03-39013

Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 03/39013

54. **TÍTULO** AGONISTAS DEL RECEPTOR ALFA ACTIVADO DEL PROLIFERADOR DE PEROXISOMAS.

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** ELI LILLY AND COMPANY.

DOMICILIO

74. **APODERADO** CARLOS R. OLARTE.

22. **BOGOTÁ, D. C.,** MAYO 9, 2003.

(FORMA P-10)

PETITORIO

1

03 039013 0

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03039013 00000000 Folios: 908
Fecha (AMD): 2003-05-09 17:09:25
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC adicación
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

[X] Patente de Invención [ ] Patente de Modelo de Utilidad
[ ] Capítulo I. [X] Capítulo II.

(2) SOLICITANTE (71)

Nombre: ELI LILLY AND COMPANY.
Dirección: Indianapolis, IN 46285 Estados Unidos de América.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Indianapolis, Estados Unidos de América.
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
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Teléfono: 634-1500 Fax: 376-2211
E-Mail: patents.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.782.747 Btá TP 74.295

(4) INVENTOR (ES) (72)

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

(5) PCT (85)

Solicitud Internacional No. PCT/US01/42928 Fecha Noviembre 9, 2001
Publicación Internacional No. WO 02/38553 Fecha Mayo 16, 2002

(6) Título (54) AGONISTAS DEL RECEPTOR ALFA ACTIVADO DEL PROLIFERADOR DE PEROXISOMAS.

(7) Clasificación Internacional (51) A 61 K 31/4196; C07D 249/12

(8) Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI [X] NO [ ]	US	Noviembre 10, 2000	60/247.317

(9) Comprobante de pago No. 16,817 **Fecha** 030703

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

(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
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [X] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Búsqueda Internacional

(11) FIGURA CARATERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 de Btá T.P. 74295

Instrucciones para la presentación de los anéxos, ver reverso de esta página

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Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03039013 00000000 Folios: 900
Fecha (AMD): 2003-05-09 17:09:35
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 16,817
FECHA : MARZO 7 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	8569193	07/03/2003	30,000,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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PODER Y CERTIFICACIÓN NOTARIAL

(nota traductor: Han sido diligenciados y suscritos en la columna izquierda (inglés) que corresponde a la columna derecha en español)

(nota traductor: punto 6- Acta del Directorio con fecha 29 de agosto de 1986 y Certificado de Constitución con fecha 17 de enero de 1901.)

EN TESTIMONIO DE LO CUAL, este Poder ha sido suscrito por Robert A. Armitage, Vicepresidente Ejecutivo y Asesor Jurídico, el 7 de enero de 2003 en Indianápolis, Indiana, Estados Unidos de América.

SUSCRITO Y JURAMENTADO ante mí el 7 de enero de 2003.

(firmado: Julie Ann Worland)
NOTARIO PUBLICO

JULIE ANN WORLAND
CONDADO MORGAN
MI COMISION VENCE:
20 DE JULIO DE 2008

ROBERTO M. OLARTE GARCIA
Traductor e Intérprete Oficial
Resolución No. 0041
Minljusticia 1996

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
11 FEB 2003
BOGOTA D.C. - COLOMBIA
NOTARIA ONCE (11)

8

SECRETARÍA DE ESTADO
ESTADO DE INDIANA

APOSTILLA
(Convención de la Haya del 5 de octubre de 1961)

1. País: ESTADOS UNIDOS DE AMERICA

2. Este documento público ha sido suscrito por: Julie A. Worland

3. en calidad de Notario Público para el Condado de Morgan

4. y lleva el sello de Notario Público del Estado de Indiana

Certificó

5. en la ciudad de Indianápolis, Indiana

6. el ocho de enero de 2003,

7. por el Secretario del Estado de Indiana

8. No. A2002-31613

9. Sello: Sello del Estado de Indiana - 1816

10. Firma: (Todd Rokita)
Todd Rokita
Secretario del Estado de Indiana

ROBERTO M. OLARTE GARCIA
Traductor e Intérprete Oficial
Resolución No. 0041
Minijusticia 1996

DOMO NOTARIO ONCE DE ESTE CIRCULO HACE CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
10 FEB 2003
COLOMBIA
NOTARIA ONCE (11)

POD-02236

SECRETARY OF STATE
STATE OF INDIANA

Todd Rokita
Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. **Country: United States of America**
2. **This public document has been signed by** *Julie A. Worland*
3. **acting in the capacity of Notary Public in & for** *Morgan* **County**
4. **and bears the seal/stamp of notary public in & for the State of Indiana**

Certified

5. **at Indianapolis, Indiana**
6. **this** *Eighth* **day of** *January, 2003*
7. **by Secretary of State of Indiana**
8. **No. A2002-** *31613*

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
19 FEB 2003
BOGOTA, D.C. - COLOMBIA
NOTARIA ONCE (11)

9. **Seal/Stamp:**

10. **Signature**

Todd Rokita
Indiana Secretary of State

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IN WITNESS WHEREOF, this Power of Attorney has been signed by Robert A. Armitage, Senior Vice President and General Counsel this 7th day of January, 2003 at Indianapolis, Indiana USA.

SUBSCRIBED AND SWORN to be before me this 7th day of January, 2003.

Julie Ann Worland
NOTARY PUBLIC

JULIE ANN WORLAND
MORGAN COUNTY
MY COMMISSION EXPIRES:
JULY 20, 2009

DOMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
19 FEB 2003
BOGOTA D.C. - COLOMBIA
TRUJILLO MANCERO DE BAUTISTA
NOTARIA ONCE (11)

RAISBECK, LARA, RODRIGUEZ & RUEDA
MEMBERS OF THE FIRM
BAKER & McKENZIE
ATTORNEYS AT LAW

AV 82 No. 10-62, 6TH FLOOR
BOGOTA, D.C. COLOMBIA
TELEPHONE (57-1) 634-1500
FACSIMILE (57-1) 376-2211
NIT 860.068.840-3
OFFICE.BOGOTA@BAKERNET.COM
WWW.BAKERNET.COM

11

POWER OF ATTORNEY

The undersigned.

(name of the company) Eli Lilly and Company

located in *(full street address)* Lilly Corporate Center

(city, state) Indianapolis, Indiana U.S.A.

declares that it hereby grants to

CARLOS REINALDO OLARTE AND/OR

ALVARO CORREA ORDOÑEZ

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of:

Patents of Invention, Patents for Utility Models, Industrial Design Registrations, mergers, changes of name, assignments, filing and prosecution of oppositions, changes of address.

to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds. To the said mandatories sufficient power is granted hereby to receive notifications for and on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the patents, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary.

Done and subscribed in

Indianapolis, Indiana U.S.A.

On the *(day)* 7th day of *(month)* January

2003

(signature) _____

Robert A. Armitage
Senior Vice President
and General Counsel

RAS

PODER

La abajo firmada.

domiciliada en _____

_____

declara por el presente otorgar a

CARLOS REINALDO OLARTE Y/O

ALVARO CORREA ORDOÑEZ

poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de :
Patentes de invención, Patentes de Modelo de Utilidad, Registro de Diseños Industriales, fusiones, cambios de nombre, cesiones, presentación y trámite de oposiciones, cambios de dirección.

a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones , protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de las patentes se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

Dado y firmado en

_____

A los ____ días del mes de _____

2002

DOMO NOTARIO ONCE DE ESTE CIRCUITO QUE ESTA COPIA COINCIDE CON EL ORIGINAL QUE TENGO A LA VISTA.
13 FEB 2003
BOGOTA D.C. - COLOMBIA
TYLMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

RAISBECK, LARA, RODRIGUEZ & RUEDA
MEMBERS OF THE FIRM
BAKER & McKENZIE
ATTORNEYS AT LAW

AV 82 No. 10-62, 6TH FLOOR
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OFFICE.BOGOTA@BAKERNET.COM
WWW.BAKERNET.COM

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NOTARIAL CERTIFICATION

On this *(day)* 7th day of *(month)* January 2003 the undersigned Notary Julie Ann Worland *(name of the notary)*

CERTIFIES

1. That *(name of the officer)* Robert A. Armitage of legal age and domiciled in *(city, state)* Indianapolis, Indiana set his hand on the foregoing document.

2. That the grantor is to me personally know and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as *(officer's title/position)* Senior Vice President and General Counsel of the judicial person Eli Lilly and Company *(name of the company)*

4. That the judicial person Eli Lilly and Company *(name of the company)* having its home office in *(full street address)* Lilly Corporate Center, Indianapolis, Indiana 46285 U.S.A. is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:

(provide name of documents and their dates) Board Meeting Minutes dated August 29, 1986 and Certificate of Incorporation dated January 17, 1901.

Notary Public

CERTIFICACION NOTARIAL

A los _____ dias del mes de _____ de 2002, el suscrito Notario

DA FE

1. Que _____ mayor y domiciliado en _____ suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3. Que el otorgante ha suscrito el referido documento en su carácter de _____ de la persona jurídica _____

4. Que la persona jurídica _____ con sede en _____ está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se ha otorgado el poder está comprendido entre los que constituyen su objeto social.

5. Que el otorgante tiene efectivamente la representación que ostenta, y que esta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:

_____

El Notario Público

COMO NOTARIO ONCE DE ESTE CIRCULO HE PODIDO CONSTATAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
9 FEB 2003
BOGOTA, D.C. - COLOMBIA
NOTARIA ONCE (11)

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

(19) World Intellectual Property Organization
International Bureau

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16 May 2002 (16.05.2002)

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(51) International Patent Classification[7]: C07D 249/12, A61K 31/4196, C07D 401/06, 413/06, 409/06, 409/12, 417/12, 405/06, A61K 31/4439, 31/427, C07C 257/22, 281/04, 281/06

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9 November 2001 (09.11.2001)

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(26) Publication Language: English

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60/247,317 10 November 2000 (10.11.2000) US

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, DC 1104, Indianapolis, IN 46285 (US).

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(74) Agents: VORNDRAN-JONES, MaCharri et al.; Eli Lilly and Company, Lilly Corporate Center, DC 1104, Indianapolis, IN 46285 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE,*

[Continued on next page]

(54) Title: PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR ALPHA AGONISTS

(57) Abstract: The present invention is directed to compounds represented by the following structural formula, and pharmaceutically acceptable salts, solvates and hydrates thereof, R1 is a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-2}-alkyl, heteroaryl-C_{0-2}-alkyl, C_3-C_8 cycloalkylaryl-C_{0-2}-alkyl or phenyl. W is O or S. R2 is H or a substituted or unsubstituted group selected from C_1-C_8 alkyl, C_3-C_6 cycloalkyl and heteroaryl. X is a C_2-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S. Y is C, , S, NH or a single bond. Furthermore, E is $(CH_2)_nCOOH$, wherein n is 0, 1, 2 or 3, or C(R3)(R4)A, wherein A is an acidic functional group such as carboxyl, carboxamide substituted or unsubstituted sulfonamide, or substituted or unsubstituted tetrazole. R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy. Additionally, R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, arylC_0-C_6alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_6 cycloalkyl.

WO 02/38553 A2

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR ALPHA AGONISTS

BACKGROUND OF THE INVENTION

Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Various subtypes of PPARs have been discovered. These include PPARα, NUC1, PPARγ and PPARδ.

The PPARα receptor subtypes are reported to be activated by medium and long-chain fatty acids. They are involved in stimulating beta-oxidation of fatty acids and with the activity of fibrates which reportedly produce a substantial reduction in plasma triglycerides and moderate reduction in low density lipoprotein (LDL) cholesterol.

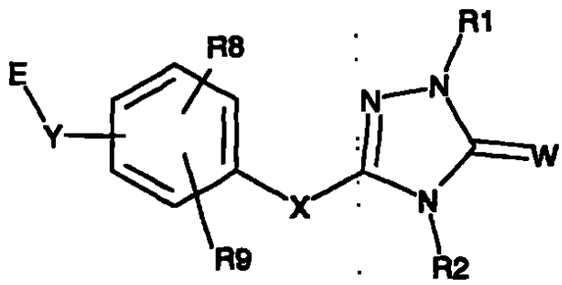
PPARα, PPARγ and PPARδ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, Syndrome X and gastrointestinal disease, such as, inflammatory bowel disease. Syndrome X is the combination of symptoms which include hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL.

Current PPAR agonist treatment for Syndrome X relates to the use of thiazolidinediones (TZDs) or other insulin sensitivity enhancers (ISEs). TZDs are a class of PPAR gamma agonists which have been shown to increase the sensitivity of insulin sensitive cells. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. However, TZDs and ISEs typically have little effect in preventing the cardiovascular part of Syndrome X in that their administration usually dose not result in the lowering of

triglycerides and LDL-cholesterol while raising HDL-cholesterol. Furthermore, side effects commonly associated with treatment with TZDs include significant weight gain, and, for troglitazone, liver toxicity. Therefore, a need exists for new pharmaceutical agents which affect treat or prevent cardiovascular disease, particularly that associated with Syndrome X, while preventing or minimizing weight gain, and more preferably while improving insulin sensitivity.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by the following structural Formula I:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and $-CH_2-C(O)-R17-R18$, wherein R17 is O or NH and R18 is optionally substituted benzyl;

(b) W is O or S;

(c) R2 is H or a substituted or unsubstituted group

selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(d) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(e) Y is C, O, S, NH or a single bond; and

(f) E is selected from the group consisting of hydrogen, C(R3)(R4)A, A, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is an functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

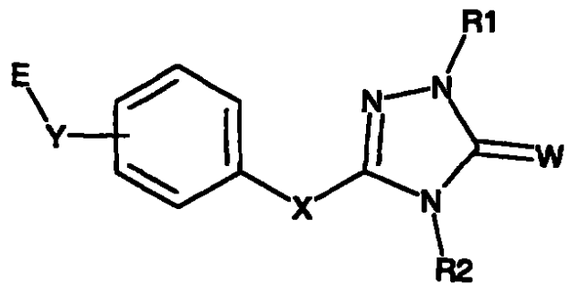
(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4alkyl and optionally substituted arylmethyl;

(g) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(h) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl.

An additional embodiment is a compound of Structural Formula I' and pharmaceutically acceptable salts, solvates and hydrates thereof:

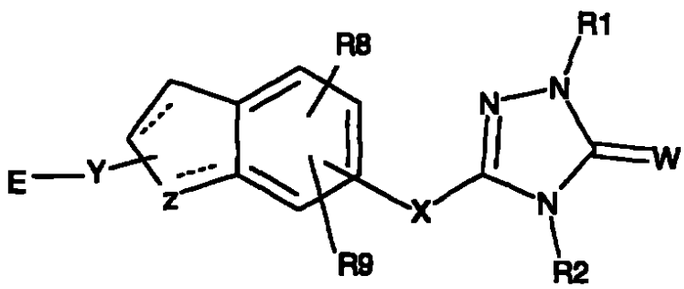


Structural Formula I'

In Structural Formula I', R1 is a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-2}-alkyl, heteroaryl-C_{0-2}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl or phenyl. W is O or S. R2 is H or a substituted or

unsubstituted group selected from C_1-C_6 alkyl and C_3-C_6 cycloalkyl. X is a C_2-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S. Y is C, O, S, NH or a single bond. Furthermore, E is $(CH_2)_nCOOH$, wherein n is 0, 1, 2 or 3, or C(R3)(R4)A, wherein A is an acidic functional group such as carboxyl, carboxamide substituted or unsubstituted sulfonamide, or substituted or unsubstituted tetrazole. R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy. Additionally, R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl.

A further embodiment of the present invention is a compound represented by the following structural formula:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and $-CH_2$-C(O)-R17-R18, wherein R17 is O or NH and R18 is optionally substituted benzyl;

(b) W is O or S;

(c) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(d) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(e) Y is C, O, S, NH or a single bond; and

(f) E is selected from the group consisting of hydrogen, C(R3)(R4)A, A, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is a functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4alkyl, and optionally substituted arylmethyl;

(g) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

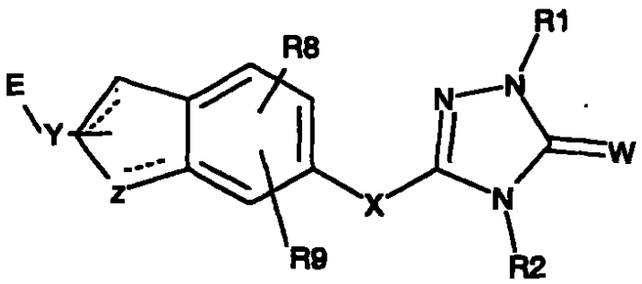
(h) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10;

(i) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

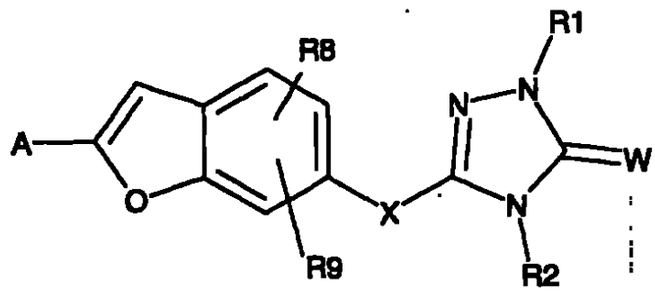
(j) Z is C_0-C_3 alkylene, O, S, N, O-(C_0-C_2 alkylene), S-(C_0-C_2 alkylene), and N-(C_0-C_2 alkylene); and

(k) --- is an optional bond to form a double bond.

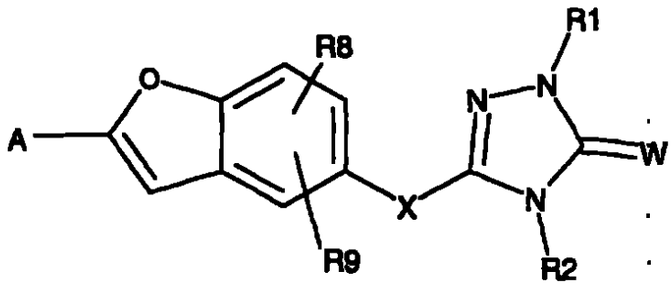
Another claimed embodiment of the present invention is a compound of the formula:



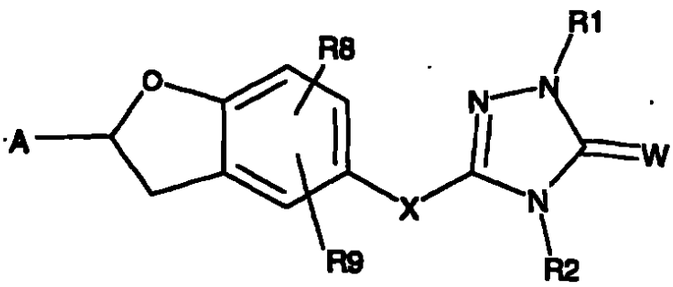
Another embodiment of this invention is compounds of the following formula, which may be preferred:



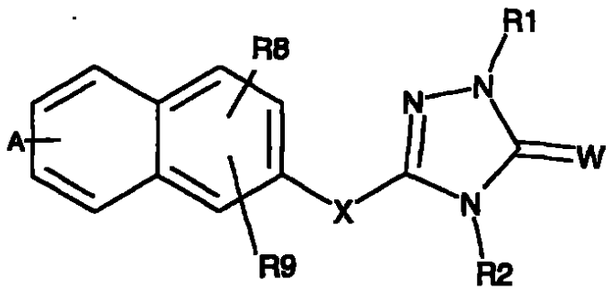
In another embodiment of the present invention, compounds represented the following structure may be preferred:



In a further embodiment of this invention, a compound the following structural formula may be preferred:



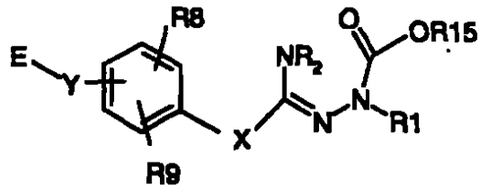
Another compound claimed by this invention that may be preferred is shown by the following structure:



In another feature of this invention, a compound claimed herein is radiolabeled.

The present invention additionally provides a process for preparing a triazolone from an acyl semicarbazide comprising contacting said acyl semicarbazide with an acid. Preferred acids for said process are sulfonic acid and pyridinium hydrochloride. It is a preferred embodiment of this invention when the triazole prepared by said process is a compound of Formula I.

Another embodiment of the present invention is a compound of the formula:



wherein

(a) R1 is hydrogen or is selected from the group consisting of a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl;

(b) R2 is H or a substituted or unsubstituted group

selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(c) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Y is C, O, S, NH or a single bond; and

(e) E is selected from the group consisting of hydrogen, $(CH_2)_n$ COOR19, C(R3)(R4)A, substituted or unsubstituted selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl,and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is a functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4alkyl and optionally substituted arylmethyl;

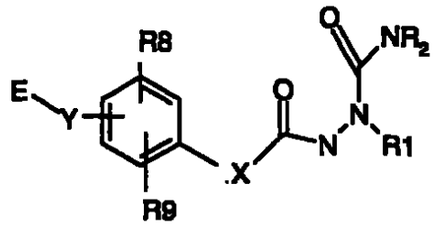
(f) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(g) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

(h) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl; and

(i) R15 is selected from the group consisting of hydrogen and an optionally substituted substituent selected from the group consisting of C_1-C_4 alkyl, aryl, and benzyl. Such compounds are particularly useful as intermediates for the preparation of compounds claimed herein.

Another embodiment of the present invention is a compound of the formula:



wherein

(a) R1 is hydrogen or is selected from the group consisting of a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl,

heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl;

(b) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(c) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Y is C, O, S, NH or a single bond; and

(e) E is selected from the group consisting of hydrogen, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C(R3)(R4)A, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is an acidic functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5

alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

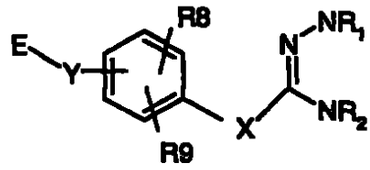
(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4alkyl and optionally substituted arylmethyl;

(f) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(g) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

(h) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl. Such compounds are particularly useful as intermediates for the preparation of compounds of Formula I.

Another embodiment of the invention claimed herei is a compound of the formula:



wherein

(a) R1 is hydrogen or is selected from the group consisting of a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl;

(b) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(c) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Y is C, O, S, NH or a single bond; and

(e) E is selected from the group consisting of hydrogen, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C(R3)(R4)A, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is an acidic functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4alkyl and optionally substituted arylmethyl;

(f) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(g) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

(h) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl. Such compounds are especially useful as intermediates for the manufacture of compounds of Formula I.

For compounds having Structural Formula I, it is preferred that E is C(R3)(R4)A. It is more preferred that A is a carboxyl group. It is even more preferred that E is C(R3)(R4)COOH and R_3 is H or CH_3.

The present invention further provides a crystalline Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl- compound of Formula I or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof.

In one embodiment, the present invention also relates to pharmaceutical compositions which comprising at least one compound of the present invention, or a pharmaceutically

acceptable salt, solvate, hydrate or prodrug thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of modulating a PPAR alpha receptor by contacting the receptor with at least one compound represented by Structural Formula I, and pharmaceutically acceptable salts, solvates and hydrates thereof

In a further embodiment, the present invention relates to a method of making a compound represented by Structural Formula I.

The compounds of the present invention and pharmaceutically acceptable salts, solvates and hydrates thereof are believed to be effective in treating and preventing Syndrome X, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagaulopathy, hypertension, atherosclerosis, and other disorders related to Syndrome X and cardiovascular diseases. In addition, the compounds exhibit fewer side effects than compounds currently used to treat these conditions. Further, compounds of this invention can be useful for lowering fibrinogen, increasing HDL levels, treating renal disease, controlling desirable weight, treating demyelinating diseases, treating certain viral infections, and treating liver disease.

DETAILED DESCRIPTION OF THE INVENTION

The terms used to describe the instant invention have the following meanings herein.

As used herein, alkyl groups include straight chained or branched hydrocarbons, which are completely saturated.

As used herein, alkylene linker is an optionally unsaturated C_1-C_5 straight or branched chain hydrocarbon group.

Cycloalkyl groups, as used herein, include cyclic hydrocarbons, which are partially or completely saturated.

As used herein, aryl groups include carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl and benzodioxyl).

Heterocyclic group, as used herein, is a ring system having at least one heteroatom such as nitrogen, sulfur or oxygen. Heterocyclic groups include benzofuranyl, benzothiazolyl, benzothienyl, isoquinolyl, isoxazolyl, morpholino, oxadiazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinolyl, tetrahydropyranyl and thienyl.

Examples of R1, R5, E, R4, R19 and R9 suitable substituents when said R1, E, R4, R5, R19 or R9 are one or more independently selected from the group consisting of C_1-C_8alkyl, aryl, $(CH_2)_nCOOR19$, C_1-C_6 allyl, thio-C_1-C_4alkyl, thioaryl, C_1-C_4alkoxyaryl, C_1-C_4alkoxy C_1-C_4alkyl, aminoaryl and aminoC_1-C_4alkyl, aryl-C_{0-4}alkyl, heteroarylC_{0-4}alkyl, heterocyclic, $-CH_2-C(O)-R17-R18$, (C_3-C_6)cycloalkylaryl-C_{0-2}-alkyl and cycloalkyl, then suitable substituted groups include, for example, C1-C5 alkyl, C1-C5 alkoxy, C1-C5 haloalkyl, C1-C5 haloalkoxy, nitro, cyano, CHO, hydroxyl, C1-C4 alkanoic acid phenyl, aryloxy, SO2R7, SR7, benzyloxy, alkylcarboxamido or COOH. R7 is an alkyl or a haloalkyl. When R1, R5, E, R4, R19 or R9 is substituted, it is preferred that there are from 1-3 substitutions on said R1, R5, E, R4, R19 or R9 group.

Examples of suitable substituents for an "optionally substituted C_2-C_5 alkylene linker", include one or more independently selected from the group consisting of C_1-C_6alkyl, oxo, substituted or unsubstituted arylC_0-C_3alkyl,

C_1-C_3alkoxy, hydroxy, C_3-C_6cycloalkyl and halo. When the alkylene linker is substituted, it is preferred that there are from one to three independent substitutions.

Examples of suitable substituents for a substituted C_1-C_3 alkylene, include one or more independently selected from C_1-C_6alkyl, oxo, aryl C_0-C_3alkyl, C_1-C_3alkoxy, hydroxy, and halo. When the alkylene is substituted it is preferred that there are from 1-3 independent substitutions.

Suitable substituents for substituted R2 groups wherein R2 is C_1-C_6alkyl, C_1-C_6allyl, arylC_0-C_4alkyl, arylC_0-C_4alkyl, sulfonamide, amide, OR10, or C_3-C_6cycloalkyl, include for example, one or more independently selected from the group consisting of OH, alkoxy, haloalkyl, amino, COOH, heteroaryl-O-, heteroaryl-C(O)-, alkyl-O-, alkyl-C(O)-, C3-C6 cycloalkyl, aryl-O-, aryl-C(O)-, heteroaryl, aryl, heterocycloalkyl, heterocycloalkyl-O-, and heterocycloalkyl-C(O)-. When R2 is substituted it is preferred that there are from 1-3 independent substitutions on the R2 group.

Examples of suitable substituents for A groups, wherein the A is a sulfonamide, include one or more independently selected from C1-C4 alkyl, C1-C4 haloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl. When the A group is substituted, it is preferred that there are from 1-3 independent substitutions on the A group.

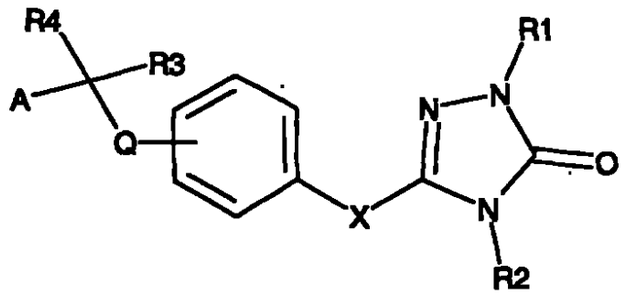
Examples of suitable substituents for A groups, wherein A is acylsulfonamide and tetrazole include, for example, one or more independently selected from C1-C4 alkyl, C1-C4 haloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl.

Suitable substitutents for R4 wherein R4 is C_1-C_5 alkyl, C_1-C_5alkoxy, C_1-C_6cycloalkyl, arylC_0-C_4alkyl or phenyl,

include, for example phenyl, C1-C4 alkoxy, hydroxy and alkoxy. When R4 is substituted, it is preferred that there are from 1-4 independent substitutions on the R4 group.

Preferably, for the compounds of the present invention, represented by Structural Formula I, and with their respective pharmaceutical compositions, W is an oxygen.

More preferably, the compounds of the present invention, and with their respective pharmaceutical compositions, have a structure represented by Structural Formula II:

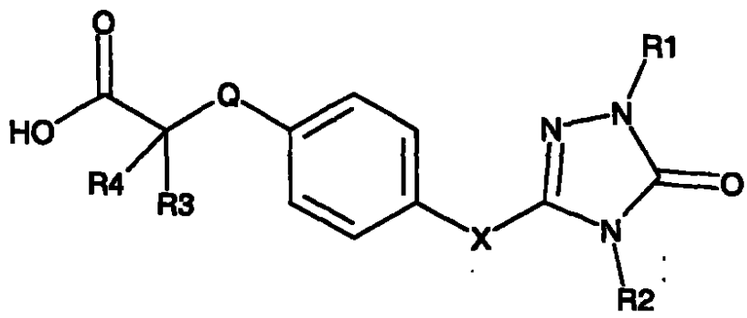


Structural Formula II

In Structural Formula II, R1, R2, X, R3, R4 and A are as defined for Structural Formula I. Q is C, O or S.

For compounds having Structural Formula I, it is preferred that R_3 is H or CH_3.

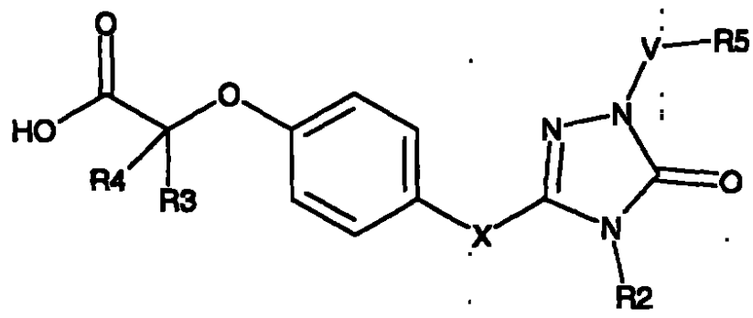
Compounds that may be especially preferred are Compounds of Formula III, and with their respective pharmaceutical compositions. Such compounds have a structure represented by Structural Formula III:



Structural Formula III

In Structural Formula III, R1, R2, X, Q, R3 and R4 are as defined for Structural Formulas I and II.

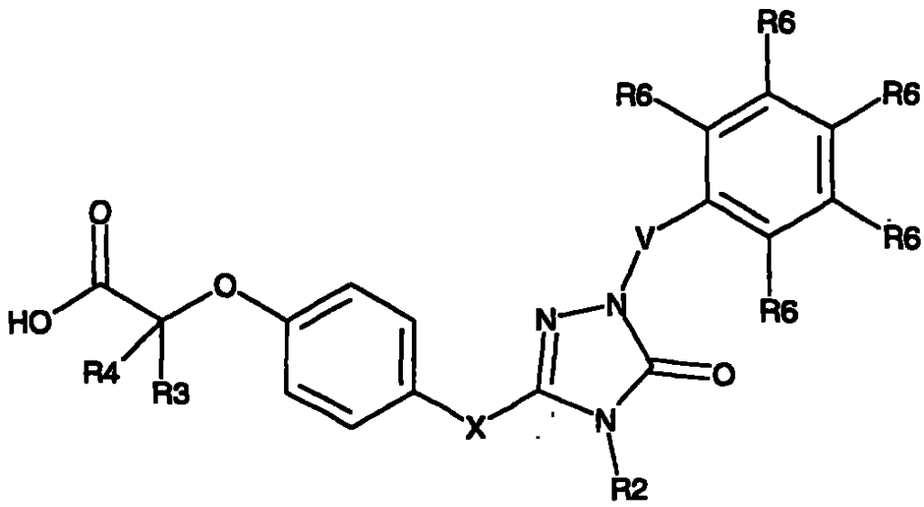
A further prefered embodiment is the compounds of the present invention having Formula IV, and their respective pharmaceutical compositions, have a structure represented by Structural Formula IV.



Structural Formula IV

In Structural Formula IV, R2, X, R3 and R4 are as defined for Structural Formulas I and II. V is a bond, C1-C3 alkylene which is unsubstituted or substituted with oxo or alkyl) group. R5 is substituted or unsubstituted group selected from aryl, heteroaryl and cycloalkyl groups.

Another prefered embodiment is the compounds of the present invention, and with their respective pharmaceutical compositions, having a structure represented by Structural Formula V.

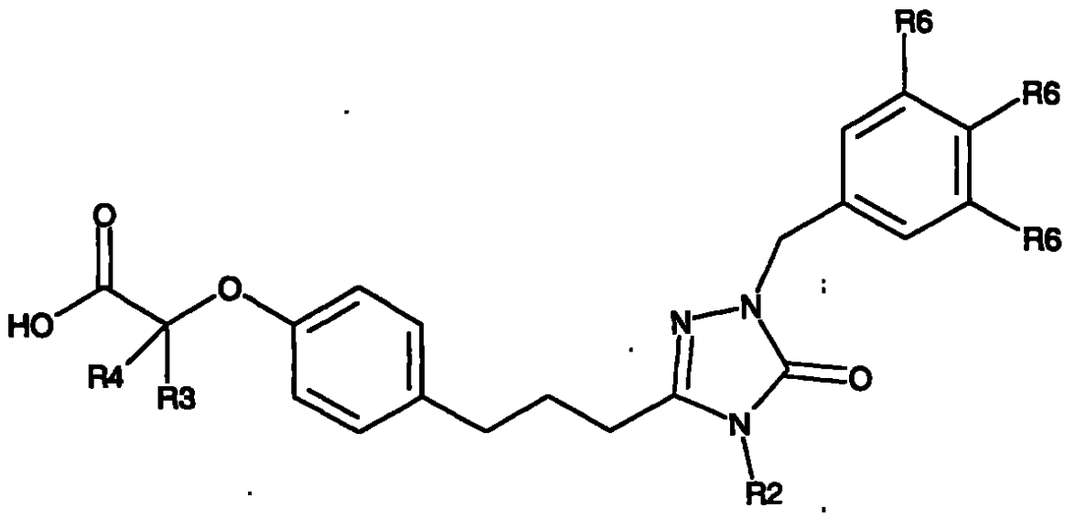


Structural Formula V

In Structural Formula V, R2, X, R3, R4 and V are as defined for Structural Formulas I, II and IV. R6 is H, OH, C1-C5 alkyl, alkoxy, halo, haloalkyl, haloalkoxy, nitro, phenyl, aryloxy, SO2R7, SR7, cyano, benzyloxy, phenoxy, alkylcarboxamido or COOH. R7 is an alkyl or a haloalkyl.

For, the compounds of the present invention, and their respective pharmaceutical compositions, having a structure represented by Structural Formula V, it is preferred that V is methylene. It is more preferred that V is methylene and X is propylene. It is even further preferred that V is methylene, X is propylene, R3 is methyl, and R4 is methyl.

Another prefered embodiment is the compounds of the present invention, and with their respective pharmaceutical compositions, have a structure represented by Structural Formula VI.



Structural Formula VI

In Structural Formula VI, R2, R3, R4 and R6 are as defined for Structural Formulas I, II, IV and V. For the compounds of Structural Formula VI, it is preferred that, independently, each R6 group is H or methyl.

The present invention further provides a desired crystalline Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl- having an X-ray diffraction pattern which comprises at least one of the following peaks: 13.2 +/- 0.2, 15.9 +/- 0.2, 20.7 +/- 0.2, and 24.1 +/- 0.2 in 2θ when obtained from a copper radiation source.

The compounds of Structural Formula I may contain one or more chiral centers, and exist in different optically active forms. When compounds of Structural Formula I contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. The enantiomers may be resolved by methods known t those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example,

by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound represented by Structural Formula I has more than one chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each

conformational isomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I which are substantially non-toxic to mammals. Typical pharmaceutically-acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as base addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically-acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

By virtue of its acidic moiety, a compound of Structural Formula I forms salts with pharmaceutically acceptable bases. Some examples of base addition salts include metal salts such as aluminum; alkali metal salts such as lithium, sodium or potassium; and alkaline earth metal salts such as calcium and magnesium; and ammonium or substituted ammonium salts. Examples of substituted ammonium salts include, for instance, those with lower alkylamines such as trimethylamine, triethylamine;

hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine or dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, glucamine, N-methylglucamine; bases of the pyridine type such as pyridine, collidine, quinine or quinoline; and salts of basic amino acids such as lysine and arginine.

Examples of inorganic bases include, without limitation, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

Compounds of Structural Formula I, which are substituted with a basic group, may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid.

These salts may be prepared by methods known to those skilled in the art.

Certain compounds of Structural Formula I and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Poorly crystalline and/or amorphous materials are typically less desirable than highly crystalline materials for formulation processing. Amorphous compounds are chemically and physically less stable as they tend to adsorb

significant amounts of water. The adsorption of water by an amorphous material in a gelatin capsule, for example, may cause the capsule to shrink or buckle as moisture is transferred from the capsule to the amorphous component. In addition, amorphous compounds have a tendency to precipitate out of solutions containing them. If an amorphous drug substance precipitates from a delivery solution, the dissolution and bioavailability properties of the drug may be negatively affected.

In addition, it is generally not desirable to formulate pharmaceuticals containing substantial amounts of organic solvent (*e.g.*, ethyl acetate) due to potential solvent toxicity to the recipient thereof and changes in potency of the pharmaceutical as a function of the solvent. In addition, from a manufacturing perspective, it is also generally less desirable to prepare non-crystalline materials whenever said preparation involves a collection of the final product via filtration. Such filtrations are often more difficult to perform when the material collected is non-crystalline. Moreover, it is also generally less desirable, from a manufacturing perspective, to formulate pharmaceuticals containing substantial amounts of water (hydrates) because the level of hydration will typically be some function of the relative humidity at which the pharmaceutical is produced and stored. In other words, potency variability is typically more problematic with a hydrate relative to its anhydrous form. The present invention provides a desired crystalline form.

Prodrugs are compounds of the present invention, which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active

in vivo. Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

Methyl ester prodrugs may be prepared by reaction of the acid form of a compound of Formula I in a medium such as methanol with an acid or base esterification catalyst (e.g., NaOH, H_2SO_4). Ethyl ester prodrugs are prepared in similar fashion using ethanol in place of methanol.

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Structural Formula I (in a medium such as dimethylformamide) 4-(2-chloroethyl)morphine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

Characterization of Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl- crystalline form

Differential scanning calorimetry/thermogravimetric analysis (DSC/TGA), moisture sorption/desorption, and X-ray powder diffraction (XRD) methods were used to characterize Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl-. TGA is a measure of the

thermally induced weight loss of the material as a function of temperature. It is most commonly used to study desolvation processes and quantatively determine the total volatile content of a solid. DSC is a technique that is often used to screen compounds for polymorphism because the temperatures(s) at which a physical change in a material occurs is usually characteristic of that material. Moisture sorption isotherms provide evaluation of the degree of hydroscopicity associated with a given material and characterization of non-hydrates and hydrates. Lastly, XRD is a technique that detects long-range order in a crystalline material.

The thermodynamically favorable crystalline Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl-polymorph was characterized using a Siemens D5000 diffractometer equipped with a CuKα radiation source (λ =1.54056 Angstroms) and a solid state detector.

It is well known in the crystallography art that, for any given crystal form, the relative intensities of the diffraction peaks may vary due to preferred orientation resulting from factors such as crystal morphology and habit. Where the effects of preferred orientation are present, peak intensities are altered, but the characteristic peak positions of the polymorph are unchanged. See, *e.g.*, The United States Pharmacopeia #23, National Formulary #18, pages 1843-1844, 1995. Furthermore, it is also well known in the crystallography art that, for any given crystal form, the angular peak positions may vary slightly. For example, peak positions can shift due to a variation in the temperature at which a sample is analyzed, sample displacement, or the presence or absence of an internal

standard. In the present case, a peak position variability of ± 0.2 in 2θ will take into account these potential variations without hindering the unequivocal identification of the desired crystalline form.

A well known and accepted method for searching crystal forms in the literature is the "Fink" method. The Fink method uses the four most intense lines for the initial search followed by the next four most intense lines. In accord with the Fink method, based on peak intensities as well as peak position, the desired crystalline form of Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl- may be identified by the presence of peaks at 13.2 +/- 0.2, 15.9 +/- 0.2, 20.7 +/- 0.2, and 24.1 +/- 0.2 in 2θ; when the pattern is obtained from a copper radiation source. The presence of desired Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl- crystalline form may be further verified by peaks at 7.9 +/- 0.2, 17.37 +/- 0.2, and 19.5 7 +/- 0.2 in 2θ; when the pattern is obtained from a copper radiation source.

The term, "active ingredient" means the compounds generically described by Structural Formula I as well as the salts, solvates, and prodrugs of such compounds.

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients and salt must be compatible with the other ingredients of the composition, and not deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein.

"Treating" refers to mediating a disease or condition and preventing, or mitigating, its further progression or ameliorate the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of a compound, or of its salt, solvate, hydrate or prodrug thereof, that will elicit the biological or medical response of a tissue, system, or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount which is sufficient to modulate a PPAR alpha receptor or to prevent or mediate a disease or condition. Conditions prevented or treated by PPARα receptors include diabetes mellitus, cardiovascular disease, Syndrome X, obesity and gastrointestinal disease.

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

Administration to a human is most preferred. The compounds and compositions of the present invention are useful for the treatment and/or prophylaxis of cardiovascular disease, for raising serum HDL cholesterol levels, for lowering serum triglyceride levels and for lower serum LDL cholesterol levels. Elevated triglyceride and LDL levels, and low HDL levels, are risk factors f r the

development of heart disease, stroke, and circulatory system disorders and diseases.

The compounds and compositions of the present invention are also useful for treating and/or preventing obesity.

Further, these compounds and compositions are useful for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus (NIDDM) with reduced or no body weight gains by the patients. Furthermore, the compounds and compositions of the present invention are useful to treat or prevent acute or transient disorders in insulin sensitivity, such as sometimes occur following surgery, trauma, myocardial infarction, and the like. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective, non-toxic amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycemic human or non-human mammal in need thereof.

They are useful as therapeutic substances in preventing or treating Syndrome X, diabetes mellitus and related endocrine and cardiovascular disorders and diseases in human or non-human animals.

The invention also relates to the use of a compound of Formula I as described above, for the manufacture of a medicament for treating a PPARα mediated condition.

A therapeutically effective amount of a compound of Structural Formula I can be used for the preparation of a

medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, lowering serum LDL levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of the present invention typically reduces serum triglyceride levels of a patient by about 20% or more, and increases serum HDL levels in a patient. Preferably, HDL levels will be increased by about 30% or more. In adition, a therapeutically effective amount of a compound, used to prevent or treat NIDDM, typically reduces serum glucose levels, or more specifically HbA1c, of a patient by about 0.7% or more.

Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of the compound or compounds of Structural Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances.

When used herein Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis f any one of or any combination of the

following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially atherosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition which contains a compound of Structural Formula I and one or more additional active agents, as well as administration of a compound of Structural Formula I and each active agent in its own separate pharmaceutical dosage formulation. For example, a compound of Structural Formula I or thereof and an insulin secretogogue such as biguanides, thiazolidinediones, sulfonylureas, insulin, or α-glucosidose inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, a compound of Structural Formula I and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of atherosclerosis may be wherein a compound of Structural Formula I or salts thereof is administered in combination with one or more of the following active agents:

antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As noted above, the compounds of Structural Formula I can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the compounds of Structural Formula I, salts thereof can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating atherosclerosis.

The compounds of the present invention, and the pharmaceutically acceptable salts, solvates and hydrates thereof, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the active ingredient which is a compound of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete

unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically-acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the invention can

also be administered in a targeted drug delivery system, such as, for example, in a liposome coated with endothelial cell-specific antibody.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, powders, sachets, granules, dragees, capsules, liquids, elixers, tinctures, gels, emulsions, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

For oral administration in the form of a tablet or capsule, the active ingredient may be combined with an oral, non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, methyl cellulose, calcium carbonate, calcium phosphate, calcium sulfate, sodium carbonate, mannitol, sorbitol, and the like; together with, optionally, disintegrating agents, such as, without limitation, cross-linked polyvinyl pyrrolidone, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid, or a salt thereof such as sodium alginate, and the like; and, optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example,

without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substance which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the

finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

All formulations for oral administration should be in dosages suitable for such administration. Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules.

For parental administration the compounds of the present invention, or salts thereof, can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Formulations for injection may be presented in unit dosage form, such as in ampoules or in multi-dose containers, with an added preservative. Th

compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that each syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against any contamination. The carrier can be solvent or dispersion medium containing, for example, water, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in a conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of a dry powder inhaler, or an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilized solid or paste, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

The following pharmaceutical formulations 1 through 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active Ingredient", refers to a compound according to Structural Formula I or salts thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg .

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Active Ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The Active Ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The Active Ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed

with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of Active Ingredient, are made as follows:

Active Ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The Active Ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of Active Ingredient, are made as follows:

Active Ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The Active Ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of Active Ingredient per 5 ml dose, are made as follows:

Active Ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active Ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Active Ingredient	100 mg
Isotonic saline	1,000 ml

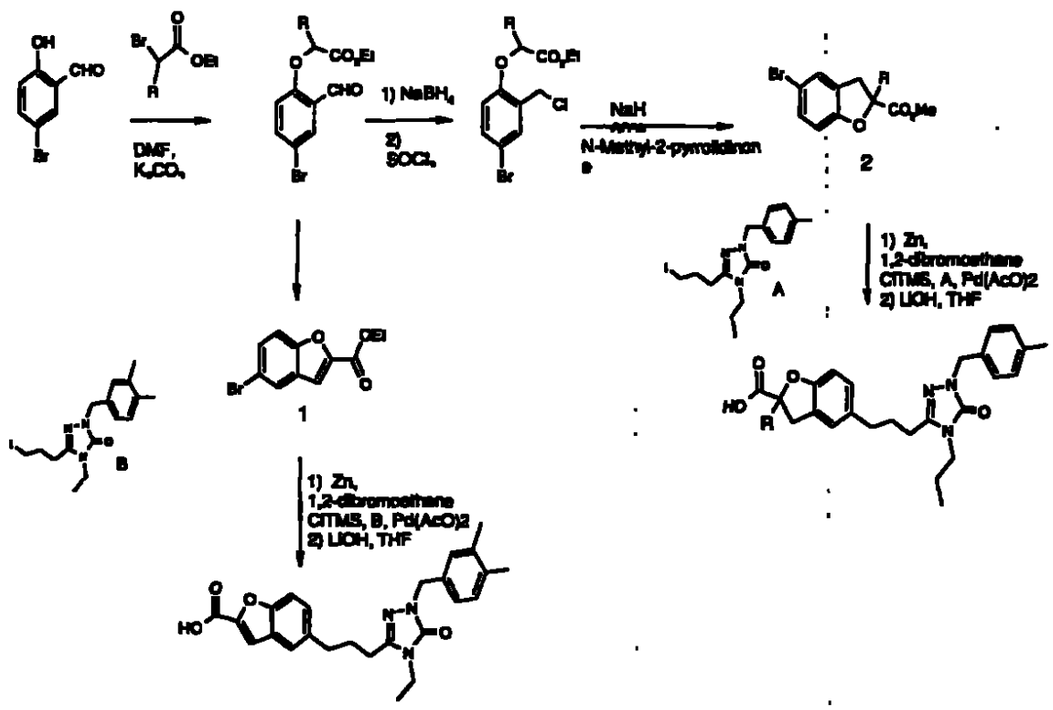
The solution of the above materials generally is administered intravenously to a subject at a rate of 1 ml per minute.

