptable del mismo.

18.- Un método de tratamiento de la obesidad, que comprende administrar a un humano en necesidad del mismo una cantidad eficaz de un

compuesto como el que se reclama en cualquiera de las reivindicaciones anteriores.

19.- Una composición farmacéutica que comprende un compuesto como el que se reclama en cualquiera de las reivindicaciones 1 a 17, y un vehículo farmacéuticamente aceptable.

20.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 17.

RESUMEN DE LA INVENCIÓN

Esta invención se refiere a compuestos novedosos que son inhibidores de acil coenzima A: diacilglicerol aciltransferasa 1 (DGAT-1), a composiciones farmacéuticas que los contienen, a procedimientos para su preparación, y a su uso en terapia para la prevención o tratamiento de enfermedades relacionadas con disfunción de DGAT-1, o en donde la modulación de la actividad de DGAT-1 puede tener un beneficio terapéutico, que incluyen, sin limitación, obesidad, trastornos relacionados con la obesidad, hipertrigliceridemia, hiperlipoproteinemia, quilomicronemia, dislipidemia, esteatohepatitis no alcohólica, diabetes, resistencia a la insulina, síndrome metabólico, infección por virus de hepatitis C y acné u otros trastornos de la piel.

EA

P13/1502F

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

FITCH, Duke M.
GlaxoSmithKline
709 Swedeland Road, P.O. Box 1539
King of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
02 July 2013 (02.07.2013)

Applicant's or agent's file reference
PU64641

IMPORTANT NOTIFICATION

International application No.
PCT/US2012/038520

International filing date *(day/month/year)*
18 May 2012 (18.05.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.: 610-270-5030
Facsimile No.: 610-270-5090
E-mail address: us_cipkop@gsk.com

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
GLAXOSMITHKLINE INTELLECTUAL PROPERTY (No.2) LIMITED
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.: 610-270-5030
Facsimile No.: 610-270-5090
E-mail address: us_cipkop@gsk.com
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Safi Horiya
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

PENG, Tony, W.
GlaxoSmithKline
Corporate Intellectual Property, UW2220
709 Swedeland Road, P.O. Box 1539
King of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
06 March 2013 (06.03.2013)

Applicant's or agent's file reference
PU64641

IMPORTANT NOTIFICATION

International application No.
PCT/US2012/038520

International filing date *(day/month/year)*
18 May 2012 (18.05.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
GLAXOSMITHKLINE LLC
One Franklin Plaza
200 North 16th Street
Philadelphia, PA 19102
United States of America

State of Nationality: US
State of Residence: US
Telephone No.: 610-270-4918
Facsimile No.: 610-270-5090
E-mail address: us_cipkop@gsk.com

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

State of Nationality: GB
State of Residence: GB
Telephone No.:
Facsimile No.:
E-mail address:
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Campin Helene
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

PENG, Tony, W.
GlaxoSmithKline
Corporate Intellectual Property, UW2220
709 Swedeland Road, P.O. Box 1539
King of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
30 November 2012 (30.11.2012)

Applicant's or agent's file reference
PU64641

IMPORTANT NOTIFICATION

International application No.
PCT/US2012/038520

International filing date *(day/month/year)*
18 May 2012 (18.05.2012)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
TANGIRALA, Reghuram
Navi-Mumbai
India

State of Nationality: IN
State of Residence: IN
Telephone No.
Facsimile No.
E-mail address

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
TANGIRALA, Raghuram
Navi-Mumbai
India

State of Nationality: IN
State of Residence: IN
Telephone No.
Facsimile No.
E-mail address
☐ Notifications by e-mail authorized

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Martin Jean-Luc
e-mail pt03.pct@wipo.int
Telephone No. +41 22 338 74 03

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PU64641	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2012/038520	International filing date *(day/month/year)* 18 May 2012	(Earliest) Priority Date *(day/month/year)* 20 May 2011
Applicant GLAXOSMITHKLINE LLC		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038520

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.: 18-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

2. ☐ As all searchable claims could be searched without effort justifying 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.:

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/038520

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/17 (2012.01)
USPC - 514/598
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)
IPC(8) - A61K 31/17, 4418, 444, 472, 4725, 4965, 497 (2012.01)
USPC - 514/255.05, 255.06, 307, 309, 352, 353, 596, 598

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 practicable, search terms used)
PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CURTIN et al. Isoindolinone ureas: a novel class of KDR kinase inhibitors. Bioorganic & Medicinal Chemistry Letters 14 (2004). Pgs. 4505–4509. entire document	1-17
A	US 2007/0249620 A1 (KURATA et al) 25 October 2007 (25.10.2007) entire document	1-17
A	US 2010/0041590 A1 (BOUILLOT) 18 February 2010 (18.02.2010) entire document	1-17
A, P	US 2011/0245247 A1 (BRAJE et al) 06 October 2011 (06.10.2011) entire document	1-17
A, P	WO 2011/080718 A1 (JADHAV et al) 07 July 2011 (07.07.2011) entire document This document can be viewed by entering the doc number at the following url: http://worldwide.espacenet.com/numberSearch?locale=en_EP	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* 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 application or patent 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
27 July 2012	26 SEP 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774