In yet another embodiment of the compounds of the present invention, the compound is radiolabelled, such as with carbon-14, or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new PPARα agonists.

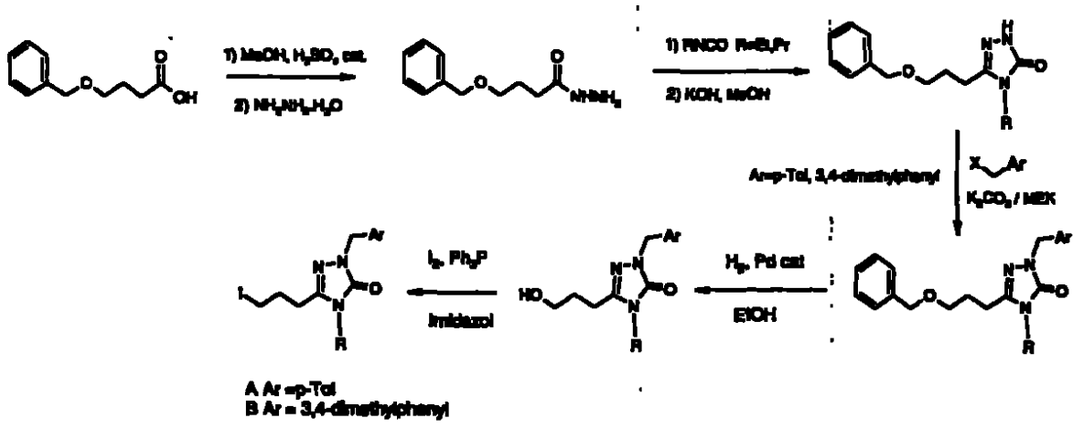
SYNTHESIS

Compounds of the present invention have been formed as specifically described in the examples. Further, many compounds were prepared as more generally as shown in the following schematic. Alternative synthesis methods may also be effective and known to the skilled artisan.

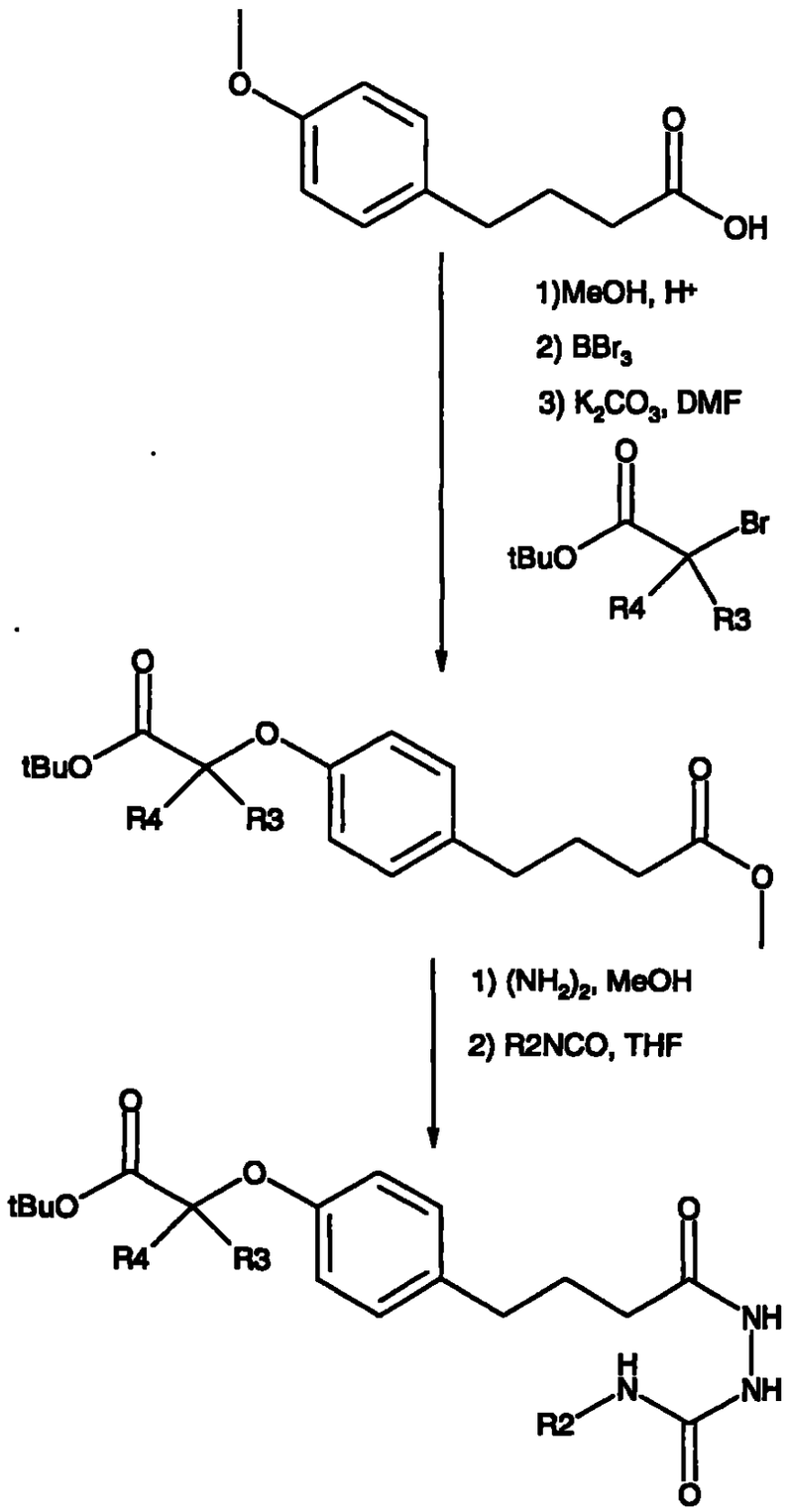
Certain compounds of this invention were prepared as shown in scheme 1. Intermediates 1, 2 were obtained from commercially available p-bromo salicyl aldehyde and alpha-bromo esters. Intermediates A and B were obtained following the reaction sequence shown in scheme 2. The final compounds were obtained through a palladium catalized coupling reaction between 1and 2 with A or B, followed by basic hydrolysis of the ester to the acid.

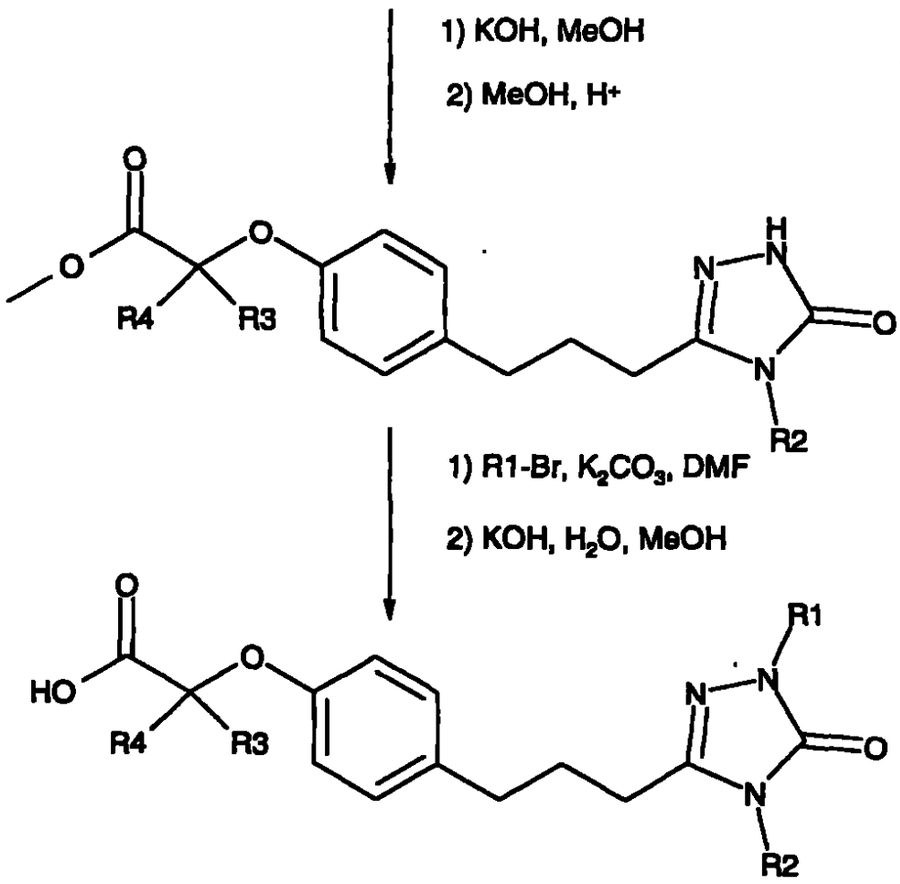


Scheme 2

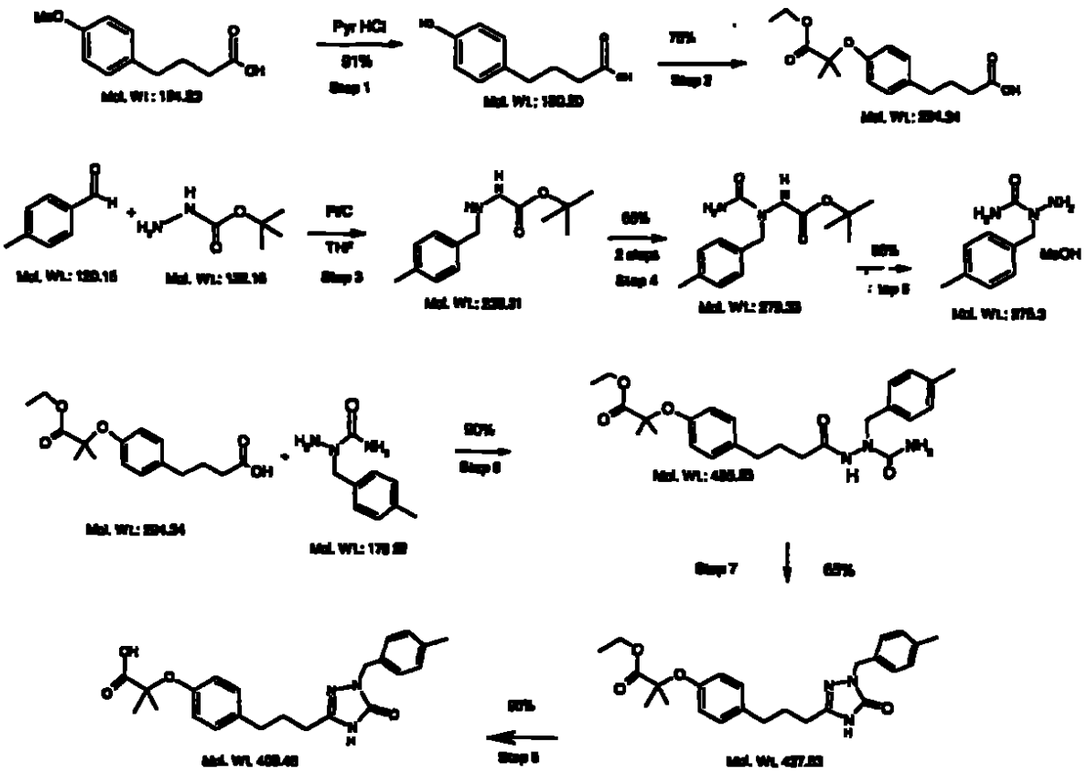


61


O
O
OH
1)MeOH, H+
2) BBr3
3) K2CO3, DMF
O
Br
tBuO
R4
R3
O
tBuO
O
R4
R3
O
O
1) (NH2)2, MeOH
2) R2NCO, THF
O
tBuO
O
R4
R3
O
NH
H
N
NH
R2
O


1) KOH, MeOH
2) MeOH, H+
1) R1-Br, K2CO3, DMF
2) KOH, H2O, MeOH

PPAR Alpha Agonist 518674 DSR 10-00



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The Examples provided herein are illustrative of the invention claimed herein and are not intended to limit the scope of the claimed invention in any way.

EXEMPLIFICATION

Instrumental Analysis

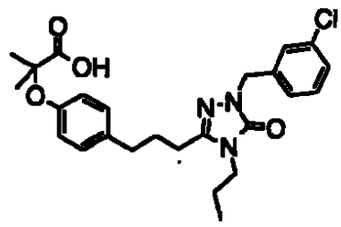
Infrared spectra were recorded on a Perkin Elmer 781 spectrometer. ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C NMR were recorded on a Varian 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale, with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.5 ppm). Combustion analyses were performed by Eli Lilly & Company Microanalytical Laboratory. High resolution mass spectra were obtained on VG ZAB 3F or VG 70 SE spectrometers. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light.

Exemplified Compounds

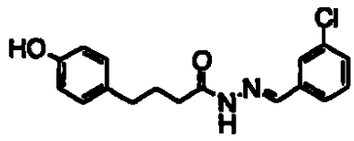
Example 1

Compound 1(1)

Compound 1, shown below, was prepared according to the Steps outlined below:

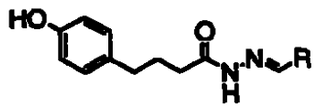


Step A: Preparation of:



To a suspension of 4-(4-hydroxyphenyl)butyrylhydrazide (0.5 g, 2.58 mmol) in isopropanol (5 mL) was added 3-chlorobenzaldehyde (Aldrich, 420 mg, 3 mmol), followed by p-toluenesulphonic acid (25 mg). The reaction mixture was stirred at room temperature for 20 h. A solid separated, which was filtered, washed with isopropanol (0.25 mL), and dried to give the product as a solid. MS: m/z (M^+ + 1): 317

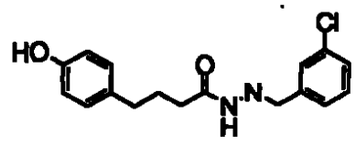
Additional compounds, shown below, were prepared by substituting the appropriate benzaldehyde for 3-chlorobenzaldehyde.



R	MS: m/z (M^+ + 1)
3-Methylphenyl	297
Phenyl	283

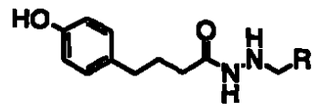
2,4-Difluorophenyl	319
2-Methylphenyl	297
3-Methoxyphenyl	313

Step B: Preparation of:



To a solution of the Step A product (650 mg, 2.05 mmol, Example 1) in a mixture of 5 mL of isopropanol, tetrahydrofuran, and acetic acid (1:1:0.3) was added sodium cyanoborohydride (1.25 g, 20 mmol). The reaction mixture was strirred at room temperature for 30 h. Reaction mixture was diluted with ethyl acetate (50 mL) and washed with water 2 x 75 mL). The organic phase was dried (Na_2SO_4) and concentrated to dryness to give the product as syrup. MS: m/z (M^+ + 1): 319

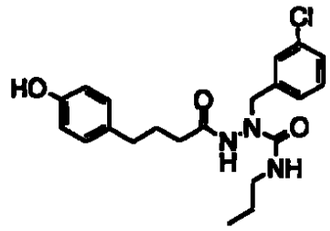
Additional compounds, shown below, were also prepared.



R	MS: m/z (M^+ + 1)
3-Methylphenyl	299
Phenyl	285

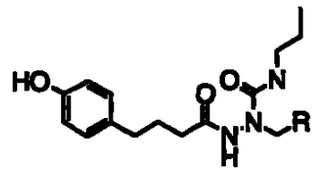
2,4-Difluorophenyl	321
2-Methylphenyl	299
3-Methoxyphenyl	315

Step C: Preparation of:



To a solution of the Step B product (400 mg, 1.26 mmol) in anhydrous THF (5 mL) was added n-propylisocyanate (213 mg, 2.52 mmol). The reaction mixture was stirred for 16 h. Methanol (1 mL) was added to the reaction mixture and the stirring was continued for an additional 30 min. The solvent was removed on a rotary evaporator to give the product as an oily residue. MS: m/z (M^+ + 1): 404

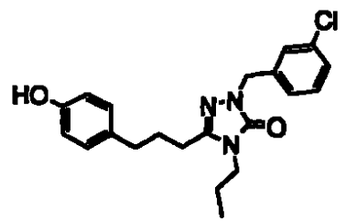
Additional compounds, shown below, were also prepared.



R	MS: m/z (M^+ + 1)
3-Methylphenyl	384
Phenyl	370

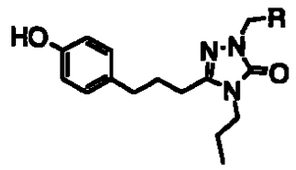
2,4-Difluorophenyl	406
2-Methylphenyl	384
3-Methoxyphenyl	400

Step D: Preparation of 2-(3-chlorobenzyl)-5-(3-(4-hydroxyphenyl)propyl)-4-n-propyltriazolin-3H-3-one:



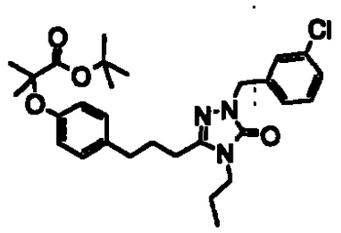
The Step C product, [1-(4-(4-hydroxyphenyl))butyryl-2-(3-chlorobenzyl)-4-n-propylcarbazate], (200 mg) was dissolved in methanol (20 mL). To this solution was added solid potassium hydroxide (0.50 g) and the reaction mixture was heated at reflux for 24 h with stirring. The reaction mixture was concentrated to a small volume (5 mL) and diluted with water (50 mL) and the aqueous layer was then acidified with 5N hydrochloric acid (pH ~ 2). The aqueous layer was extracted with ethyl acetate (2 x 50 mL), the organic layer was dried (Na_2SO_4), and the solvent was removed on a rotary evaporator to give the product as an oily residue. MS: m/z (M^+ + 1): 386

Additional compounds, shown below, were also prepared.


HO
N
N
R
O
N

R	MS: m/z (M^+ + 1)
3-Methylphenyl	366
Phenyl	352
2,4-Difluorophenyl	388
2-Methylphenyl	366
3-Methoxyphenyl	382

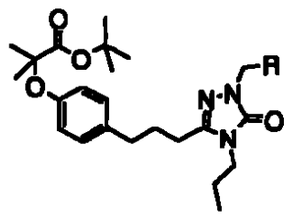
Step E: Preparation of:



To a solution of the Step D product [2-(3-chlorobenzyl)-5-(3-(4-hydroxyphenyl)propyl)-4-n-propyltriazolin-3H-3-one] (0.17 g, 0.45 mmol) in anhydrous DMF (5 mL) was added tert-butyl bromoisobutyrate (0.70 gm, 3.14 mmol) followed by anhydrous K_2CO_3 (1.0 gm, powdered). The reaction mixture was stirred at 50 °C for 64 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 x 25 mL). The ethyl acetate layer was dried (Na_2SO_4) and concentrated on a rotary evaporaor to give an oily residue

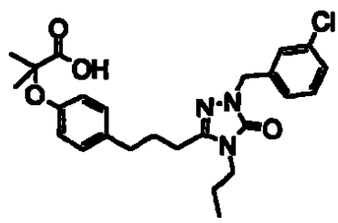
which was further purified on a silica gel column (1 cm x 7 in.) eluting with ethyl acetate -hexane mixture (20-30% v/v) to give the product as an oil. MS: m/z (M^+ + 1): 530

Additional compounds, shown below, were also prepared.



R	MS: m/z (M^+ + 1)
3-Methylphenyl	466
Phenyl	452
2,4-Difluorophenyl	530
2-Methylphenyl	466
3-Methoxyphenyl	

Step F: Preparation of:

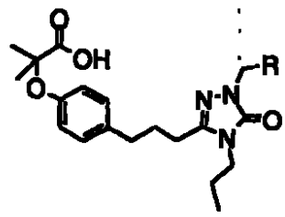


The Step E product (180 mg) was treated a mixture of triflouroacetic acid and dichloromethane (10 mL, 50% v/v)

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with stirring for 3 h. The solvent was removed on a rotary evaporator and the residue dried under high vacuum to give the title compound as an oil. MS: m/z (M^+ + 1): 472.9

Additional compounds, shown below, were also prepared.

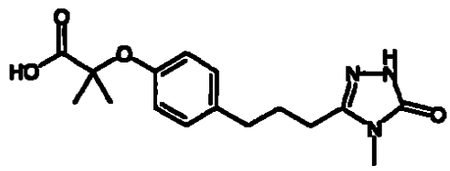


Example Number	R	MS: m/z (M^+ + 1)
1(2)	3-Methylphenyl	452
1(3)	Phenyl	438
1(4)	2,4-Difluorophenyl	473
1(5)	2-Methylphenyl	452
1(6)	3-Methoxyphenyl	468

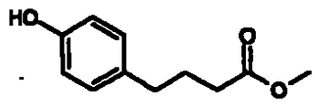
Example 2

Compound 2(1)

The compound shown below was prepared as follows:

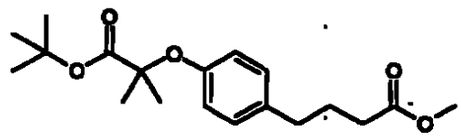


Step A: Preparation of:



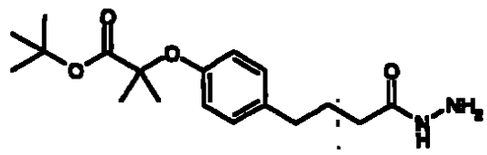
To a cooled (0°C) solution of boron tribromide (50 g, 200 mmol) in CH_2Cl_2 (50 mL) was added a solution of methyl 4-(4-methoxyphenyl)butyrate (15.5 g, 74.4 mmol) in CH_2Cl_2 (100 mL) dropwise over one hour. After stirring for an additional hour at 0°C, the reaction mixture was treated with 1:1 CH_3OH:CH_2Cl_2 (120 mL) with cooling and stirred overnight at ambient temperature. Concentration of the mixture gave an oil which was partitioned between ethyl acetate (150 mL) and water (150 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combin d organic extracts washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), then concentrated to give the desired phenol as an oil. $C_{11}H_{14}O_3$ (MW = 194.23); MS: m/z (M^+ + 1) =195

Step B: Preparation of:



The phenol from Step A (18.6 g, 96 mmol) was dissolved in DMF (300 mL) and treated with t-butyl 2-bromoisobutyrate (50 mL, 288 mmol), powdered K_2CO_3 (53.0g, 384 mmol) and $MgSO_4$ (1.6 g, 96 mmol), and the resulting mixture heated at 75°C overnight. After cooling to ambient temperature, the reaction mixture was decanted into 1N aqueous HCl (300ml) and extracted with diethyl ether (3 x 150ml). The remaining solids from the decantation were washed several times with diethyl ether. The diethyl ether extracts and washes were combined and washed with 1N aqueous HCl (150ml), dried (Na_2SO_4), and concentrated to a dark oil. Purification by flash chromatography (gradient elution, hexanes to 95:5 hexanes:ethyl acetate) gave the desired ether as an oil. $C_{19}H_{28}O_5$ (MW = 336.43); MS: m/z (M^+ + 1) = 337

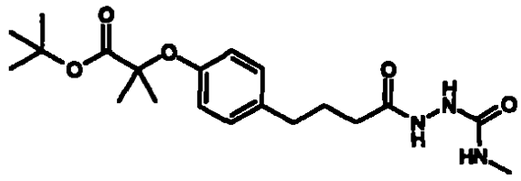
Step C: Preparation of:



A solution of the ether from Step B (21.8 g, 64 mmol) in methanol (250 mL) was treated with hydrazine hydrate (32.0 g, 650 mmol) and the mixture stirred overnight at ambient temperature. The reaction mixture was concentrated and the residue partitioned between ethyl acetate (250 mL) and water (100 mL). The aqueous layer was extracted with

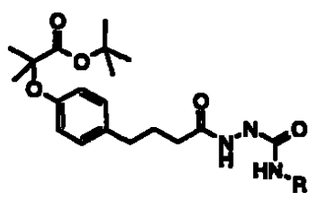
ethyl acetate (2 x 100 mL), and the combined organic extracts washed with brine (100 mL), dried (Na_2SO_4), and concentrated to give the desired acylhydrazide as an oil. $C_{18}H_{28}N_2O_4$ (MW = 336.43); MS: m/z (M^+ + 1) = 337

Step D: Preparation of:



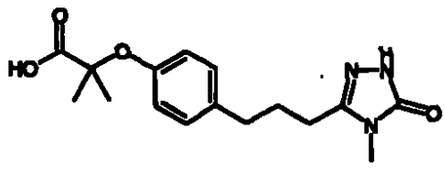
To a solution of the acylhydrazide from Step C (6.6 g, 19.6 mmol) in anhydrous THF (150 mL) was added methyl isocyanate (1.51 mL, 25.5 mmol) in one portion. The reaction mixture was stirred overnight at ambient temperature, then concentrated to give the desired acylsemicarbazate as an oil. $C_{20}H_{31}N_3O_5$ (MW = 393.49); MS: m/z (M^+ + 1) = 394

The compounds shown below were also prepared by substituting an appropriate alkylisocyanate or arylisocyanate for methylisocyanate.



R	MS: m/z (M^+ + 1)
Ethyl	408
n-Propyl	422
n-Butyl	436
n-Pentyl	450
n-Hexyl	464
2,4-Dimethoxybenzyl	530
2,4,6-Trimethoxybenzyl	664
Allyl	

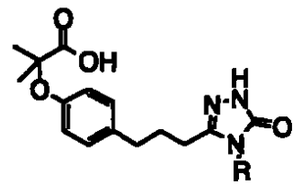
Step E: Preparation of



To a solution of the acylsemicarbazide from Step D in methanol (175 mL) was added solid potassium hydroxide (13 g, 231 mmol) and the reaction mixture heated at reflux for 48 hours. After cooling to ambient temperature, the reaction mixture was diluted with water (50 mL1) and methylene chloride (200 mL), then acidified to pH 2 with 5N

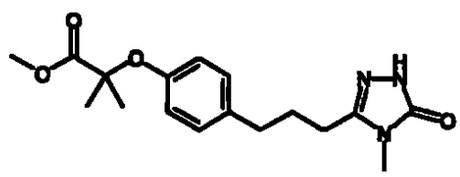
hydrochloric acid. The aqueous layer was extracted with methylene chloride (2x40 mL). The combined organic extracts were washed with water (75 mL), brine (75 mL), dried (Na_2SO_4), and concentrated to give the desired triazolinone as an oil. $C_{16}H_{21}N_3O_4$ (MW = 319.36); MS: m/z (M^+ + 1) = 320

The compounds listed below were also prepared by this cyclization procedure.



R	MS: m/z (M+1)
Ethyl	334
n-Propyl	348
n-Butyl	362
n-Pentyl	376
n-Hexyl	390
2,4-Dimethoxybenzyl	456
2,4,6-Trimethoxybenzyl	590
Allyl	

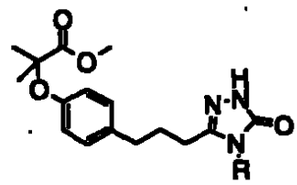
Step F: Preparation of:



78

To a solution of the triazolinone from Step E in methanol (150 mL) was added concentrated sulfuric acid (1 mL) and the reaction mixture stirred at room temperature for 18 hours. After concentration to remove methanol, the oil was dissolved in ethyl acetate (125 mL), washed with water (50ml), saturated aqueous $NaHCO_3$ (50ml), and (brine 50ml). The organic layer was dried (Na_2SO_4) and concentrated to give the methyl ester as a solid. $C_{17}H_{23}N_3O_4$ (MW = 333.39); MS: m/z (M^+ + 1) = 334

The compounds listed below were also prepared by Fisher esterification of the appropriate carboxylic acids above.

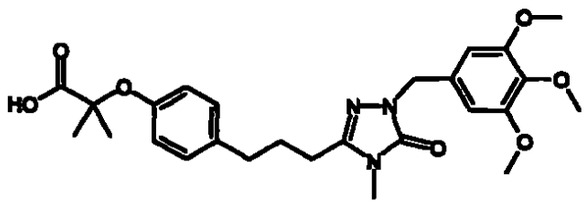


Example Number	R	MS: m/z (M^+ + 1)
2(2)	Ethyl	348
2(3)	n-Propyl	362
2(4)	n-Butyl	376
2(5)	n-Pentyl	390
2(6)	n-Hexyl	404
2(7)	2,4-Dimethoxybenzyl	470

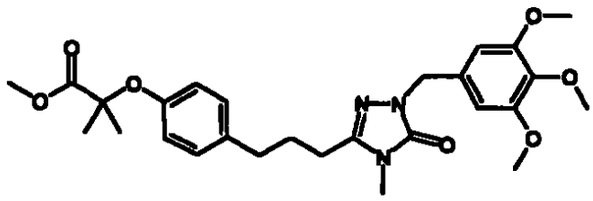
2(8)	2,4,6-Trimethoxybenzyl	604
2(9)	Allyl	

Example 3

Compound 3(1)

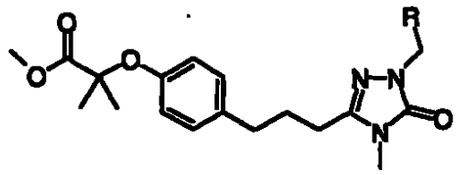


Step A: Preparation of:



To a solution of the methyl ester, specifically Compound 2(1) (100 mg, 0.29 mmol) in DMF (2 mL), was added 3,4,5-trimethoxybenzyl chloride (129 mg, 0.6 mmol) and powdered potassium carbonate (350 mg, 2.53 mmol) and the resulting mixture heated at 45 °C for 24 hours. After cooling to ambient temperature, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were concentrated to an oil which was purified by flash chromatography (gradient elution, 1:4 ethyl acetate:hexanes to 4:1 ethyl acetate:hexanes) to give the desired product as an oil. $C_{27}H_{35}N_3O_7$ (MW = 513.60); MS: m/z (M^+ + 1) = 514

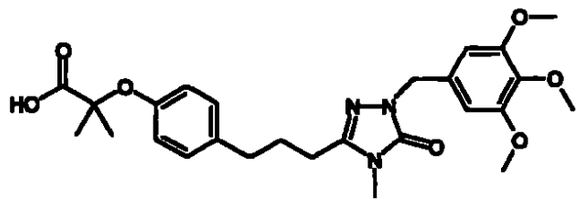
The compounds listed below were also prepared by alkylation of N-methyltriazolinone using appropriate alkylhalides in the place of 3,4,5-trimethoxybenzyl chloride.



R	MS: m/z (M^+ + 1)
3,5-Dimethoxyphenyl	484
4-Biphenyl	500
3-Chlorophenyl	458
3-Chloro-4-methylphenyl	472
Bis-trifluoromethylphenyl	560
3,4-Diflourophenyl	460
3-Phenoxyphenyl	516
4-Isopropylphenyl	468
3-triflouromethoxyphenyl	508
4-Methoxyphenyl	454
4-Trifluoromethoxyphenyl	508
4-Methylsulphonylphenyl	502
3-(triflouromethylthio)phenyl	524
4-Ethylphenyl	452
3,4-Dimethylphenyl	452
4-tert-Butylphenyl	480
2-Naphthyl	474
3-Methylphenyl	438
Phenmethyl	438
3-(5-Chloro)benzothiophene	515
4-Methylphenyl	438

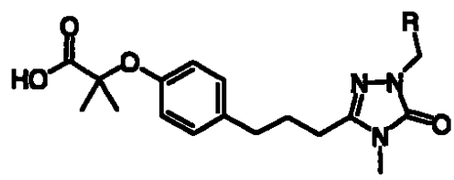
3,5-Difluorophenyl	460
3-Trifluorophenyl	492
3,4-Dichlorophenyl	493
Phenyl	424
3,5-Dimethylphenyl	452
4-Chlorophenyl	458

Step B: Preparation of:



A solution of the methyl ester from Step A (125 mg, 0.24 mmol) in methanol (3 mL) was treated with 5N aqueous NaOH (0.30 mL) and the mixture stirred overnight at ambient temperature. After concentration to dryness, the residue was dissolved in water (5 mL), the solution acidified to pH 3 with concentrated hydrochloric acid, then extracted into methylene chloride (3x2 mL). The combined organic extracts were dried by eluting through a cartridge packed with diatomaceous earth, then concentrated to provide the carboxylic acid as a waxy solid. $C_{26}H_{33}N_3O_7$ (MW = 499.57); MS: m/z (M^+ + 1) = 500

The compounds listed below were also prepared by hydrolysis of appropriate methyl ester listed above.



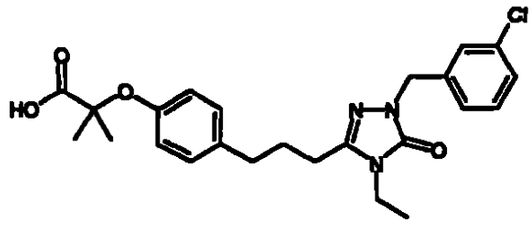
Example Number	R	MS: m/z (M^++1)
3(2)	3,5-Dimethoxyphenyl	470
3(3)	4-Biphenyl	486
3(4)	3-Chlorophenyl	444
3(5)	3-Chloro-4-methylphenyl	458
3(6)	2,4-Diflouromethylphenyl	546
3(7)	3,4-Difluorophenyl	446
3(8)	3-Phenoxyphenyl	502
3(9)	4-Isopropylphenyl	452
3(10)	3-triflouromethoxyphenyl	494
3(11)	4-Methoxyphenyl	440
3(12)	4-Trifluoromethoxy	494
3(13)	4-Methylsulphonylphenyl	488
3(14)	3-(triflouromethylthio)phenyl	510
3(15)	4-Ethylphenyl	438

3(16)	3,4-Dimethylphenyl	438
3(17)	4-tert-Butylphenyl	466
3(18)	2-Naphthyl	460
3(19)	3-Methylphenyl	424
3(20)	Phenmethyl	424
3(21)	3-(5-Chloro)benzothiophene	501
3(22)	4-Methylphenyl	424
3(23)	3,5-Difluorophenyl	446
3(24)	3-Trifluorophenyl	478
3(25)	3,4-Dichlorophenyl	479
3(26)	Phenyl	410
3(27)	3,5-Dimethylphenyl	438
3(28)	4-Chlorophenyl	444

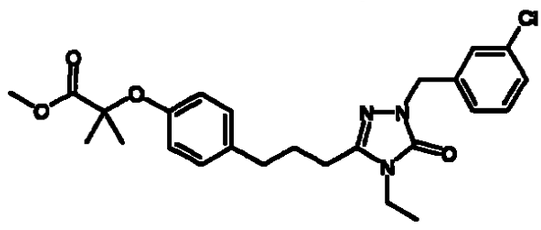
84

Example 4

Compound 4(1)

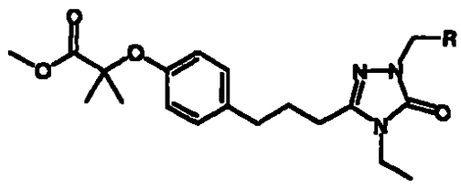


Step A: Preparation of:



To a solution of Compound 2(2) (100 mg, 0.28 mmol) in DMF (2 mL), was added m-chlorobenzyl bromide (119 mg, 0.58 mmol) and powdered potassium carbonate (350 mg, 2.53 mmol) and the resulting mixture heated at 45 °C for 24 hours. After cooling to ambient temperature, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were concentrated to an oil which was purified by flash chromatography (gradient elution, 1:4 ethyl acetate:hexanes to 4:1 ethyl acetate:hexanes) to give the desired product as an oil. $C_{25}H_{30}ClN_3O_4$ (MW = 471.99); MS: m/z (M^+ + 1) = 473.

The compounds listed below were also prepared by alkylation of Compound 2(2) using the appropriate alkylhalide in the place of m-chlorobenzyl bromide.



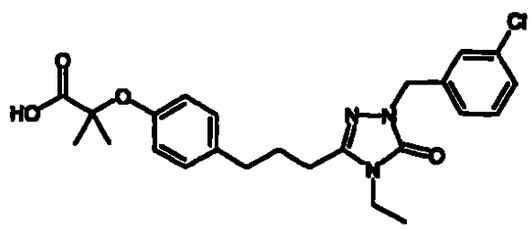
R	MS: m/z (M^+ + 1)
n-propyl	
3-chlorophenyl	472
3-methylphenyl	452
phenyl	438
2,4-difluorophenyl	
3-trifluoromethylphenyl	506
4-methylphenyl	452
2-methylphenyl	
3-nitrophenyl	
4-carboxyphenyl	
2-phenylethyl	
3,5-difluorophenyl	474

2-pyridyl	
4-pyridyl	
3-pyridyl	
2-quinolinoyl	489
6-(4-methoxy-2-trifluoromethyl)quinolinoyl	
3-(5-chloro)benzo[b]thienyl	
4-tert-butylphenyl	494
β-naphthyl	488
α-methylbenzyl	
3,5-dimethylphenyl	
2,6-dichlorophenyl	
3-cyanophenyl	463
5-(6-chloro)piperonyl	
4-cyanophenyl	463
5-piperonyl	482
3-trifluoromethoxyphenyl	522

bis-2,4-trifluoromethylphenyl	
Cyclohexyl	
4-ethylphenyl	
3,4-dimethylphenyl	466
4-trifluoromethylthiophenyl	
4-isopropylphenyl	480
4-methoxyphenyl	466
4-trifluoromethoxyphenyl	522
3,4-dichlorophenyl	507
4-chlorophenyl	
3,4-difluorophenyl	474
4-methylsulfonylphenyl	
2-methoxyphenyl	
3,5-dimethoxyphenyl	498
3,4,5-trimethoxyphenyl	528
4-tert-pentylphenyl	

2-(6-methyl)naphthyl	502
2-naphthoyl	516
5-(tert-butyl)1,2,4-oxadiazol-3-yl	486
3-methyl-4-methoxyphenyl	482
4-benzyloxyphenyl	544
3-chloro-4-methylphenyl	487
3-phenoxyphenyl	530
4-acetamidophenyl	495
4-trifluoromethylphenyl	506
p-biphenyl	514
3,5-dimethylisoxazol-4-yl	457

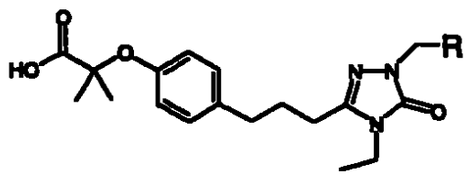
Step B: Preparation of



A solution of the product (125 mg, 0.24 mmol) from Step A in methanol (3 mL) was treated with 5N aqueous NaOH (0.30

mL) and the mixture stirred overnight at ambient temperature. After concentration to dryness, the residue was dissolved in water (5 mL), the solution acidified to pH 3 with concentrated hydrochloric acid, then extracted into methylene chloride (3 x 2 mL). The combined organic extracts were dried by eluting through a cartridge packed with diatomaceous earth, then concentrated to provide the carboxylic acid as a waxy solid. $C_{26}H_{33}N_3O_7$ (MW = 457.96); MS: m/z (M^+ + 1) = 458.

The compounds listed below were also prepared by hydrolysis of appropriate methyl ester listed above.



Example Number	R	MS: m/z (M^+ + 1)
4(2)	n-propyl	
4(3)	3-methylphenyl	438
4(4)	phenyl	424
4(5)	2,4-difluorophenyl	
4(6)	3-trifluoromethylphenyl	492
4(7)	4-methylphenyl	438
4(8)	2-methylphenyl	

4(9)	3-nitrophenyl	
4(10)	4-carboxyphenyl	
4(11)	2-phenylethyl	
4(12)	3,5-difluorophenyl	460
4(13)	2-pyridyl	
4(14)	4-pyridyl	
4(15)	3-pyridyl	
4(16)	2-quinolinoyl	475
4(17)	6-(4-methoxy-2-trifluoromethyl)quinolinoyl	
4(18)	3-(5-chloro)benzo[b]thiophenyl	515
4(19)	4-tert-butylphenyl	480
4(20)	β-naphthyl	474
4(21)	α-methylbenzyl	
4(22)	3,5-dimethylphenyl	
4(23)	2,6-dichlorophenyl	
4(24)	3-cyanophenyl	449

4(25)	5-(6-chloro)piperonyl	
4(26)	4-cyanophenyl	449
4(27)	5-piperonyl	468
4(28)	3-trifluoromethoxyphenyl	508
4(29)	bis-2,4-trifluoromethylphenyl	
4(30)	Cyclohexyl	
4(31)	4-ethylphenyl	
4(32)	3,4-dimethylphenyl	452
4(33)	4-trifluoromethylthiophenyl	
4(34)	4-isopropylphenyl	466
4(35)	4-methoxyphenyl	454
4(36)	4-trifluoromethoxyphenyl	508
4(37)	3,4-dichlorophenyl	493
4(38)	4-chlorophenyl	
4(39)	3,4-difluorophenyl	460
4(40)	4-methylsulfonylphenyl	

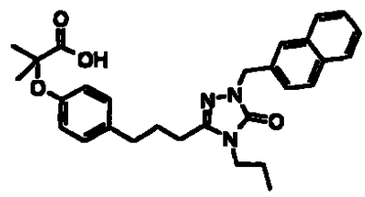
92

4(41)	2-methoxyphenyl	
4(42)	3,5-dimethoxyphenyl	484
4(43)	3,4,5-trimethoxyphenyl	514
4(44)	4-tert-pentylphenyl	
4(45)	2-(6-methyl)naphthyl	488
4(46)	2-naphthoyl	502
4(47)	5-(tert-butyl)1,2,4-oxadiazol-3-yl	472
4(48)	3-methyl-4-methoxyphenyl	468
4(49)	4-benzyloxyphenyl	530
4(50)	3-chloro-4-methylphenyl	473
4(51)	3-phenoxyphenyl	516
4(52)	4-acetamidophenyl	481
4(53)	4-trifluoromethylphenyl	492
4(54)	p-biphenyl	500
4(55)	3,5-dimethylisoxazol-4-yl	443

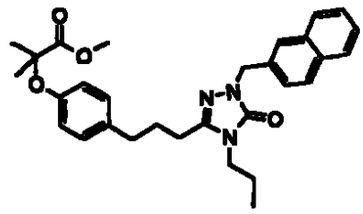
93

Example 5

Compound 5(1)

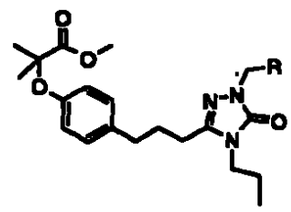


Step A: Preparation of



To a solution of triazolinone, Compound 2(3) (0.4 mmol) in anhydrous DMF (2 mL), was added the 2-bromomethyl-naphthalene (0.8 mmol), followed by anhydrous K_2CO_3 (500 mg, powdered). The reaction was strirred at 40 to 45 °C for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with ethylacetate (3 x 20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated to give an oily residue. The crude was further purified on pre-packed silica column (Biotage, Quad 3) eluting with ethyl acetate-hexane mixture to give the product. MS: m/z (M^+ + 1) = 502.

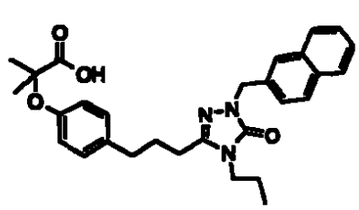
The compounds below were also prepared by alkylation of Compound 2(3) using appropriate alkylhalides in the place of 2-bromomethylnaphthalene.



R	MS: m/z (M^+ + 1)
n-ethyl	404
3-chlorophenyl	486
3-methylphenyl	466
Phenyl	452
2,4-difluorophenyl	488
3-trifluoromethylphenyl	520
4-methylphenyl	466
2-methylphenyl	466
3-nitrophenyl	497
4-carboxyphenyl	496
2-phenylmethyl	466
3,5-difluorophenyl	488
2-pyridyl	443
4-pyridyl	443
3-pyridyl	443
2-quinolinoyl	503
6-(4-methoxy-2-trifluoromethyl)quinolinoyl	601
3-(5-chloro)benzo[b]thienyl	543
4-tert-butylphenyl	508
β-naphthyl	502
α-methylbenzyl	466
3,5-dimethylphenyl	480
2,6-dichlorophenyl	521
3-cyanophenyl	477

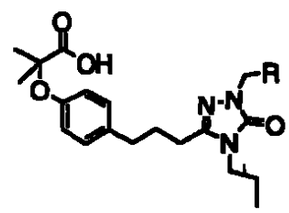
5-(6-chloro)piperonyl	531
4-cyanophenyl	477
5-piperonyl	496
3-trifluoromethoxyphenyl	536
Bis-2,4-trifluoromethylphenyl	588
Cyclohexyl	458
4-ethylphenyl	480
3,4-dimethylphenyl	480
4-trifluoromethylthiophenyl	552
4-isopropylphenyl	494
4-methoxyphenyl	482
4-trifluoromethoxyphenyl	536
3,4-dichlorophenyl	521
4-chlorophenyl	486
3,4-difluorophenyl	488
4-methylsulfonylphenyl	530
2-methoxyphenyl	482
3,5-dimethoxyphenyl	512
3,4,5-trimethoxyphenyl	542
4-tert-pentylphenyl	522
2-(6-methyl)naphthyl	516
2-naphthoyl	530
5-(tert-butyl)1,2,4-oxadiazol-3-yl	500

Step B: Preparation of:



To a solution of the methyl ester of Step A (150 mg) in methanol (2 mL) was added 1N aqueous KOH solution (2 mL). The reaction mixture was stirred at room temp for 4 h. Methanol was removed on a rotary evaporator and the aqueous layer diluted with water (1 mL). This was then acidified with 5 N aqueous HCl (pH~2). The aqueous layer was extracted with dichloromethane (3 x 20 mL), dried (Na_2SO_4) and concentrated to dryness to give the product as a foam. MS: m/z (M^+ + 1) = 488.

The compounds below were also prepared by hydrolysis of the appropriate methyl ester.



Example Number	R	MS: m/z (M^+ + 1)
5(2)	n-Ethyl	390
5(3)	3-chlorophenyl	472
5(4)	3-methylphenyl	452
5(5)	Phenyl	438
5(6)	2,4-difluorophenyl	474
5(7)	3-trifluoromethylphenyl	506

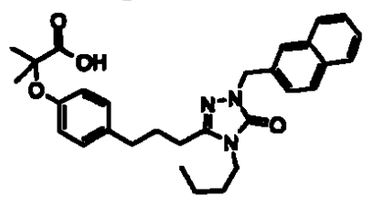
5(8)	4-methylphenyl	452
5(9)	2-methylphenyl	452
5(10)	3-nitrophenyl	483
5(11)	4-carboxyphenyl	482
5(12)	phenylmethyl	452
5(13)	3,5-difluorophenyl	474
5(14)	2-pyridyl	439
5(15)	4-pyridyl	439
5(16)	3-pyridyl	439
5(17)	2-quinolinoyl	489
5(18)	6-(4-methoxy-2-trifluoromethyl)quinolinoyl	587
5(19)	3-(5-chloro)benzo[b]thienyl	529
5(20)	4-tert-butylphenyl	494
5(21)	α-methylbenzyl	452
5(22)	3,5-dimethylphenyl	466
5(23)	2,6-dichlorophenyl	507

5(24)	3-cyanophenyl	463
5(25)	5-(6-chloro)piperonyl	517
5(26)	4-cyanophenyl	463
5(27)	5-piperonyl	482
5(28)	3-trifluoromethoxyphenyl	522
5(29)	Bis-2,4-trifluoromethylphenyl	574
5(30)	Cyclohexyl	444
5(31)	4-ethylphenyl	466
5(32)	3,4-dimethylphenyl	466
5(33)	4-trifluoromethylthiophenyl	538
5(34)	4-isopropylphenyl	480
5(35)	4-methoxyphenyl	468
5(36)	4-trifluoromethoxyphenyl	522
5(37)	3,4-dichlorophenyl	507
5(38)	4-chlorophenyl	472
5(39)	3,4-difluorophenyl	474

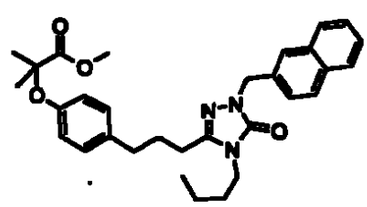
5(40)	4-methylsulfonylphenyl	516
5(41)	2-methoxyphenyl	468
5(42)	3,5-dimethoxyphenyl	498
5(43)	3,4,5-trimethoxyphenyl	528
	4-tert-pentylphenyl	508
5(45)	2-(6-methyl)naphthyl	502
5(46)	2-naphthoyl	516
5(47)	5-(tert-butyl)1,2,4-oxadiazol-3-yl	486

Example 6

Compound 6(1)



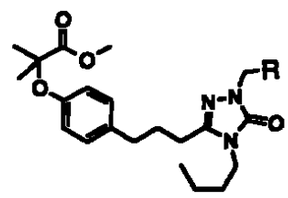
Step A: Preparation of:



To a solution of 4-butyltriazolinone derivative, Compound 2(4) (188 mg, 0.4 mmol) in anhydrous DMF (3 mL),

was added the 2-bromethylnaphthalene (265 mg, 1.2 mmol), followed by anhydrous K_2CO_3 (500 mg, powdered). The reaction was strirred at 40 to 45 °C for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with ethylacetate (3 x 20 mL). The combined organic layers were concentrated to give an oily residue. The crude was purified on pre-packed silica column (Biotag, Quad 3) eluting with ethyl acetate-hexane mixture to give the product. MS: m/z (M^+ + 1) = 516.

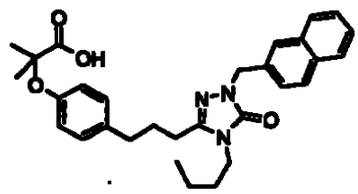
The compounds below were also prepared by alkylation of the 4-butyltriazolinone derivative using the appropriate alkylhalide in place of 2-bromethylnaphthalene.



R	MS: m/z (M^+ + 1)
3-Trifluoromethylphenyl	534
3-Cyanophenyl	491
3,5-Bistrifluoromethylphenyl	502
Phenyl	466
4-Cyanophenyl	491
3,5-Dimethylphenyl	494

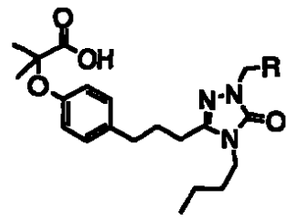
4-tert-Butylphenyl	522
4-Methylphenyl	480
2-Biphenyl	542
3,5-Diflourophenyl	502
Piperonyl	510
Phenylmethyl	480

Step B: Preparation of



To a solution of ester from Step A (150 mg) in 2 mL of methanol was added 2N aqueous NaOH solution (2 mL). The reaction mixture was stirred at room temperature for 2 h. Methanol was removed on the rotary evaporator. The reaction mixture was acidified with 5N aqueous HCl (pH ~3) and extracted with dichloromethane (2 x 25 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness to give the product as an oily residue. MS: m/z (M^+ + 1) = 502.

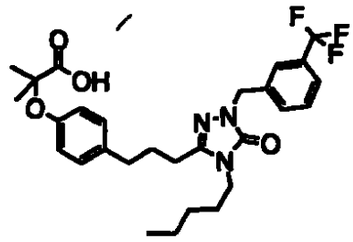
The compounds below were also prepared by hydrolysis of appropriate methyl ester.



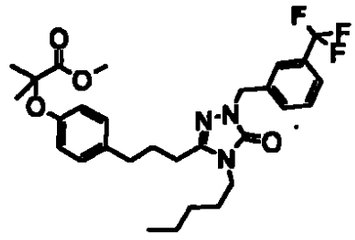
Example Number	R	MS: m/z (M^+ + 1)
6(2)	3-Trifluoromethylphenyl	520
6(3)	3-Cyanophenyl	477
6(4)	3,5-Bistrifluoromethylphenyl	588
6(5)	Phenyl	452
6(6)	4-Cyanophenyl	477
6(7)	3,5-Dimethylphenyl	480
6(8)	4-tert-Butylphenyl	508
6(9)	4-Methylphenyl	466
6(10)	2-Biphenyl	528
6(11)	3,5-Diflourophenyl	488
6(12)	Piperonyl	496
6(13)	Phenylmethyl	466

Example 7

Compound 7(1)

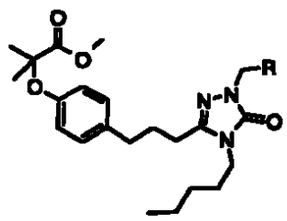


Step A: Preparation of



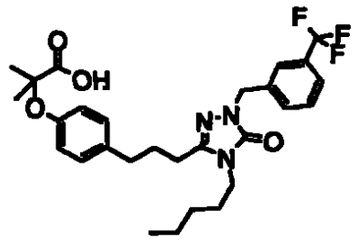
To a solution of the 4-n-pentyltriazolinone derivative, Compound 2(5) (150 mg, 0.39 mmol) in anhydrous DMF (3 mL), was added the 3-trifluoromethylbenzyl bromide (286 mg, 1.2 mmol), followed by anhydrous K_2CO_3 (500 mg, powdered). The reaction was strirred at 40 to 45 °C for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were concentrated to give an oily residue. The crude was purified on pre-packed silica column (Biotage, Quad 3) eluting with ethyl acetate-hexane mixture to give the product. MS: m/z (M^+ + 1) = 548.

The compounds below were also prepared in the same manner by alkylation of the 4-n-pentyltriazolinone derivative using the appropriate alkylhalide in the place of 3-trifluoromethylbenzyl bromide.



R	MS: m/z (M^+ + 1)
3,5-bis-triflouromethylphenyl	616
phenyl	480
4-cyanophenyl	505
3,5-dimethylphenyl	508
4-tert-butylphenyl	536
4-methylphenyl	494
2-biphenyl	556
3,5-difluorophenyl	516
piperanyl	524
3-heptyl	502
2-naphthyl	
3-cyanophenyl	

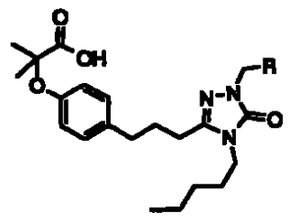
Step B: Preparation of:



To a solution of the Step A ester (170 mg) in 2 mL of methanol was added 2N aqueous NaOH solution (2.5 mL). The reaction mixture was stirred at room temperature for 2 h. Methanol was removed on the rotary evaporator. The reaction mixture was acidified with 5N aqueous HCl (pH ~3) and

extracted with dichloromethane (2 x 25 mL). The oraganic layer was dried over Na_2SO_4 and concentrated to dryness to give the product as an oily residue. MS: m/z (M^+ + 1) = 534.

The compounds below were also prepared by hydrolysis of the appropriate methyl ester.

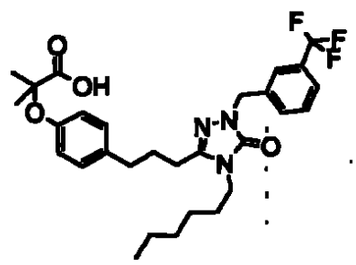


Example Number	R	MS: m/z (M^+ + 1)
7(2)	3,5-bis-triflouromethylphenyl	602
7(3)	phenyl	466
7(4)	4-cyanophenyl	491
7(5)	3,5-dimethylphenyl	494
7(6)	4-tert-butylphenyl	522
7(7)	4-methylphenyl	480
7(8)	2-biphenyl	542
7(9)	3,5-difluorophenyl	502
7(10)	piperanyl	510

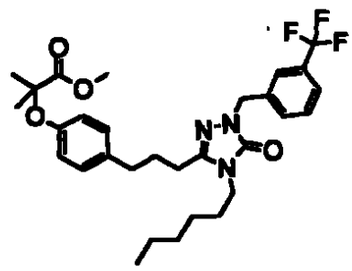
7(11)	3-heptyl	488
7(12)	2-naphthyl	516
7(13)	3-cyanophenyl	491

Example 8

Compound 8(1)



Step A: Preparation of



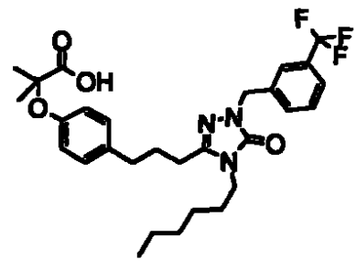
To a solution of the 4-hextyltriazolinone derivative, Compound 2(6) (150 mg, 0.39 mmol) in anhydrous DMF (3 mL), was added the 3-trifluoromethylbenzyl bromide (286 mg, 1.2 mmol), followed by anhydrous K_2CO_3 (500 mg, powdered). The reaction was strirred at 40 to 45 °C for 18 h. The reaction mixture was diluted with water (20 mL) and extracted with

ethyl acetate (3 x 20 mL). The combined organic layers were concentrated to give an oily residue. The crude product was further purified on pre-packed silica column (Biotage, Quad 3) eluting with ethyl acetate-hexane mixture to give the products as oils.

The compounds listed below were prepared by alkylation of Compound 2(6) and using the appropriate alkylhalide in the place of 3-trifluoro-methylbenzyl bromide.

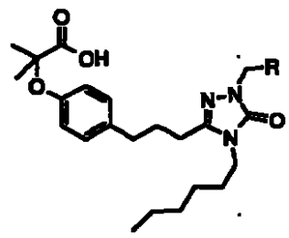
R	MS: m/z (M^+ + 1)
2-naphthyl	
3-cyanophenyl	
3,5-bis-trifluoromethylphenyl	

Step B: Preparation of:



To a solution of the Step A ester (204 mg) in 2 mL of methanol was added 2N aqueous NaOH solution (2.5 mL). The reaction mixture was stirred at room temperature for 2 h. Methanol was removed on the rotary evaporator. The reaction mixture was acidified with 5N aqueous HCl (pH ~3) and extracted with dichloromethane (2 x 25 mL). The oraganic layer was dried over Na_2SO_4 and concentrated to dryness to give the product as an oily residue. MS: m/z (M+1) 548.

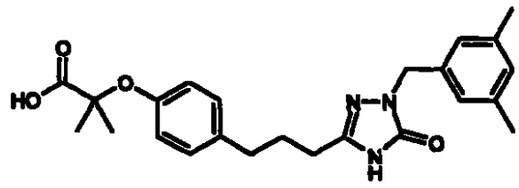
The compounds listed below were prepared by hydrolysis of appropriate methyl ester.



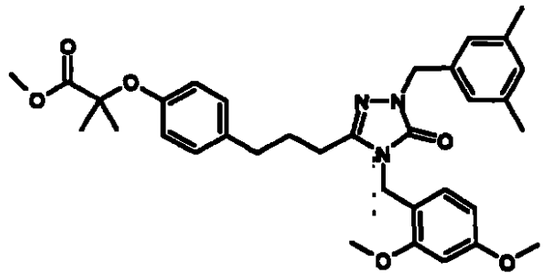
Example Number	R	MS: m/z (M^+ + 1)
8(2)	2-naphthyl	530
8(3)	3-cyanophenyl	505
8(4)	3,5-bis-trifluoromethylphenyl	616

Example 9

Compound 9(1)

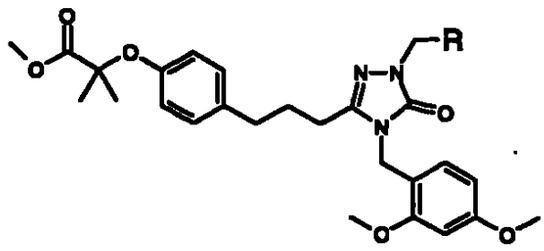


Step A: Preparation of:



To a solution of the 4-(2,4-dimethoxybenzyl)-triazolinone derivative from Compound 2(7) (190 mg, 0.40 mmol) in DMF (2 mL), was added 3,5-dimethylbenzyl bromide (159 mg, 0.80 mmol) and powdered potassium carbonate (350 mg, 2.53 mmol), and the resulting mixture heated at 45 °C for 24 hours. After cooling to ambient temperature, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 3 mL). The combined organic extracts were concentrated to an oil which was purified by flash chromatography (gradient elution, 1:4 ethyl acetate:hexanes to 4:1 ethyl acetate:hexanes) to give the desired product as an oil. $C_{34}H_{41}N_3O_6$ (MW = 587.72); MS: m/z (M^+ + 1) = 588.

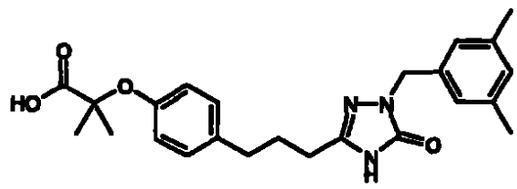
The following compounds were prepared utilizing the appropriate bromide in the place of 3,5-dimethylbenzyl bromide, as shown in the table.



R	MS: m/z (M^+ + 1)
4-t-butylphenyl	616
3-phenoxyphenyl	652
3-methylphenyl	574
3-trifluoromethylphenyl	628
2-naphthyl	610
3,5-dimethylphenyl	588

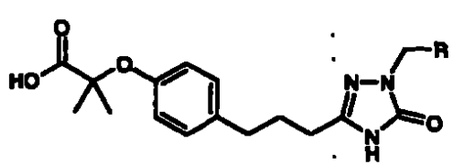
110

Step B: Preparation of:



A solution of the Step A product (157mg, 0.26mmol) in 33%(wt) hydrogen bromide in acetic acid (3 ml) was stirred at ambient temperature for 24 hours. The reaction mixture was treated with ice (30 g) and the mixture extracted with ethyl acetate (2 x 15 mL). The combined ethyl acetate extracts were washed with water, brine, dried and concentrated to an oil. The oil was dissolved in methanol (3 mL), treated with 5N aqueous NaOH (0.5 mL), and the resulting solution was stirred at ambient temperature for 18 hours. Concentration to remove methanol gave a residue which was dissolved in water (10 mL) and the resulting solution acidified to pH3 with concentrated hydrochloric acid. The suspension was extracted with methylene chloride (3 x 4 mL). The combined organic extracts were purified by reverse phase HPLC to give the desired product as a foam after lyophilization. $C_{24}H_{29}N_3O_4$ (MW = 423.52); mass spectroscopy (MH^+) = 424.

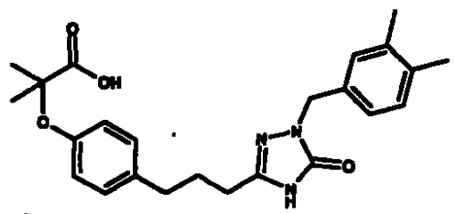
The compounds listed below were prepared from the corresponding methyl esters.



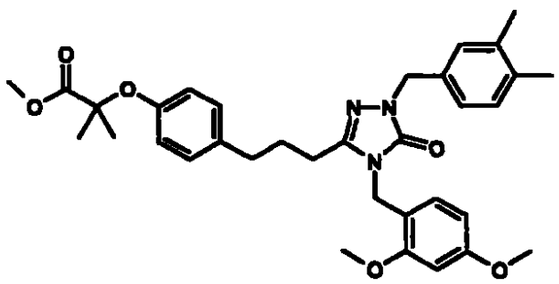
Example Number	R	MS: m/z (M^+ + 1)
9(2)	4-t-butylphenyl	452
9(3)	3-phenoxyphenyl	488
9(4)	3-methylphenyl	410
9(5)	3-trifluoromethylphenyl	464
9(6)	2-naphthyl	446

Example 10

Compound 10



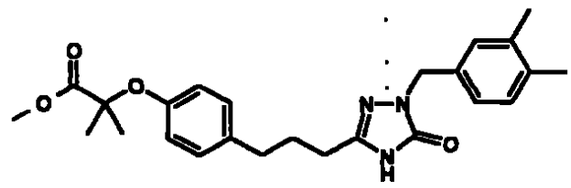
Step A: Preparation of:



To a solution of the 4-(2,4-dimethoxybenzyl)-triazolinone derivative from Compound 2(7) (9.0, 21.3 mmol) in DMF (25 mL), was added 3,4-dimethylbenzyl bromide (4.62 g, 25 mmol) and powdered potassium carbonate (10 g), and the resulting mixture stirred at ambient temperature for 24 hours. The reaction mixture was diluted with water (100mL) and extracted with ethyl acetate (3 x 75 mL). The combined

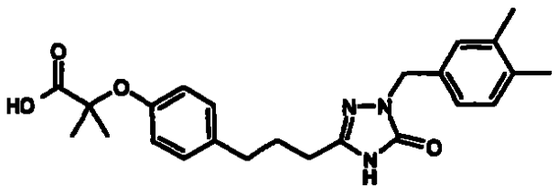
organic extracts were concentrated to an oil. Alternatively the product could be further purified by flash chromatography (gradient elution, 1:4 ethyl acetate:hexanes to 4:1 ethyl acetate:hexanes) to give the desired product as an oil. MS: m/z (M^+ + 1) = 588.

Step B: Preparation of:



A solution of the Step A product (9.5 gm) in 33%(wt) hydrogen bromide in acetic acid (50 mL) was stirred at ambient temperature for 24 hours. The reaction mixture was treated with ice (100 g) and the mixture extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate extracts were washed with water, brine, dried and concentrated to an oil. The oil was dissolved in methanol (200 mL), treated with 2 mL of concentrated H_2SO_4, and the resulting solution was stirred at ambient temperature for 18 hours. Concentration to remove methanol gave a residue which was dissolved in methylene chloride (200 mL) and washed with water (2 x 100 mL) followed by saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (SiO_2, EtOAc/Heanes) to give the desired product as a solid. MS: m/z (M^+ + 1) = 438.

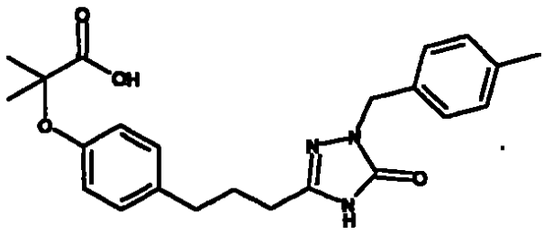
Step C: Preparation of:



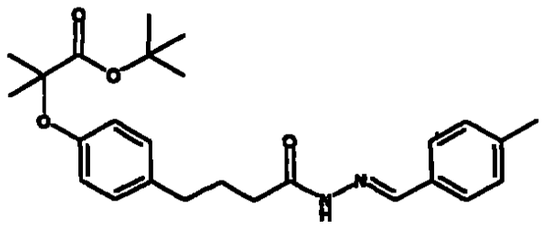
A solution of the Step B product (150 mg) in methanol (3 mL) was added 2N NaOH (2 mL) and the mixture was stirred at ambient temperature for 4 hours. The reaction mixture concentrated, diluted with methylene chloride (25 mL), water (5 mL) was added, and the mixture was acidified with concentrated HCl to pH ~ 2. The layers were separated, and the aqueous layer was extracted (2 x 25 mL) methylene chloride. The combined organic extracts were dried (Na_2SO_4) and concentrated, to give the desired product as a solid. MS: m/z (M^+ + 1) = 424.

Example 11

Compound 11

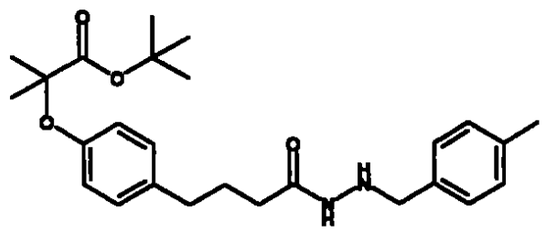


Step A: Preparation of:



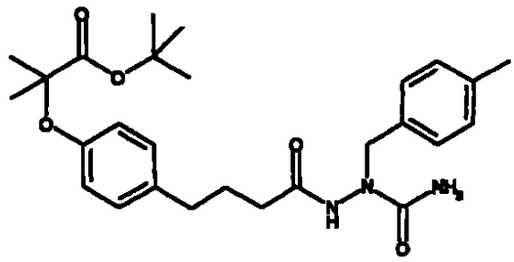
To the acyl hydrazide product of Example 2, Step C (5.4079 g, 16.07 mmol) in ethyl acetate (15 mL) was added *p*-methyl benzaldehyde (1.90 mL, 1.936 g, 16.11 mmol) via syringe. The resulting solution was stirred at room temperature and hexanes (30 mL) was added. Precipitate began to form and the resulting slurry was stirred for 16 h, then cooled to 0 °C and filtered. The filter cake was rinsed with cold hexanes and air dried to afford the desired imine (6.49 g, 92.1%) as a white solid. Anal. Calcd. for $C_{26}H_{34}N_2O_4$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.90; H, 7.79; N, 6.45.

Step B: Preparation of:



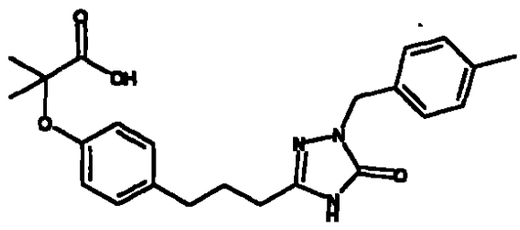
To the product of Step A (4.0 g, 9.12 mmol) in THF (40 mL) was added platinum oxide (0.2012 g) and the resulting slurry hydrogenated at room temperature and 40 psi for 3 h. The solution was filtered and an additional charge of platinum oxide (0.303 g) was added, and the resulting slurry was hydrogenated at room temperature and 40 psi for 16 h. The slurry was filtered and concentrated in vacuo at 60 °C to afford the desired acyl hydrazide (3.88 g, 96.6%) as a viscous oil. $C_{26}H_{36}N_2O_4$ (MW = 440.58); MS: m/z (M^+ + 1) = 441.

Step C: Preparation of:



Acyl hydrazide from Step B (287 g, 0.65 mol, 1 equiv) and isopropanol (1.7 L) were combined and heated to 50 °C. Trimethylsilylisocyanate (85%, 112 g, 0.98 mol, 1.5 equiv) was added rapidly. The reaction was stirred for 45 min, then cooled to 0 °C and stirred for 30 min. Colorless crystalline solid was collected by filtration and dried to provide product acyl semicarbazide (253.7 g, 81%). $C_{27}H_{37}N_3O_5$ (MW = 483.60); MS: m/z (M^+ + 1) = 484.

Step D: Preparation of:



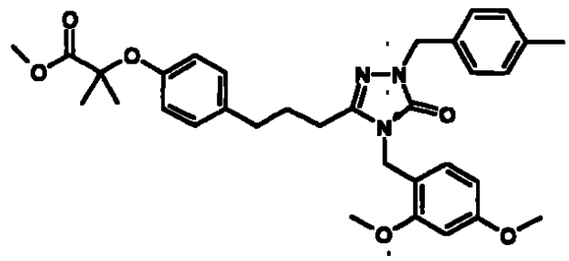
Acylsemicarbazide product from Step C (25.0 g, 0.0517 mol, 1.0 equiv), toluene (250 mL) and methanesulfonic acid (1.68 mL, 0.0258 mol, 0.5 equiv) were combined and the resulting solution was heated at reflux with azeotropic removal of water for 4 hrs. The reaction was concentrated in vacuo and the residue partitioned between CH_2Cl_2 (250 mL) and water (50 mL). The layers were separated and the organic phase was washed with 1N HCl (3 X 50 mL), dried (Na_2SO_4), filtered and the filter cake washed with CH_2Cl_2 (3 X 30 mL). The filtrate was concentrated to a white foamy film, dissolved in CH_2Cl_2 (200 mL) and washed with 1 N HCl (4 X 100 mL, then 5 X 200 mL), dried (Na_2SO_4) and concentrated to a white foam. Crude product was diss lved

in warm ethyl acetate (75 mL) and seeded with authentic product. The resulting slurry was allowed to stand at rt for 1 h, then refrigerated overnight. Colorless crystals were collected by filtration, washed with a minimal amount of cold ethyl acetate and dried to afford desired triazolone (12.5 g, 59%). $C_{23}H_{27}N_3O_4$ (MW = 409.48); MS: m/z (M^+ + 1) = 410.

Example 12

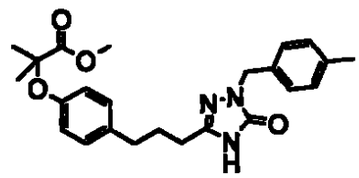
Compound 12(1)

Step A: Preparation of:



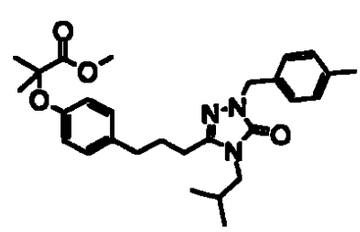
To a solution of the 4-(2,4-dimethoxybenzyl)-triazolinone derivative from Compound 2(7) (9.0, 21.3 mmol) in DMF (25 mL), was added 4-methylbenzyl bromide (4.62 g, 25 mmol) and powdered potassium carbonate (10 g), and the resulting mixture stirred at ambient temperature for 24 hours. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3x75 mL). The combined organic extracts were concentrated to an oil. Alternatively the product could be further purified by flash chromatography (gradient elution, 1:4 ethyl acetate:hexanes to 4:1 ethyl acetate:hexanes) to give the desired product as an oil. MS: m/z (M^+ + 1) = 588.

Step B. Preparation of:



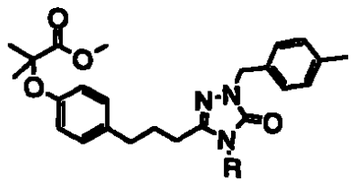
A mixture of 4-(2,4-dimethoxylbenzyl)triazolinone derivative, from Step A, (12.6 gm, 21.9 mmol) and HBr solution (50 mL, 32% w/v in glacial acetic acid) was stirred at room temp. for 24 h. Crushed ice (50 gm) was added to the reaction mixture and diluted with water (100 mL). The aqueous layer was extracted with ethyl acetate (400 mL). Wash ethyl acetate layer with water (2 x 250 mL), brine (100 mL), and dry over Na_2SO_4. The ethyl acetate layer was concentrated to dryness on a rotary evaporator to give an oily residue. The residue was taken up in methanol (300 mL). To this solution was added conc. Sulfuric acid (5 mL) with stirring. The reaction mixture was stirred at room temperature for 18 h. Methanol was removed to a small volume (25 mL) and the reidue was diluted with ethyl acetate (200 mL), washed with water (2 x 200 mL), saturated $NaHCO_3$ solution (2 x 100 mL), brine (100 mL) and dried over Na_2SO_4. The ethyl acetate layer was concentrated to dryness to give a residue which was purified on a flash silica column to give the product as an oily residue. MS: m/z (M+1) 424.

Step C: Preparation of:



To a solution of the Step B product (50 mg, 0.12 mmol) in DMF (1 mL) was added isopropylmethyliodide followed by anhydrous (250 mg, powdered). The reaction mixture was stirred at 40-45 °C for 18 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). Combined organic layer was concentrated to drynes on a rotary evaporator and then under high vacuum for 2 h. The crude was chromatographed on a prepacked silica column using Biotage Quad3 parallel chromatographic system eluting with ethyl acetate -hexane mixture (30-40 % v/v) to give the product as an oily residue. MS: m/z (M+1) 480

The compounds below were prepared by alkylation of the Step B product, using the appropriate alkylhalide listed in the table.

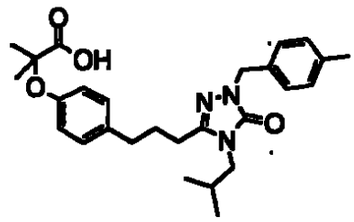


Alkyl halide	R	MS:m/z (M+1)
1-Iodo-2-methylpropane	Isobutyl	480
2-bromoethyl methyl ether	2-Methoxyethyl	482
2-Bromoethyl ethyl ether	2-Ethoxyethyl	496
1-bromobutan-2-one	2-Oxobutyl	494
4-bromobutyl benzoate	4-Hydroxybutyl	496
2-bromoethyl acetate	2-Hydroxyethyl	468

	2-(N,N-Diethyl)ethyl	523
1-bromo-3,3-dimethylbutan-2-one	3,3-Dimethyl-2-oxobutyl	522
Bromomethylcyclopropane	Cyclopropylmethyl	478
	1-Morpholinocarbonyl-2-isopropylmethyl	593
Methyl bromopropanoate	2-methoxycarbonylethyl	510
	3-(2-tetrahydro-pyranyloxy)prop-1-yl	566
1-bromo-3-hydroxypropane	3-Hydroxypropyl	482
Methyl bromoacetate	2-methoxycarbonylmethyl	496
Isopropyliodide	Isopropyl	466
	methoxyethoxyethyl	526
	3-Methoxy-2-hydroxypropyl	512
2-chloromethylpyridien	2-Pyridylmethyl	515
4-chloromethyl pyridine	4-Pyridylmethyl	515
Benzyl bromide	Benzyl	514
	2,2,2-trifluroethyl	
	3,3,3-trifluropropyl	
	4,4,4-triflurobutyl	

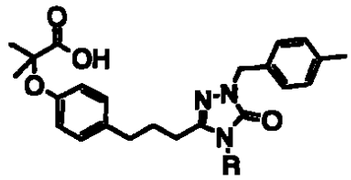
120
127

Step D: Preparation of:



To a solution of the Step C product (15 mg,) in MeOH (1 mL) was added 2N NaOH (2 mL) and the mixture was stirred at ambient temperature for 16 hrs. The reaction mixture was concentrated, diluted with 15 mL water, and acidified to pH ~2 with concentrated HCl and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give the product as an oil. MS: m/z (M+1) 466.

The compounds below were prepared from the corresponding methyl esters.

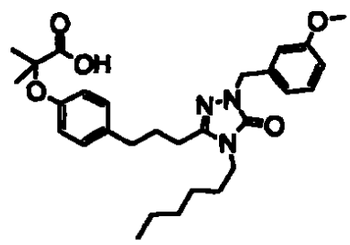


Example Number	R	MS:m/z (M+1)
12(2)	2-Methoxyethyl	468
12(3)	2-Ethoxyethyl	482
12(4)	2-Oxobutyl	480
12(5)	4-Hydroxybutyl	482
12(6)	2-Hydroxyethyl	454
12(7)	2-(N,N-Diethyl)ethyl	509
12(8)	3,3-Dimethyl-2-oxobutyl	508
12(9)	Cyclopropylmethyl	464
12(10)	1-Morpholinocarbonyl-2-methylpropyl	579
12(11)	2-Carboxyethyl	482
12(12)	THPether	552
12(13)	3-Hydroxypropyl	468
12(14)	Carboxymethyl	468
12(15)	Isopropyl	452
12(16)	methoxyethyloxyethyl	512

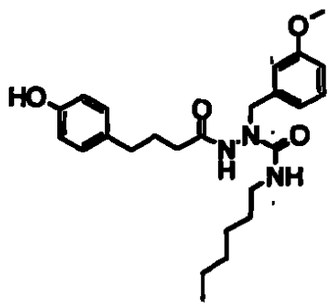
12(17)	3-Methoxy-2-hydroxypropyl	498
12(18)	2-Pyridylmethyl	501
12(19)	4-Pyridylmethyl	501
12(20)	Benzyl	500
12(21)	2,2,2-trifluoroethyl	492
12(22)	3,3,3-trifluoropropyl	506
12(23)	4,4,4-trifluorobutyl	520

Example 13

Compound 13



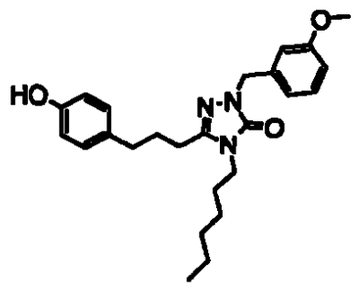
Step A: Preparation of



123

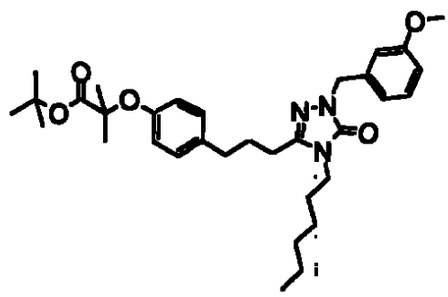
To a solution of hydrazide, specifically the 3-methoxyphenyl compound of Example 1, Step B (250 mg, 0.79 mmol) in anhydrous THF (5 mL) was added n-hexylisocyanate (202 mg, 1.59 mmol). The reaction mixture was stirred at room temp for 18 h. Methanol (1 mL) was added to the reaction mixture and it was stirred for an additional 30 min. The solvent was evaporated on a rotary evaporator to give the semicarbazate. MS: m/z (M+1) 442

Step B: Preparation of



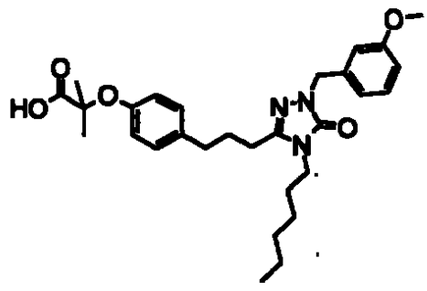
To a solution of the Step A product, in methanol (20 mL) and water (0.5 mL) was added KOH (500 mg). The reacion mixture was heated at reflux with stirring for 48 h. The reaction mixture was cooled to room temp and concentrated on a rotary evaporator to a small volume (5 mL). The reaction mixture was diluted with water (30 mL) and acidified with 5N HCl (pH 2-3) and extracted with ethyl acetate (2 x 35 mL). The combined organic layers were dried over Na_2SO_4 and concentrated on a rotary evaporator to give product as a colorless oily residue. MS: m/z (M+1) 424.

Step C: Preparation of



To a solution of the Step B product (300 mg, 0.71 mmol) in anhydrous DMF (5 mL) was added tert-butyl bromoisobutyrate (1 gm, 4.48 mmol) followed by powdered anhydrous K_2CO_3 (20 mmol). The reaction mixture was heated at 50 °C with stirring for 64 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 x 30 mL). Combined ethyl acetate layer dried (Na_2SO_4) and concentrated to dryness on rotary evaporator to give an oily residue. The crude was purified on a flash silica column eluting with 20% ethyl acetate-hexane mixture giving the product as a colorless oil. MS: m/z (M+1) 566

Step D: Preparation of

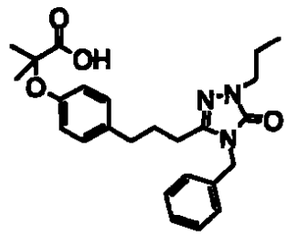


The Step C product (225 mg) was treated with a 50:50 mixture of TFA and dichloromethane (10 mL). The reaction was stirred at room temperature for 2 h. The solvent was removed on a rotary evaporator and the residue was dried under high vacuum to give the product as a colorless oil. MS: m/z (M+1) 510.

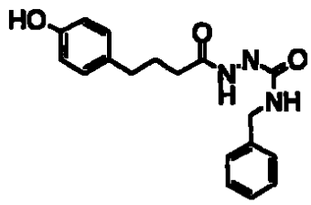
125

Example 14

Compound 14(1)

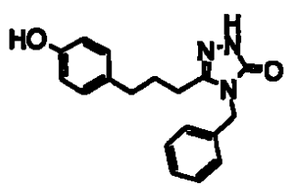


Step A: Preparation of



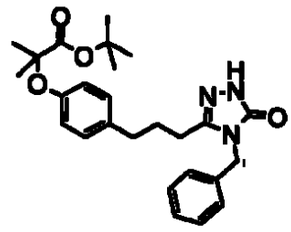
To a solution of 4-(4-hydroxyphenyl)butyrylhydrazine (200 mg, 1.03 mmol) in THF (5 mL) was added benzylisocyanate (200 mg, 1.5 mmol). The reaction mixture was stirred at room temperature for 48 h. Methanol (1 mL) was added to the reaction mixture and stirred for and additional 30 minutes. Solvent was removed on rotary evaporator to give the product as a white solid. MS: m/z (M+1) 328

Step B: Preparation of



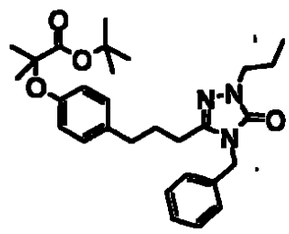
To a solution of the Step A semicarbazate (315 mg) in methanol (20 mL) was added solid KOH (1 gm). The reaction was heated at reflux with stirring for 20 h. The reaction mixture was concentrated to small volume (5 mL), acidified with 5N HCl to pH 3. It was then extracted with ethyl acetate (2 x 30 mL). Ethyl acetate layer was dried (Na2SO4) and concentrated to dryness to give the product as gummy solid. MS: m/z (M+1) 310

Step C: Preparation of

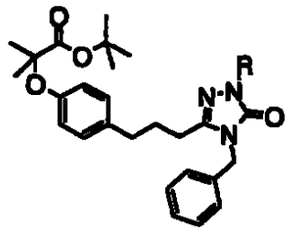


To a solution of the Step B benzyl triazolinone (270 mg) in DMF (7.5 mL) was added tert-butyl isobutyrate (1.1 g) followed by solid powdered anhydrous K2CO3 (500 mg). The reaction mixture was heated at 50 oC with stirring for 3 days. The reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 x 40 mL). Ethyl acetate layer dried (Na2SO4) and concentrated on a rotary evaporator to give a crude residue. The crude was purified on a flash silica column eluting with 60 % ethyl acetate-hexane to give the product. MS: m/z (M+1) 452

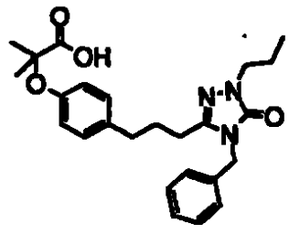
Step D: Preparation of



To a solution of the Step C benzyltriazolinone (30 mg) in anhydrous THF (1 mL) was added 1-iodoproapane followed by 1M methanolic KOH solution (1 mL). Reaction initially stirred at room temp for 24 h. The reaction was then heated at 50 oC for and 18 h. The reaction mixture was diluted with water 920 mL) and extracted with ethyl acetate (2 x 20 mL). Ethyl acetate layer was dried (Na2SO4) and concentrated to dryness to give a residue. The residue was purified on flash silica column eluting with 40% ethyl acetate -hexane mixture to give the product.
MS: m/z (M+1) = 494.



Step E: Preparation of



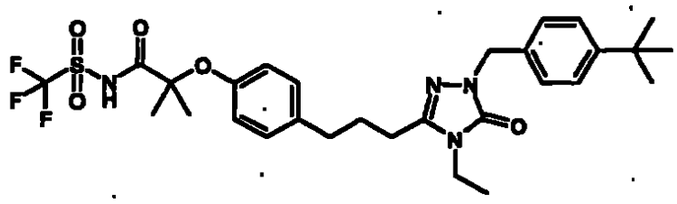
The Step D tert-butyl ester, descibed (16 mg) was treated with a 50% mixture of trifluoroacetic acid and dichloromethane (2 mL) for 2 h with stirring. The solvent was removed on a rotary evaporator and the residue dried under high vacuum to give the product as an oil.
MS: m/z (M+1) 438

The compounds below were synthesized by alkylating benzyltriazolinone, using appropriate bromides to give the corresponding products.

Example Number	R	MS: m/z (M+1)$^+$
14(2)	H	
14(3)	Benzyl	
14(4)	4-tert-butylbenzyl	

Example 15

Compound 15(1)

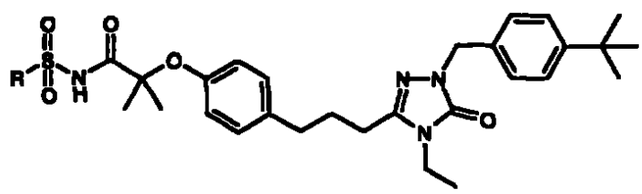


To a solution of the compound described in Example 4, Compound 4(19) (120 mg, 0.25 mmol), trifluoromethanesulfonamide (37 mg, 0.25 mmol), and 4-dimethylaminopyridine (31 mg, 0.25 mmol) in methylene chloride (2 mL) at ambient temperature was added N,N-diisopropylethylamine (65 mg, 0.50 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbo-diimide hydrochloride (77 mg, 0.40 mmol). After stirring for 24 hours, the reaction mixture was concentrated in vacuo to give a residue which was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to an oil which was purified by flash chromatography (gradient

elution, 1:4 ethyl acetate:hexanes to 100% ethyl acetate) to give the desired product as a white solid.

$C_{29}H_{37}N_4O_5SF_3$ (MW = 610.70); mass spectroscopy (MH^+) = 611.

The following compounds were also prepared utilizing the appropriate sulfonamide (listed in the table) by the procedure of Compound 15(1).

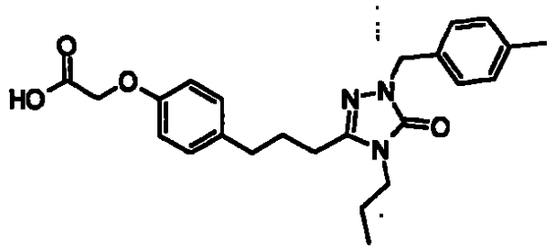


Example Number	RSO_2NH_2	R	$(MH)^+$
15(2)	benzenesulfonamide	phenyl	619
15(3)	α-toluenesulfonamide	benzyl	633
15(4)	4-methoxybenzenesulfonamide	4-methoxyphenyl	649
15(5)	naphthalene-2-sulfonamide	β-naphthyl	669
15(6)	Methanesulfonamide	Methyl	557
15(7)	5-bromothiophene-2-sulfonamide	5-bromo-2-thienyl	704
15(8)	3-chlorobenzenesulfonamide	3-chlorophenyl	654

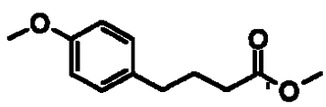
15(9)	6-ethoxy-2-benzothiazolesulfonamide	6-ethoxy-2-benzothiazolyl	720

Example 16

Compound 16

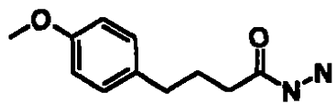


Step A: Preparation of methyl 4-(4-methoxyphenyl)-butyrate



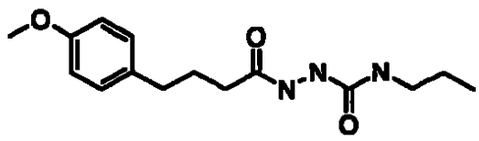
To a solution of 4-(4-methoxyphenyl)-butyric acid (25.1 g, 0.129 mol) in methanol (130 mL), was added sulfuric acid (concentrated, 1.0 mL) dropwise and it was stirred at room temperature overnight under nitrogen. The reaction mixture was concentrated on a rota-vapor, the residue was then partitioned between ethyl acetate (200 mL) and saturated sodium bicarbonate aqueous solution (200 mL). The organic phase was separated, washed with brine (3 x 200 mL), then dried over Na_2SO_4 and filtered. Evapbration of solvent gave the titled compound as an oil (26.8 g, 99%). Mass (MH+) = 209.

Step B: Preparation of



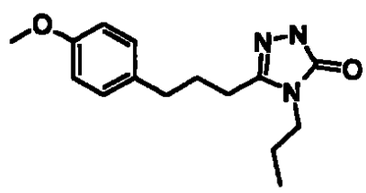
A mixture of methyl 4-(4-methoxyphenyl)-butyrate (10.4 g, 0.0500 mol) from Step A and hydrazine hydrate (25.0 g, 0.500 mol) in methanol (250 mL) was heated under reflux for an hour. It was then cooled down to room temperature and stirred overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The organic layer was washed with brine (3 x 200 mL), dried over Na_2SO_4, filtered and concentrated to dryness to give the titled compound as a white crystal (8.79 g, 85%). Mass (MH+) = 209.

Step C: Preparation of



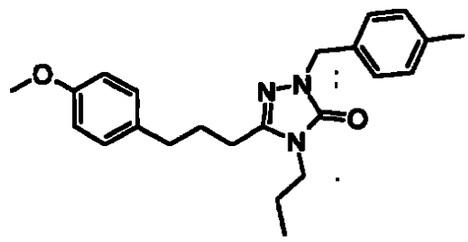
To a solution of the Step B product (8.76 g, 0.0421 mol) in THF (200 mL), was added n-propyl isocyanate (Aldrich, 4.34 mL, 0.0463 mol) dropwise and the mixture was stirred at room temperature for an hour. Evaporation of solvent gave the titled compound as an off-white powder (12.4 g, 100%). Mass (MH+) = 294.

Step D: Preparation of



To a solution of the Step C product (12.4 g, 0.0421 mol) in methanol (200 mL), was added potassium hydroxide in one portion (35.4 g, 0.632 mol). The reaction mixture was heated at 70 °C for 36 hours. It was then concentrated on a rota-vapor, the residue was then partitioned between methylene chloride (150 mL) and water (150 mL), it was brought to pH = 7 by concentrated HCl before the two layers was separated. The aqueous layer was extracted with more methylene chloride (150 mL). The combined organic layers was dried over Na_2SO_4 and filtered. Evaporation of solvent gave the titled compound as a off-white solid (11.2 g, 97%). Mass (MH+) = 276.

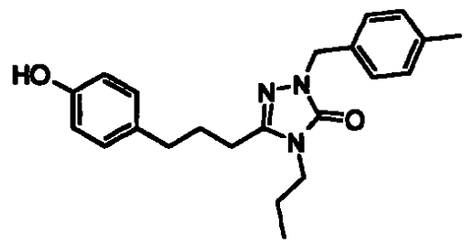
Step E: Preparation of



To a solution of the Step D product (5.51 g, 0.0200 mol) in DMF (100 mL), was added α-bromo-p-xylene (8.30 g, 0.0440) followed by potassium carbonate powder (13.8 g, 0.100 mol). It was heated to 70 °C under nitrogen overnight. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (200 mL), the aqueous layer was extracted with ethyl acete (200 mL) one more time. The organic phase was combined, washed with brine (4 x 200 mL), then dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 20-60% ethyl acetate in hexane to give

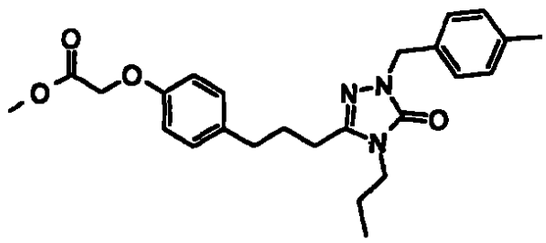
the titled compound as colorless oil (6.59 g, 87%). Mass (MH+) = 380.

Step F: Preparation of



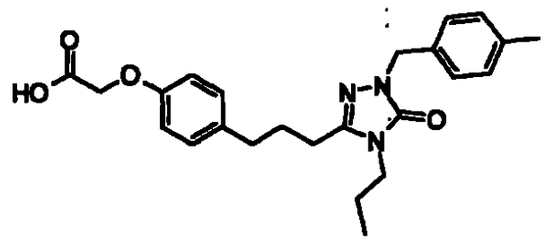
To a solution of the Step E product (6.55 g, 0.0173 mol) in DCM (100 mL) at 0 °C, was added dropwise the solution of BBr_3 (4.91 mL, 0.0519 mL) in methylene chloride (25 mL). The reaction was kept at 0 °C and stirred for an hour. It was then quenched by 1:1 MeOH/DCM (20 mL), stirred for another hour at 0 °C, then room temperature overnight. The reaction mixture was washed with water (3 x 100 mL), and the organic layer was separated, dried over Na_2SO_4, filtered and concentrated to an yellow oil, which was purified by chromatography on a silica gel column eluting with 20-60% ethyl acetate in hexane to give the titled compound as a white solid (2.39 g, 39%). Alternatively, the titled compound can also be made at -78 °C instead of 0 °C on the same scale, white solid (4.89g, 78%). Mass (MH+) = 366.

Step G: Preparation of



The Step F product (0.100 g, 0.000274 mol) was dissolved in DMF (1.0 mL), to it was added methyl bromoacetate (0.103 g, 0.000548 mol) followed by potassium carbonate (0.189 g, 0.00137 mol). After heated at 50 °C over weekend, the reaction mixture was diluted with ethyl acetate (2 mL), washed with water (2 mL), the separated organic layer was pass through a chem elut 1005 tube, and the tube was washed with more ethyl acetate (50 mL). Evaporation of solvent gave the methyl ester as an oil, which was purified on Biotage Quad3 (silica gel, 20-60% ethylacetate in hexane). Mass (MH+) 438.

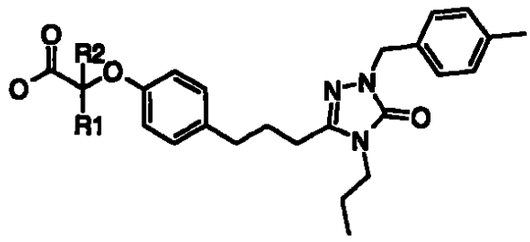
Step H: Preparation of



The methyl ester obtained from Step G was treated with 1:1 MeOH/5.0N NaOH (6 mL) at room temperature overnight, and then concentrated. The resulting residue was diluted with water (2 mL), cooled down to 0 °C, acidified to pH = 2 by adding concentrated HCl dropwise. The aqueous suspension was loaded on a Chem elut 1005 tube, eluted with DCM (50 mL). Evaporation of methylene chloride gave the titled compound as an il (0.103 g, 89%). Mass (MH+) = 424.

135
137

The compounds listed below were prepared according to the procedure outlined above by using the appropriate methyl or ethyl α-substituted-α-bromo ester in Step G.



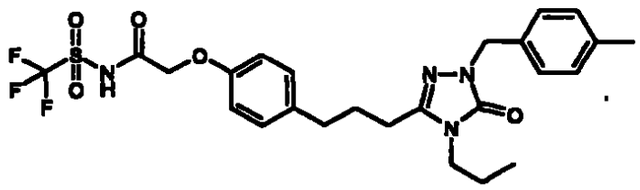
Example Number	R1	R2	MS (m/z)
16(2)	Methyl	H	438
16(3)	Ethyl	H	452
16(4)	Isopropyl	H	466
16(5)	F	F	460
16(6)	$-(CH_2)_3-$		464
16(7)	Cyclohexyl	H	506
16(8)	Phenyl	H	500
16(9)	Hydroxyethyl	H	468
16(10)	F	H	442
16(11)	n-Butyl	H	480

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16(12)	n-Pentyl	H	494
16(13)	4-fluoro phenyl	H	518

Example 17

Compound 17

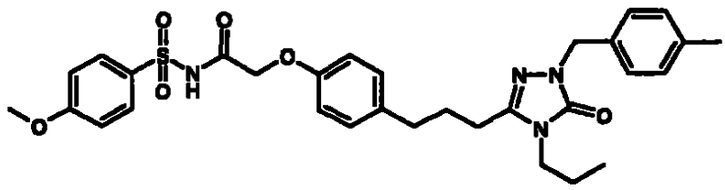


To a solution of the compound described in Example 16, **clarify, please (45 mg, 0.10 mmol), trifluoromethanesulfonamide (15 mg, 0.10 mmol), and 4-dimethylaminopyridine (12 mg, 0.10 mmol) in methylene chloride (1 mL) at ambient temperature was added N,N-diisopropylethylamine (26 mg, 0.20 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (31 mg, 0.16 mmol). After stirring for 24 hours, the reaction mixture was concentrated in vacuo to give a residue which was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated to an oil which was purified by flash chromatography (gradient elution, 1:4 ethyl acetate:hexanes to 100% ethyl acetate) to give the desired product as a white solid. $C_{25}H_{29}F_3N_4O_5S$ (MW = 554.59); mass spectroscopy (MH^+) = 555.

137

Example 18

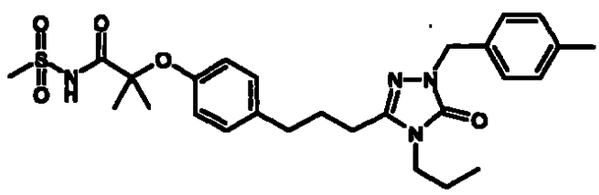
Compound 18



The title compound was prepared utilizing the Example 16 product and 4-methoxybenzenesulfonamide according to the procedure described in Example 17. $C_{31}H_{36}N_4O_6S$ (MW = 592.72); mass spectroscopy (MH^+) = 593.

Example 19

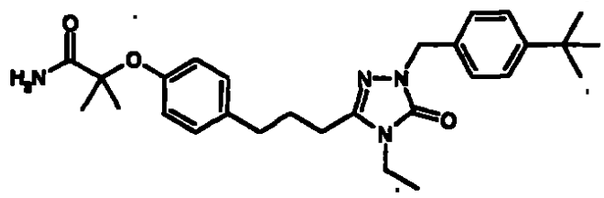
Compound 19



The title compound was prepared utilizing the compound described in Example 5, Compound 5(8), and methane sulfonamide according to the procedure described in Example 17. $C_{27}H_{36}N_4O_5S$ (MW = 528.68); mass spectroscopy (MH^+) = 529

Example 20

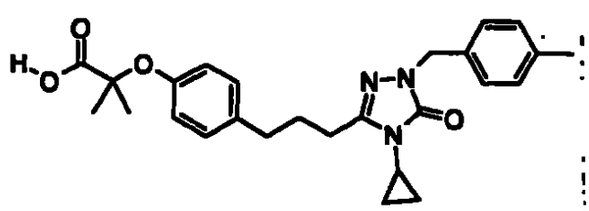
Compound 20



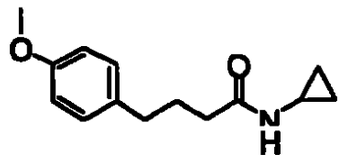
To a cooled (0 °C) solution of the compound described in Example 4, Compound 4(19)(164 mg, 0.34 mmol) in methylene chloride (3 mL) was added oxalyl chloride (178 µL, 2.0 mmol) followed by N,N-dimethylformamide (1 drop). After stirring in cold bath for 0.25 hour, the reaction mixture was stirred at room temperature for one hour, then concentrated to dryness. The residue was dissolved in tetrahydrofuran (15 mL) and the resulting solution added dropwise to chilled (0 °C) concentrated ammonium hydroxide (30 mL) with vigorous stirring. The mixture was stirred at 0 °C for one hour, then stirred at room temperature for 20 hours. Concentration gave a residue which was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The ethyl acetate layer was washed with water, brine, dried (Na_2SO_4), and concentrated to give the desired product as a foam. $C_{28}H_{38}N_4O_3$ (MW = 478.64); mass spectroscopy (MH^+) = 479.

Example 21

Compound 21

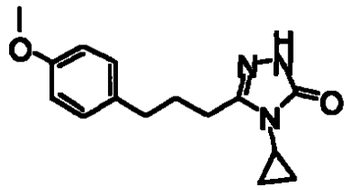


Step A: Preparation of:



To a solution of 4-(4-methoxyphenyl)-butyric acid (2.13 g, 11 mmol), cyclopropylamine (1.14 mL, 16 mmol), HOAt (1.49 g, 11 mmol) and DMAP (134 mg, 1 mmol) in 70 mL of dry DMF, 3.07 g of EDC (16 mmol) was added in one portion. The resulting mixture was allowed to stand under N_2 for 8 h. Then the mixture was diluted with 50 mL of Et_2O. Organic layer was washed with 1N HCl (3 x 20 mL), brine (3 x 20 mL) and dried over Na_2SO_4, filtered. The organic solvent was then removed under vacuum. Residue was purified by column chromatography to give the title compound. MS ($M+1^+$) m/z 234.

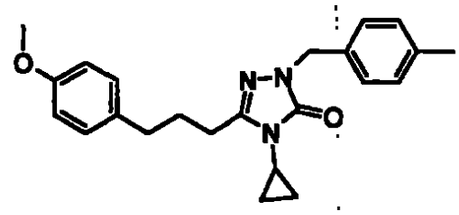
Step B: Preparation of:



To a solution of the Step A product (1.72 g, 7.37 mmol) in 9 mL of dry CH_2Cl_2, 2.18 g of trimethyl-oxonium tetrafluoroborate (14.7 mmol) was added in one portion. The mixture was allowed to stand at r.t. for 4 h. Organic solvent was then removed under vacuum. Residue was redissolved in 50 mL of Et_2O and washed with cold sat' aq. K_2CO_3 (3 x 10 mL), brine (3 x 10 mL). The ether layer was then dried over Na_2SO_4, filtered and concentrated. The

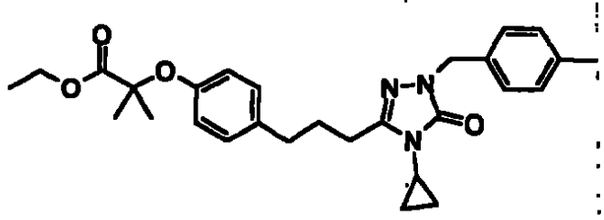
residue was dissolved in 30 mL of dry toluene. To the solution, 0.79 g of ethylcarbazate was added. The mixture was heated to reflux for 38 h. Organic solvent was then removed under vacuum. Residue was purified by chromatography to give the title compound. MS (M+1$^+$) m/z 274.

Step C: Preparation of



A mixture of the Step B product (1.53 g, 5.6 mmol), 4-methylbenzyl bromide (2.1 g, 11.2 mmol) and K_2CO_3 (7.7 g, 56 mmol) in 25 mL of dry DMF was heated at 60 °C for 12 h. The mixture was then diluted with 75 mL of Et_2O and filtered. Organic layer was washed with 1N HCl (3 x 15 mL), brine (3 x 15 mL), dried over $MgSO_4$, filtered and concentrated. Residue was purified by chromatography to give the title compound. MS (M+1$^+$) m/z 377.

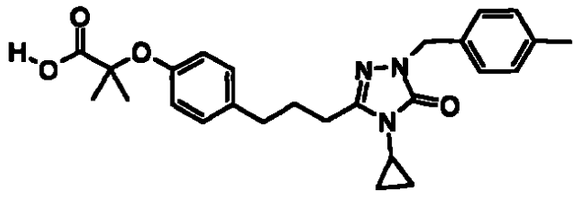
Step D: Preparation of



To a solution of the Step C product (1.01 g, 2.7 mmol) in 50 mL of dry CH_2Cl_2 at -78 °C, 0. 8 mL of BBr_3 (8.1 mmol)

was added dropwise. The resulting solution was warmed up to 0 °C in 10 min. and maintained at same temperature for 2h. The mixture was then diluted with 200 mL of Et_2O. Organic layer was washed with H_2O (3 x 20 mL), brine (3 x 20 mL) and dried over Na_2SO_4, filtered. Organic solvent was removed under vacuum. Residue was dissolved in 25 mL of absolute EtOH. To the solution, 3.1 mL of 2-bromo-ethylbutyrate (21.2 mmol), 1.26 g of K_2CO_3 (9.1 mmol) and 365 mg of $MgSO_4$ (3.03 mmol) were added. The resulting mixture was heated to 70 °C for 12 h. Solid was filtered off and organic solvent was removed under vacuum. The residue was then dissolved in 75 mL of CH_2Cl_2. The organic layer was washed with 1N HCl (3 x 10 mL), brine (3 x 10 mL), dried over Na_2SO_4, filtered and then concentrated. Residue was purified by chromatography to give the title compound. MS ($M+1^+$) m/z 478.

Step E: Preparation of



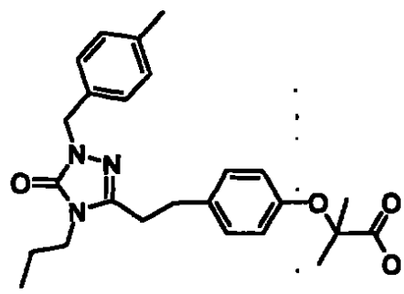
To a solution of the Step D product (490 mg, 1.03 mmol) in 20 mL of EtOH, 1.0 mL of 5N NaOH was added. The resulting solution was heated to reflux for 30 min. Organic solvent was removed under vacuum. Residue was dissolved in 30 mL of CH_2Cl_2 and washed with 1N HCl (2 x 10 mL), brine (2 x 10 mL). Organic layer was then dried over Na_2SO_4, filtered and concentrated. Residue was purified by

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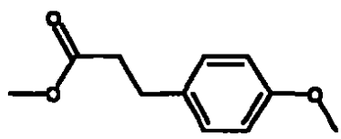
chromatography to give the title compound. MS ($M+1^+$) m/z 450.

Example 22

Compound 22

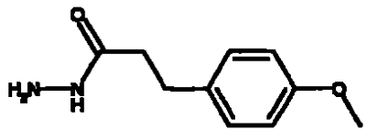


Step A: Preparation of



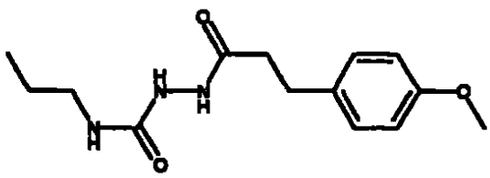
A methanol solution (500 mL) of 3-(4-methoxyphenyl)propionic acid (Aldrich, 10.15 g, 0.056 mol) was treated with H_2SO_4 (concentrated, 3 mL) and stirred at room temperature overnight. The solvent was evaporated and the residue diluted with CH_2Cl_2 (150 mL). The resulting solution was extracted with saturated aqueous sodium bicarbonate (1X150 mL) followed by brine (1X150 mL), then dried over Na_2SO_4. Upon evaporation of the solvent the desired methyl ester was obtained as a colorless oil. $C_{11}H_{14}O_3$ (MW = 194.23); mass spectroscopy (MH^+) = 195.1

Step B: Preparaion of



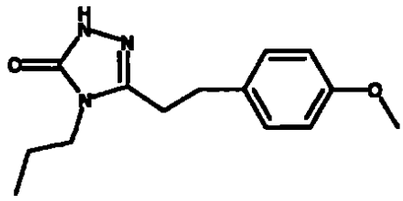
A methanol solution (60 mL) of methyl ester from Step A (10.6 g, 0.055 mol) was treated with hydrazine hydrate (30 g, 0.60 mol) and stirred overnight. The solvent was evaporated and the residue dissolved in ethyl acetate (300 mL). The resulting solution was extracted with H_2O (300 mL). The aqueous extract was back extracted with ethyl acetate (300 mL) then the combined organic extracts were dried over Na_2SO_4 and concentrated to give a white solid. The product was suspended in hexane (100 mL) then filtered to give the desired acyl hydrizide as a white solid. $C_{10}H_{14}N_2O_2$ (MW = 194,23); mass spectroscopy (MH^+) = 195.1

Step C: Preparation of



A THF solution (125 mL) of the acyl hydrizide from Step B (9.2 g, 0.047 mol) was treated with a THF solution (50 mL) of n-propyl isocyanate (Aldrich, 5.3 mL, 0.057 mol) - added dropwise over 15 minutes. The mixture was stirred overnight during which a thick precipitate formed. The resulting suspension was treated with methanol (100 mL) and stirred approximately 2 hours. The solvent was then concentrated to give the desired acyl semicarbazide as a white solid which was used without further purification.

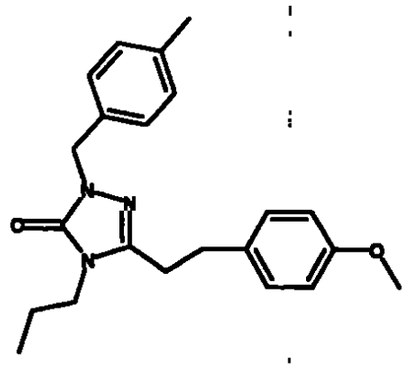
Step D: Preparation of



The acyl semicarbazide from Step C (13.4 g, 0.048 mol) was dissolved in methanol (100 mL), treated with KOH (27 g, 0.48 mol), then heated to 60 °C for 16 hr and 85 °C for an additional 6 hr. The reaction mixture was cooled to room temperature, poured into H_2O, then extracted with ethyl acetate (3X500 mL). The combined organic extracts were dried over Na_2SO_4 then concentrated to give the desired N4-propyl triazolinone as a slightly yellow solid.

$C_{14}H_{19}N_3O_2$ (MW = 261.33); mass spectroscopy (MH^+) = 262.1

Step E: Preparation of

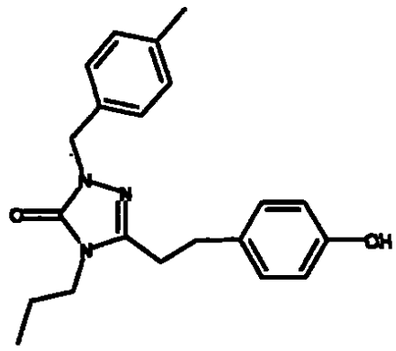


The N4-propyl triazolinone from Step D (1.05 g, 4.0 mmol) was dissolved in DMF (25 mL) and treated with α-bromo-p-xylene (1.17 g, 6.3 mmol) and powdered K_2CO_3 (3.17 g, 0.023 mol). The resulting mixture was heated to 50 °C under a drying tube overnight. The reaction mixture was cooled to room temperature, poured into aqueous HCl (1N, 75 mL) and extracted into ethyl acetate (75 mL). The organic extract was washed with brine, dried over Na_2SO_4, then concentrated to give the crude product. Purification by flash

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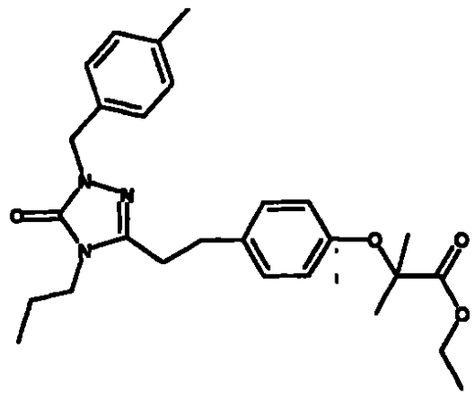
chromatography (1:1 hexanes:ethyl acetate) gave the desired N2-p-methylbenzyl triazolinone as a slightly yellow oil. $C_{22}H_{27}N_3O_2$ (MW = 365.48); mass spectroscopy (MH^+) = 366.1.

Step F: Preparation of



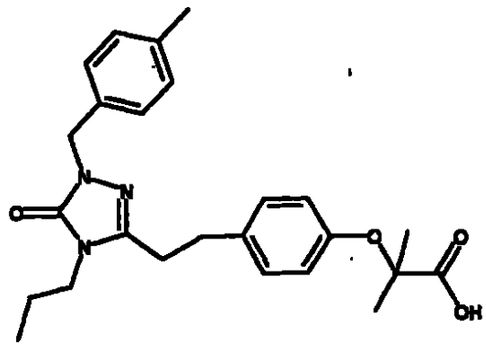
The N2-p-methylbenzyl triazolinone from Step E (0.95 g, 2.6 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C under N_2. To this solution was added, dropwise, a CH_2Cl_2 solution (10 mL) of BBr_3 (1.0 mL, 10.6 mmol). After stirring for 2 hr at 0 °C, the reaction mixture was quenched by the dropwise addition of methanol/CH_2Cl_2. The resulting mixture was poured into H_2O and extracted with additional CH_2Cl_2 (50 mL). The organic extract was washed with brine, dried over Na_2SO_4, then concentrated to give the desired phenol as a slightly yellow oil. $C_{21}H_{25}N_3O_2$ (MW = 351.45); mass spectroscopy (MH^+) = 352.2.

Step G: Preparation of



The phenol from Step F (0.81 g, 2.3 mmol) was dissolved in ethanol (absolute, 15 mL) and treated with ethyl 2-bromoisobutyrate (1.2 mL, 8.2 mmol), powdered K_2CO_3 (1.4 g, 10.1 mmol), and $MgSO_4$ (1.0 g, 8.3 mmol). The resulting mixture was heated to 60 °C under a drying tube overnight. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated. The resulting residue was dissolved in CH_2Cl_2 (100 mL) and washed with aqueous HCl (1N, 100 mL) followed by brine. The organic extract was dried over Na_2SO_4 then concentrated to give the crude product. Purification by flash chromatography (1:1 hexanes:ethyl acetate) gave the desired ethyl ester as an oil. $C_{27}H_{35}N_3O_4$ (MW = 465.60); mass spectroscopy (MH^+) = 466.2.

Step H: Preparation of

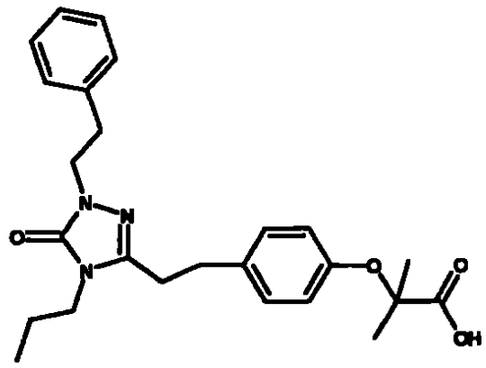


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The ethyl ester from Step G (277.3 mg, 0.60 mmol) was dissolved in dioxane/H_2O (10 mL/3 mL) and treated with LiOH (44 mg, 1.8 mmol). The resulting mixture was stirred overnight then concentrated. The resulting residue was diluted with CH_2Cl_2 (25 mL) and extracted with aqueous NaOH (1N, 2X25 mL). The combined aqueous extracts were acidified by the careful addition of aqueous HCl (5N) then extracted into CH_2Cl_2 (2X25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give the desired carboxylic acid an a colorless oil. $C_{25}H_{31}N_3O_4$ (MW= 437.54); Mass spectroscopy (MH^+)=438.2 (MH^-)=436.3

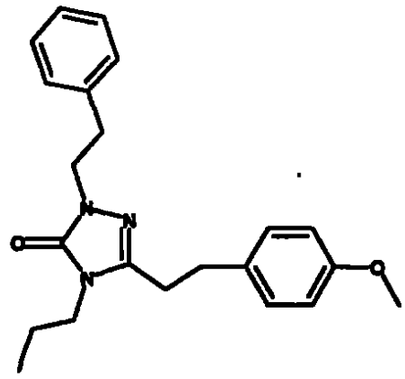
Example 23

Compound 23



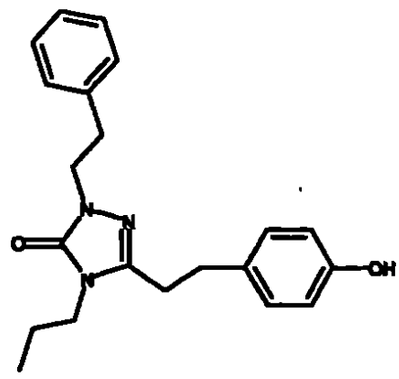
Step A: Preparation of

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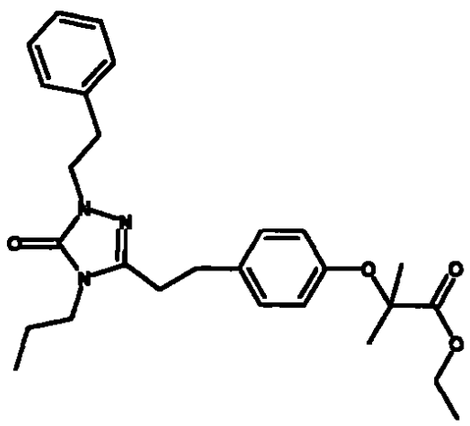
The N4-propyl triazolinone from Example 22, Step D (1.13 g, 4.3 mmol) was dissolved in DMF (25 mL) and treated with phenethylbromide (710 □L, 5.2 mmol) and powdered K_2CO_3 (1.25 g, 9.0 mmol). The resulting mixture was heated to 50-60 °C under a drying tube overnight. The reaction mixture was cooled to room temperature, poured into aqueous HCl (1N, 75 mL) and extracted into ethyl acetate (100 mL). The organic extract was washed with brine, dried over Na_2SO_4, then concentrated to give the crude product. Purification by flash chromatography (gradient 2:1 to 1:1 hexanes:ethyl acetate) gave the desired N2-phenethyl triazolinone as an oil. $C_{22}H_{27}N_3O_2$ (MW = 365.48); mass spectroscopy (MH^+) = 366.1.

Step B: Preparation of



The N2-phenethyl triazolinone from Step A (0.83 g, 2.3 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C under N_2. To this solution was added, dropwise, a CH_2Cl_2 solution (10 mL) of BBr_3 (1.0 mL, 10.6 mmol). After stirring for 2 hr at 0 °C, the reaction mixture was quenched by the dropwise addition of methanol/CH_2Cl_2. The resulting mixture was poured into H_2O and extracted with additional CH_2Cl_2 (50 mL). The organic extract was washed with brine, dried over Na_2SO_4, then concentrated to give the desired phenol as a slightly yellow oil. $C_{21}H_{25}N_3O_2$ (MW = 351.45); mass spectroscopy (MH^+) = 352.2.

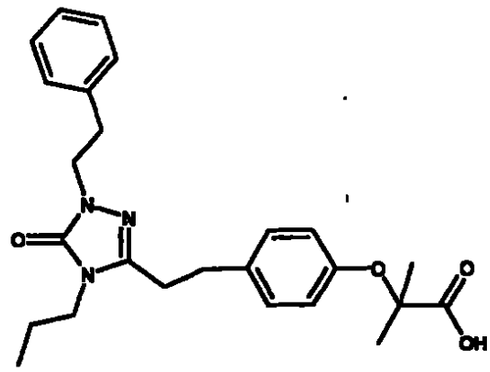
Step C: Preparation of



The phenol from Step B (0.78 g, 2.2 mmol) was dissolved in ethanol (absolute, 15 mL) and treated with ethyl 2-bromoisobutyrate (1.2 mL, 8.2 mmol), powdered K_2CO_3 (1.4 g, 10.1 mmol), and $MgSO_4$ (1.0 g, 8.3 mmol). The resulting mixture was heated to 60 °C under a drying tube overnight. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated. The resulting residue was dissolved in CH_2Cl_2 (100 mL) and washed with aqueous HCl (1N, 100 mL) followed by brine. The organic extract was dried over Na_2SO_4 then

concentrated to give the crude product. Purification by flash chromatography (1:1 hexanes:ethyl acetate) gave the desired ethyl ester as an oil. $C_{27}H_{35}N_3O_4$ (MW = 465.60); mass spectroscopy (MH^+) = 466.3.

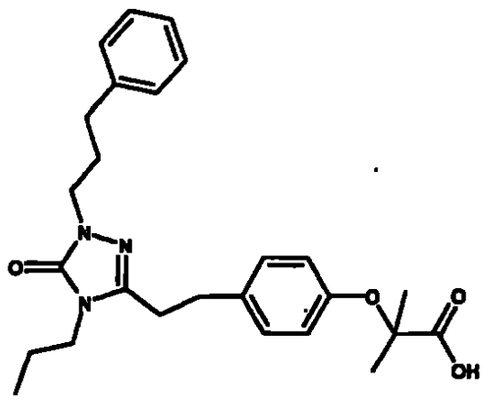
Step D: Preparation of



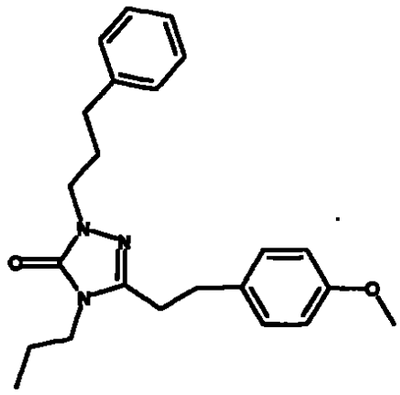
The ethyl ester from Step C (0.78 g, 1.7 mmol) was dissolved in dioxane/H_2O (20 mL, 3/1) and treated with LiOH (122 mg, 5.1 mmol). The resulting mixture was stirred overnight then concentrated. The resulting residue was diluted with ethyl acetate (50 mL) and extracted with aqueous HCl (1N, 50 mL). The organic extract was reextracted with aqueous NaOH (1N, 1 X 50 mL). The resulting aqueous washing was acidified by the addition of aqueous HCl (5N) then extracted with ethyl acetate (2X50 mL). The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to give the desired carboxylic acid an a colorless oil. $C_{25}H_{31}N_3O_4$ (MW = 437.54); mass spectroscopy (MH^+) = 438.2; (MH^-) = 436.3

Example 24

Compound 24

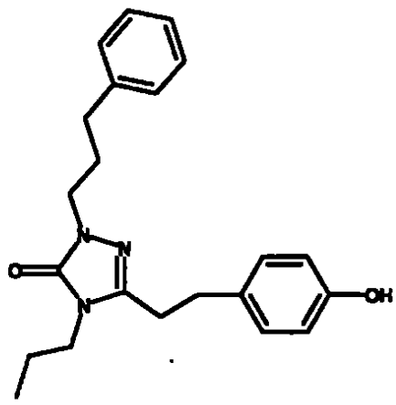


Step A: Preparation of



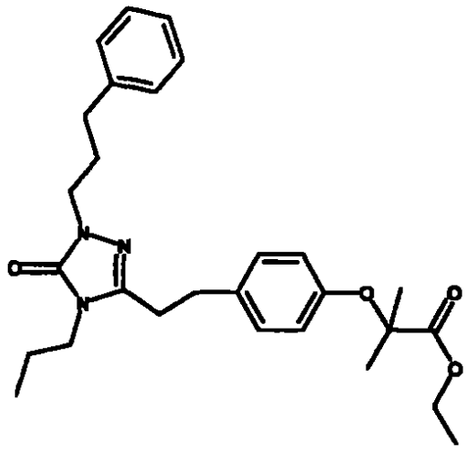
The N4-propyl triazolinone from Example 22, Step D (1.07 g, 4.1 mmol) was dissolved in DMF (25 mL) and treated with 3-phenylpropyl bromide (750 µL, 4.9 mmol) and powdered K_2CO_3 (1.2 g, 8.7 mmol). The resulting mixture was heated to 50-60 °C under a drying tube overnight. The reaction mixture was cooled to room temperature, poured into aqueous HCl (1N, 75 mL) and extracted into ethyl acetate (100 mL). The organic extract was washed with brine, dried over Na_2SO_4, then concentrated to give the crude product. Purification by flash chromatography (1:1 hexanes:ethyl acetate) gave the desired N2-(3-phenylpropyl) triazolinone as a slightly yellow oil. $C_{23}H_{29}N_3O_2$ (MW = 379.51); mass spectroscopy (MH^+) = 380.1

Step B: Preparation of



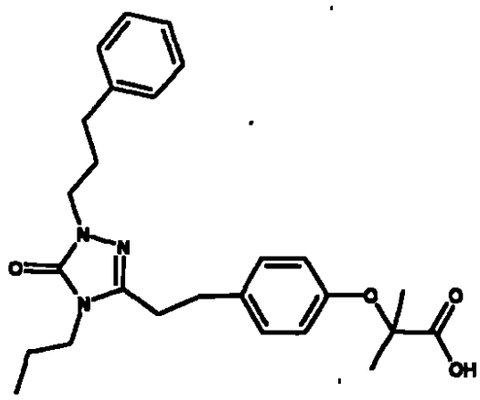
The N2-(3-phenylpropyl) triazolinone from Step A (0.92 g, 2.4 mmol) was dissolved in CH_2Cl_2 and cooled to 0 °C under N_2. To this solution was added, dropwise, a CH_2Cl_2 solution (10 mL) of BBr_3 (0.60 mL, 5.6 mmol). After stirring for approximately 1.5 hr at 0 °C, the reaction mixture was quenched by the dropwise addition of methanol/CH_2Cl_2. The resulting mixture was poured into H_2O and extracted with additional CH_2Cl_2 (2 X 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, then concentrated to give the crude phenol as a colorless oil (used without further purification). $C_{22}H_{27}N_3O_2$ (MW = 365.48); mass spectroscopy (MH^+) = 366.2.

Step C: Preparation of



The phenol from Step B (0.91 g, 2.5 mmol) was dissolved in ethanol (absolute, 15 mL) and treated with ethyl 2-bromoisobutyrate (1.2 mL, 8.2 mmol), powdered K_2CO_3 (1.4 g, 10.1 mmol), and $MgSO_4$ (0.62 g, 5.2 mmol). The resulting mixture was heated to 60 °C under a drying tube overnight. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated. The resulting residue was diluted with aqueous HCl (0.5N, 75 mL) and extracted with CH_2Cl_2 (2 X 75 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 then concentrated to give the crude product. Purification by flash chromatography (gradient 5:1 to 1:1 hexanes:ethyl acetate) gave the desired ethyl ester as a colorless oil. $C_{28}H_{37}N_3O_4$ (MW = 479.62); mass spectroscopy (MH^+) = 480.2.

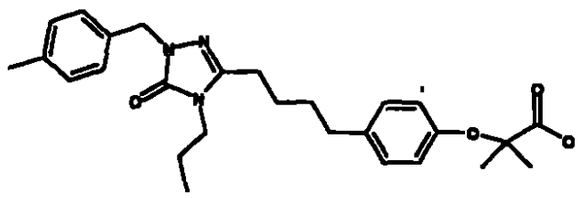
Step D: Preparation of



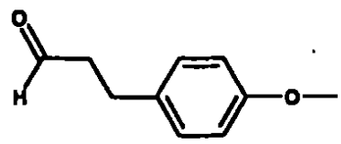
The ethyl ester from Step C (0.82 g, 1.7 mmol) was dissolved in dioxane/H_2O (16 mL, 3/1) and treated with LiOH (140 mg, 5.8 mmol). The resulting mixture was stirred at room temperature for 2 hr then 45 °C for an additional 2 hr. The mixture was concentrated and the resulting residue was diluted with ethyl acetate (50 mL) and extracted with aqueous HCl. The organic extract was reextracted with aqueous NaOH (1N, 1 X 50 ml). The resulting aqueous washing was acidified by the addition of aqueous HCl (5N) then extracted with ethyl acetate (1 X 50 mL). The organic extract was dried over Na_2SO_4 and concentrated to give the desired carboxylic acid an a colorless oil. $C_{26}H_{33}N_3O_4$ (MW = 451.25); mass spectroscopy (MH^+) = 452.3; (MH^-) = 450.3.

Example 25

Compound 25

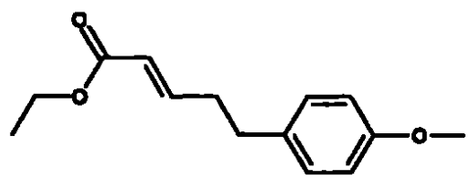


Step A: Preparation of



A methylene chloride solution (300 mL) of 3-(4-methoxyphenyl)-1-propanol (Aldrich, 15.0 g, 0.090mol) was cooled to 0 ^{0}C and stirred. Pyridinium chlorochromate (Aldrich, 23.4 g, 0.108 mol) was slowly added to the solution which was then warmed to room temperature, placed under a drying tube and stirred over a weekend (approx. 72 hrs.). The reaction mixture was filtered through a pad of Florisil (Aldrich) and the filtrate was concentrated to give the crude product as a dark oil. Purification by flash chromatography (6:1 hexanes:ethyl acetate) gave the desired 3-(4-methoxyphenyl)propionaldehyde as a pale yellow oil.

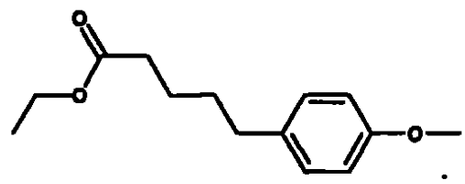
Step B: Preparation of



An aqueous (18 mL) solution of the aldehyde from Step A (8.5 g, 0.052 mol) was treated with triethylphosphonoacetate (Aldrich, 14.0 g, 0.062 mol) and potassium carbonate (14.4 g, 0.104 mol). The bi-phasic solution is stirred at room temperature overnight. Additional water (60 mL) was added to the mixture which was extracted with hexanes (3X). The combined organic layers were washed with brine then dried over sodium sulfate. Evaporation of the solvent gave

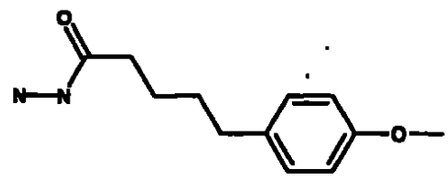
the crude product as an oil. Purification by flash chromatography (10:1 hexanes:ethyl acetate) gave the desired unsaturated ethyl ester.

Step C: Preparation of



An ethyl acetate solution (100 mL) of the unsaturated ethyl ester from Step B (6.2 g, 0.026 mol) was stirred in a 3-neck flask. The atmosphere of the flask was replaced with nitrogen by alternating vacuum and nitrogen into the flask. Palladium on carbon (5%) was added, the atmosphere purged again then introduced to a balloon of hydrogen while stirring overnight. The hydrogen atmosphere was replaced with nitrogen as above, the resulting mixture was filtered through a pad of Celite and the filter cake washed with ethyl acetate. The filtrate was concentrated to give the desired saturated product as a clear oil.

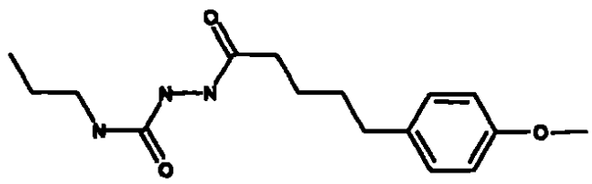
Step D: Preparation of



An ethanol solution of the ester from Step C (6.0 g, 0.025 mol) and hydrazine hydrate (EM Sciences, 12.7 g, 0.254 mol) was stirred and heated to 60^0 C for 4 hours then cooled to r om

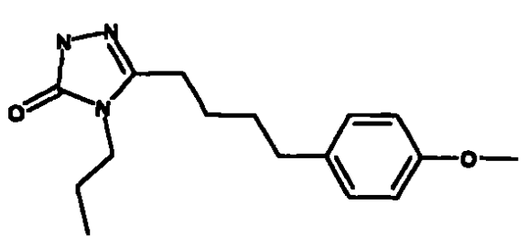
temperature and stirred over the weekend (about 72 hrs.). The resulting solution was concentrated, added to water and extracted with ethyl acetate (2X). The organic layers were combined and washed with brine then dried over sodium sulfate. Evaporation of the solvent gave a solid product which was washed with hexanes and filtered to give the desired acyl hydrazide as a white solid. $C_{12}H_{18}O_2N_2$ (MW = 222.29); mass spectroscopy (MH^+) = 223.2.

Step E: Preparation of



A tetrahydrofuran solution (25 mL) of the acyl hydrazide from Step D (2.6 g, 0.012 mol) was treated with propyl isocyanate (Aldrich, 1.2 g, 0.014 mol) and stirred at room temperature overnight, during which a precipitate forms. The resulting suspension was treated with methanol and stirred for an additional 30 minutes. The solvent was then evaporated to give the desired acyl semicarbazide as a white solid, which was used without further purification.

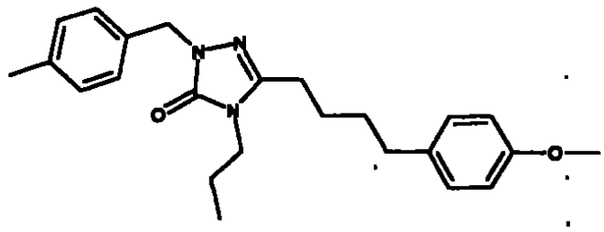
Step F: Preparation of



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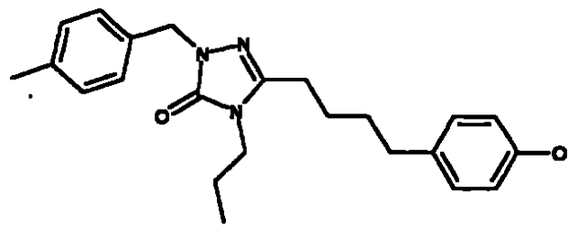
A methanol solution (50 mL) of the acyl semicarbazide from Step E (3.4 g, 0.011 mol) was stirred and treated with solid potassium hydroxide (6.2 g, 0.110 mol). The mixture was heated at 60° C for 48 hrs. The resulting mixture was cooled, added to water (150 mL) and extracted with ethyl acetate (3X). The organic layers were combined, washed with brine and dried over sodium sulfate. Evaporation of the solvent gave a solid which was washed with hexane to give the desired N4-propyl triazolinone as a white solid. $C_{16}H_{23}N_3O_2$ (MW = 289); mass spectroscopy (MH+) = 290.2.

Step G: Preparation of



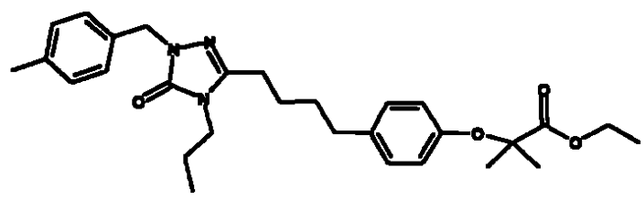
The N4-propyl triazolinone from Step F (1.2 g, 0.0042 mol) was dissolved in DMF (25 mL) and treated with α-bromo-p-xylene (Aldrich, 1.2 g, 0.0063 mol) and powdered potassium carbonate (Aldrich, 2.3 g, 0.0168 mol). The resulting mixture was heated to 45° C for 2 hrs and then allowed to cool to room temperature and stir overnight. The reaction mixture was added to aqueous HCl (1N, 75 mL) and extracted with ethyl acetate (3X). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to give the crude product as an oil. Purification by flash chromatography (gradient: hexanes to 1:1 hexanes:ethyl acetate) gave the desired N2-p-methyl-benzyl triazolinone.

Step H: Preparation of



The N2-p-methylbenzyl triazolinone from Step G (1.2 g, 0.0031 mol) was dissolved in methylene chloride (25 mL) and cooled to 0 °C under a drying tube. A solution of boron tribromide (0.6 mL, 0.006 mol) in methylene chloride (5 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hr. An additional two equivalents of boron tribromide (0.6 mL, 0.006 mol) was added and stirring continued for an additional 0.5 hr. The reaction was quenched by the dropwise addition of methanol (4 mL) in methylene chloride (4 mL). The reaction was added to an additional 60 mL of methylene chloride and washed with water. The organic layer was then dried over sodium sulfate and concentrated to give the desired phenol as a yellow solid. $C_{23}H_{29}N_3O_2$ (MW = 379.5); mass spectroscopy (MH^+) = 380.3.

Step I: Preparation of

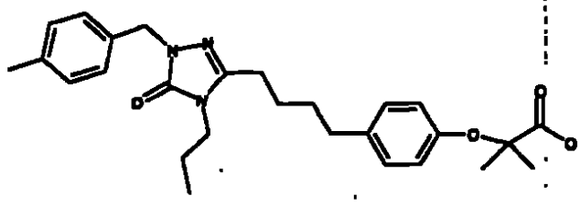


The phenol from Step H (1.0 g, 0.0026 mol) was dissolved in ethanol (absolute, 25 mL) and treated with ethyl 2-bromoisobutyrate (Aldrich, 1.5 g, 1.1 mL, 0.0078 mol), powdered potassium carbonate (Aldrich, 1.4 g, 0.010 mol) and magnesium sulfate (0.3 g, 0.0026 mol). The resulting mixture was stirred and heated to 60 °C, under a drying tube, for 16 hrs. The reaction mixture was filtered through a pad of Celite and the

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filtrate was concentrated. The resulting residue was dissolved in ethyl acetate and washed with HCl (1N) and brine. The organic layer was then dried over sodium sulfate and concentrated to give the crude product. Purification by flash chromatography (1:1 hexanes:ethyl acetate) gave the desired ethyl ester. $C_{29}H_{39}N_3O_4$ (MW = 493.6); mass spectroscopy (MH^+) = 494.3.

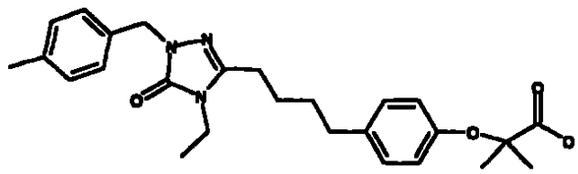
Step J: Preparation of



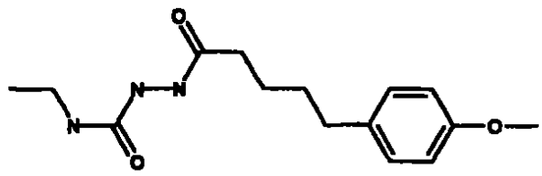
The ethyl ester from Step I (0.6 g, 0.0012 mol) was dissolved in methanol (6 mL) and an aqueous solution of lithium hydroxide (0.06 g, 0.0024 mol) in water (6 mL) added. The resulting mixture was heated to 60 ^{0}C for 2 hrs. After cooling to room temperature, the reaction mixture was added to ethyl acetate (70 mL) and washed with water, resulting in an emulsion, which was broken up by the addition of HCl(1N). This was extracted with ethyl acetate (2X). These two layers were combined and extracted with NaOH (1N), the aqueous layer was acidified with HCl (5N) and extracted with ethyl acetate (2X). These two organic layers were combined, dried over sodium sulfate and concentrated to give the desired carboxylic acid as an oil. $C_{27}H_{35}N_3O_4$ (MW = 465.6); mass spectroscopy (MH^+) = 466.3; (MH^-) = 464.3.

Example 26

Compound 26

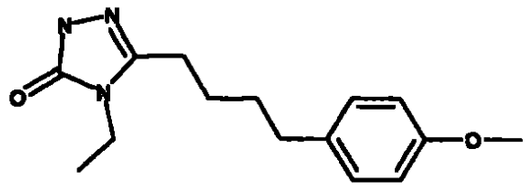


Step A: Preparation of



The acyl hydrazide from Example 25, Step D (2.6 g, 0.012 mol) was dissolved in tetrahydrofuran (25 mL) and treated with ethyl isocyanate (Aldrich, 1.2 g, 0.014 mol). The resulting mixture was stirred at room temperature overnight. The resulting suspension was treated with methanol and stirred for an additional 30 minutes. The solvent was then evaporated to give the desired acyl semicarbazide as a white solid which was used without further purification.

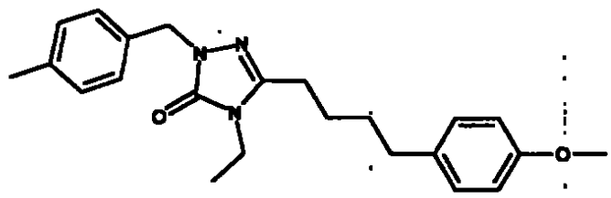
Step B: Preparation of



A methanol solution (50 mL) of the acyl semicarbazide from Step A (3.3 g, 0.011 mol) was stirred and treated with solid potassium hydroxide (6.2 g, 0.11 mol). The mixture was heated at 60^0 C overnight. The resulting mixture was cooled, added t water (125 mL) and extracted with ethyl acetate (3X). The organic layers were combined, washed with brine and dried over sodium sulfate. Evaporation of the solvent gave the desired

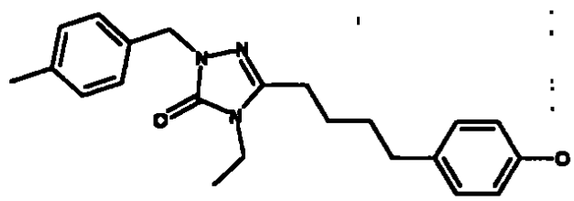
N4-ethyl triazolinone as a white solid. $C_{15}H_{21}N_3O_2$ (MW = 275.35); mass spectroscopy (MH+) = 276.1.

Step C: Preparation of



The N4-ethyl triazolinone from Step B (1.2 g, 0.0044 mol) was slowly added to a slurry of sodium hydride (60% dispersion in mineral oil, 0.3 g, 0.009 mol), under a stream of nitrogen. The resulting slurry was stirred for 45 min. and then treated with α-bromo-p-xylene (Aldrich, 1.2 g, 0.006 mol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was added slowly to aqueous HCl (1N, 100 mL) and extracted with ethyl acetate (3X). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated to give the crude product as an oil. Purification by flash chromatography (gradient: 1:1 hexanes:ethyl acetate to 4:1 ethyl acetate:hexanes) gave the desired N2-p-methylbenzyl triazolinone.

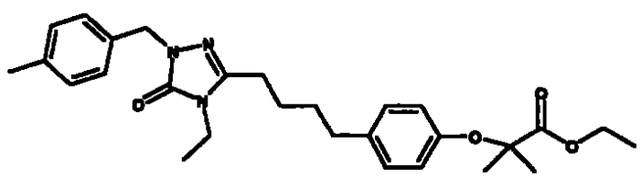
Step D: Preparation of



The N2-p-methylbenzyl triazolinone from Step C (1.1 g, 0.0029 mol) was dissolved in methylene chloride (25 mL) and cooled to 0 °C under a drying tube. A solution of boron tribromid (0.4 mL, 0.004 mol) in methylene chloride was added dropwise over 5 min. The reaction mixture was stirred at 0 °C

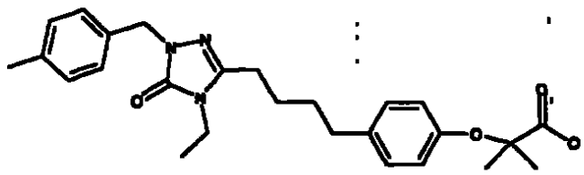
for 10 min. then an additional solution of boron tribromide (0.4 mL, 0.004 mol) in methylene chloride was added and stirring continued for 1 hr. The reaction was quenched by the dropwise addition of methanol (2 mL). The reaction was added to an additional 100 mL water and extracted with methylene chloride (3X). The organic layers were combined, washed with brine and dried over sodium sulfate. Evaporation of the solvent gave the desired phenol as a white solid. $C_{22}H_{27}N_3O_2$ (MW = 365.48); mass spectroscopy (MH+) = 366.2.

Step E: Preparation of



The phenol from Step D (0.8 g, 0.0022 mol) was dissolved in ethanol (absolute, 20 mL) and treated with ethyl 2-bromo-isobutyrate (Aldrich, 1.3 g, 0.0066 mol), powdered potassium carbonate (Aldrich, 1.2 g, 0.0088 mol) and magnesium sulfate (0.2 g, 0.002 mol). The resulting mixture was stirred and heated to 65 ^{0}C, under a drying tube, for 48 hrs. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to give the crude product. Purification by flash chromatography (gradient: 3:2 hexanes:ethyl acetate t 1:1 hexanes:ethyl acetate) gave the desired ethyl ester. $C_{28}H_{37}N_3O_4$ (MW = 479.62); mass spectroscopy (MH^+) = 480.3.

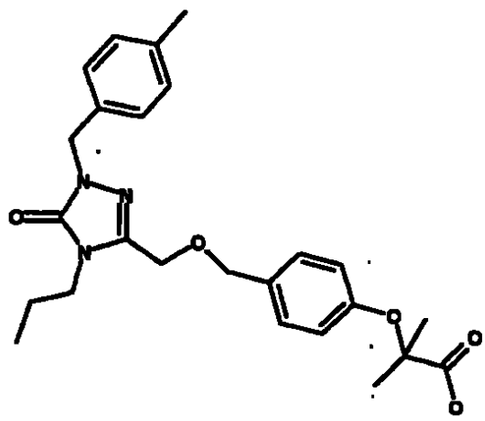
Step F: Preparation of:



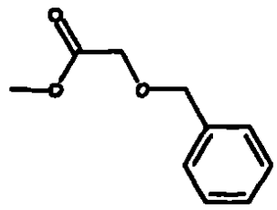
The ethyl ester from Step E (0.75 g, 0.0016 mol) was dissolved in methanol (7 mL) and an aqueous solution of lithium hydroxide (0.08 g, 0.0032 mol) in water (7 mL) added. The resulting mixture was heated to 60 °C for 1 hr. The reaction mixture was added to water (60 mL) and washed with ether. The aqueous layer was acidified with aqueous HCl (conc.) to a pH of 4 and extracted with ethyl acetate (2X). These two layers were combined, washed with brine and dried over sodium sulfate. The solvent was evaporated to give the desired carboxylic acid as an oil. $C_{26}H_{33}N_3O_4$ (MW = 451.57); mass spectroscopy (MH^+) = 452.2; (MH^-) = 450.3.

Example 27

Compound 27

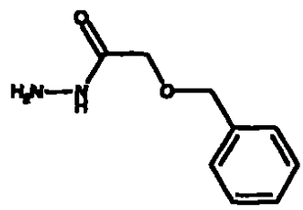


Step A: Preparation of



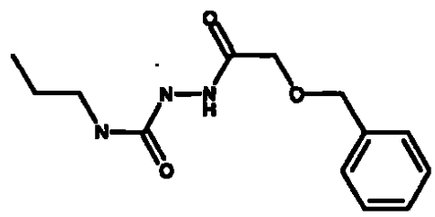
A methanol solution (75 mL) of benzyloxyacetic acid (Aldrich, 15.0 g, 0.090 mol) was treated with H_2SO_4 (concentrated, 1 mL) and stirred at room temperature overnight. The solvent was evaporated and the residue diluted with CH_2Cl_2 (150 mL). The resulting solution was extracted with saturated aqueous sodium bicarbonate (1X150 mL) followed by brine (1X150 mL), then dried over Na_2SO_4. Upon evaporation of the solvent the desired methyl ester was obtained as a colorless oil. $C_{10}H_{12}O_3$ (MW = 180.21); mass spectroscopy (MH^+) = 195.1.

Step B: Preparation of



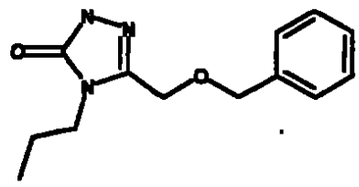
A methanol solution (100 mL) of methyl ester from Step A (6.45 g, 0.036 mol) was treated with hydrazine hydrate (20 mL, 0.41 mol) and stirred at room temperature several days. The solvent was evaporated and the residue dissolved in ethyl acetate (200 mL). The resulting solution was extracted with H_2O (200 mL). The organic extract was dried over Na_2SO_4 and concentrated to give the desired acyl hydrizide as an oil.

Step C: Preparation of



A THF solution (50 mL) of the acyl hydrizide from Step B (3.56 g, 0.020 mol) cooled to 0 °C and treated with a THF solution (25 mL) of n-propyl isocyanate (Aldrich, 2.3 mL, 0.024 mol) - added dropwise over 15 minutes. The mixture was warmed to room temperature and stirred overnight during which a thick precipitate formed. The resulting suspension was treated with methanol (25 mL) and stirred approximately 1 hour. The solvent was then concentrated to give the desired acyl semicarbazide as a white solid which was used without further purification. $C_{13}H_{19}N_3O_3$ (MW = 265.31); mass spectroscopy (MH^+) = 266.1.

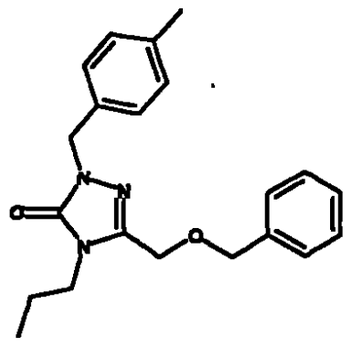
Step D: Preparation of



The acyl semicarbazide from Step C (5.02 g, 18.9 mmol) was dissolved in methanol (75 mL), treated with KOH (10.2 g, 18.2 mmol), then heated to reflux overnight. The reaction mixture was cooled to room temperature, poured into H_2O (300 mL), then extracted with ethyl acetate (3 X 300 mL). The combined rganic extracts were washed with brine (1 X 300

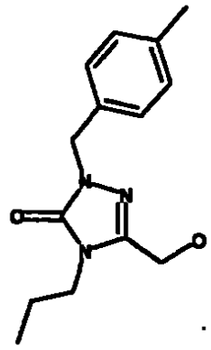
mL), dried over Na_2SO_4 then concentrated to give the desired N4-propyl triazolinone as a slightly yellow solid. $C_{13}H_{17}N_3O_2$ (MW = 247.30); mass spectroscopy (MH^+) = 248.1.

Step E: Preparation of



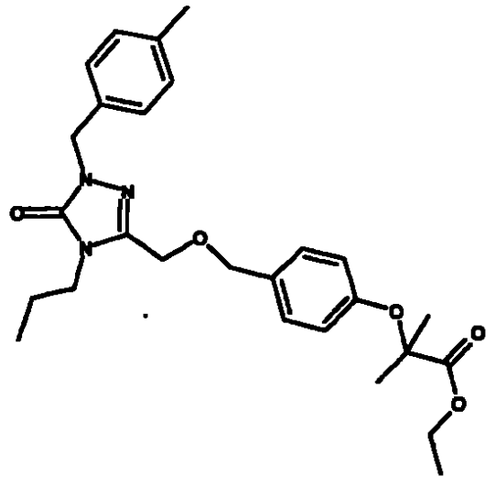
The N4-propyl triazolinone from Step D (4.32 g, 17.5 mmol) was dissolved in DMF (100 mL) and treated with α-bromo-p-xylene (4.0 g, 21.6 mmol) and powdered K_2CO_3 (5.2 g, 38 mmol). The resulting mixture was heated to 50 °C under a drying tube overnight. The reaction mixture was cooled to room temperature, poured into aqueous HCl (1N, 200 mL) and extracted into ethyl acetate (200 mL). The organic extract was washed with brine, dried over Na_2SO_4, then concentrated to give the crude product. Purification by flash chromatography gave the desired N2-p-methylbenzyl triazolinone as a slightly yellow oil. $C_{21}H_{25}N_3O_2$ (MW = 351.45); mass spectroscopy (MH^+) = 352.2.

Step F: Preparation of



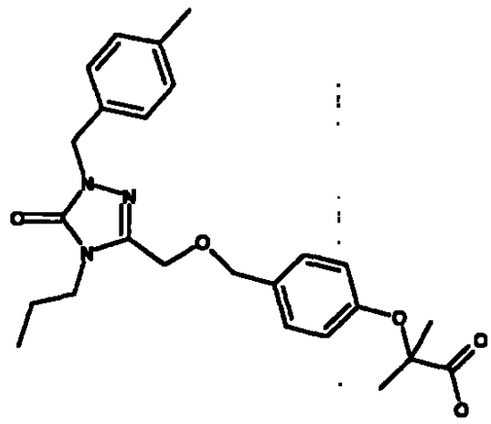
To a slurry containing 5% Pd/C (320 mg) in ethanol (50 mL) was added the benzyl ether from Step E (2.9 gm, 8.25 mmol) as a THF solution (50 mL). The resulting mixture was purged with nitrogen and then with hydrogen. An atmosphere of hydrogen was maintained over the reaction mixture by means of a balloon. After 48 hours, the reaction was judged (TLC and MS) to be only 50% complete. The catalyst was removed via filtration through a pad of celite. The resulting filtrate was concentrated to an oil and redissolved in CH_3OH (50 mL). A slurry containing 5% Pd/C (210 mg) in CH_3OH (10 mL) was added and the mixture was purged with nitrogen. An atmosphere of hydrogen was established as before and maintained for 5 days. Again the catalyst was removed via filtration through a pad of celite. Concentration of the filtrate gave the crude product which was purified by flash chromatography (gradient: 5:1 to 1:2 hexanes:ethyl acetate) to provide the desired alcohol as a white solid. $C_{14}H_{19}N_3O_2$ (MW = 261.33); mass spectroscopy (MH^+) = 262.0.

Step G: Preparation of



To a suspension of NaH (60% in oil, 130 mg, 3,25 mmol) in DMF (10 mL) at 0 °C was added a DMF solution (5 mL) of the alcohol from Step F (383.7 mg, 1.47 mmol). The resulting mixture was stirred 5 minutes then treated with a DMF solution (5 mL) of ethyl 2-[4-(bromomethyl)phenoxy]-2-methyl-propionate (registry 58336-71-3, 457.2 mg, 1.52 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The mixture was then poured into aqueous HCl (1 N, 100 mL) and extracted into CH_2Cl_2 (100 mL). The organic extract was washed a second time with aqueous HCl (1 N) followed by brine, dried over Na_2SO_4, and concentrated. Flash chromatography (3:1 hexanes: ethyl acetate) gave the desired product as a yellow oil. NMR analysis indicated the presence of DMF so the oil was dissolved in Et_2O (50 mL) and washed with aqueous HCl (1 N, 50 mL) followed by brine (1 X 50 mL). The organic solution was dried over Na_2SO_4 then concentrated. Purification by flash chromatography (3:1 hexanes:ethyl acetate) gave the desired ethyl ester. $C_{27}H_{35}N_3O_5$ (MW = 481.60); mass spectroscopy (MH^+) = 482.2.

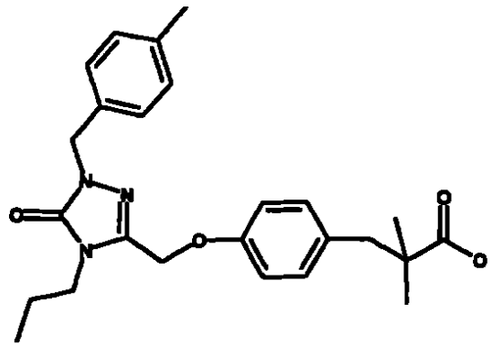
Step H: Preparation of



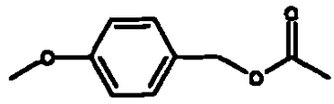
The ethyl ester from Step G (252.9 mg, 0.53 mmol) was dissolved in dioxane/H_2O (15 mL/5 mL) and treated with LiOH (50 mg, 2.1 mmol). The resulting mixture was stirred overnight then concentrated. The resulting residue was diluted with H_2O (70 mL) and washed with Et_2O (1 X 75 mL). The aqueous extract was acidified with aqueous HCl then extracted with ethyl acetate (2X70 mL). The combined organic extracts were dried over Na_2SO_4 then concentrated t give the desired carboxylic acid as a thick, colorless oil. $C_{25}H_{31}N_3O_5$ (MW = 453.54); mass spectroscopy (MH^+) = 454.2; (MH^-) = 452.2.

Example 28

Compound 28

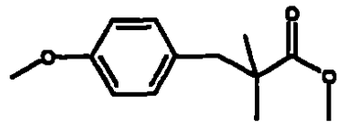


Step A: Preparation of



A solution of 4-methoxy benzyl alcohol (11 mL, 0.088 mol) in methylene chloride (865 mL) was cooled to 0 °C then treated with triethyl amine (18 mL, 0.129 mol). Acetyl chloride (7.2 mL, 0.101 mol) was added to the mixture. The reaction was allowed to stir for an hour: The solution was washed with 1N HCl, saturated $NaHCO_3$, and brine then dried over Na_2SO_4. The organic layer was concentrated to give the desired compound as a brown oil.

Step B: Preparation of

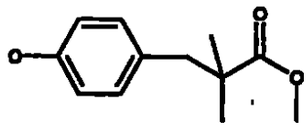


The acetate from Step A (13 g, 0.072 mol) was dissolved in methylene chloride (600 mL) and treated with 1-methoxy-1-trimethyl siloxy-2-methyl-1-propene (Aldrich, 29 mL, 0.193 mol) followed by $Mg(ClO_4)_2$ (1.7 g, 0.0073 mol). The mixture was stirred overnight at room temperature. The solution was washed with water then brine. The organic layer was

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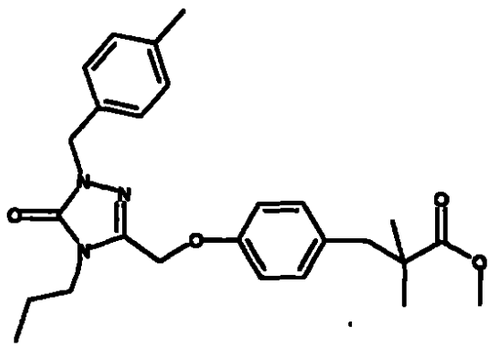
concentrated to yield to a yellow oil. The material was carried forth without further purification.

Step C: Preparation of



A solution of BBr_3 (9 mL, 0.048 mol) in methylene chloride (180 mL) was cooled to 0 °C and treated with a solution of the methyl ester from Step B (10.56 g, 0.095 mol) in methylene chloride (180 mL). The reaction was allowed to stir for thirty minutes. Methylene chloride and methanol (1:1, 70 ml) was added to quench the reaction. The solvent was concentrated. Purification of the residue by flash chromatography (3:1 hexanes:ethyl acetate) afforded the phenol as a colorless oil.

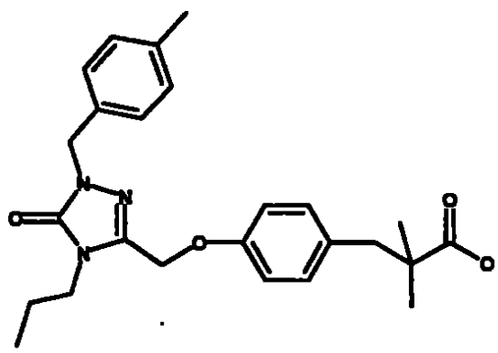
Step D: Preparation of



A THF solution of the phenol from Step C (173.3 mg, 0.83 mmol) and the alcohol from Example 27, Step F (204.5 mg, 0.78 mmol) was treated with triphenylphosphine (218.5 mg, 0.83 mmol) and diethyl azodicarboxylate (145 µL, 0.92 mmol). The resulting mixture was stirred overnight at room temperature under N_2. The mixture was concentrated and the residue dissolved in CH_2Cl_2 (50 mL). The organic solution

was washed with H_2O (1 X 50 mL) and brine (1 X 50 mL), dried over Na_2SO_4, and then concentrated to give the crude product. Purification by flash chromatography (4:1 hexanes:ethyl acetate) gave the desired methyl ester as an oil. $C_{26}H_{33}N_3O_4$ (MW = 451.57); mass spectroscopy (MH^+) = 452.2.

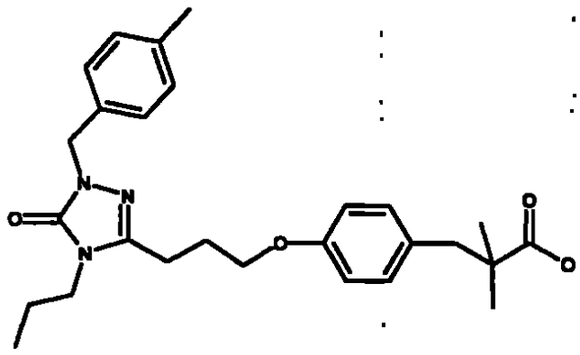
Step E: Preparation of



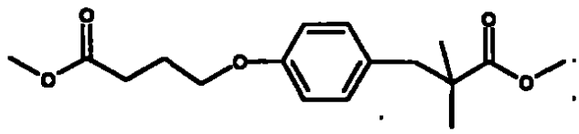
The methyl ester from Step D (190 mg, 0.42 mmol) was dissolved in dioxane/H_2O (6 mL/3 mL) and treated with LiOH (50 mg, 2.1 mmol). The resulting mixture was stirred overnight then concentrated. The resulting residue was diluted with H_2O (50 mL) and washed with Et_2O (1 X 50 mL). The aqueous extract was acidified with aqueous HCl then extracted with ethyl acetate (1 X 50 mL). The organic extract was washed with brine (1 X 50 mL), dried over Na_2SO_4 then concentrated to give the crude product. Purification by flash chromatography (gradient 1:1 to 1:2 hexanes:ethyl acetate) gave the desired carboxylic acid as a colorless oil. $C_{25}H_{31}N_3O_4$ (MW = 437.54); mass spectroscopy (MH^+) = 438.1; (MH^-) = 436.1.

Example 29

Compound 29

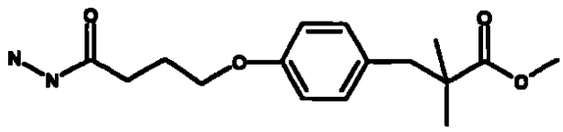


Step A: Preparation of



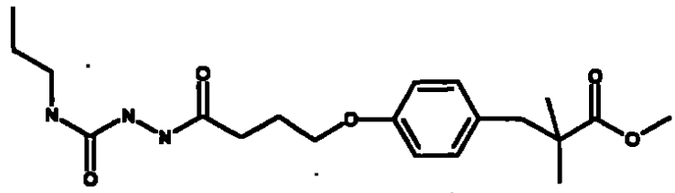
A DMF solution (65 mL) of the phenol from Example 28, Step C (2.1 g, 0.010 mol) and methyl 4-bromobutyrate (2.2 g, 0.012 mol) was treated with powdered K_2CO_3, (4.0 g, 0.030 mol) and $MgSO_4$ (4.0 g, 0.033 mol). The resulting mixture was heated to 60-70 °C under a drying tube. After heating overnight the mixture was cooled to room temperature and filtered through a pad of celite. The filtrate was diluted with aqueous HCl (1 N, 150 mL) and extracted with Et_2O. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (10:1 hexanes:ethyl acetate) provided the desired methyl ester as a slightly yellow oil. $C_{17}H_{24}O_5$ (MW = 308.38); mass spectroscopy (MH^+) = 309.1.

Step B: Preparation of



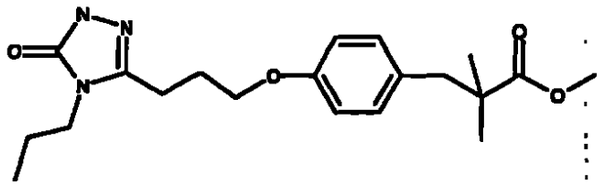
A methanol solution (76 mL) of the methyl ester from Step A (2 g, 0.0065 mol) was treated with hydrazine hydrate (0.95 mL, 0.019 mol) and stirred overnight. Additional hydrazine hydrate (0.95 mL, 0.019 mol) was added to drive the reaction to completion. The solvent was concentrated and the resulting residue was diluted with ethyl acetate. The organic layer was washed with water followed by brine then evaporated to yield the desired acyl hydrizide as a yellow oil. $C_{16}H_{24}N_2O_4$ (MW = 308.38); mass spectroscopy (MH^+) = 309.2.

Step C: Preparation of



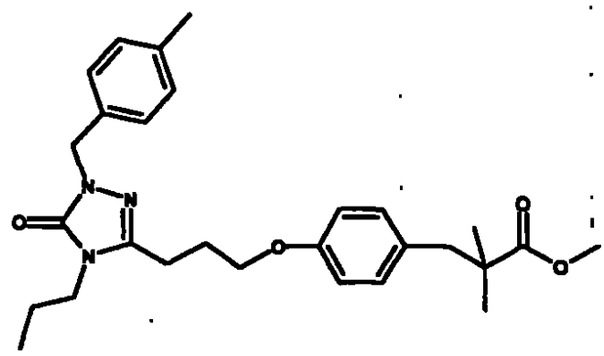
A THF solution (20 mL) of the acyl hydrizide from Step B (2 g, 0.006 mol) was treated with a THF solution (20 mL) of n-propyl isocyanate (Aldrich, 0.791 ml, 0.0084 mol), added dropwise. The mixture was stirred overnight. The solvent was concentrated to give a quantitative yield of the desired acyl semicarbazide which was carried forth without further purification.

Step D: Preparation of



The acyl semicarbazide from Step C (2.68 g, 0.0068 mol) was dissolved in methanol and treated with KOH (3.82 g, 0.068 mol). The reaction was refluxed overnight. Upon cooling, water was added to the reaction mixture and the solution was then acidified using 1N HCl to pH = 3. The acidified layer was then extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated. The resulting material was diluted with methanol and treated with a catalytic amount of conc. H_2SO_4. The solution stirred overnight. The solvent was evaporated then the residue was diluted with methylene chloride and washed with water. The organic layer was concentrated to give the methyl ester. $C_{20}H_{29}N_3O_4$ (MW = 375.47); mass spectroscopy (MH^+) = 376.2.

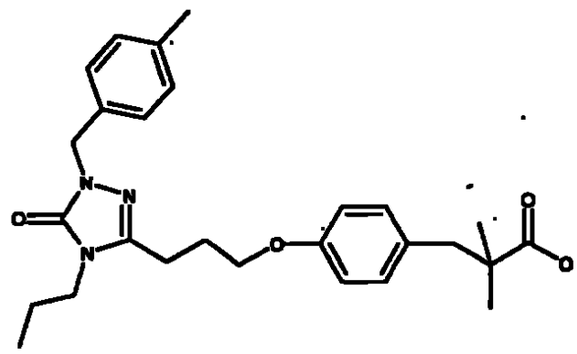
Step E: Preparation of



The N4-propyl triazolinone from Step D (1.5 g, 0.004 mol) was dissolved in DMF (7 ml) and treated with α-bromo-p-xylene (1.11 g, 0.006 mol) and powdered K_2CO_3. The resulting mixture was stirred overnight at 67 °C. The heating source

was removed and ethyl acetate was added to the reaction mixture. The organic layer was extracted with water followed by brine, dried then concentrated. Purification of the yellow oil by flash chromatography (4:1 hexanes: ethyl acetate) yielded the desired N4-p-methyl benzyl triazolinone. $C_{28}H_{37}N_3O_4$ (MW = 479.62); mass spectroscopy (MH^+) = 480.3.

Step F:

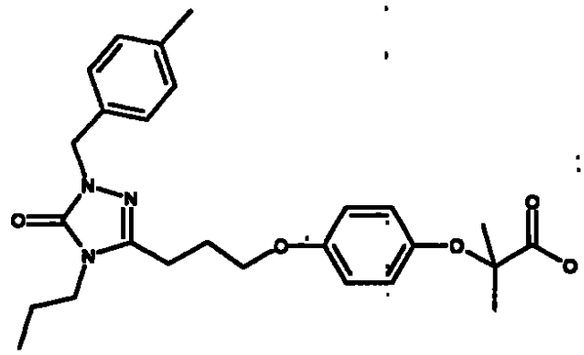


The methyl ester from Step E (0.160 g, 0.00033 mol) was dissolved in ethanol (6 mL) and treated with 2N NaOH (3 mL). The reaction was refluxed for one hour. The reaction was cooled and water (20 mL) was added to the solution. The solution was then acidified using 1N HCl to pH = 3 then extracted with ethyl acetate. The organic layer was concentrated to afford the desired carboxylic acid as a colorless oil. $C_{27}H_{35}N_3O_4$ (MW = 465.60); mass spectroscopy (MH^+) = 466.3.

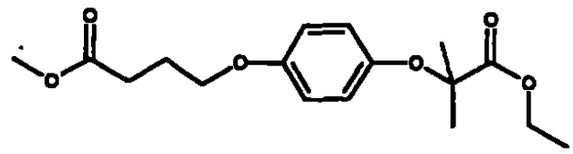
Example 30

Compound 30

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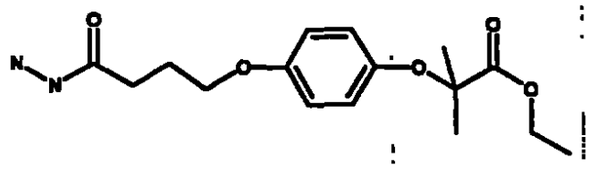


Step A: Preparation of



Methyl-4-bromo butyrate (3 g, 0.0166 mol) and 2-(4-hydroxyphenyl)-2-methyl propanoic acid ethyl ester (American Home Products US Pat. No 3795691, 3.13 g, 0.014 mol) were combined in a flask and heated to 70 °C. The reaction was stirred overnight. Upon cooling, the reaction mixture was filtered through celite. The filtrate was diluted with water and extracted with ethyl ether. The organic layer was washed with brine, then concentrated. Purification by flash chromatography (4:1 hexanes:ethyl acetate) provided the desired diester as a yellow oil. $C_{17}H_{24}O_6$ (MW = 324.38); mass spectroscopy (MH^+) = 325.2.

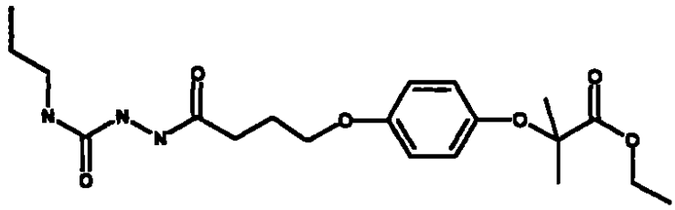
Step B: Preparation of



A methanol solution (60 mL) of the diester from Step A (1.64 g, 0.005 mol) was treated with hydrazine hydrate (1.23 mL, 0.025 mol) and stirred overnight. Additional hydrazine hydrate (2.46 mL, 0.050 mol) was added and the reaction was

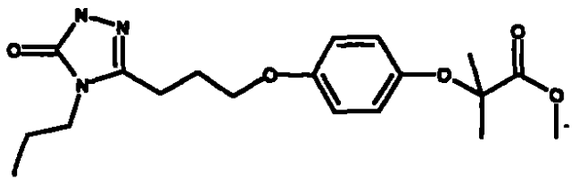
stirred overnight. The solvent was evaporated. The resulting residue was diluted with ethyl acetate and washed with water followed by brine. Concentration of the organic layer gave the acyl hydrizide.

Step C: Preparation of



A THF solution (10 mL) of the acyl hydrizide from Step B (0.860 g, 0.00265 mol) was treated with a THF solution (10 mL) of n-propyl isocyanate (Aldrich, 0.323 ml, 0.00345 mol) added dropwise. The mixture was stirred overnight. The solvent was concentrated to give a quantitative yield of the desired acyl semicarbazide which was carried forth without further purification.

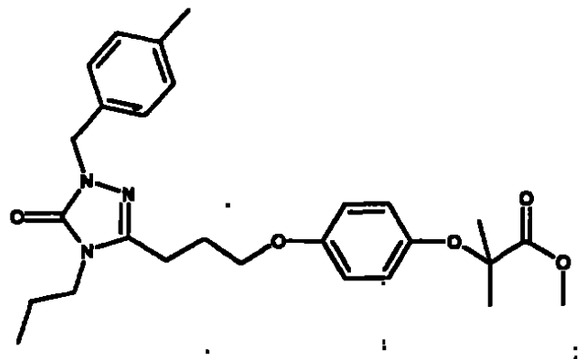
Step D: Preparation of



The acyl semicarbazide from Step C (1 g, 0.0026 mol) was dissolved in methanol and treated with KOH (1.48 g, 0.026 mol). The reaction was refluxed overnight. Upon cooling, water was added to the reaction mixture and the solution was then acidified using 1N HCl to pH = 3. The acidified layer was then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting material was diluted with

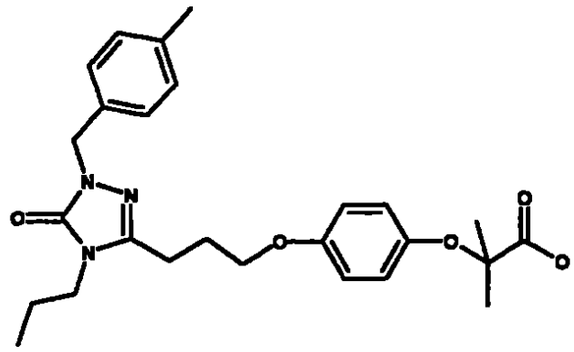
methanol and treated with a catalytic amount of conc. H_2SO_4. The solution was stirred overnight. The solvent was evaporated then the residue was diluted with methylene chloride and washed with water. The organic layer was concentrated to give the desired N4-propyl-triazolinone. $C_{19}H_{27}N_3O_5$ (MW = 377.44); mass spectroscopy (MH^+) = 378.2.

Step E: Preparation of



The N4-propyl triazolinone from Step D (0.92 g, 0.0024 mol) was dissolved in DMF (7 mL) and treated with α-bromo-p-xylene (0.476 mL, 0.0036 mol) and powdered K_2CO_3 (1.68 g, 0.012 mol). The resulting mixture was stirred for two hours at 67 °C. The heating source was removed and ethyl acetate was added to the reaction mixture. The organic layer was extracted with water followed by brine, dried over Na_2SO_4, then concentrated. Purification of the yellow oil by flash chromatography (1:1 hexanes: ethyl acetate) yielded the desired N2-p-methyl benzyl triazolinone as a yellow oil. $C_{27}H_{35}N_3O_5$ (MW = 481.60); mass spectroscopy (MH^+) = 482.3.

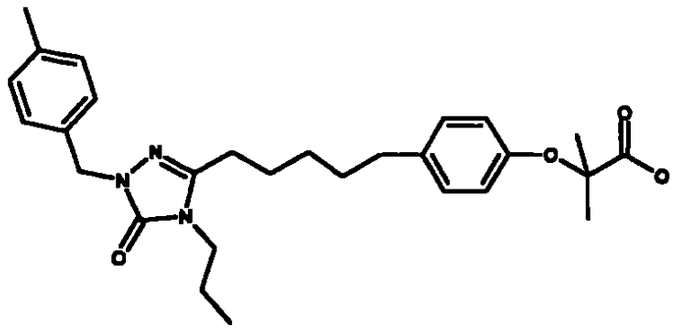
Step F: Preparation of



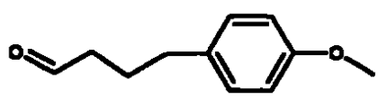
The methyl ester from Step E (0.250 g, 0.0005 mol) was dissolved in ethanol (8 mL) and treated with 2N NaOH (4 mL). The reaction was refluxed for thirty minutes. The reaction was cooled and water (10 mL) was added to the solution. The solution was then acidified using 1N HCl to pH = 3 then extracted with ethyl acetate. The organic layer was concentrated to afford the desired carboxylic acid. $C_{26}H_{33}N_3O_5$ (MW = 467.57); mass spectroscopy (MH^+) = 468.2.

Example 31

Compound 31



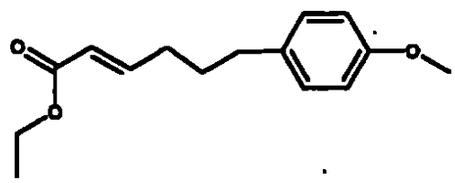
Step A: Preparation of



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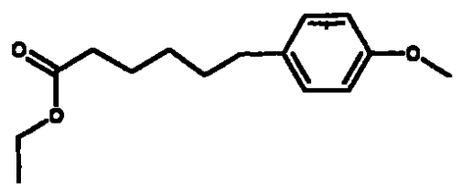
Pyridinium chlorochromate (14.2 g, 0.066 mol) was added slowly to a solution of 4-(4-methoxyphenyl)-1-butanol (10 g, 0.055 mol) in methylene chloride at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was filtered through a pad of Florisil and the solvent was evaporated. Purification by flash chromatography (4:1 hexanes: ethyl acetate) yielded the desired aldehyde as a colorless oil.

Step B: Preparation of



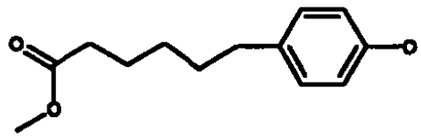
The aldehyde from Step A (6.28 g, 0.035 mol) was combined with triethyl phosphonoacetate (Aldrich, 8.39 mL, 0.042 mol) and potassium carbonate (9.66 g, 0.07 mol) in water (120 mL) and stirred overnight. Dioxane (120 mL) was added and the reaction was stirred for several days. The solution was extracted with hexanes. The organic layer was evaporated. The resulting material was purified by flash chromatography (4:1 hexanes:ethyl acetate) to give the olefin.

Step C: Preparation of



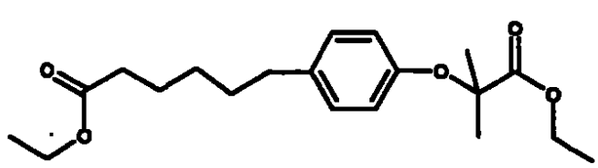
The olefin from Step B (2.5 g, 0.010 mol) was dissolved in ethyl acetate (40 mL) and purged with nitrogen. Upon the addition of the 5% Pd/C (0.40 g), the solution was purged with nitrogen and then H_2 gas was released across the system. The reaction was stirred overnight. The solution was filtered through a pad of celite. The solvent was concentrated to give the desired methy ether which was used without further purification.

Step D: Preparation of



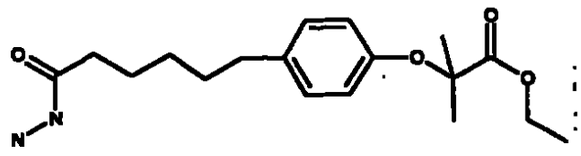
The methy ether, prepared as described in Step C (3.92 g, 0.016 mol), was dissolved in methylene chloride (50 mL) and cooled to 0 °C. To this solution was added, dropwise, a solution of BBr_3 (4.5 mL, 0.48 mol) in methylene chloride. (20 mL). After stirring for about 45 minutes at room temperature, the reaction mixture was cooled to 0 °C and quenched by the dropwise addition of methanol/methylene chloride. During quenching, transesterification from the ethyl ester to the methyl ester occurred. The solvent was concentrated to give a dark oil. Purification by flash chromatography (4:1 hexanes:ethyl acetate) gave the desired phenol.

Step E: Preparation of



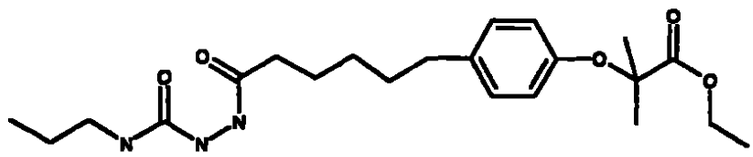
The phenol from Step D (2.5 g, 0.011 mol) was dissolved in ethanol (absolute, 40 mL) and treated with ethyl 2-bromoisobutyrate (11.56 mL. 0.079 mol), powdered K_2CO_3 (4.55 g, 0.033 mol), and $MgSO_4$. The reaction was stirred overnight at 75 °C. Upon cooling, the reaction mixture was filtered and the filtrate was concentrated. The resulting residue was diluted with ethyl acetate and extracted with water followed by brine. The organic layer was concentrated to dryness. Purification by flashed chromatography (9:1 hexanes:ethyl acetate) gave the desired diester.

Step F: Preparation of



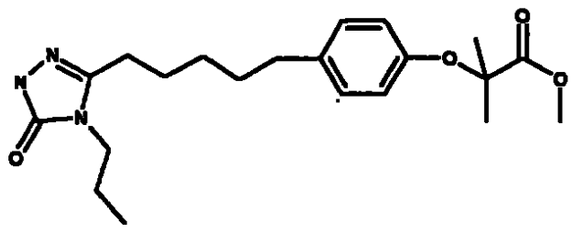
A methanol solution (76 mL) of the diester from Step E (2.65g, 0.0076 mol) was treated with hydrazine hydrate (1.84 mL, 0.038 mol) and stirred overnight. After about six hours, additional hydrazine hydrate (1.84 mL, 0.038 mol) was added and the reaction was stirred overnight. Again, additional hydrazine hydrate (1.84 mL, 0.038 mol) was added. After several hours, the reaction was stopped and the solvent was evaporated. The resulting mixture was purified by flash chromatography (gradient 100% ethyl acetate to 6:1 ethyl acetate:methanol) to give the desired acyl hydrizide.

Step G: Preparation of



A THF solution (7 mL) of the acyl hydrizide from Step F (0.5 g, 0.0015 mol) was treated with a THF solution (7 mL) of n-propyl isocyanate (Aldrich, 0.181 mL, 0.0019 mol) added dropwise. The mixture was stirred overnight. The solvent was concentrated to give a quantitative yield of the desired acyl semicarbazide which was carried forth without further purification.

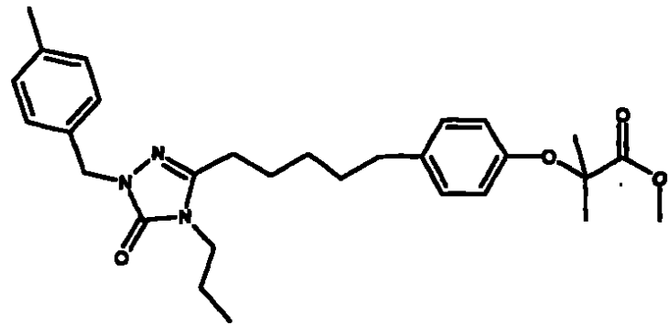
Step H: Preparation of



The acyl semicarbazide from Step G (1 g, 0.0024 mol) was dissolved in methanol and treated with KOH (1.34 g, 0.024 mol). The reaction was refluxed overnight. Upon cooling, water was added to the reaction mixture and the solution was then acidified using 1N HCl to pH = 3. The acidified layer was then extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated. The resulting material was diluted with methanol and treated with a catalytic amount of conc. H_2SO_4. The solution stirred overnight. The solvent was evaporated then the residue was diluted with methylene chloride and washed with water. The organic layer was concentrated to

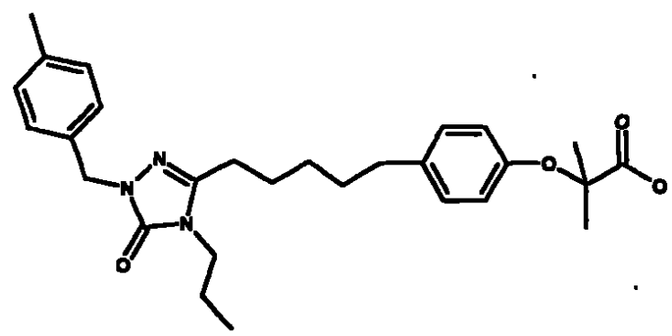
give the desired N4-propyl triazolinone. $C_{21}H_{31}N_3O_4$ (MW = 389.50); mass spectroscopy (MH^+) = 390.3.

Step I: Preparation of



The N4-propyl triazolinone from Step H (0.5 g, 0.0013 mol) was dissolved in DMF (7 mL) and treated with α-bromo-p-xylene (0.885 g, 0.0064 mol) and powdered K_2CO_3 (0.885 g, 0.0064 mol). The resulting mixture was stirred for ninety minutes at 67 °C. The heating source was removed and ethyl acetate was added to the reaction mixture. The organic layer was extracted with water followed by brine, dried then concentrated. Purification of the yellow oil by flash chromatography (2:1 hexanes:ethyl acetate) yielded the desired N2-p-methyl benzyl triazolinone. $C_{29}H_{39}N_3O_4$ (MW = 493.65); mass spectroscopy (MH^+) = 494.3.

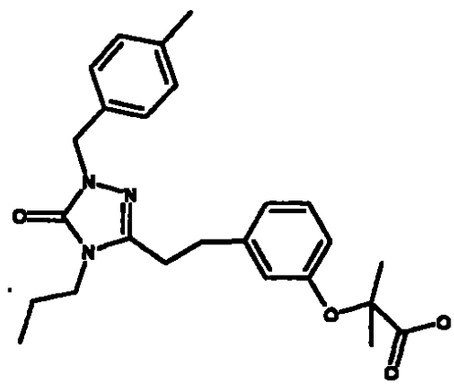
Step J: Preparation of



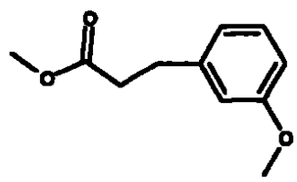
The methyl ester from Step I (0.129 g, 0.00026 mol) was dissolved in ethanol (4 mL) and treated with 2N NaOH (2 mL). The reaction was refluxed for forty-five minutes. The reaction was cooled and water (10 mL) was added to the solution. The solution was then acidified using 1N HCl to pH = 3 then extracted with ethyl acetate. The organic layer was concentrated to afford the desired carboxylic acid as a colorless oil. $C_{28}H_{37}N_3O_2$ (MW = 479.62); mass spectroscopy (MH^+) = 480.3.

Example 32

Compound 32



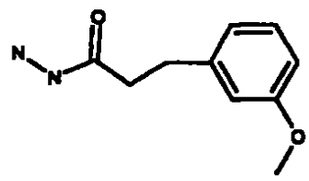
Step A: Preparation of



A methanol solution (75 mL) of 3-(3-methoxyphenyl)-propionic acid (Aldrich, 10.0 g, 0.055 mol) was treated with H_2SO_4 (concentrated, 2 mL) and stirred at room temperature for 2 days. The solvent was evaporated and the residue diluted with CH_2Cl_2 (150 mL). The resulting solution was

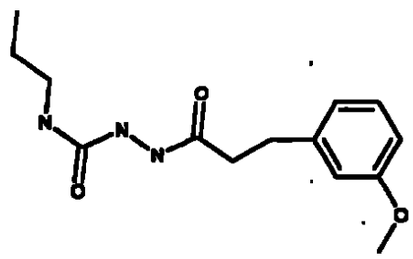
extracted with saturated aqueous sodium bicarbonate (1 X 150 mL) followed by brine (1 X 150 mL), then dried over Na_2SO_4. Upon evaporation of the solvent the desired methyl ester was obtained as a yellowish oil. $C_{11}H_{14}O_3$ (MW = 194.23); mass spectroscopy (MH^+) = 195.0.

Step B: Preparation of



A methanol solution (100 mL) of methyl ester from Step A (10.3 g, 0.053 mol) was treated with hydrazine hydrate (30 mL, 0.60 mol) and stirred overnight. The solvent was evaporated and the residue dissolved in ethyl acetate (200 mL). The resulting solution was washed with H_2O (200 mL), dried over Na_2SO_4 and concentrated to give the desired acyl hydrizide as a white solid. $C_{10}H_{14}N_2O_2$ (MW = 194,23); mass spectroscopy (MH^+) = 195.1.

Step C: Preparation of

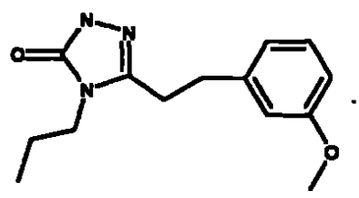


A THF solution (125 mL) of the acyl hydrizide from Step B (7.3 g, 0.038 mol) was treated with a THF solution (25 mL) of n-propyl isocyanate (Aldrich, 4.5 mL, 0.048 mol) - added dropwise over 15 minutes. The mixture was stirred overnight during which a thick precipitate formed. The resulting

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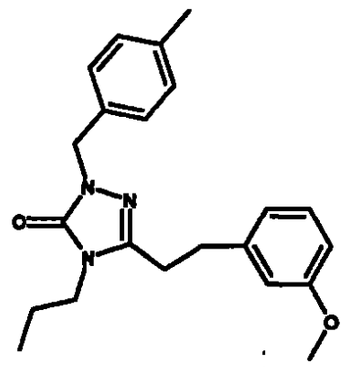
suspension was treated with methanol (100 mL) and stirred approximately 2 hours. The solvent was then concentrated to give the desired acyl semicarbazide as a white solid which was used without further purification. $C_{14}H_{21}N_3O_3$ (MW = 279.34); mass spectroscopy (MH^+) = 280.2.

Step D: Preparation of



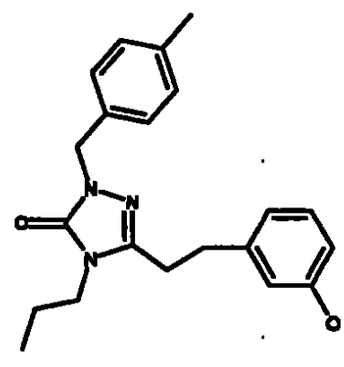
The acyl semicarbazide from Step C (10.0 g, 0.036 mol) was dissolved in methanol (200 mL), treated with KOH (20 g, 0.36 mol), then heated reflux overnight. The reaction mixture was cooled to room temperature, poured into H_2O (500 mL) and extracted with ethyl acetate (2 X 500 mL). The combined organic extracts were washed with brine (1 X 500 mL), dried over Na_2SO_4 then concentrated to give the desired N4-propyl triazolinone as a yellow oil. $C_{14}H_{19}N_3O_2$ (MW = 261.33); mass spectroscopy (MH^+) = 262.1.

Step E: Preparation of



The N4-propyl triazolinone from Step D (1.25 g, 4.8 mmol) was dissolved in DMF (25 mL) and treated with α-bromo-p-xylene (1.36 g, 7.3 mmol) and powdered K_2CO_3 (4.2 g, 0.030 mol). The resulting mixture was heated to 50 °C under a drying tube overnight. The reaction mixture was cooled to room temperature, poured into aqueous HCl (1N, 200 mL) and extracted into ethyl acetate (200 mL). The organic extract was washed with brine (1X200 mL), dried over Na_2SO_4, then concentrated to give the crude product. Purification by flash chromatography (gradient 2:1 to 1:1 hexanes:ethyl acetate) gave the desired N2-p-methylbenzyl triazolinone as a colorless oil. $C_{22}H_{27}N_3O_2$ (MW = 365.48); mass spectroscopy (MH^+) = 366.1.

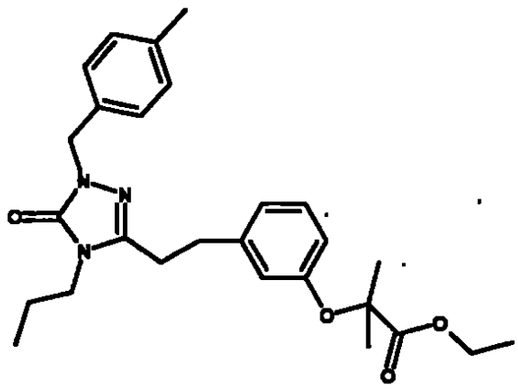
Step F: Preparation of



The N2-p-methylbenzyl triazolinone from Step E (1.06 g, 0.0029 mol) was dissolved in methylene chloride (15 mL) and

cooled to 0 °C. To this solution was added, dropwise, a solution of BBr_3 (0.548 mL, 0.0058 mol) in methylene chloride. (5 mL). After stirring for two hours, the reaction mixture was cooled to 0 °C and quenched by the dropwise addition of methanol/methylene chloride. The solvent was concentrated and the resulting material was dissolved in methylene chloride. The organic layer was extracted with water followed by brine. Upon evaporation of the solvent, the desired phenol was obtained. $C_{21}H_{25}N_3O_2$ (MW = 351.45); mass spectroscopy (MH+) = 352.19.

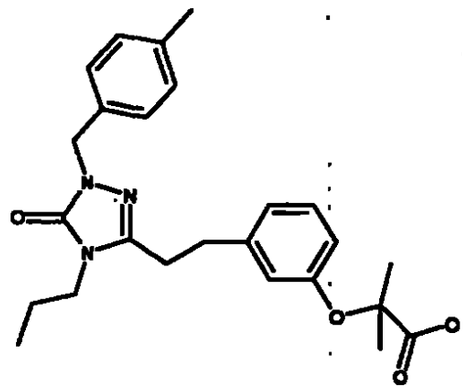
Step G: Preparation of



The phenol from Step F (1 g, 0.0028 mol) was dissolved in ethanol (absolute, 15 mL) and treated with ethyl 2-bromoisobutyrate (2.88 mL, 0.0196 mol), powdered K_2CO_3 (1.157 g, 0.0084 mol), and $MgSO_4$. The reaction was stirred overnight at 71 °C. Upon cooling, the reaction mixture was filtered and the filtrate was concentrated. The resulting residue was diluted with methylene chloride and extracted with water followed by brine. An emulsion occurred. The organic layer was separated by the addition of brine then concentrated to dryness. Purification by flashed chromatography (gradient: 3:1 hexanes:ethyl acetate to 2:1

hexanes: ethyl acetate) gave the desired ester. $C_{27}H_{35}N_3O_4$ (MW = 465.60); mass spectroscopy (MH^+) = 466.3.

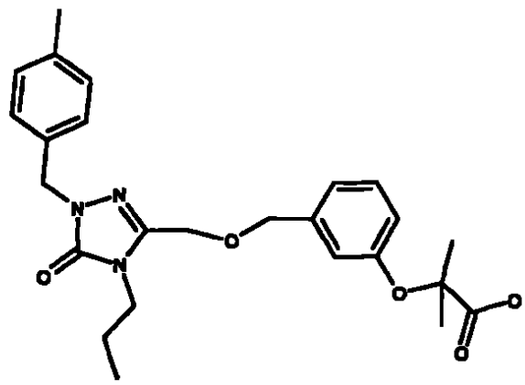
Step H: Preparation of



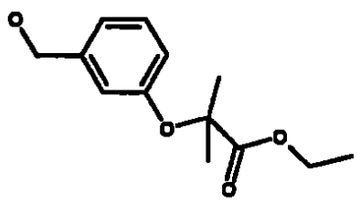
The ester from Step G (0.600 g, 0.0013 mol) was dissolved in methanol (6 mL) and treated with an aqueous solution of LiOH (0.062 g, 0.0026 mol). The reaction was stirred overnight at room temperature. Water (20 mL) was added to the reaction mixture and the solution was extracted with ethyl acetate. The aqueous layer was then acidified using 1N HCl to pH = 3 then extracted with ethyl acetate. The organic layer was concentrated to afford the desired carboxylic acid. $C_{25}H_{31}N_3O_4$ (MW = 437.54); mass spectroscopy (MH^+) = 438.2.

Example 33

Compound 33

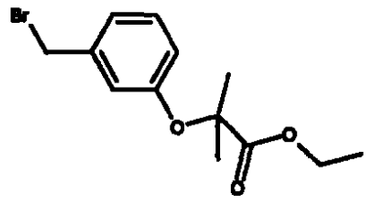


Step A: Preparation of



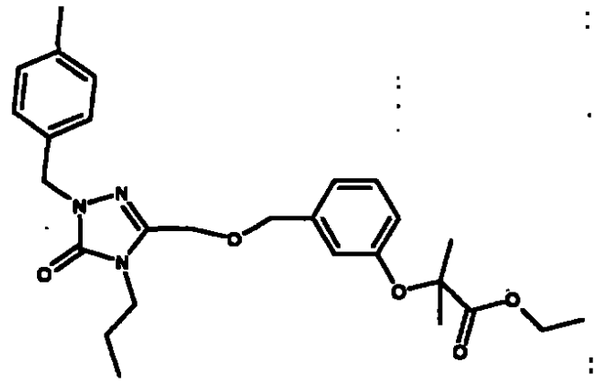
An ethanol solution of 3-hydroxybenzyl alcohol (Aldrich, 5 g, 0.040 mol) was combined with potassium carbonate (powdered, 18 g, 0.130 mol), ethyl 2-bromoisobutyrate (17 mL, 0.116 mol), and magnesium sulfate (15 g). The reaction was stirred overnight at 50 °C. The reaction mixture was filtered and the filtrate was concentrated. The resulting residue was dissolved in methylene chloride and extracted with water followed by brine. Purification by flash chromatography (gradient 5:1 hexanes:ethyl acetate to 2:1 hexanes:ethyl acetate) gave the desired alcohol as a yellow oil.

Step B: Preparation of



The alcohol from Step A (8.68 g, 0.036 mol) was dissolved in methylene chloride (150 mL) and cooled to 0 °C. Carbon tetrabromide (14.5 g, 0.044 mol) was added to the solution followed by the slow addition of triphenylphosphine (11.5 g, 0.044 mol). The solvent was evaporated and the resulting material was diluted with ethyl ether causing the triphenylphosphine oxide by-product to precipitate from the solution. The by-product was filtered and filtrate was concentrated. The resulting material was dissolved in hexane causing additional by-product to precipitate. A second filtration was performed and the filtrate was concentrated. A 5 g portion of the crude material was purified by flash chromatography (gradient 95:5 hexanes:ethyl acetate to 9:1 hexanes:ethyl acetate) to afford the ester. $C_{13}H_{17}BrO_3$ (MW = 301.18); mass spectroscopy (MH^+) = 302.0.

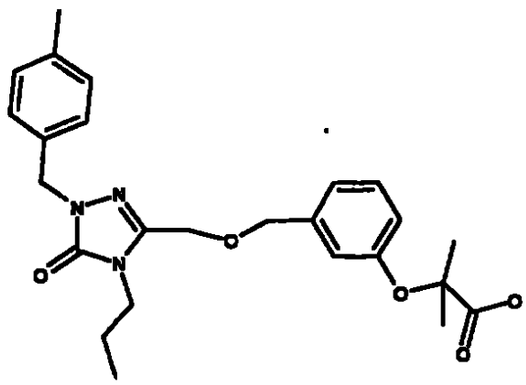
Step C: Preparation of



To a dry three-neck round bottom flask was added sodium hydride (60% oil dispersion, 0.134 g, 0.0033 mol) in THF (12

mL) and cooled to 0 °C. A solution of the alcohol (0.4 g, 0.0015 mol) from Example 27, Step F in THF (12 mL) was added and the mixture was stirred for 5 minutes. The bromide from Step B was then added as a solution in THF (12 mL) and the resulting mixture was stirred overnight. The reaction mixture was poured into 1N HCl and extracted with methylene chloride. The organic layer was washed with water then brine. Purification by flash chromatography (1:1 hexanes:ethyl acetate) yielded the desired product. $C_{27}H_{35}N_3O_5$ (MW = 481.60); mass spectroscopy (MH^+) = 482.1.

Step D: Preparation of

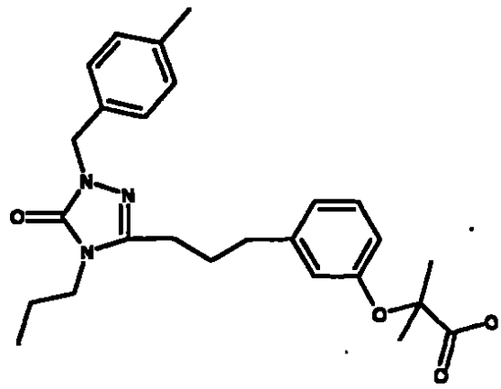


The ethyl ester from Step C (0.270 g, 0.00056 mol) was dissolved in ethanol (12 mL) and treated with 2N NaOH (6 mL). The reaction was refluxed for one hour. The reaction was cooled and water (25 mL) was added to the solution. The solution was then acidified using 1N HCl to pH = 3 then extracted with ethyl acetate. The organic layer was concentrated to afford the desired carboxylic acid as a thick oil. $C_{25}H_{31}N_3O_5$ (MW = 453.54); mass spectroscopy (MH^+) = 454.2.

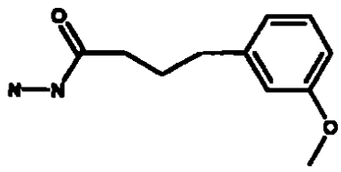
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Example 34

Compound 34

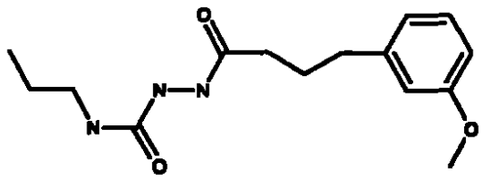


Step A: Preparation of



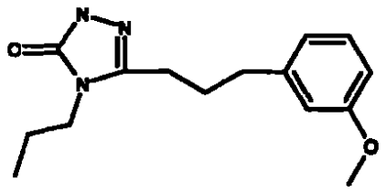
A methanol solution (15 mL) of ethyl 3-(3-methoxyphenyl)butyrate (Registry 57816-01-0, 1.91 g, 0.0086 mol) was treated with hydrazine hydrate (4.2 mL, 0.086 mol) and stirred overnight. The solvent was evaporated and the residue dissolved in ethyl acetate (50 mL). The resulting solution was washed with H_2O (50 mL) and brine (50 mL), then dried over Na_2SO_4 and concentrated to give the desired acyl hydrizide as a white solid. $C_{11}H_{16}N_2O_2$ (MW = 208.26); mass spectroscopy (MH^+) = 209.0.

Step B: Preparation of



A THF solution (20 mL) of the acyl hydrizide from Step A (1.03 g, 0.0050 mol) was treated with a THF solution of n-propyl isocyanate (Aldrich, 0.60 mL, 0.0064 mol) - added dropwise over 15 minutes. The mixture was stirred then treated with H_2O (50 mL) and stirred approximately 2 hours. The mixture was concentrated to an aqueous solution which was extracted with CH_2Cl_2 (2 X 75 mL). The combined organic extracts were dried over Na_2SO_4 then concentrated to give the desired acyl semicarbazide as a white solid, which was used without further purification. $C_{15}H_{23}N_3O_3$ (MW = 293.37); mass spectroscopy (MH^-) = 292.2.

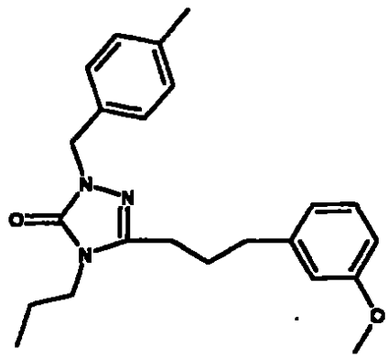
Step C: Preparation of



The acyl semicarbazide from Step B was dissolved in methanol (60 mL), treated with KOH (3.0 g, 0.053 mol), then heated to reflux for 48 hours. The reaction mixture was cooled to room temperature, poured into H_2O (200 mL), then extracted with ethyl acetate (2 X 200 mL). The combined organic extracts were washed with brine (250 mL), dried over Na_2SO_4 then concentrated to give the desired N4-propyl triazolinone as a solid. $C_{15}H_{21}N_3O_2$ (MW = 275.35); mass spectroscopy (MH^+) = 276.1.

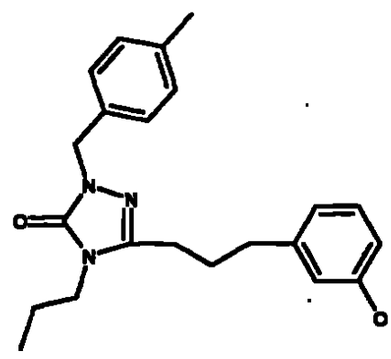
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Step D: Preparation of



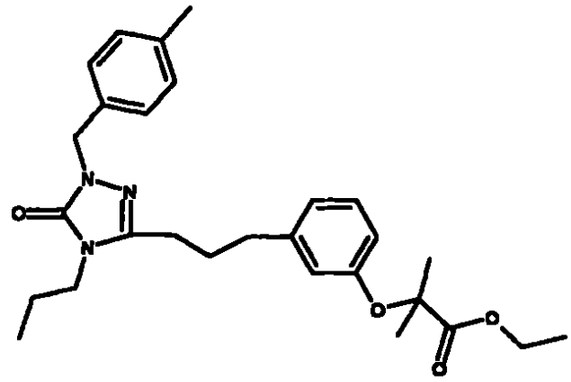
The N4-propyl triazolinone from Step C (1.20 g, 4.4 mmol) was dissolved in DMF (20 mL) and treated with p-methylbenzyl bromide (1.60 g, 8.6 mmol), powdered K_2CO_3 (3.2 g, 0.023 mol), and $MgSO_4$ (1.2 g, 0.010 mol). The resulting mixture was heated to 80 °C under a drying tube overnight. The reaction mixture was cooled to room temperature, poured into aqueous HCl (1N, 100 mL) and extracted into Et_2O (2 X 100 mL). The combined organic extracts were washed with brine (1 X 200 mL), dried over Na_2SO_4, then concentrated to give the crude product. Purification by flash chromatography (2:1 hexanes:ethyl acetate) gave the desired N2-p-methylbenzyl triazolinone as a colorless oil. $C_{23}H_{29}N_3O_2$ (MW = 379.51); mass spectroscopy (MH^+) = 380.2.

Step E: Preparation of



The N2-p-methylbenzyl triazolinone from Step D (0.7879 g, 0.002 mol) was dissolved in methylene chloride (15 mL) and cooled to 0 °C. To this solution was added, dropwise, a solution of BBr_3 (0.392 mL, 0.004 mol) in methylene chloride (5 mL). After stirring for about 90 minutes, the reaction mixture was cooled to 0 °C and quenched by the dropwise addition of methanol/methylene chloride. The solvent was concentrated and the resulting material was dissolved in methylene chloride. The organic layer was extracted with water followed by brine. Upon evaporation of the solvent, the desired phenol was obtained. $C_{22}H_{27}N_3O_2$ (MW = 365.48); mass spectroscopy (MH+) = 366.3.

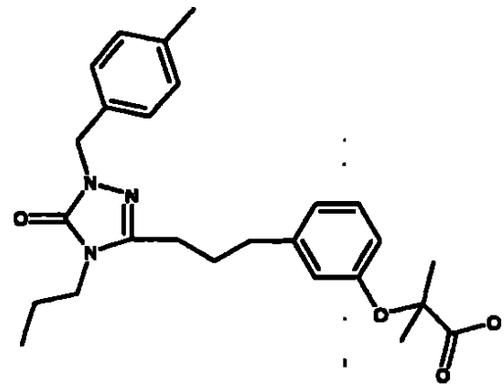
Step F: Preparation of



The phenol from Step E (0.70 g, 0.0019 mol) was dissolved in DMF (40 mL) and treated with ethyl 2-bromoisobutyrate (1.97 mL, 0.013 mol), powdered K_2CO_3 (0.797 g, 0.0057 mol), and $MgSO_4$. The reaction was stirred overnight at 75 °C. Upon cooling, the reaction mixture was filtered and the filtrate was concentrated. The resulting residue was diluted with ethyl acetate and extracted with water followed by brine. The organic layer was concentrated to dryness. Purification by flashed chromatography (1:1

hexanes:ethyl acetate) gave the desired ester. $C_{28}H_{37}N_3O_4$ (MW = 479.62); mass spectroscopy (MH^+) = 480.3.

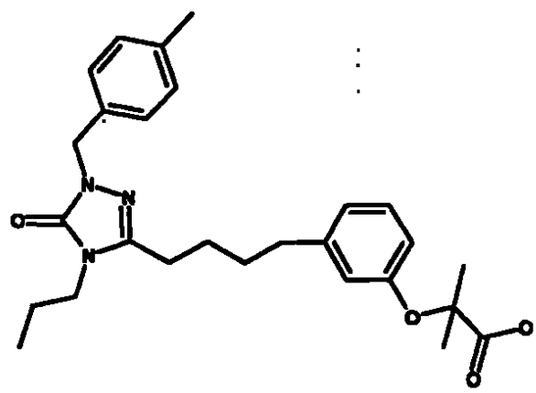
Step G: Preparation of



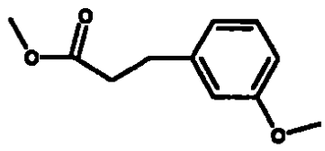
The ester from Step F (0.250 g, 0.00052 mol) was dissolved in ethanol (8 mL) and treated with 2N NaOH (4 mL). The reaction was refluxed for thirty minutes. The reaction was cooled and water (20 mL) was added to the solution. The solution was then acidified using 1N HCl to pH = 3 then extracted with ethyl acetate. The organic layer was concentrated to afford the desired carboxylic acid. $C_{26}H_{33}N_3O_4$ (MW = 451.57); mass spectroscopy (MH^+) = 452.3.

Example 35

Compound 35

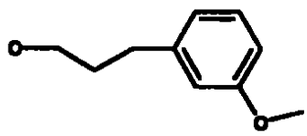


Step A: Preparation of



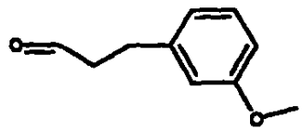
A methanol solution (75 mL) of 3-(3-methoxyphenyl)-propionic acid (Aldrich, 10 g, 0.055 mol) was treated with a catalytic amount of concentrated H_2SO_4 and stirred at room temperature overnight. The solvent was concentrated and the residue was diluted with methylene chloride (150 mL). The resulting solution was extracted with saturated aqueous sodium bicarbonate (1X150 mL) followed by brine (1 X 150 mL), then dried over Na_2SO_4. Upon evaporation of the solvent, the desired methyl ester was obtained as a colorless oil. $C_{11}H_{14}O_3$ (MW = 194.23); mass spectroscopy (MH^+) = 195.1.

Step B: Preparation of



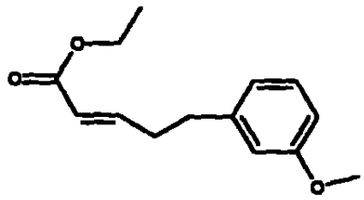
The ester from Step A (5 g, 0.0257 mol) was dissolved in toluene (100 mL) and cooled to 0 °C. An excess of DIBAL (1M, 50 mL, 0.050 mol) was slowly added to the solution. The reaction stirred for 1 hour. An aqueous solution of Rochelle's salt (saturated) was added and the mixture was stirred over the weekend. The resulting biphasic solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, then concentrated. Purification by flash chromatography (gradient 4:1 to 3:1 hexanes:ethyl acetate) gave the desired alcohol.

Step C: Preparation of



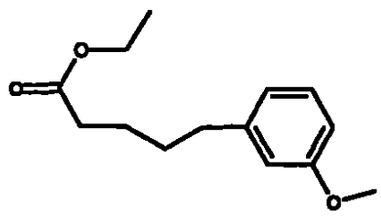
The alcohol, prepared as described in Step B (5.5 g, 0.033 mol), was dissolved in methylene chloride (165 mL) and cooled to 0 °C. Pyridinium chlorochromate (8.57 g, 0.040 mol) was added slowly to the solution. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was filtered through a pad of celite then concentrated. Purification by flash chromatography (4:1 hexanes:ethyl acetate) yielded the desired aldehyde.

Step D: Preparation of



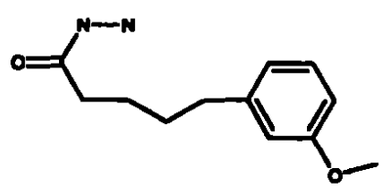
The aldehyde (3.73 g, 0.023 mol) from Step C was combined with triethyl phosphonoacetate (Aldrich, 6.12 g, 0.027 mol) and potassium carbonate (6.26 g, 0.045 mol) in water and stirred overnight. Dioxane was added and the reaction was stirred overnight again. The reaction solution was diluted with hexanes and extracted. The organic layer was concentrated. Purification by flash chromatography (15:1 hexanes:ethyl acetate) gave the desired olefin.

Step E: Preparation of



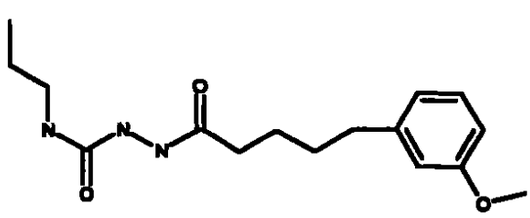
The olefin from Step D (2.5 g, 0.010 mol) was dissolved in ethyl acetate and purged with nitrogen. Upon the addition of 5% Pd/C (0.250 g), the solution was purged with nitrogen then subjected to H_2 gas. The reaction was stirred overnight. The solution was filtered through a pad of celite. The solvent was concentrated to give the saturated ester which was used without further purification.

Step F: Preparation of



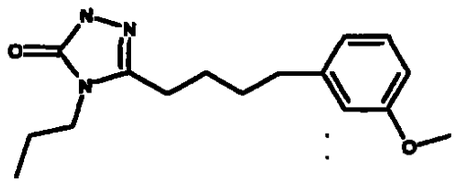
A methanol solution (60 mL) of the ester from Step E (2.5 g, 0.0105 mol) was treated with hydrazine hydrate (5.14 mL, 0.105 mol) and stirred for three days. The solvent was evaporated. The resulting mixture was dissolved in ethyl acetate and the solution was extracted with water then brine. The organic layer was concentrated to give the desired acyl hydrizide. $C_{12}H_{18}N_2O_2$ (MW = 222.29); mass spectroscopy (MH^+) = 223.

Step G: Preparation of



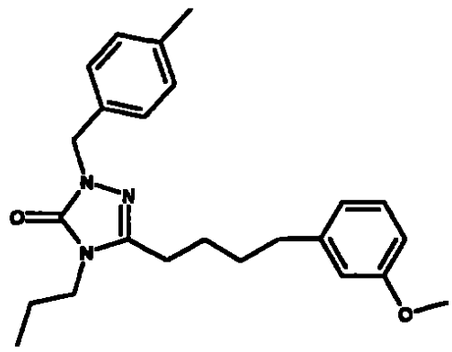
A THF solution (20 mL) of the acyl hydrizide from Step F (2.1 g, 0.0095 mol) was treated with a THF solution (20 mL) of n-propyl isocyanate (Aldrich, 1.15 mL, 0.012 mol) added dropwise. The mixture was stirred overnight. The solvent was concentrated to give the desired acyl semicarbazide which was carried forth without further purification. $C_{16}H_{25}N_3O_3$

Step H: Preparation of



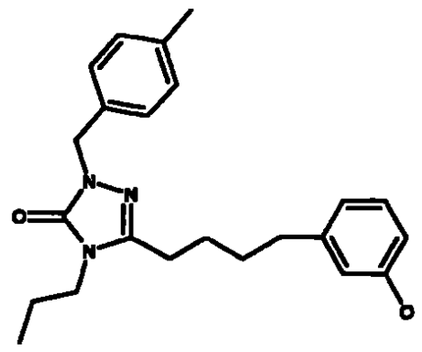
The acyl semicarbazide from Step G (2.95 g, 0.0096 mol) was dissolved in methanol and treated with KOH (5.39 g, 0.096 mol). The reaction was refluxed overnight. Upon cooling, water was added to the reaction mixture and the solution was then acidified using 1N HCl to pH = 3. The acidified layer was then extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated. Purification by flash chromatography (1:1 hexanes:ethyl acetate) gave the desired N4-propyl triazolinone. $C_{16}H_{23}N_3O_2$ (MW = 289.38); mass spectroscopy (MH^+) = 290.2.

Step I: Preparation of



The N4-propyl triazolinone from Step H (2.13 g, 0.0073 mol) was dissolved in DMF (75 mL) and treated with α-chloro-p-xylene (1.54, 0.0110 mol) and powdered K_2CO_3 (5.09 g, 0.037 mol). The resulting mixture was stirred overnight at 67 °C. The heating source was removed and ethyl acetate was added to the reaction mixture. The organic layer was extracted with water followed by brine, dried over Na_2SO_4 then concentrated. Purification of the residue by flash chromatography (2:1 hexanes:ethyl acetate) yielded the desired N2-p-methyl benzyl triazolinone. $C_{24}H_{31}N_3O_2$ (MW = 393.53); mass spectroscopy (MH^+) = 394.3.

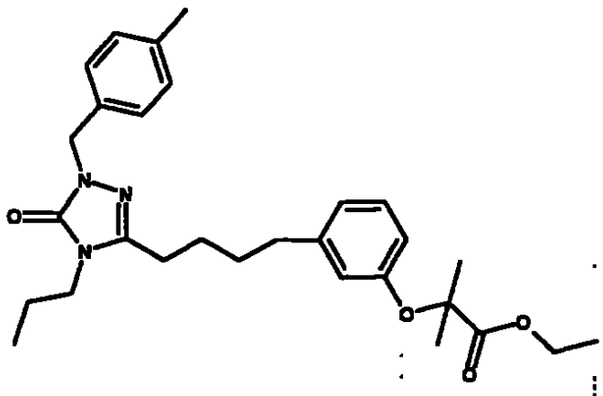
Step J: Preparation of



The N2-p-methyl benzyl triazolinone from Step I (1.96 g, 0.005 mol) was dissolved in methylene chloride (30 mL)

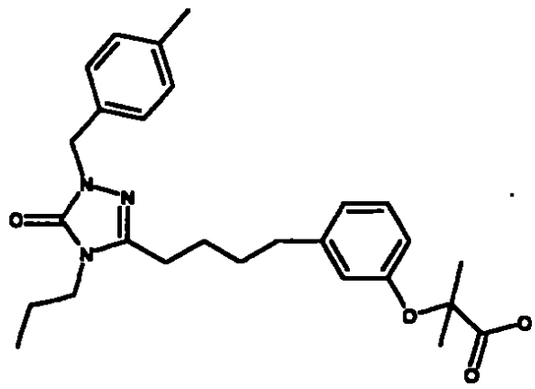
and cooled to 0 °C. To this solution was added, dropwise, a solution of BBr_3 (0.942 mL, 0.010 mol) in methylene chloride (10 mL). After stirring for about one hour, two additional equivalents of BBr_3 was added. The reaction mixture was cooled to 0 °C and quenched by the dropwise addition of methanol/methylene chloride. The solvent was concentrated to give the desired phenol which was used without further purification. $C_{23}H_{29}N_3O_2$ (MW = 379.51); mass spectroscopy (MH^+) = 380.3.

Step K: Preparation of



The phenol from Step J (1.75 g, 0.0046 mol) was dissolved in ethanol (absolute, 20 mL) and treated with ethyl 2-bromoisobutyrate (4.74 mL, 0.032 mol), powdered K_2CO_3 (1.90 g, 0.014 mol), and $MgSO_4$. The reaction was stirred overnight at 77 °C. Upon cooling, the reaction mixture was filtered and the filtrate was concentrated. The resulting residue was diluted with ethyl acetate and extracted with water followed by brine. The organic layer was concentrated to dryness. Purification by flashed chromatography (1:1 hexanes:ethyl acetate) gave the ester as a colorless oil. $C_{29}H_{39}N_3O_4$ (MW = 493.65); mass spectroscopy (MH^+) = 494.3.

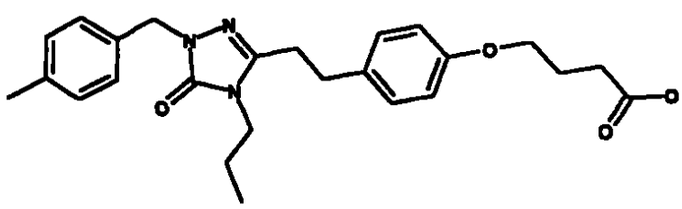
Step L: Preparation of



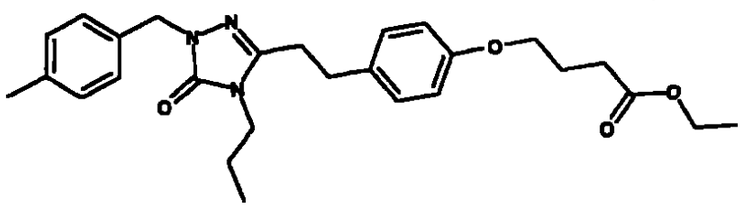
The ethyl ester from Step K (1 g, 0.002 mol) was dissolved in ethanol (24 mL) and treated with 2N NaOH (12 mL). The reaction was refluxed for one hour. The reaction was cooled and water (25 mL) was added to the solution. The solution was then acidified using 1N HCl to pH = 3 then extracted with ethyl acetate. The organic layer was concentrated to afford the desired carboxylic acid as a colorless oil. $C_{27}H_{35}N_3O_4$ (MW = 465.6); mass spectroscopy (MH^+) = 466.7.

Example 36

Compound 36

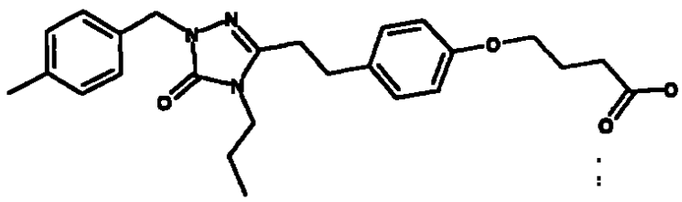


Step A: Preparation of



The phenol (2.1 g, 0.0060 mol), prepared as in Example 22, Step F, was dissolved in DMF (25 mL) and treated with ethyl 4-bromobutyrate (Aldrich, 1.4 g, 0.0072 mol), powdered potassium carbonate (Aldrich, 3.3 g, 0.0240 mol) and small amount of magnesium sulfate. The resulting mixture was stirred and heated to 65° C for 18 hrs. The resulting reaction mixture was added slowly to HCl (1N, 100 mL) and extracted with ether (3X). the ether layers were combined, washed with water and dried over sodium sulfate. Evaporation of the solvent gave the crude product. Purification by flash chromatography (1:1 hexanes:ethyl acetate) gave the desired ethyl ester as a clear oil.

Step B: Preparation of

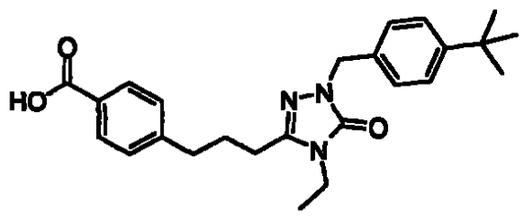


The ethyl ester from Step A (0.1 g, 0.0002 mol) was dissolved in methanol (2 mL) and treated with an aqueous solution of lithium hydroxide (0.01 g, 0.0004 mol) in water (2 mL). The resulting mixture was heated to 50 °C for 2 hrs., then stirred at room temperature overnight. The reaction mixture was added to water and acidified with aqueous HCl (conc.) to a pH of 3 and extracted with ethyl acetate (2X). These two layers were combined, washed with brine and dried

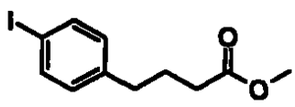
over sodium sulfate. The solvent was evaporated to give the desired carboxylic acid as an oil. $C_{25}H_{31}N_3O_4$ (MW = 437.54); mass spectroscopy (MH^+) = 438.1.

Example 37

Compound 37

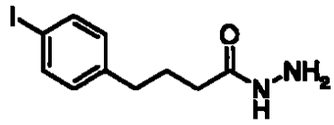


Step A: Preparation of methyl 4-(4-iodophenyl)-butyrate



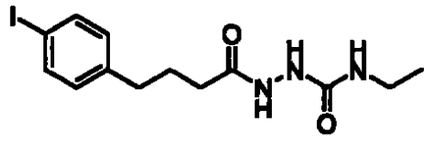
To a solution of 4-(p-iodophenyl)-butyric acid (45.0 g, 0.155 mol) in methanol (1.3 L), was added sulfuric acid (concentrated, 8.4 mL) dropwise and it was stirred at room temperature under nitrogen for 3 hours. The reaction mixture was concentrated on a rota-vapor, the residue was then partitioned between ethyl acetate (700 mL) and saturated sodium bicarbonate aqueous solution (500mL). The organic phase was separated, washed with brine (2x200 mL), then dried over Na_2SO_4 and filtered. Evaporation of solvent gave the titled compound as an oil that was used in step B without further purification.

Step B: Preparation of



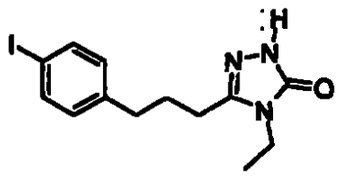
A mixture of methyl 4-(4-iodophenyl)-butyrate (47.0 g, 0.155 mol) from Step A and hydrazine hydrate (38.8 g, 0.775 mol) in methanol (200 mL) at room temperature was stirred overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate (500mL) and water (100 mL). The organic layer was washed water (3x100 mL) and brine (2x100 mL), dried over Na_2SO_4, filtered and concentrated to dryness to give the titled compound as a white crystal that was used in step C without further purification.

Step C: Preparation of



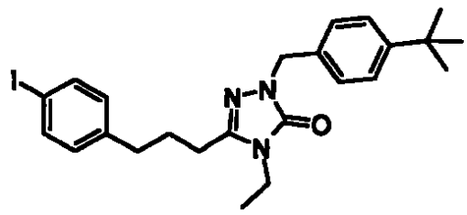
To a solution of the Step B product (47.0 g, 0.155 mol) in THF (500mL), was added a solution of ethyl isocyanate (Aldrich, 14.7 mL, 0.186 mol) in THF (200 mL) dropwise and the mixture was stirred at room temperature for an hour. Evaporation of solvent gave the titled compound as an off-white powder that was used in step D without further purification.

Step D: Preparation of



To a solution of the Step C product (58 g, 0.155 mol) in methanol (775 mL), was added potassium hydroxide in one portion (43.5 g, 0.775 mol). The reaction mixture was heated at 85°C for 48 hours. Half of the volume was then evaporated on a rota-vapor, the residue was then partitioned between ethyl acetate (1.0 L) and water (500 mL), and the two layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 200 mL). The combined organic layers was dried over Na_2SO_4 and filtered. Evaporation of solvent gave the titled compound as a white solid.

Step E: Preparation of

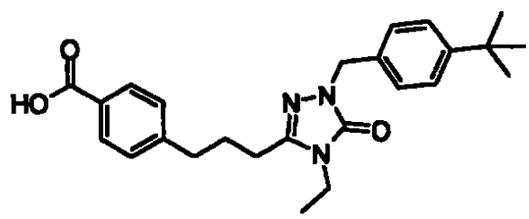


To a solution of the Step D product (2.05 g, 0.00574 mol) in methyl ethyl ketone (60 mL), was added 4-(tert-butyl)benzyl bromide (1.93 mL, 0.00861 mol) followed by potassium carbonate powder (4.75 g, 0.0344 mol).The resulting mixture was stirred under reflux under a drying tube for 24 hours. The reaction mixture was cooled to room temperature and then partitioned between ethyl acetate (100 mL) and NH_4Cl saturated aqueous solution (100 mL). The aqueous layer was extracted with ethyl acete (100 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50% ethyl

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acetate in hexane to give the titled compound as colorless oil.

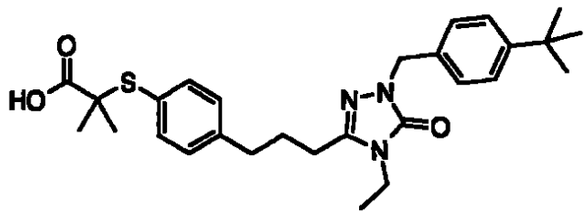
Step F: Preparation of



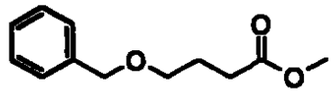
To a solution of the Step E product (2.4 g, 0.0048 mol) in benzene (5 mL) at room temperature, a solution of KOH (5.35 g, 0.0953 mol) in water (8.9 mL), chloroform (19.2 mL) and $Pd(Ph_3P)_2Cl_2$ (0.34 g, 0.00048 mol) were added and mixture stirred for 24 hours. Then, mixture was diluted with diethyl ether (20 mL) and pH adjusted to pH=1-2 by addition of 1N HCl. Layers were separated and the aqueous layer extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give a crude product, which was purified on a silica gel column eluting, first with 70% ethyl acetate in hexane and then with ethyl acetate. The titled compound was obtained as white solid. Mass (MH+ = 422.5).

Example 38:

Compound 38

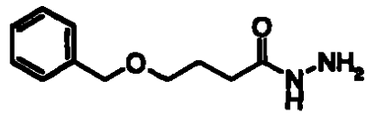


Step A: Preparation of methyl 4-benzyloxybutyrate



To a solution of 4-benzyloxybutyric acid (54.8 g, 0.282 mol) in methanol (1.4 L), was added sulfuric acid (concentrated, 1.4 mL) dropwise and it was stirred at room temperature under nitrogen overnight. The reaction mixture was concentrated on a rota-vapor, the residue was then partitioned between ethyl acetate (700 mL) and saturated sodium bicarbonate aqueous solution (200 mL). The organic phase was separated, washed with brine (2 x 100 mL), then dried over Na_2SO_4 and filtered. Evaporation of solvent gave the titled compound as an oil that was used in step B without further purification.

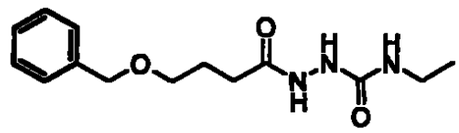
Step B: Preparation of



A mixture of methyl 4-benzyloxybutyrate (58.7 g, 0.282 mol) from Step A and hydrazine hydrate (56.4 g, 1.13 mol) in methanol (300 mL) at room temperature was stirred overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate (1 L) and water (100 mL). The organic layer was washed water (3 x 100 mL) and brine (2 x 100 mL),

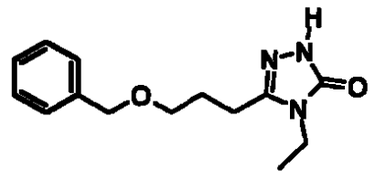
dried over Na_2SO_4, filtered and concentrated to dryness to give the titled compound as a white crystal that was used in step C without further purification.

Step C: Preparation of



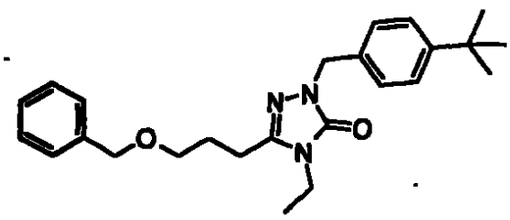
To a solution of the Step B product (58.7 g, 0.282 mol) in THF (600mL), was added a solution of ethyl isocyanate (Aldrich, 26.8 mL, 0.338 mol) in THF (300 mL) dropwise and the mixture was stirred at room temperature for an hour. Evaporation of solvent gave the titled compound as an off-white powder that was used in step D without further purification.

Step D: Preparation of



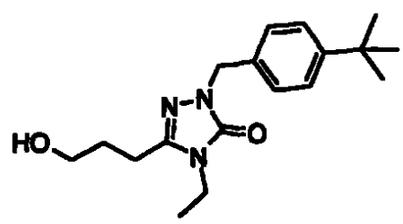
A suspension of the Step C product (78.6 g, 0.282 mol) in a solution of KOH (19.0 g, 0.339 mol) in water (380 mL) (1.2 eq of 5% KOH aqueous solution) was heated at 110 °C for 1 hour (as soon as the temperature is increased, suspension disappear). At that time, TLC showed no starting material remained and reaction was cooled to room temperature. Then, pH was adjusted to pH=6-7 by addition of 1N HCl, and extracted with AcOEt (3 x 500 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give the titled compound as white solid.

Step E: Preparation of



To a solution of the Step D product (9.7 g, 0.00374 mol) in methyl ethyl ketone (400 mL), was added 4-(tert-butyl)benzyl bromide (17.2 mL, 0.00935 mol) followed by potassium carbonate powder (25.8 g, 0.187 mol).The resulting mixture was stirred at 80-85 °C under a drying tube for 24 hours. The reaction mixture was cooled to room temperature and then partitioned between ethyl acetate (300 mL) and NH_4Cl saturated aqueous solution (300 mL). The aqueous layer was extracted with ethyl acetate (200 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50% ethyl acetate in hexane to give the titled compound as colorless oil.

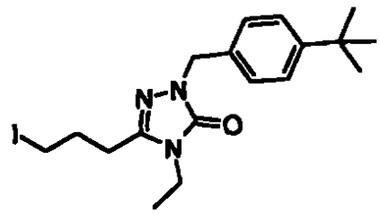
Step F: Preparation of



To a solution of the Step E product (4.2 g, 0.0103 mol) in ethanol (100 mL) at r om temperature, palladium, 10% on

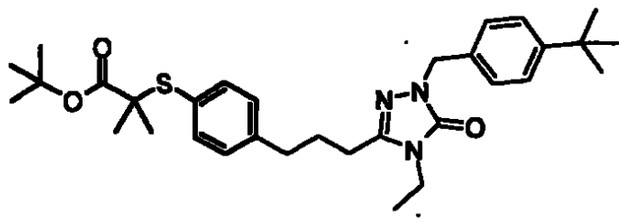
activated carbon (1.03 g) was added. Mixture was stirred under hydrogen atmosphere (balloon) for 3 hours and then filtered through a plug of celite. Evaporation of the solvent gave the titled compound as white solid that was used in Step G without further purification.

Step G: Preparation of



To a solution of triphenylphosphine (1.23 g, 4.68 mmol) and imidazole (0.32 g, 4.68 mmol) in a 3:1 mixture of Et_2O-CH_3CN (20 mL) at 0 °C under nitrogen atmosphere, iodine (1.19 g, 4.68 mmol) was added in small portions with vigorous stirring. The resulting mixture was warmed at room temperature and stirred for 30 minutes. Then, mixture was cooled to 0°C and a solution of the Step F product (1.35 g, 4.25 mmol) in a 1:1 mixture of Et_2O-CH_3CN (5 mL) was added. Reaction was stirred at 0 °C for 15 min and at room temperature for 30 minutes and then poured onto 0.5N HCl (50 mL). The aqueous layer was extracted twice with a 1:1 mixture of Et_2O-hexanes (100 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50% ethyl acetate in hexane to give the titled compound as yellow oil.

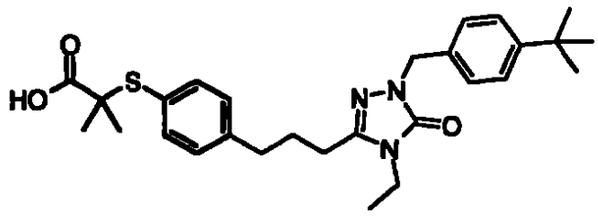
Step H: Preparation of



To a stirred slurry of zinc dust (0.21 g, 3.22 mmol) in anhydrous THF (0.5 mL) under nitrogen atmosphere at 60 °C was added 1,2-dibromoethane (13.9 µL, 0.16 mmol). After 15 minutes of vigorous stirring, the slurry was allowed to cool to room temperature and chlorotrimethylsilane (17.1 µL, 0.135 mmol) was added. Mixture was stirred for 30 minutes and then was reheated to 60°C. Then, a solution of the Step G product (0.23 g, 0.54 mmol) in anhydrous THF (1 mL) was added dropwise and mixture stirred for 30 minutes. A solution of tert-butyl 2-(4-bromophenylsulfanyl)-2-methylpropionate (0.36 g, 1.08 mmol), $Pd(dba)_2$ (0.0155 g, 0.027 mmol) and tri-o-tolylphosphine (0.0164 g, 0.054 mmol) in anhydrous THF (1 mL) was added and the resulting solution maintained at 60 °C for 2 h. Reaction was then cooled at room temperature and poured onto saturated NH_4Cl aqueous solution (20 mL). The aqueous layer was extracted with ethyl acetate (50 mL) and the organic layer washed with saturated NH_4Cl aqueous solution (2 x 10 mL). The combined aqueous phase was extracted with ethyl acetate (50 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 40% ethyl acetate in hexane to give the titled compound as colorless oil. MS: m/z (M^+ + 1): 552.4.

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221

Step I: Preparation of

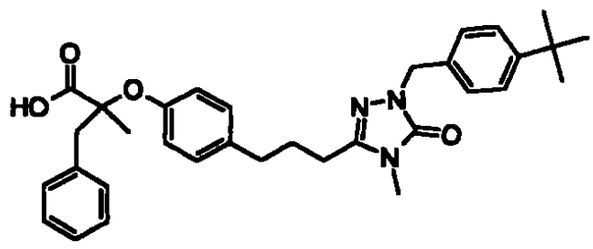


The Step I product (180 mg) was treated a mixture of triflouroacetic acid and dichloromethane (10 mL, 50% v/v) with stirring for 3 h. The solvent was removed on a rotary evaporator and the residue dried under high vacuum to give the titled compound.

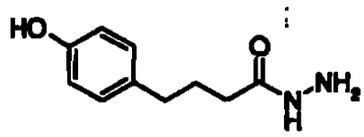
Example 39

Compound 39

2-(4-{3-[1-(4-tert-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-2-methyl-3-phenylpropionic acid



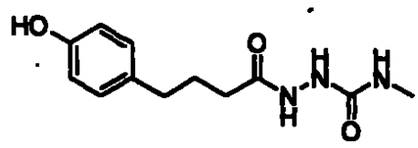
Step A: Preparation of 4-(4-Hydroxyphenyl)butyric acid hydrazide



A mixture of methyl 4-(4-hydroxyphenyl)butyrate (4.93 g, 0.025 mol) and hydrazine hydrate (25.4 g, 0.254 mol) in

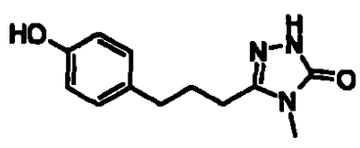
methanol (64 mL) was heated under reflux for an hour. It was then cooled down to room temperature and stirred overnight. The solvent was evaporated and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness to give the titled compound as a white crystal (3.30 g, 67%). 400 MHz ^1H NMR (DMSO-d^6) δ 9.10 (s, 1H), 8.89 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 3.32 (s, 2H), 2.40 (t, J = 7.6 Hz, 2H), 1.97 (t, J = 7.2 Hz, 2H), 1.71-1.67 (m, 2H); Mass ($M-H^-$) = 193.27.

Step B: Preparation of



To a solution of the Step A product (3.49 g, 0.0180 mol) in THF (900 mL), was added methyl isocyanate (Aldrich, 1.17 mL, 0.0198 mol) dropwise and the mixture was stirred at room temperature for an hour. Evaporation of solvent gave the titled compound as an off-white powder (3.2 g, 71%). Mass ($M-H^-$) = 250.30.

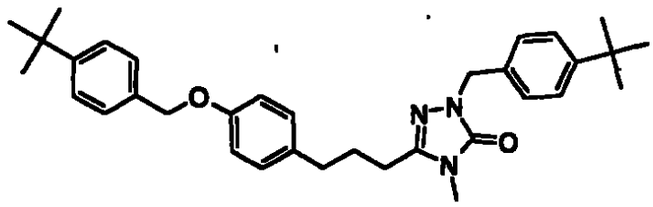
Step C: Preparation of 5-[3-(4-hydroxyphenyl)propyl]-4-methyl-2,4-dihydro-[1,2,4]triazol-3-one



To a solution of the Step B product (3.21 g, 0.0128 mol) in methanol (64 mL), was added potassium hydroxide in one portion (10.8 g, 0.181 mol). The reaction mixture was

heated at 70 °C for 36 hours. The residue was concentrated under reduced pressure and dissolved in water (80 mL). The aqueous solution was acidified to pH = 2 by concentrated HCl, resulting in product precipitation. The heterogeneous mixture was stirred for 18h, and the product was collected by filtration, yielding the titled compound as an off-white solid (4.5 g, in excess of theoretical yield). 400 MHz ^{1}H NMR (DMSO-d^6) δ 11.37 (s, 1H), 6.97 (d, J = 8.0 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 3.01 (s, 3H), 2.50 (t, J = 7.6 Hz, 2H), 2.42 (t, J = 7.6 Hz, 2H), 1.80-1.77 (m, 2H); Mass ($M+H^+$) = 234.21, ($M-H^-$) = 232.29.

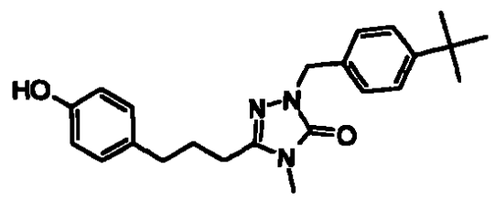
Step D: Preparation of 2-(4-tert-Butylbenzyl)-5-{3-[4-(4-tertbutylbenzyloxy)- phenyl]propyl}-4-methyl-2,4-dihydro[1,2,4]triazol-3-one



To a solution of the Step C product (1.00 g, 4.3 mmol) in DMF (21.2 mL), was added 4-t-butylbenzyl bromide (3.86 g, 17 mmol) followed by potassium carbonate powder (2.92 g, 22 mmol). The mixture was stirred at rt under nitrogen overnight. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic phase was dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 20% ethyl acetate in hexane to give the titled compound as colorless oil (1.12 g, 59%). 400 MHz ^{1}H

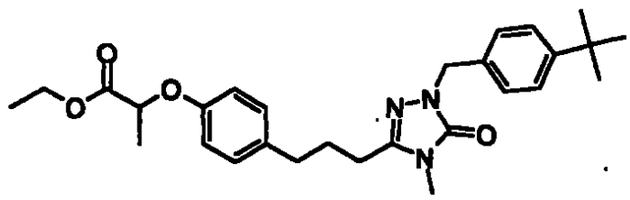
NMR ($CDCl_3$) δ 7.42-7.26 (m, 8H), 7.06 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.00 (s, 2H), 4.89 (s, 2H), 3.15 (s, 3H), 2.63 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 7.6 Hz, 2H), 1.95 (quintet, J = 7.6 Hz, 2H); 1.29 (m, 18H); Mass ($M+H^+$) = 526.43.

Step E: Preparation of 2-(4-tert-butylbenzyl)-5-[3-(4-hydroxyphenyl)propyl]-4-methyl-2,4-dihydro-[1,2,4]triazol-3-one



To a solution of the Step D product (1.12 g, 2.1 mmol) in EtOH (21 mL) was added 5% Pd/C (22 mg) and a hydrogen balloon. The reaction was stirred for 18 h. After filtering away the catalyst on celite, the filtrate was concentrated to produce the titled compound as a white solid (0.746 mg, 92%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), δ 6.99 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.89 (s, 2H), 3.15 (s, 3H), 2.61 (t, J = 7.6 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 1.97-1.92 (m, 2H); 1.28 (s, 9H); Mass ($M+H^+$) = 380.26.

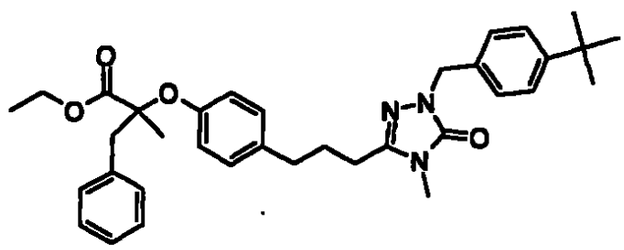
Step F: Preparation of 2-(4-{3-[1-(4-tert-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)propionic acid ethyl ester



To a solution of the Step E product (0.746 g, 1.97 mmol) in DMF (7.9 mL) was added ethyl bromopropionate (0.713 g, 3.94 mmol) followed by powdered potassium carbonate (1.36 g, 9.85 mmol). The reaction was stirred at rt overnight, then diluted with ethyl acetate (20 mL) and washed with water (10 mL). The aqueous layer was back-extracted with ethyl acetate (20 mL), then the combined organics were dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (90 g SiO_2, 50% ethyl acetate in hexane to 100% ethyl acetate) providing the ethyl ester as an oil (0.754g, 80%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.33 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 4.89 (s, 2H), 4.70 (q, J = 6.8 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.15 (s, 3H), 2.62 (t, J = 7.6 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 1.94 (quintet, J = 7.2 Hz, 2H), 1.60 (d, J = 6.8 Hz, 3H), 1.28-1.23 (m, 12H); Mass ($M+H^+$) = 480.2.

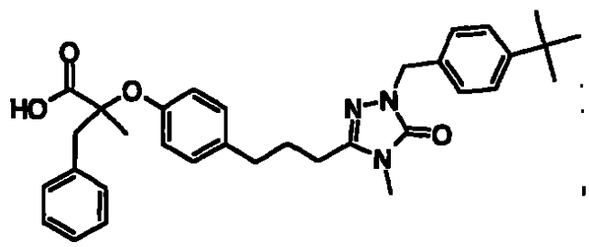
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Step G: Preparation of 2-(4-{3-[1-(4-tert-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-2-methyl-3-phenyl-propionic acid ethyl ester



A magnetically stirred solution of the Step F product (0.752 g, 1.6 mmol) in THF (12 mL) was cooled to -78 °C under nitrogen. LHMDS (1M solution in THF, 1.96 mL) was added dropwise via syringe, followed by syringe addition of a mixture of benzyl bromide (0.992 g, 5.8 mmol) and tetrabutyl ammonium iodide (57 mg, 0.15 mmol). The reaction proceeded for 1h at -78 °C, then for 4h at -20 °C, and finally for 1h at rt. The reaction was quenched with saturated aqueous ammonium chloride, and ethyl acetate was added. Layers were separated, and the organic phase was washed with brine, dried over Na_2SO_4, then concentrated. The product was purified by column chromatography (50 g SiO_2, 50% ethyl acetate in hexane to 100% ethyl acetate) providing the ethyl ester as an oil (0.224 g, 25%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.34-7.25 (m, 9H), 6.99 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 4.88 (s, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.31 (d, J = 9.6 Hz, 2H), 3.16 (d, J = 9.6 Hz, 2H), 3.14 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 1.95-1.91 (m, 2H), 1.34 (s, 3H), 1.27-1.20 (m, 12H); Mass ($M+H^+$) = 570.3, ($M+NH_4^+$) = 587.3.

Step H: Preparation of 2-(4-{3-[1-(4-tert-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-2-methyl-3-phenyl-propionic acid

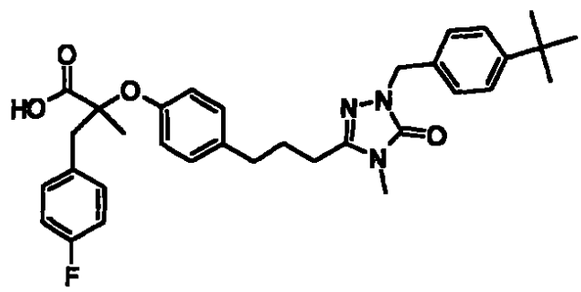


A magnetically stirred solution of the Step G product (0.073 g, 0.13 mmol) in EtOH (1.3 mL) was treated with NaOH (5M aqueous solution, 0.128 mL) and heated at reflux for 18h. The reaction mixture was acidified to pH = 1 using 1M HCl, and cooled to rt. Ethyl acetate was added (10 mL), layers were separated, and the aqueous phase was back-extracted with EtOAc (3 x 10 mL). Combined organic phases were dried over Na_2SO_4, and concentrated to provide the product as a tacky solid (0.054 g, 77%). Mass ($M+H^+$) = 542.2, ($M-H^-$) = 540.2.

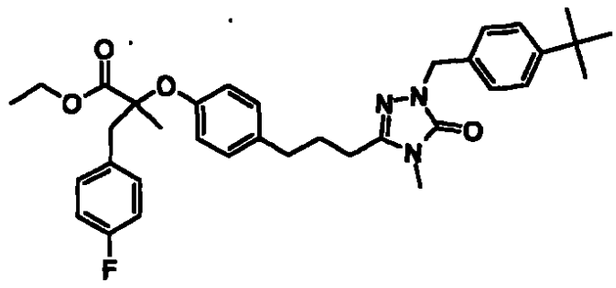
Example 40

Compound 40

<u>2-(4-{3-[1-(4-tert-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-3-(4-fluorophenyl)-2-methylpropionic acid ethyl ester</u>



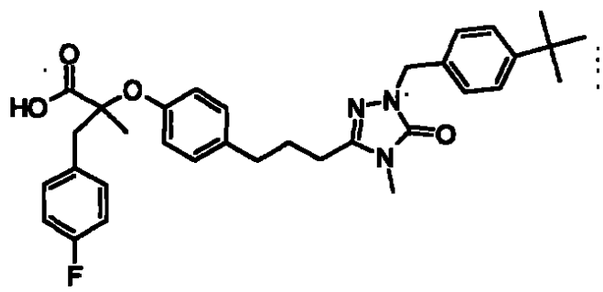
Step A: Preparation of 2-(4-{3-[1-(4-tert-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-3-(4-fluorophenyl)-2-methylpropionic acid ethyl ester



A magnetically stirred solution of the 2-(4-{3-[1-(4-tert-butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)propionic acid ethyl ester (Example 1, step F)(0.119 g, 0.25 mmol) in THF (1.7 mL) was cooled to -78 °C under nitrogen. LHMDS (1M solution in THF, 0.31 mL) was added dropwise via syringe, followed by syringe addition of a mixture of 4-fluorobenzyl bromide (0.173 g, 0.91 mmol) and tetrabutyl ammonium iodide (10 mg, 0.03 mmol). The reaction proceeded for 1h at -78 °C, then for 4h at -20 °C, and finally for 1h at rt. The reaction was quenched with saturated aqueous ammonium chloride, and

ethyl acetate was added. Layers were separated, and the organic phase was washed with brine, dried over Na_2SO_4, then concentrated. The product was purified by column chromatography (30 g SiO_2, 50% ethyl acetate in hexane) providing the ethyl ester as an oil (0.051 g, 35%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.34-7.22 (m, 8H), 7.00 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.88 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.28 (d, J = 14.0 Hz, 2H), 3.14 (s, 3H), 3.12 (d, J = 14.0 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 1.95-1.91 (m, 2H), 1.28-1.22 (m, 18H).

Step B: Preparation of 2-(4-{3-[1-(4-tert-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}-phenoxy)-3-(4-fluorophenyl)-2-methylpropionic acid



A magnetically stirred solution of the Step A product (54 mg, 0.09 mmol) in EtOH (0.9 mL) was treated with NaOH (5M aqueous solution, 0.091 mL) and heated at reflux for 18h. The reaction mixture was acidified to pH = 1 using 1M HCl, and cooled to rt. Ethyl acetate was added (10 mL), layers were separated, and the aqueous phase was back-extracted with EtOAc (3 x 10 mL). Combined organic phases were dried over Na_2SO_4, and concentrated to provide the product as a tacky solid (0.029 g, 57%). 400 MHz ^1H NMR (DMSO-d^6) δ 7.15 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 4.76 (s,

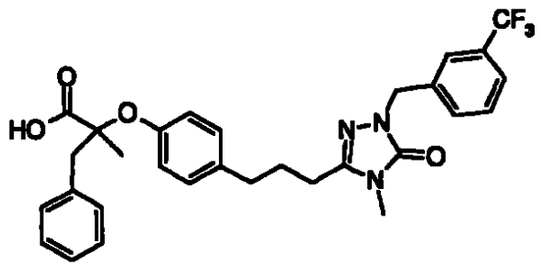
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2H), 3.08 (s, 2H), 2.53-2.45 (m, 4H), 1.82-1.78 (m, 2H), 1.25 (s, 3H), 1.22 (s, 9H); Mass ($M+H^+$) = 560.3, ($M-H^-$) = 558.3.

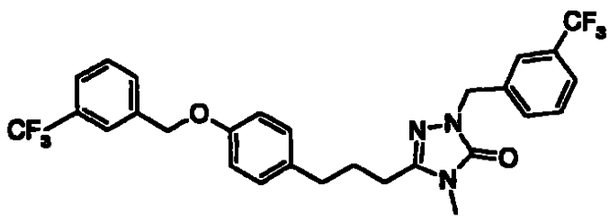
Example 41

Compound 41

2-Methyl-2-(4-{3-[4-methyl-5-oxo-1-(3-trifluoromethyl-benzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-3-phenyl-propionic acid



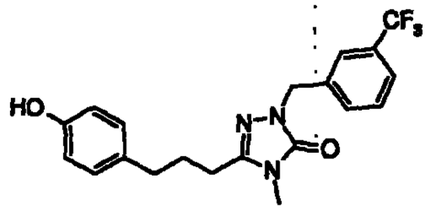
Step A: Preparation of 4-Methyl-2-(3-trifluoromethyl-benzyl)-5-{3-[4-(3-trifluoromethyl-benzyloxy)-phenyl]-propyl}-2,4-dihydro-[1,2,4]triazol-3-one



To a solution of 5-[3-(4-hydroxyphenyl)propyl]-4-methyl-2,4-dihydro-[1,2,4]triazol-3-one (Example 1, step C) (0.350 g, 1.50 mmol) in DMF (5 mL), was added 3-trifluorobenzyl bromide (1.03 g, 4.29 mmol) followed by potassium carbonate powder (0.74 g, 5.35 mmol). The mixture was stirred at rt under nitrogen overnight. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ and

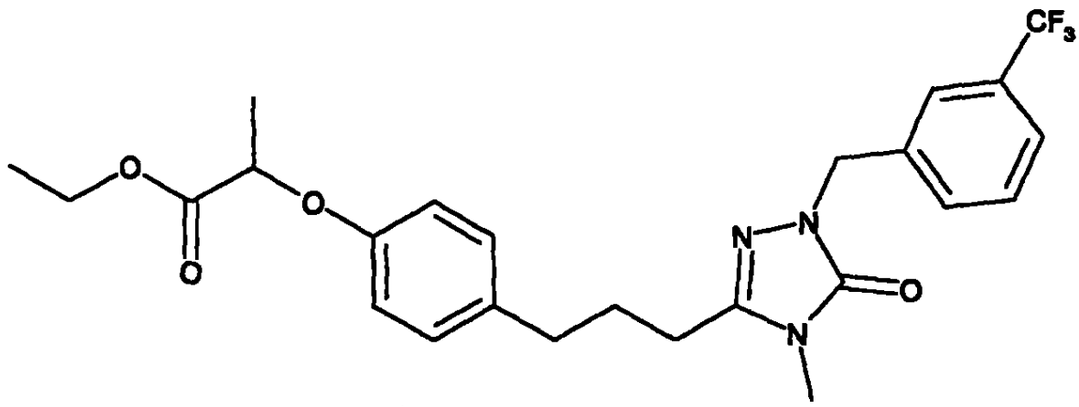
filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column (125 mL SiO_2) eluting with 50% EtOAc/hexanes to give the titled compound as colorless oil (0.675 g, 82%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.63-7.42 (m, 7H), 7.08 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.09 (s, 2H), 4.98 (s, 2H), 3.18 (s, 3H), 2.64 (t, J = 7.2 Hz, 2H), 2.48 (t, J = 7.6 Hz, 2H), 1.97 (quintet, J = 7.6 Hz, 2H); Mass ($M+H^+$) = 550.3.

Step B: Preparation of 5-[3-(4-Hydroxy-phenyl)-propyl]-4-methyl-2-(3-trifluoromethyl-benzyl)-2,4-dihydro-[1,2,4]triazol-3-one



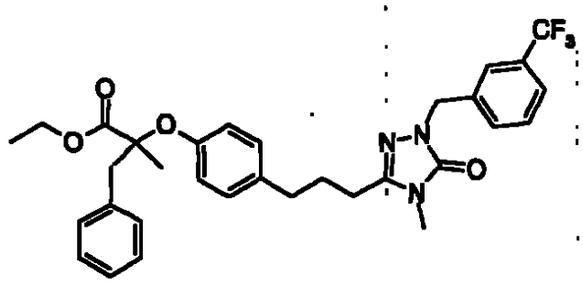
To a solution of the Step A product (0.67 g, 1.22 mmol) in EtOH (50 mL) was added 5% Pd/C (85 mg) and a hydrogen balloon. The reaction was stirred for 18 h. After filtering away the catalyst on celite, the filtrate was concentrated to produce the titled compound (oil, 0.29 g, 60%). Mass ($M+H^+$) = 392.2.

Step C: Preparation of 2-Methyl-3-(4-{3-[4-methyl-5-ox -1-(3-trifluoromethyl-benzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid ethyl ester



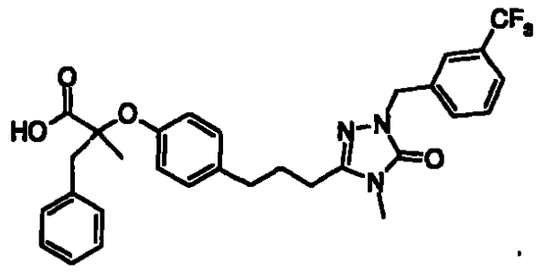
To a solution of the Step B product (0.29 g, 0.74 mmol) in DMF (3 mL) was added ethyl bromopropionate (0.27 g, 1.47 mmol, 0.19 mL) followed by powdered potassium carbonate (0.51 g, 3.7 mmol). The reaction was stirred at rt overnight, then diluted with ethyl acetate (20 mL) and washed with water (10 mL). The aqueous layer was back-extracted with ethyl acetate (20 mL), then the combined organics were dried over $MgSO_4$ and concentrated. The product was purified by column chromatography (100 mL SiO_2, 50% ethyl acetate in hexane to 100% ethyl acetate) providing the ethyl ester as an oil (0.754g, 80%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.51-7.49 (m, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 4.95 (s, 2H), 4.68 (q, J = 7.2 Hz, 2H), 4.19 (q, J = 7.2 Hz, 2H), 3.15 (s, 3H), 2.60 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 1.93 (quintet, J = 7.6 Hz, 2H), 1.58 (d, J = 6.8 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H); Mass ($M+H^+$) = 492.1.

Step D: Preparation 2-Methyl-2-(4-{3-[4-methyl-5-oxo-1-(3-trifluoromethyl-benzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-3-phenyl-propionic acid ethyl ester



A magnetically stirred solution of the part C product (0.22 g, 0.45 mmol) in THF (2.8 mL) was cooled to -78 °C under nitrogen. LHMDS (1M solution in THF, 0.56 mL) was added dropwise via syringe, followed by syringe addition of a mixture of benzyl bromide (0.27 g, 1.6 mmol) and tetrabutyl ammonium iodide (16 mg, 0.045 mmol). The reaction proceeded for 1 h at -78 °C, then for 4 h at -20 °C, and finally for 1 h at rt. The reaction was quenched with saturated aqueous ammonium chloride, and ethyl acetate was added. Layers were separated, and the organic phase was washed with brine, dried over Na_2SO_4, then concentrated. The product was purified by column chromatography (100 mL SiO_2, 15% EtOAc/hexanes to 70% EtOAc/hexanes) providing the ethyl ester as an oil (23 mg, 9%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.34-7.22 (m, 9H), 7.00 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 4.97 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.28 (d, J = 14.0 Hz, 2H), 3.14 (s, 3H), 3.12 (d, J = 14.0 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 1.95-1.91 (m, 2H), 1.38 (s, 3H), 1.28 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H); Mass ($M+H^+$) = 582.4; ($M+NH_4^+$) = 599.4.

Step E: Preparation of 2-Methyl-2-(4-{3-[4-methyl-5-oxo-1-(3-trifluoromethyl-benzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-3-phenyl-propionic acid

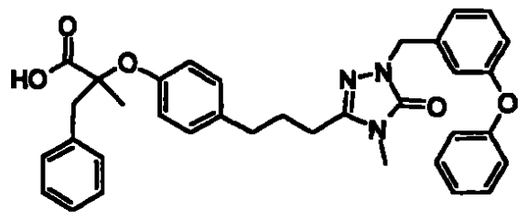


A magnetically stirred solution of the Step D product (20 mg, 0.034 mmol) in EtOH (2 mL) was treated with NaOH (5M aqueous solution, 40 µL) and heated at reflux for 18h. The reaction mixture was acidified to pH = 1 using 1M HCl, and cooled to rt. Ethyl acetate was added (10 mL), layers were separated, and the aqueous phase was back-extracted with EtOAc (3 x 10 mL). Combined organic phases were dried over $MgSO_4$, and concentrated to provide the product as a tacky solid (10.3 mg, 54%). Mass ($M+H^+$) = 554.3, ($M-H^-$) = 552.3.

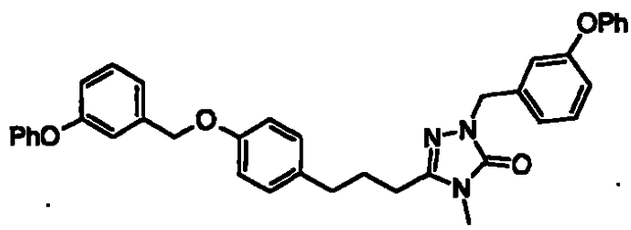
Example 42

Compound 42

2-Methyl-2-(4-{3-[4-methyl-5-oxo-1-(3-phenoxybenzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-3-phenylpropionic acid

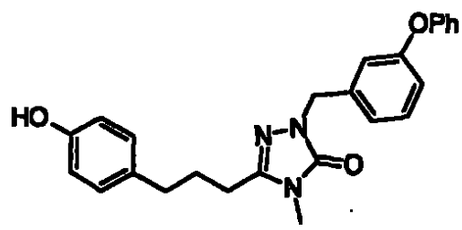


Step A: Preparation of 4-Methyl-2-(3-phenoxy-benzyl)-5-{3-[4-(3-phenoxy-benzyloxy)-phenyl]-propyl}-2,4-dihydro-[1,2,4]triazol-3-one



To a solution of 5-[3-(4-hydroxyphenyl)propyl]-4-methyl-2,4-dihydro-[1,2,4]triazol-3-one (Example 1, step C) (0.350 g, 1.50 mmol) in DMF (5 mL), was added 3-phenoxybenzyl chloride (0.94 g, 4.29 mmol) followed by potassium carbonate powder (0.74 g, 5.35 mmol). The mixture was stirred at rt under nitrogen overnight. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column (125 mL SiO_2) eluting with 50% EtOAc/hexanes to give the titled compound as colorless oil (0.0.78 g, 87%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.32 (q, J = 7.6 Hz, 4H), 7.30-7.25 (m, 3H), 7.20-6.90 (m, 10H), 6.97 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.01 (s, 2H), 4.91 (s, 2H), 3.16 (s, 3H), 2.63 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 7.6 Hz, 2H), 1.94 (quintet, J = 7.6 Hz, 2H); Mass ($M+H^+$) = 598.4.

Step B: Preparation of 5-[3-(4-Hydroxy-phenyl)-propyl]-4-methyl-2-(3-phenoxy-benzyl)-2,4-dihydro-[1,2,4]triazol-3-one

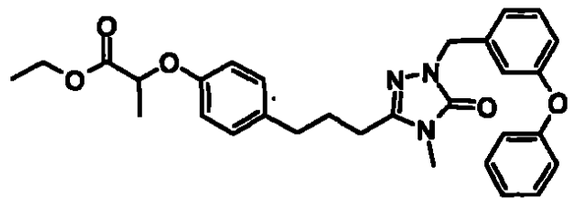


To a solution of the Step A product (0.78 g, 1.30 mmol) in EtOH (10 mL) and EtOAc (2 mL) was added 5% Pd/C (85 mg) and a hydrogen balloon. The reaction was stirred for 72 h.

233
224

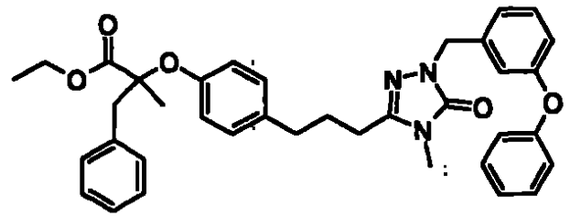
After filtering away the catalyst on celite, the filtrate was concentrated to produce the titled compound as a oil (0.138 g, 25%). Mass ($M+H^+$) = 416.1.

Step C: Preparation of 2-(4-{3-[4-Methyl-5-oxo-1-(3-phenoxybenzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)propionic acid ethyl ester



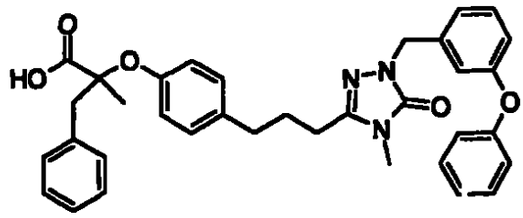
To a solution of the Step B product (0.138 g, 0.33 mmol) in DMF (1.3 mL) was added ethyl bromopropionate (0.120 g, 0.66 mmol) followed by powdered potassium carbonate (0.23 g, 0.0017 mol). The reaction was stirred at rt overnight, then diluted with ethyl acetate (20 mL) and washed with water (10 mL). The aqueous layer was back-extracted with ethyl acetate (20 mL), then the combined organics were dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (20 g SiO_2, 50% ethyl acetate in hexane) providing the ethyl ester as an oil (0.144g, 84%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.22-7.15 (m, 4H), 7.00-6.69 (m, 9H), 4.81 (s, 2H), 4.61 (q, J = 6.8 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 3.07 (s, 3H), 2.52 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.86-1.82 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 7.2 Hz, 3H); Mass ($M+H^+$) = 516.3, ($M+NH_4^+$) = 533.3.

Step D: Preparation of 2-Methyl-2-(4-{3-[4-methyl-5-oxo-1-(3-phenoxybenzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-3-phenylpropionic acid ethyl ester



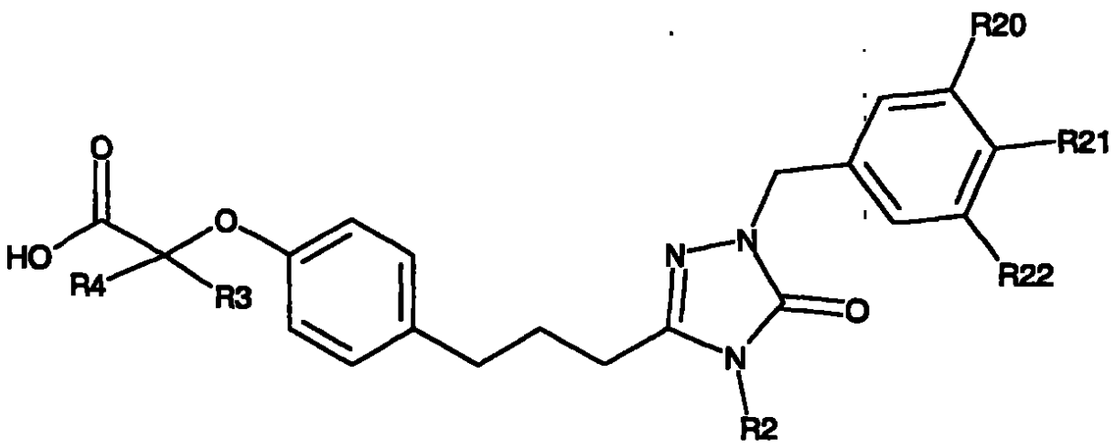
A magnetically stirred solution of the Step C product (0.144 g, 0.00028 mol) in THF (2 mL) was cooled to -78 °C under nitrogen. LHMDS (1M solution in THF, 0.348 mL) was added dropwise via syringe, followed by syringe addition of a mixture of benzyl bromide (0.176 g, 0.00103 mol) and tetrabutyl ammonium iodide (0.010 g, 0.00003 mol). The reaction proceeded for 1h at -78 °C, then for 4h at -20 °C, and finally for 1h at rt. The reaction was quenched with saturated aqueous ammonium chloride, and ethyl acetate was added. Layers were separated, and the organic phase was washed with brine, dried over Na_2SO_4, then concentrated. The product was purified by column chromatography (50 g SiO_2, 50% ethyl acetate in hexane) providing the ethyl ester as an oil (0.146 g, 87%). 400 MHz ^1H NMR ($CDCl_3$) δ 7.31-7.24 (m, 8H), 7.09-6.74 (m, 10 H), 4.90 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.30-3.15 (m, 5H), 2.60 (t, J = 7.2 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 1.94-1.91 (m, 2H), 1.38 (s, 3H), 1.27-1.20 (m, 3H); Mass ($M+H^+$) = 606.2, ($M+NH_4^+$) = 623.2.

Step E: Preparation of 2-Methyl-2-(4-{3-[4-methyl-5-oxo-1-(3-phenoxybenzyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-3-phenylpropionic acid



A magnetically stirred solution of the Step D product (0.120g, 0.00020 mol) in EtOH (2.0 mL) was treated with NaOH (5M aqueous solution, 0.198 mL) and heated at reflux for 48h. The reaction mixture was acidified to pH = 1 using 1M HCl, and cooled to rt. Ethyl acetate was added (10 mL), layers were separated, and the aqueous phase was back-extracted with EtOAc (3 x 10 mL). Combined organic phases were dried over Na_2SO_4, and concentrated to provide the product as a tacky solid (0.097 g, 85%). 400 MHz ^1H NMR (DMSO-d^6) δ 7.38-7.24 (m, 8H), 7.14-6.73 (m, 10 H), 4.81 (s, 2H), 3.25-3.07 (m, 5H), 2.52 (m, 4H), 1.82-1.76 (m, 2H), 1.26 (s, 3H); Mass ($M+H^+$) = 578.3, ($M-H^-$) = 576.3.

Additional compounds of the present invention, having the structural formula shown below, were synthesized by methods similar to those described in the previous examples.



These additional compounds are further exemplified in the following table.

Table I

Example Number	R4	R3	R2	R20	R21	R22
43	CH3	CH3	propyl	OH	H	H
44	CH3	CH3	butyl	H	H	OCH3
45	CH3	CH3	CH3	H	H	OCH3
46	CH3	CH3	propyl	H	NO2	H
47	CH3	CH3	ethyl	H	H	OCH3
48	ethyl	CH3	propyl	H	CH3	H
49	benzyl	CH3	propyl	H	CH3	H
50	H	H	propyl	CH3	CH3	H

51	CH3	H	propyl	CH3	CH3	H
52	ethyl	H	propyl	CH3	CH3	H
53	isopropyl	H	propyl	CH3	CH3	H
54	F	F	propyl	CH3	CH3	H
55	cyclohexyl	H	propyl	CH3	CH3	H
56	phenyl	H	propyl	CH3	CH3	H
57	2-hydroxy ethyl	H	propyl	CH3	CH3	H
58	F	H	propyl	CH3	CH3	H
59	butyl	H	propyl	CH3	CH3	H
60	pentyl	H	propyl	CH3	CH3	H
61	H	H	propyl	H	t-butyl	H
62	CH3	H	propyl	H	t-butyl	H
63	ethyl	H	propyl	H	t-butyl	H
64	isopropyl	H	propyl	H	t-butyl	H
65	F	F	propyl	H	t-butyl	H
66	cyclohexyl	H	propyl	H	t-butyl	H

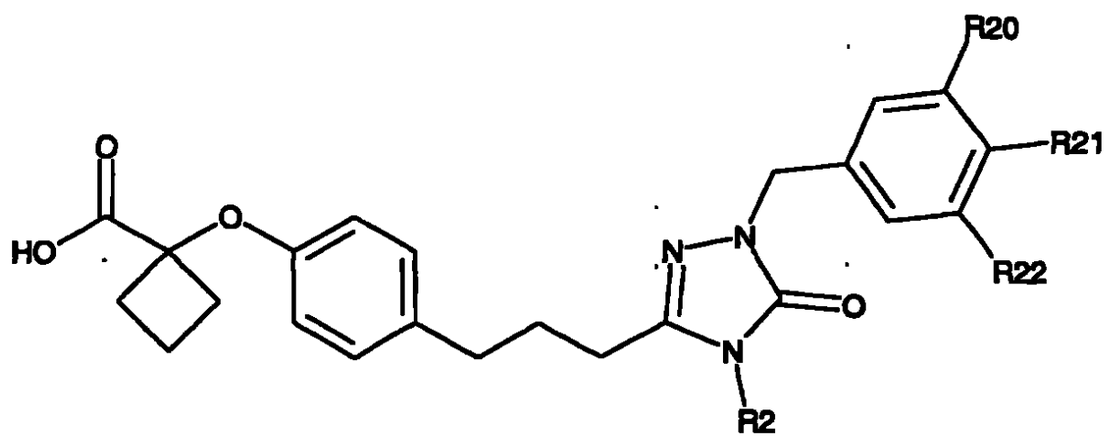
238

67	phenyl	H	propyl	H	t-butyl	H
68	2-hydroxy ethyl	H	propyl	H	t-butyl	H
69	butyl	H	propyl	H	t-butyl	H
70	pentyl	H	propyl	H	t-butyl	H
71	CH3	CH3	2-methoxy ethyl	CH3	CH3	H
72	H	H	ethyl	H	CH3	H
73	CH3	H	ethyl	H	CH3	H
74	ethyl	H	ethyl	H	CH3	H
75	isopropyl	H	ethyl	H	CH3	H
76	cyclohexyl	H	ethyl	H	CH3	H
77	phenyl	H	ethyl	H	CH3	H
78	CH3	CH3	t-butyl	CH3	CH3	H
79	CH3	CH3	i-propyl	CH3	CH3	H
80	CH3	CH3	H	H	H	Cl
81	CH3	CH3	H	CF3	H	CF3
82	CH3	CH3	H	H	Cl	Cl

83	CH3	CH3	H	H	F	F
84	OCH3	H	propyl	H	t-butyl	H
85	CH3	CH3	H	H	t-amyl	H
86	CH3	CH3	H	H	CF3	H
87	CH3	CH3	H	H	OCF3	H
88	CH3	CH3	H	H	CF3	F
89	CH3	CH3	2-phenoxy ethyl	CH3	CH3	H
90	CH3	CH3	cyclo-propyl-methyl	CH3	CH3	H
91	CH3	CH3	propyl	H	amino	H
92	CH3	CH3	2,4-dimethoxy-benzyl	H	CH3	H
93	CH3	CH3	2,4-dimethoxy-benzyl	CH3	H	CH3
94	CH3	CH3	2,4-dimethoxy-benzyl	H	t-butyl	H
95	CH3	CH3	2,4-dimethoxy-benzyl	H	H	phenoxy

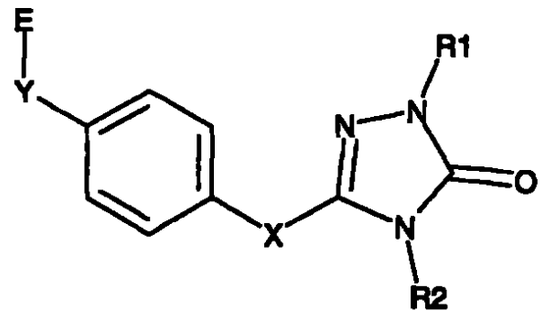
96	CH3	CH3	2,4-dimethoxy-benzyl	H	H	CH3
97	CH3	CH3	2,4-dimethoxy-benzyl	H	H	CF3
98	CH3	CH3	2,4-dimethoxy-benzyl	CH3	CH3	H
99	CH3	CH3	2,4,6-trimethoxy-benzyl	H	CH3	H

Other compounds of the present invention, having the structural formula shown below, were also synthesized by methods similar to those described in the previous examples.



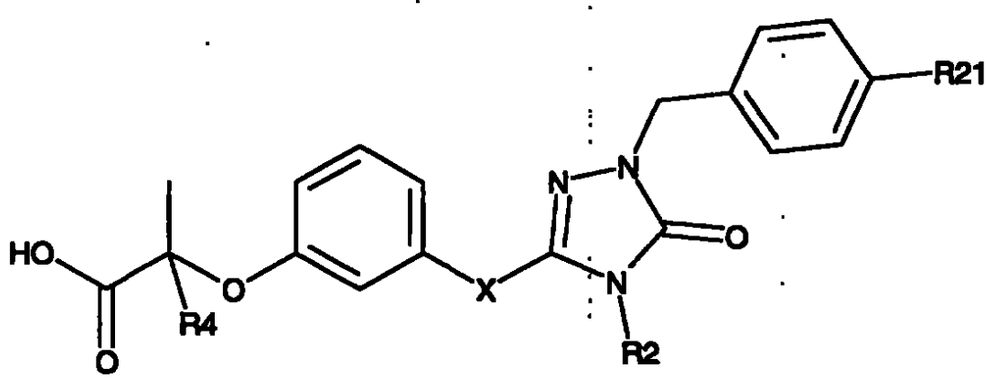
Example	R2	R20	R21	R22
100	propyl	CH3	CH3	H
101	propyl	H	t-butyl	H

102	ethyl	H	CH3	H
103	methyl	H	CH3	H



Example	E	Y	X	R1	R2
104	2(2-methyl) propanoic acid	O	butylene	4-methyl benzyl	ethyl
105	2(2-methyl) propanoic acid	O	butylene	4-methyl benzyl	propyl
106	ethanoic acid	O	propylene	phenyl	propyl
107	2(2-methyl) propanoic acid	O	propylene	phenyl	propyl
108	2(2-methyl) propanoic acid	O	propylene	β-naphthyl methyl	CH3
109	2(2-tetrazole)	O	proplyene	4-t-butyl benzyl	propyl

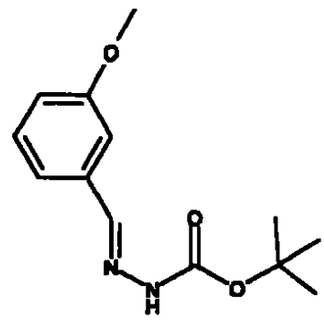
	ethyl				
110	2(2-methyl) propanoic acid	O	ethylene	3-methoxy benzyl	hexyl
111	COOH	-	propylene	4-t-butyl benzyl	ethyl
112	2(2-methyl-3-tetrazole) ethyl	O	propylene	3,4-dimethoxy benzyl	CH3



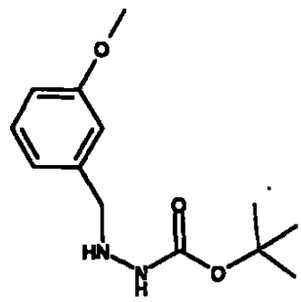
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Example	R4	X	R2	R21
113	CH3	propylene	CH3	t-butyl
114	benzyl	propylene	CH3	t-butyl
115	CH3	butylene	propyl	methyl

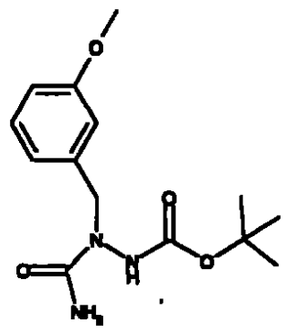
Example 116



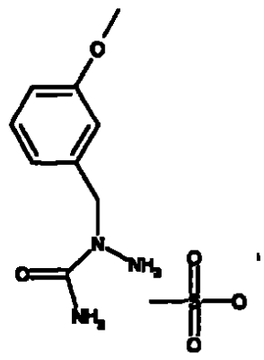
(3-methoxyphenyl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of *t*-butyl carbazate (5.59 g, 42.3 mmol) in ethyl acetate (15 mL) was added with stirring *m*-anisaldehyde (5.17 mL, 5.76 g, 42.3 mmol). Hexanes (70 mL) was added slowly and crystallization occurred. The resulting slurry was stirred at rt for 45 min and then cooled to 0 °C. The slurry was stirred at 0 °C for 60 min, then filtered and rinsed with cold hexanes (20 mL), and dried in vacuo at 40 °C to afford the title compound as a solid (9.68 g, 91.4%): mp 135.6-137.4 °C; ^{1}H NMR (DMSO-d_6) δ 10.93 (s, 1H), 7.29 (t, 1 H, *J* = 8 Hz), 7.14 (d, 2 H, *J* = 7 Hz), 6.92 (q, 1 H, *J* = 7 Hz), 3.75 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 160.2, 153.1, 143.7, 136.8, 130.5, 120.0, 116.2, 111.3, 80.1, 55.7, 28.7; IR (KBr mull): 3360, 3010, 2982, 2838, 1510, 1487 cm^{-1}; A portion was recrystallized from ethyl acetate and submitted for elemental analysis. Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.34.; H, 7.46; N, 11.19.



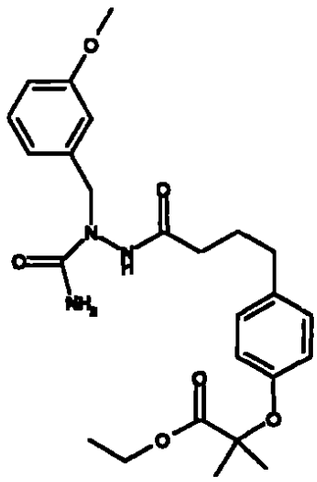
(3-methoxybenzyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester (3-methoxyphenyl) methylenehydrazinecarboxilic acid, 1,1-dimethylethyl ester (7.03 g, 28.1 mmol) and Pt/C (5%, dry, 5.07g) were slurried in THF (80 mL) and hydrogenated at rt and 50 psig for 8 hr. The slurry was then filtered through celite and concentrated in vacuo at 50 °C to afford the title compound as a clear oil (6.68 g, 94.0%): ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1H), 7.19 (t, 1 H, J = 8 Hz), 6.85 (d, 1 H, J = 7 Hz), 6.77 (d, 1 H, J = 7 Hz), 3.84 (s, 2 H), 3.72 (s, 3 H), 1.37 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 159.9, 157.1, 141.1, 129.7, 121.1, 114.1, 113.1, 78.9, 55.5, 54.9, 28.9; IR ($CHCl_3$): 3008, 2982, 2935, 1712 cm^{-1}; Exact Mass: Calc'd. m/z for $C_{13}H_{20}N_2O_3Na$: 275.1372, Found: 275.1381.



3-(aminocarbonyl)-2-(3-methoxyphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (3-methoxybenzyl) hydrazinecarboxilic acid, 1,1-dimethylethyl ester (6.30 g, 25.0 mmol) was dissolved in isopropyl alcohol (IPA, 65 mL). Trimethylsilyl isocyanate (4.73g, 34.9 mmol) was added in one portion via syringe and the solution was allowed to stir at ambient temperature for 7 h. The slurry was cooled to 0-5 °C, filtered, and the solids rinsed with cold IPA. The solids were dried in vacuo at 40 °C overnight to afford the title compound as a white solid (4.71 g, 63.9%). The filtrate was concentrated and purified by column chromatography (SiO_2, EtOAc) to afford additional compound (0.91 g, 12.3%). These two portions were combined to yield 5.82 g (76.2%) of the title compound: mp 136.3-138.5°C; ^1H NMR (DMSO-d_6, 60°C) δ 8.70 (s, 1H), 7.20 (t, 1 H, J = 8 Hz), 6.80 (m, 3 H), 5.90 (s, 2 H), 4.50 (s, 2 H), 3.74 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR (DMSO-d_6, 20°C) δ 159.9, 159.6, 155.0, 140.2, 129.8, 120.9, 114.0, 113.2, 80.2, 55.6, 51.1, 28.7; IR ($CHCl_3$): 3003, 2984, 2938, 1745, 1680 cm^{-1}; Anal. Calcd. for $C_{14}H_{21}N_3O_4$: C, 56.94; H, 7.17; N, 14.23. Found: C, 56.54; H, 7.17; N, 13.98.

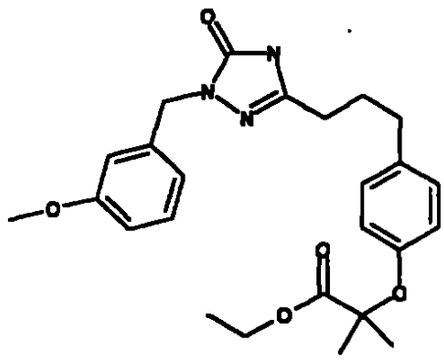


1-(3-methoxyphenylmethyl)hydrazine carboxamide methanesulfonate 3-(aminocarbonyl)-2-(3-methoxyphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (5.30 g, 17.9 mmol) was dissolved in dichloromethane (60 mL). Methanesulfonic acid (1.93g, 19.9 mmol) was added in one portion and the solution was allowed to stir at rt overnight. The resulting slurry was cooled to 0-5 °C, filtered, and the solids rinsed with cold dichloromethane. The solids were dried in vacuo at 40 °C overnight to afford the title compound as a white solid (5.05 g, 96.6%). mp 130.3-132.1 °C; ^{1}H NMR (DMSO-d_6) δ 9.7 (broad s, 3 H), 7.30 (t, 1 H, J = 8 Hz), 7.05 (broad s, 2 H), 6.88 (s, 3 H), 4.69 (s, 2 H), 3.74 (s, 3 H), 3.34 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 160.1, 158.2, 137.3, 130.5, 120.7, 114.3, 114.0, 55.7, 52.7, 40.4; IR (KBr mull): 3186, 2939, 1719, 1707, 1168 cm^{-1}; Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 41.23.; H, 5.88; N, 14.42. Found: C, 40.86.; H, 5.92; N, 14.61.



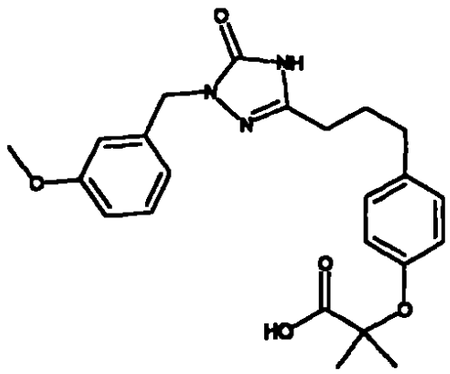
1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3-methoxyphenylmethyl)semicarbazide 4-[4-(1-Ethoxycarbonyl-1-methyl-ethoxy)-phenyl] butyric acid (4.86 g, 16.5 mmol) was dissolved in ethyl acetate (40 mL). Oxalyl chloride (2.43 g, 19.14 mmol) was added to this solution dropwise in the presence of a catalytic amount of N,N-dimethylformamide (100 mg, 1.37 mmol). Completion of acid chloride formation was verified by HPLC. This solution was then added dropwise to a suspension of 1-(3-methoxyphenylmethyl)hydrazine carboxamide methanesulfonate (4.80 g, 16.5 mmol) and pyridine (1.30 g, 16.5 mmol) in ethyl acetate (55 mL) at 0-5 °C. After stirring at 0-5 °C for 6 h, an additional charge of pyridine was added (1.30 g, 16.5 mmol) and the solution was stirred at 0-5 °C for 1 h at which time the reaction was complete. The solution was warmed to rt and washed twice with 1N HCl (80 mL) and twice with 5% aq. $NaHCO_3$ (80 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to a waxy solid. The solids were recrystallized from a mixture of toluene (17 mL) and n-heptane (7 mL) at 60 °C, cooled to 0-5 °C and filtered. The solids were dried in vacuo at 40 °C overnight, affording the title compound as a white solid (5.05 g, 65%): ^1H NMR (DMSO-d_6, 60°C) δ 9.60 (s, 1 H), 7.19 (t, 1 H, J = 8 Hz), 7.00 (d, 2 H), 6.80 (m, 3 H), 6.71 (d, 2

H, J = 8 Hz), 5.92 (s, 2 H), 4.52 (s, 2 H), 4.15 (q, J = 7 Hz), 3.71 (s, 3 H), 2.45 (t, 2 H, J = 7 Hz), 2.07 (t, 2 H, J = 7 Hz), 1.73 (quint, 2 H, J = 7 Hz), 1.48 (s, 6 H), 1.17 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 171.9, 159.9, 159.3, 153.7, 140.5, 135.9, 129.9, 129.7, 120.9, 119.4, 114.1, 113.1, 79.2, 61.6, 55.5, 50.9, 34.3, 33.4, 27.2, 25.7, 14.6; IR (KBr mull): 3450, 3320, 3275, 3202, 2997, 2940, 1730, 1646, 1511 cm^{-1}; Anal. Calcd. for $C_{25}H_{33}N_3O_6$: C, 63.68; H, 7.05; N, 8.91. Found: 63.49; H, 7.02; N, 8.99.



2-(4-{3-[1-(3-Methoxy-benzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester 1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3-methoxyphenylmethyl)semicarbazide (4.08 g, 8.65 mmol) was dissolved in ethyl acetate (7.5 mL). 1S (+)-10-camphorsulfonic acid (2.21 g, 9.51 mmol) was added in one portion and the solution was heated to reflux overnight. The solution was cooled to rt and washed with sat'd aq. $NaHCO_3$ (40 mL x 2) followed by 1N HCl (40 mL x 2). The organic was concentrated to an orange oil. This oil was redissolved in ethyl acetate (40 mL). Amberlyst-15 resin (4.41 g) was added and the mixture was heated to 50 °C and stirred f r 4 hours to remove de-ureated impurity. The

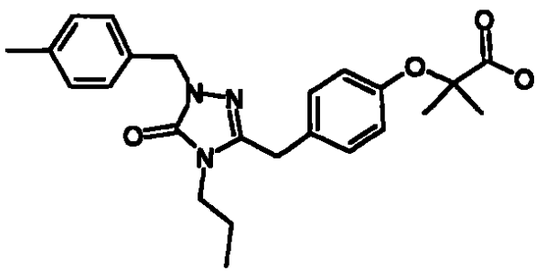
mixture was then cooled to ambient temperature, filtered, concentrated, and purified by column chromatography (SiO_2, 9:1 ethyl acetate: hexanes) to afford the title compound as an orange oil (1.93 g, 49.2%). ^1H NMR (DMSO-d_6) δ 11.47 (s, 1 H), 7.22 (t, 1 H, J = 8 Hz), 7.04 (d, 2 H, J = 8 Hz), 6.82 (d, 1 H, J = 2 Hz), 6.76 (m, 2 H), 6.68 (d, 2 H, J = 2 Hz), 4.73 (s, 2 H), 4.13 (q, 2 H, J = 7 Hz), 3.69 (s, 3 H), 2.48 (t, 2 H, J = 8 Hz), 2.36 (t, 2 H, J = 8 Hz), 1.80 (quint, 2 H, J = 7 Hz), 1.47 (s, 6 H), 1.14 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 160.0, 155.0, 153.8, 146.7, 139.8, 135.5, 130.2, 129.8, 120.1, 119.5, 113.8, 113.2, 79.2, 61.6, 55.6, 47.8, 34.0, 28.4, 26.2, 25.7, 14.6; IR ($CHCl_3$) 2940, 1692, 1508, 1467 cm^{-1}; Anal. Calcd. for $C_{25}H_{31}N_3O_5$: C, 66.21.; H, 6.89; N, 9.26. Found: C, 66.29; H, 6.75; N, 9.19.



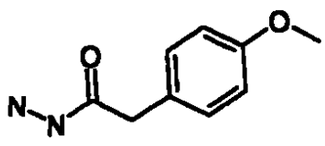
2-(4-{3-[1-(3-Methoxy-benzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid 2-(4-{3-[1-(3-Methoxy-benzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester (1.55 g, 3.42 mmol) was dissolved in a mixture of ethanol (7.5 mL) and deionized water (7.5 mL).

Solid sodium hydroxide (0.36 g, 8.73 mmol) was added in one portion and the solution was warmed to 70 °C and stirred for one hour. The solution was cooled to ambient temperature and the pH adjusted to 7 with 6N HCl. The solution was concentrated to a hazy yellow oil. This oil was partitioned between 1N HCl (10 mL) and ethyl acetate (15 mL). The aqueous layer was then re-extracted with ethyl acetate (15 mL) and the organic layers combined, dried ($MgSO_4$), filtered and concentrated in vacuo at 50 °C overnight to afford the title compound as a clear oil (1.41 g, 97.0%). ^1H NMR (DMSO-d_6) δ 13.0 (broad s, 1 H), 11.47 (s, 1 H), 7.23 (t, 1 H, J = 8 Hz), 7.03 (d, 2 H, J = 8 Hz), 6.82 (d, 1 H, J = 2 Hz), 6.75 (m, 5 H), 4.73 (s, 2 H), 3.70 (s, 3 H), 3.35 (broad s, 1 H), 2.48 (t, 2 H, J = 8 Hz), 2.36 (t, 2 H, J = 8 Hz), 1.80 (quint, 2 H, J = 7 Hz), 1.46 (s, 6 H); ^{13}C NMR (DMSO-d_6, 20°C) δ 175.8, 160.0, 155.0, 154.1, 146.8, 139.8, 135.0, 130.3, 129.7, 120.1, 119.1, 113.8, 113.2, 78.9, 55.6, 47.8, 40.6, 40.5, 34.0, 28.4, 27.5, 26.2, 25.7; IR (CHCl3) 1707, 1603, 1509, 1159 cm^{-1}; Anal. Calcd. for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 65.02; H, 6.65; N, 9.57.

Example 117



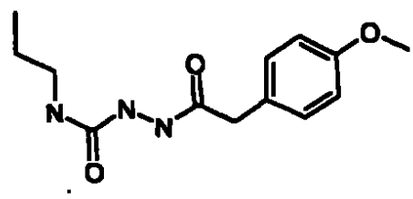
Step A:



A methanol solution of methyl 4-methoxyphenylacetate (Aldrich, 10.0 g, 0.056 mol) and hydrazine hydrate (EM Sciences, 27.8 g, 0.556 mol) was stirred at ambient temperature overnight. The resulting solution was concentrated, added to water and extracted with ethyl acetate (2X). The organic layers were combined and washed with aqueous brine then dried over sodium sulfate. Evaporation of the solvent gives a solid product which is washed with hexanes/ether and filtered to give the desired acyl hydrazide as a white solid.

$C_9H_{12}O_2N_2$ (MW = 180.21); mass spectroscopy (MH^+) = 181.0

Step B:

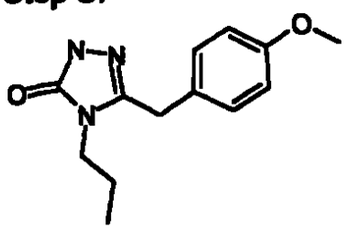


A tetrahydrofuran solution (150 mL) of the acyl hydrazide from **Step A** (8.0 g, 0.044 mol) was treated with propyl isocyanate (Aldrich, 1.2 g, 0.014 mol) and stirred at room temperature overnight, during which a precipitate forms. The resulting suspension was treated with methanol (20ml) and stirred for an additional 30 minutes. Hexane was then added and the mixture was filtered to give the desired acyl semicarbazide as a white solid which was used without further purification.

$C_{13}H_{19}N_3O_3$ (MW = 265.31)

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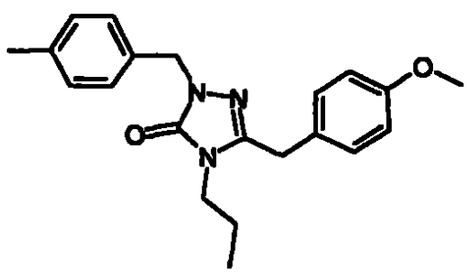
Step C:



A methanol solution (150 mL) of the acyl semicarbazide from **Step B** (10.0 g, 0.038 mol) was stirred and treated with solid potassium hydroxide (21.1 g, 0.377 mol). The mixture was heated at 60°C for 24 hrs then cooled to ambient temperature and stirred for 48 hrs. The solvent was reduced to about 75 ml, added to water, acidified to pH 6 with conc. HCl and extracted with ethyl acetate (3X). The organic layers were combined, washed with aqueous brine and dried over sodium sulfate. Evaporation of the solvent gives a solid that was washed with hexane/ether to give the desired N4-propyl triazolinone as a white solid.

$C_{13}H_{17}N_3O_2$ (MW = 247.30); mass spectroscopy (MH+) = 248.1

Step D:



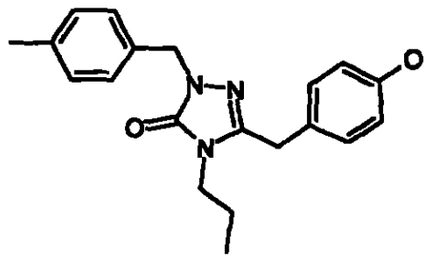
The N4-propyl triazolinone from **Step C** (7.0 g, 0.028 mol) is dissolved in DMF (75 mL) and treated with chloro-p-xylene (Aldrich, 6.0 g, 0.043 mol) and powdered potassium carbonate (Aldrich, 15.6 g, 0.113 mol). The resulting mixture was heated to 60°C overnight. The cooled reaction mixture was added to aqueous HCl (1N, 200 mL) and extracted with ethyl acetate (3X).

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The combined organic layers were washed with aqueous brine, dried over sodium sulfate and concentrated to give the crude product as an oil. Purification by flash chromatography (gradient: 100% hexanes to 2:1 hexanes:ethyl acetate) gives the desired N2-*p*-methylbenzyl triazolinone.

$C_{21}H_{25}N_3O_2$ (MW = 351.45); mass spectroscopy (MH+) = 352.2

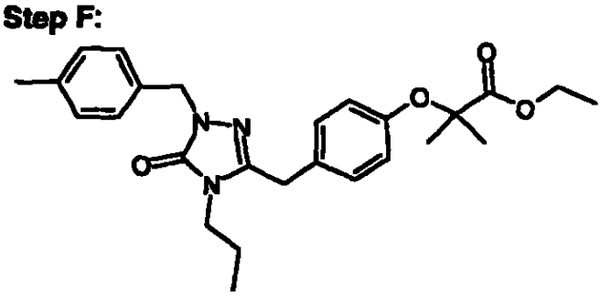
Step E:



The N2-*p*-methylbenzyl triazolinone from **Step D** (1.5 g, 0.004 mol) was dissolved in methylene chloride (25 mL) and cooled under a drying tube. A solution of boron tribromide (3.1 g, 1.2 mL, 0.013 mol) was added dropwise. The reaction mixture was then allowed to warm to ambient temperature and stirred for 2 hrs. The reaction was quenched by the dropwise addition of methanol (5 mL), added to water and extracted with methylene chloride (2X). The organic layers were combined, dried over sodium sulfate and concentrated to give the desired phenol as an oil which is used without purification.

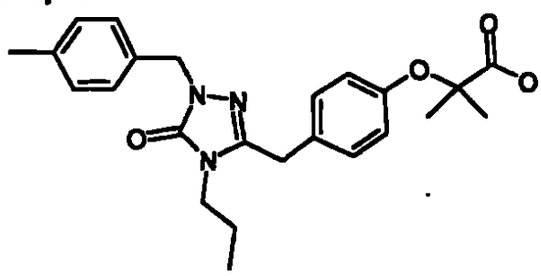
$C_{20}H_{23}N_3O_2$ (MW = 337.4); mass spectroscopy (MH^+) = 338.3

Step F:

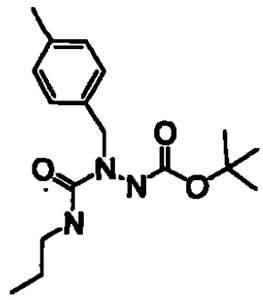


The phenol from **Step E** (1.3 g, 0.004 mol) was dissolved in ethanol (50 mL) and treated with ethyl 2-bromoisobutyrate (Aldrich, 2.3 g, 1.7 mL, 0.012 mol), powdered potassium carbonate (Aldrich, 2.2 g, 0.016 mol) and magnesium sulfate (0.6 g, 0.005 mol). The resulting mixture was stirred and heated to 55°C, under a drying tube, overnight. The cooled reaction mixture was added to HCl (5N. 70ml) and extracted with ethyl acetate (2X). The combined organic layers were dried over sodium sulfate and concentrated to give the crude product. Purification by flash chromatography (gradient: 100% hexanes to 3:2 ethyl acetate:hexanes) gives the desired ethyl ester.
$C_{26}H_{33}N_3O_4$ (MW = 451.6); mass spectroscopy (MH^+) = 452.3

Step G:

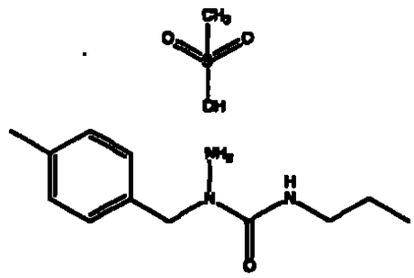


The ethyl ester from **Step F** (0.8 g, 0.002 mol) was dissolved in methanol (12 mL) and sodium hydroxide (2N, 3.0 ml, 0.006 mol) added. The resulting mixture was stirred at ambient temperature overnight. The reaction mixture was added to HCl (5N, 15ml) and extracted with ethyl acetate (2X). The organic layers were combined, dried over sodium sulfate and concentrated to give the crude product. Purification by flash chromatography (gradient: 100% hexanes to 1:1 ethyl acetate/hexane then 10% methanol in ethylacetate) gives the desired carboxylic acid as a white foam.
$C_{24}H_{29}N_3O_4$ (MW = 423.5); mass spectroscopy (MH^+) = 424.3; (MH^-) = 422.1

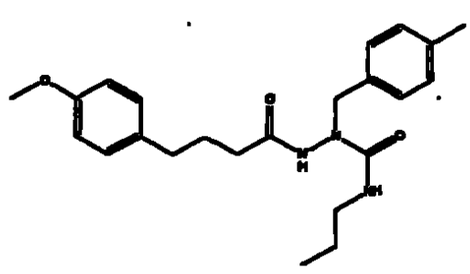


EXAMPLE 118

2-(n-Propylaminocarbonyl)-2-(4-methylphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester 4-Methylphenylmethyl hydrazine carboxylic acid, 1,1-dimethylethyl ester (5.02 g, 21.2 mmol) was dissolved in isopropanol (50 mL). Propyl isocyanate (2.71g, 31.9 mmol) was added in one portion via syringe and the solution was allowed to stir at ambient temperature for 1 h. The solution was concentrated to a clear yellow oil, and purified by column chromatography (SiO_2, 2:3 ethyl acetate:hexanes) to afford the title compound as a white solid (5.58g, 82%): mp 87.8-89.4 °C; ^{1}H NMR (DMSO-d_6, 60°C) δ 8.45 (s, 1H), 7.10 (d-d, 4 H, J = 8.2 Hz), 6.21 (s, 1 H), 4.43 (s, 1 H), 3.01 (q, 2 H, J = 6.4 Hz), 2.27 (s, 3 H), 1.41 (sext., 2 H, J = 7.3 Hz), 1.35 (s, 9 H), 0.82 (t, 3 H, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6, 20°C) δ 158.6, 155.1, 136.6, 135.5, 129.3, 129.0, 80.2, 51.0, 42.2, 28.6, 23.7, 21.4, 11.8; Anal. Calcd. for $C_{17}H_{27}N_3O_3$: C, 63.53; H, 8.47; N, 13.07.

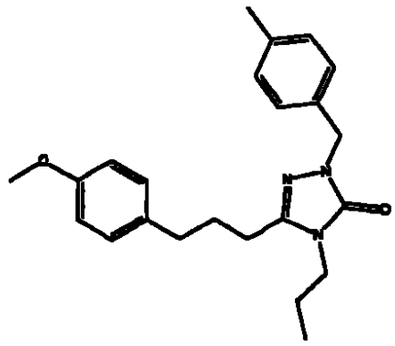


N-Propyl-1-(4-methylphenylmethyl)hydrazinecarboxamide methanesulfonate To a solution of 2-(propylaminocarbonyl)-2-(4-methylphenylmethyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester (3.0204 g, 9.397 mmol) in dichloromethane (25 mL) was added methanesulfonic acid (762 µL, 11.7 mmol) and the mixture stirred for 21 h. The mixture was then concentrated in vacuo to an oil and recrystallized (ethyl acetate) to afford the title compound as a white solid (2.0639 g, 6.502 mmol, 69%): mp 108.5-111.4 °C; ^{1}H NMR (DMSO-d_6) δ 7.56 (s, 1 H), 7.18 (s, 4 H), 4.67 (s, 2 H), 3.06 (t, 2 H, J = 7.0 Hz), 2.35 (s, 3 H), 2.81 (s, 3 H), 1.44 (m, 2 H), 0.82 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 157.7, 138.0, 132.5, 129.9, 128.8, 52.7, 42.7, 40.6, 23.3, 21.4, 11.9; IR ($CHCl_3$) 3416, 3009, 2967, 2936, 2877, 1691, 1543 cm^{-1}. Anal. Calcd. for $C_{12}H_{19}N_3O \cdot CH_4O_3S$: C, 49.19; H, 7.30; N, 13.24. Found: C, 48.87; H, 7.32; N, 13.28.

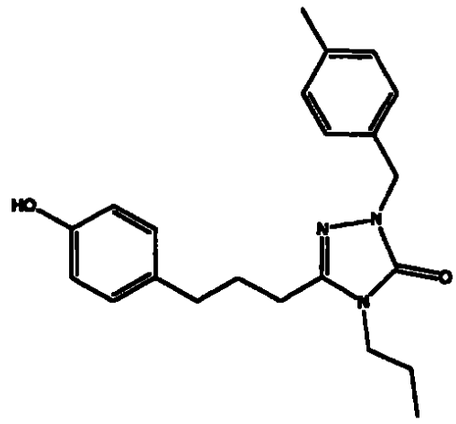


1-[(4-Methoxyphenyl)butyryl]-2-(4-methylphenylmethyl)-4-propyl)semicarbazide To a solution of 4-(4-methoxyphenyl)butyric acid (2.0207 g, 10.42 mmol) and *N,N*-

dimethylformamide (2 drops) in ethyl acetate (25 mL) was added dropwise over 5 min oxalyl chloride (1.13 mL, 13.02 mmol). The resulting mixture was stirred for 30 min and then concentrated in vacuo to remove excess oxalyl chloride. The resulting oil was redissolved in ethyl acetate (15 mL) and then added in one portion to a solution of *N*-Propyl-2-(4-methylphenylmethyl)hydrazinecarboxamide methanesulfonate (3.1578 g, 9.95 mmol,) and pyridine (2 mL, 24 mmol) in ethyl acetate (10 mL) at 0-5 °C. The reaction was stirred for 1 hour at room temperature, then washed with 1N HCl (2 x 50 mL), saturated aq. $NaHCO_3$ (2 x 50 mL), and saturated aq. NaCl (25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated and purified by silica gel chromatography (3:1 ethyl acetate:hexanes) to afford the title compound as a white solid (3.76 g, 9.47 mmol, 95%): mp 86.5-88.2 °C; ^1H NMR (DMSO-d_6, 60 °C) δ 9.45 (s, 1 H), 7.10 (m, 4 H), 6.92 (AB, 4 H, *J* = 8.0 Hz), 6.25 (s, 1 H), 4.50 (s, 1 H), 3.71 (2, 3 H), 2.99 (m, 2 H), 2.45 (t, 2 H, *J* = 8.0 Hz), 2.26 (s, 3 H), 2.06 (t, 2 H, *J* = 7.5 Hz), 1.72 (t, 2 H, *J* = 7.5 Hz), 1.40 (m, 2 H), 0.81 (t, 3 H, *J* = 8.0 Hz); ^{13}C NMR (DMSO-d_6) δ 172.0, 158.2, 158.1, 136.7, 135.8, 134.1, 129.9, 129.4, 128.9, 114.3, 55.6, 50.8, 42.3, 34.3, 33.4, 27.3, 23.7, 21.4, 11.9; IR ($CHCl_3$) 3456, 2996, 2963, 2936, 2876, 1708, 1669 cm^{-1}. Anal. Calcd. for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.36; H, 7.71; N, 10.54.



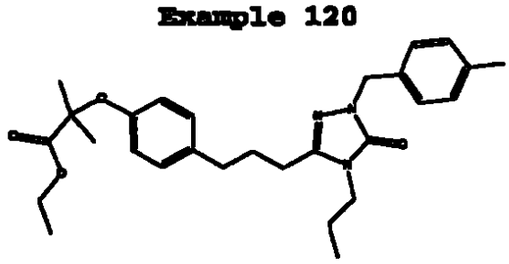
5-[3-(4-Methoxyphenyl)-propyl]-2-(4-methylbenzyl)-4-propyl-2,4-dihydro[1,2,4]tria-zol-3-one To a solution of 1-[(4-methoxyphenyl)butyryl]-2-(4-methylphenylmethyl)-4-propyl)semicarbazide (1.24 g, 3.12 mmol) in ethyl acetate (25 mL) was added camphorsulfonic acid (0.80g, 3.43 mmol) and the resulting mixture stirred at reflux for 2 hours. The organic layer was washed with saturated aq. $NaHCO_3$ (2 x 25 mL) and 1 N HCl (2 x 25 mL) followed by saturated aq. NaCl (25 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated to afford the title compound as an oil (1.14 g, 3.00 mmol, 96%): ^1H NMR (DMSO-d_6) δ 7.10 (s, 4 H), 7.06 (d, 2 H, J = 8.5 Hz), 6.81 (q, 2 H, J = 5.0 Hz), 4.77 (s, 2 H), 3.69 (s, 3 H), 3.46 (t, 2 H, J = 7.5 Hz), 2.54 (t, 2 H, J = 7.5 Hz), 2.47 (t, 2 H, J = 7.5 Hz), 2.23, (s, 3 H), 1.82 (m, 2 H), 1.52 (m, 2 H), 0.79 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 158.2, 154.1, 146.8, 137.2, 135.1, 133.9, 129.9, 129.7, 128.1, 114.4, 55.6, 48.3, 42.8, 34.0, 28.1, 24.8, 22.5, 21.3, 11.5; IR ($CHCl_3$) 1691, 1513, 1465, 1247, 1225 cm^{-1}. Anal. Calcd. for $C_{23}H_{29}N_3O_2$: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.82; H, 7.87; N, 11.11.



Example 119

5-[3-(4-Hydroxyphenyl)-propyl]-2-(4-methylbenzyl)-4-propyl-2,4-dihydro-[1,2,4]triazol-3-one 5-[3-(4-Methoxyphenyl)-propyl]-2-(4-methylbenzyl)-4-propyl-2,4-dihydro[1,2,4]triazol-3-one (0.770 g, 2.03 mmol) and excess pyridine hydrochloride were melted together for 2 hours with stirring at 180 °C. After cooling to room temperature, the contents were diluted in ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organics were washed with 5 N HCl (50 mL), saturated aq. NaCl (25 mL), dried ($MgSO_4$), filtered and concentrated to afford the title compound as a yellow oil (0.670 g, 1.83 mmol, 90%): ^1H NMR (DMSO-d_6) δ 9.13 (s, 1 H), 7.10 (q, 4 H, J = 3.0 Hz), 6.79 (AB, 4 H, J = 8.5 Hz), 4.77 (s, 2 H), 2.5 (t, 2 H, J = 7.5 Hz), 2.46 (t, 2 H, J = 7.5 Hz), 2.24 (s, 3 H), 1.79 (m, 2 H), 1.51 (m, 2 H), 0.79 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 156.1, 154.1, 146.8, 137.2, 135.1, 132.1, 129.9, 129.7, 128.1, 115.7, 48.3, 42.8, 34.1, 28.2, 24.7, 22.5, 21.3, 11.5; IR ($CHCl_3$) 3007, 2937, 1690, 1515, 1463 cm^{-1}. Exact Mass Calcd. for $C_{22}H_{28}N_3O_2$: 366.2182. Found: 366.2191.

Example 120

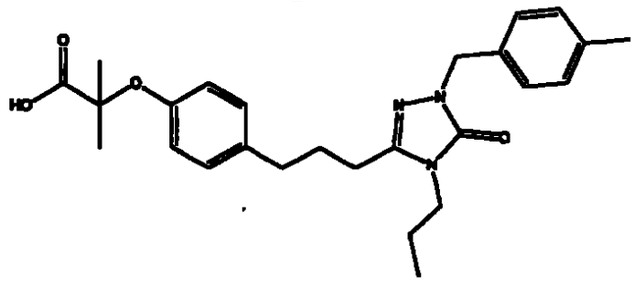


2-Methyl-2-(4-{3-[1-(4-methylbenzyl)-5-oxo-4-propyl-4,5-dihydro-1*H*-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid ethyl ester To a mixture of sodium ethoxide (1.22 mL, 3.28mmol) and ethyl acetate (322 µL, 3.28 mmol) was added 5-[3-(4-hydroxyphenyl)-propyl]-2-(4-methylbenzyl)-4-propyl-2,4-dihydro-[1,2,4]triazol-3-one (1.2 g, 3.28 mmol) in ethanol (10 mL) and the resulting mixture stirred at reflux for 1 hour. Then ethyl-2-butyl isobutyrate (1.08 mL, 7.38 mmol) was added and the reaction continued at reflux for 1 hour. Then sodium ethoxide (1.22 mL, 3.28 mmol) was added dropwise over 5 min and the reaction continued at reflux for 4.5 hour. Additional sodium ethoxide (520 µL, 1.4 mmol) and ethyl-2-butyl isobutyrate (205 µL, 1.4 mmol) were added and reaction continued at reflux for 4 hour. Additional sodium ethoxide (336 µL, 0.903 mmol) and ethyl-2-butyl isobutyrate (132 µL, 0.903 mmol) were added and the reaction continued at reflux for 3 hours. Finally, additional sodium ethoxide (200 µL, 0.54 mmol) and ethyl-2-butyl isobutyrate (100 µL, 0.133 mmol) were added and the reaction continued at reflux for 1.5 hours. The mixture was allowed to cool to room temperature and is then quenched into a solution of conc. HCl (1.5 g, 41 mmol) in water (50 mL). The resulting solution was then concentrated in vacuo, taken up in ethyl acetate (100 mL) and the aqueous layer was discarded. The rganic layer was washed with saturated aq. $NaHCO_3$ (2 x 50 mL) followed by saturated aq. NaCl (2 x 25 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel chromatography (1:1 ethyl acetate:hexanes) to afford the title compound as a yellow oil (990 mg, 2.06 mmol, 63%):

^{1}H NMR (DMSO-d_6) δ 7.10 (s, 4 H), 6.87 (AB, 4 H, *J* = 8.0 Hz), 4.77 (s, 2 H), 4.14 (q, 2 H, *J* = 7.0 Hz), 3.46 (t, 2 H, *J* = 6.5 Hz), 2.54 (t, 2 H, *J* = 7.5 Hz), 2.47 (t, 2 H, *J* = 7.5 Hz), 2.24 (s, 3 H), 1.82 (m, 2 H), 1.51 (m, 2 H), 1.47 (s, 6 H), 1.14 (t, 3 H, *J* = 7.5 Hz), 0.79 (t, 3 H, *J* = 7.0 Hz);

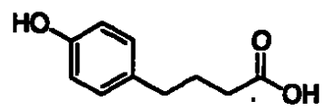
^{13}C NMR (DMSO-d_6) δ 174.0, 154.1, 153.8, 146.7, 137.2, 135.6, 135.1, 129.75, 129.66, 128.1, 119.6, 79.2, 61.6, 48.3, 42.8, 34.0, 27.8, 25.7, 24.8, 22.5, 21.3, 14.5, 11.5; IR ($CHCl_3$) 3005, 2939, 2878, 1729, 1692, 1509 cm^{-1}. Anal. Calcd. for $C_{28}H_{37}N_3O_4$: C, 70.12; H, 7.78; N, 8.76. Found: C, 69.92; H, 7.84; N, 8.77.

Example 121



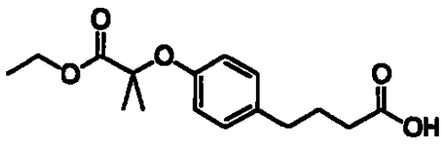
To a solution of 2-methyl-2-(4-{3-[1-(4-methylbenzyl)-5-oxo-4-propyl-4,5-dihydro-1*H*-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid ethyl ester (0.45g, 0.938 mmol) in methanol (7 mL) was added with stirring aq. 1N NaOH (2 mL, 2 mmol) at room temperature for 18 hours. The reaction mixture was concentrated to a thin film and partitioned between ethyl acetate (25 mL) and 1N HCl (25 mL). The organic layer was washed with saturated aq. NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated to afford the title compound as a yellow solid (0.400 g, 0.886 mmol, 94%): mp 94.0-96.5 °C; ^1H NMR (DMSO-d_6) δ 12.92 (br. s, 1 H), 7.10 (s, 4 H), 6.88 (AB, 4 H, J = 8.5 Hz), 4.77 (s, 2 H), 3.46 (t, 2 H, J = 7.5 Hz), 2.54 (t, 2 H, J = 7.5 Hz), 2.48 (m, 2 H), 2.24 (s, 3 H), 1.82 (m, 2 H), 1.52 (t, 2 H, J = 7.5 Hz), 1.46 (s, 6 H), 0.79 (t, 3 H, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6) δ 175.8, 154.1, 146.8, 137.2, 135.2, 135.1, 129.7, 128.1, 119.3, 79.0, 60.4, 48.3, 42.8, 34.0, 27.9, 25.7, 24.8, 22.5, 21.3, 14.8, 11.5; IR ($CHCl_3$) 3007, 2939, 2878, 1692, 1573, 1508 cm^{-1}; Anal. Calcd. for $C_{26}H_{33}N_3O_4$: C, 69.16; H, 7.37; N, 9.31. Found: C, 68.90; H, 7.55; N, 9.14.

EXAMPLE 122



4-(4-Hydroxyphenyl)butyric Acid. A 22-L 4-necked round bottom flask was equipped with a condenser, nitrogen inlet, thermometer lead and overhead stirring apparatus. The flask was charged with 4-(4-methoxyphenyl)butyric acid (2250 g, 11.58 moles) followed by pyridine hydrochloride (5360 g, 46.34 moles, 4 eq). The resulting mixture of the two solids was heated under nitrogen to 185-195 °C, with stirring commencing by 50 °C. The flask contents were held at 185-195 °C, and reaction progress was monitored by TLC (50/50 v/v hexanes/ethyl acetate + 1% v/v acetic acid, *p*-anisaldehyde stain for visualization). After two hours, TLC analysis indicated complete consumption of starting material. The heat source was removed and the mixture allowed to cool to 90 °C, after which 5N HCl (2900 mL, 14.47 moles, 1.25 eq) and H_2O (2700 mL) were added sequentially. Stirring was continued until the pot temperature reached 35 °C. The mixture was transferred to a 22-L bottom-outlet flask and diluted with *t*-butyl methyl ether (MTBE, 6000 mL). The layers were separated and the aqueous portion was reextracted with MTBE (3 x 4000 mL). The organic portions were combined and back-washed with 5N HCl (750 mL). After drying (Na_2SO_4) and filtration, the solution was concentrated in vacuo to afford the title compound as a

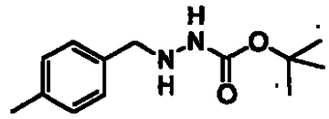
white solid (2020g, 96.7%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.70 (m, 2 H), 2.15 (t, 2 H), 2.45 (t, 2 H), 3.33 (s, 1 H), 6.65 (d, 2 H), 6.95 (d, 2 H). ^{13}C NMR (DMSO-d_6) δ 26.5, 32.5, 33.5, 114.6, 129.0, 131.2, 155.3, 174.2.



4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyric acid

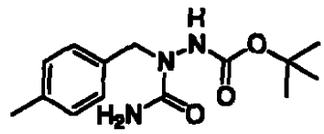
A 12-L 3-neck round-bottom flask was equipped with an overhead air-driven stirrer apparatus, condenser, nitrogen inlet, thermometer/thermocouple, and heating mantle. The flask was charged with ethyl acetate (450 mL) and 21% (wt.) sodium ethoxide in ethanol solution (3318 mL, 8.87 moles, 2 eq). The resulting mixture was heated to reflux under a nitrogen atmosphere and maintained at reflux for 30 min. The mixture was then allowed to cool slightly below reflux, and 4-(4-hydroxyphenyl)butyric acid (800 g, 4.43 moles) was added. The flask contents were re-heated to reflux for 30 min, at which point ethyl 2-bromoisobutyrate (EBIB, 1954 mL, 13.32 moles, 3.0 eqs.) was added. After 1 h at reflux, the flask was equipped with a 2-L addition funnel, which was charged sodium ethoxide in ethanol solution (1660 mL, 4.43 moles, 1 eq.). The sodium ethoxide solution was added dropwise to the refluxing reaction over 1 h. After an additional 30 min at reflux, HPLC analysis showed the reaction was complete. The heat source was removed and the flask contents were cooled to 5-10 °C and then transferred to a 22-L bottom-outlet flask. While stirring, the mixture was quenched with dilute phosphoric acid (6000 mL), transferred t a 20-L Buchi flask, and concentrated in vacuo to remove ethanol. The resulting aqueous mixture of

crystals and excess EBIB was refrigerated overnight. The crystals were then filtered and washed with water (2000 mL). The solids were removed from the funnel and placed in a 20-L Buchi flask equipped with an overhead stirring apparatus. After the addition of water (2000 mL), the solids were stirred at ambient temperature for 30 min, then filtered and washed with heptane (2 x 2500 mL). The solids were then placed in the vacuum oven and dried at 45 °C to afford the title compound as an off-white solid (1247 g, 95.5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, 3 H), 1.57 (s, 6 H), 1.92 (m, 2 H), 2.35 (t, 2 H), 2.60 (t, 2 H), 4.23 (q, 2 H), 6.76 (d, 2 H), 7.03 (d, 2 H). ^{13}C NMR ($CDCl_3$) δ 14.1, 25.4, 26.3, 33.3, 34.2, 61.4, 119.4, 129.1, 134.9, 153.7, 174.4, 179.7.

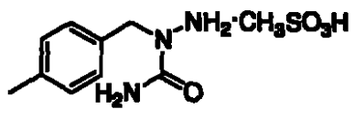


(4-Methylbenzyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester To a 10-gal stainless steel autoclave containing isopropanol (10 L) under nitrogen was charged *t*-butyl carbazate (1.25 kg, 9.46 mol)followed by isopropanol (2 L). The contents were stirred and heated at 35 °C for 30 min, then 4-methylbenzaldehyde (1.142 kg, 9.51 mol) was added, followed by isopropanol (0.3 L). The contents were heated to 45 oC, and a slurry of 5% Pd/C (0.3 kg) in water (0.3 L) and isopropanol (4 L) was added, followed by rinses of isopropanol (2 x 1 L). The contents were hydrogenated at 40 psig and 45 °C for 4 h, then a second charge of 5% Pd/C (0.3 kg) in water (0.3 L) and isopropanol (4 L) was added, followed by rinses of isopropanol (2 x 1 L). Hydrogenation was continued at 40 psig and 45 oC for 14 h, at which the

reaction was determined to be complete by HPLC. The contents were then cooled to 15 oC and filtered, and the filter cake rinsed with isopropanol (15 L). The filtrate was concentrated in vacuo to afford the title compound (1.97 kg, 88.2%) as a 33.8 wt-% solution in isopropanol.

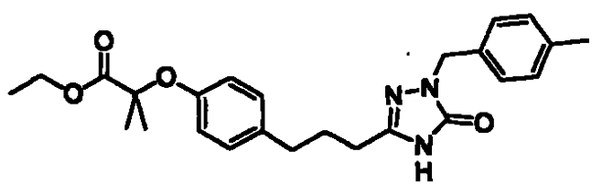


2-(Aminocarbonyl)-2-(4-methylphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester A 22-L 4-neck flask was equipped with an overhead stirring apparatus, cooling bath, thermometer probe, and 2-L addition funnel. The flask was charged with a solution of (4-methylbenzyl)hydrazinecarboxylic acid, 1,1-dimethyl-ethyl ester in isopropanol (4988 g of a 31.73% wt/wt solution, 1583 g, 6.70 moles). Additional isopropanol (3130 mL) was added to dilute the solution to a total volume of 8933 mL. Trimethylsilyl isocyanate (1179 mL, 8.71 mol, 1.3 eq) was charged to the 2-L addition funnel and was added dropwise to the stirring reaction solution over 45 minutes, while the temperature was maintained between 15-25 °C using a cool water bath. Reaction progress was monitored by TLC (50/50 v/v hexane/ethyl acetate, I_2; Rf(sm) = 0.6, Rf(prod)= 0.1). After overnight stir at room temperature, TLC indicated the reaction was essentially complete. The reaction mixture was treated with heptane (7800 mL), cooled to 5-10 °C and stirred for 0.5 hr. The mixture was filtered and the cake was washed with heptane (2 x 1000 mL). The material was dried in a vacuum oven at 30-35 °C to yield the title compound as a white solid (1423 g, 96%). ^{1}H NMR (DMSO-d_6, 300MHz): □ 1.35 (s, 9 H), 2.26 (s, 1 H), 4.45 (br s, 2 H), 6.06 (s, 2 H), 7.10 (s, 4 H), 8.88 (br s, 1 H); Anal. Calcd. for $C_{14}H_{21}N_3O_3$: C, 60.20; H, 7.58; N, 15.04. Found: C, 59.65; H, 7.34; N, 14.87.



1-(4-Methylphenylmethyl)hydrazinecarboxamide methanesulfonate

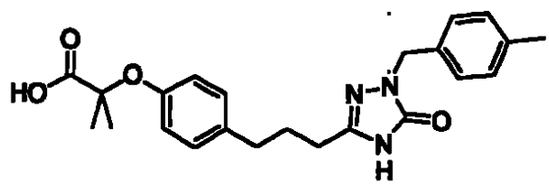
A 22-L 4-neck flask was equipped with an overhead stirring apparatus, warming/cooling bath, thermometer probe, condenser, and 500-mL addition funnel. The flask was charged with 2-(Aminocarbonyl)-2-(4-methylphenylmethyl)-hydrazine carboxylic acid, 1,1-dimethylethyl ester (1100 g, 3.94 moles) and dichloromethane (12 L). The mixture was warmed to 30-35 °C to completely dissolve all solids, then cooled to 25-30 °C and methanesulfonic acid (MsOH) (398 g, 4.14 moles) was added over 30 min. The water bath was replaced with a heating mantle and the reaction solution was heated at reflux for 12-20 hours, and monitored by TLC analysis (Ethyl Acetate 100%; I_2, Rf(sm) = 0.3, Rf(prod)= 0.1) When complete, the reaction mixture was diluted with heptane (4000 mL), cooled to 10-20 °C, and stirred for 30 min. After filtration, the cake was washed with heptane (2 x 1000 mL) and dried in vacuo at 35-45 °C, to afford the title compound as a white solid (1070 g, 98.6%). ^{1}H NMR (DMSO-d_6, 300MHz): δ 1.35 (s, 9 H), 2.26 (s, 1 H), 4.45 (br s, 2 H), 6.06 (s, 2 H), 7.10 (s, 4 H), 8.88 (br s, 1 H); Anal. Calcd. for $C_{10}H_{17}N_3O_4$ S,: C, 43.62; H, 6.22; N, 15.26; S, 11.64. Found: C, 43.33; H, 6.21; N, 14.97.



2-(4-(3-[1-(4-Methylphenylmethyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]propyl}phenoxy)-2-methylpropionic acid ethyl ester A 22-L 4-neck flask was equipped with a thermometer/thermocouple, addition funnel, overhead stirring apparatus, nitrogen inlet, and cooling bath. The flask was charged with 4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyric acid (1250 g, 4.247 moles), ethyl acetate (11,250 mL) and DMF (16.4 mL), and the resulting mixture was stirred to dissolve solids. Oxalyl chloride (426 mL, 4.88 moles, 1.15 eq) was added dropwise to the reaction mixture over 45 min, using a water bath to keep the temperature below 30 °C. The reaction mixture was then concentrated in vacuo to remove both the solvent and excess oxalyl choride to afford crude 4-[4-(1-ethoxycarbonyl-1-methylethoxy)phenyl]butyric acid chloride. A separate 22-L 4-neck flask was equipped with a thermometer/thermocouple, addition funnel, nitrogen inlet, overhead stirring apparatus, and cooling bath. The flask was charged with 1-(4-methylphenylmethyl)hydrazine-carboxamide methanesulfonate (1169 g, 4.247 moles, 1 eq.), ethyl acetate (8750 mL), and pyridine (790 mL, 9.77 moles, 2.3 eqs.). The contents of the flask were cooled to 0-5 °C. The crude acid chloride was dissolved in ethyl acetate (1000 mL) and added dropwise to the mixture containing 1-(4-methylphenylmethyl)hydrazinecarboxamide methanesulfonate over 20 min, while maintaining the pot temperature below 25 °C. The resulting mixture was stirred at ambient temperature for 1 h, then (±)-camphorsulfonic acid (1973 g, 8.494 moles, 2 eq) was added. The flask contents were then heated to reflux for 16 h. The reaction was cooled to 20 °C and transferred into a flask containing 1N HCl (7500 mL).

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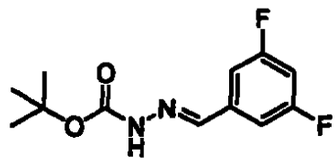
After stirring, the layers were separated and the organic layer was washed with saturated Na_2CO_3 solution (7500 mL) and water (1000 mL), then dried over $MgSO_4$. The ethyl acetate solution was transferred to a 4-neck flask equipped with a condenser, nitrogen inlet, thermometer/thermocouple, and a heating mantle. The flask was charged with Amberlyst-15 resin (1975 g) and the mixture was heated to reflux for 1 h. After cooling to 20 °C, the material was filtered to remove the resin and the resin was washed with ethyl acetate (2 x 2000 mL). The filtrate was concentrated in vacuo to afford a tan solid. MTBE (5000 mL) was added to the crude material and the mixture warmed to 45-50 °C until all solids were dissolved. While slowly rotating the flask, the solution was allowed to cool, whereupon crystallization occurred. The slurry was cooled to 0-5 °C for 1 hour, filtered, rinsed with cold MTBE (1500 mL) and dried in vacuo at 45 °C to afford the title compound as a white solid (1027 g, 55.2%). ^1H NMR (500 MHz, DMSO-d_6) δ 1.14 (t, 3 H), 1.47 (s, 6 H), 1.76, (m, 2 H), 2.26 (t, 2 H), 2.49 (t, 2 H), 3.55 (s, 3 H), 4.15 (q, 2 H), 6.69 (d, 2 H), 7.05 (d, 2 H).). ^{13}C NMR ($CDCl_3$) δ 14.0, 21.0, 25.3, 26.1, 28.1, 34.1, 48.3, 61.2, 79.0, 119.3, 127.8, 128.1, 129.0, 129.3, 133.2, 134.8, 137.5, 147.2, 148.3, 153.6, 155.8, 174.3.



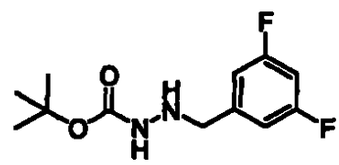
2-[4-[3-[2,5-dihydro-1-[(4-Methylphenyl)methyl]-5-oxo-1H-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl-propanoic Acid A 4-n ck flask was equipped with overhead stirring apparatus

and thermometer probe. The flask was charged with 2-(4-{3-[1-(4-Methylphenylmethyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}phenoxy)-2-methyl-propionic acid, ethyl ester (800 g, 1.828 moles), and toluene (4000 mL) followed by 1N NaOH (4023 mL, 2.194 mol, 1.2 eq). The resulting mixture was stirred at ambient temperature for 5 h. The mixture was transferred to a 22-L bottom outlet flask and layers separated. The aqueous layer from the above layer separation was charged to the flask and acidified to pH 2 with concentrated HCl (337 mL). Ethyl acetate was added (8000 mL) and the mixture was transferred to a 22-L bottom-outlet flask. The layers were separated and the organic solution was transferred to a 22- L 3-neck round-bottom flask equipped with a distillation head and overhead stirring apparatus. The mixture was concentrated by distillation of the ethyl acetate to approximately 4000 mL, and fresh ethyl acetate (3600 mL) was added to the reaction vessel. Distillation was continued until 3600 mL of distillate were recovered. Heating was stopped and the mixture was allowed to cool slowly to 60-65 °C, at which point seed crystals (0.8 g) of the desired product were added. The flask contents were allowed to cool slowly until crystallization initiated (55-57 °C), then the mixture was cooled to 0-5 °C and stirred for 1 h. The product was filtered, washed with cold ethyl acetate, and dried in vacuo at 55 °C to afford the title compound as a white solid (713.6 g, 95.3%). ^{1}H NMR (DMSO-d_6, 500MHz): δ 1.46 (s, 6 H), 1.79 (m, 2 H), 2.25 (s, 3H), 2.35 (t, 2 H), 2.47 (t, 2 H), 4.70 (s, 2 H), 6.71 (d, 2H), 7.03 (d, 2H), 7.10 (m, 4 H). ^{13}C NMR (DMSO-d_6), δ 20.6, 25.0, 25.5, 27.7, 47.0, 78.3, 118.6, 127.4, 127.7, 128.9, 128.9, 134.4, 134.5, 136.4, 145.9, 153.4, 154.3, 175.0.

Example 123

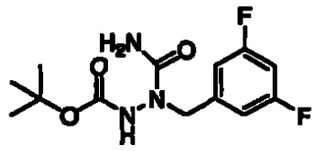


(3,5-Difluorophenyl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of t-butyl carbazate (4.99 g, 37.76 mmol) in ethyl acetate (10 mL) was added with stirring 3,5-difluorobenzaldehyde (5.50 g, 38.7 mmol) followed by hexanes (50 mL). Crystallization occurred and the resulting slurry was stirred at rt for 15 min, then cooled to 0 °C. and held at that temperature for 45 min. The solids were filtered, rinsed with cold hexanes and dried in vacuo at 60 °C to afford the title compound as a solid (9.04 g, 93.3%): mp 196.4-196.8 °C (dec); ^{1}H NMR (DMSO-d_6) δ 11.16 (br s, 1 H), 7.96 (s, 1 H), 7.28 (m, 2 H), 7.21 (t, 1 H, J = 2.2 Hz), 1.45 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 163.3 (dd, J = 246.1, 13.5 Hz), 152.9, 141.2, 139.2 (t, J = 9.6 Hz), 109.9 (dd, J = 20.2, 5.8 Hz), 105.1 (t, J = 25.9 Hz), 80.5, 28.7; IR (KBr mull) 3263, 2987, 1709, 1584, 1536 cm^{-1}. A portion was recrystallized (ethyl acetate) for analysis. Anal. Calcd. for $C_{12}H_{14}F_2N_2O_2$: C, 56.25; H, 5.51; F, 14.83; N, 10.93. Found: C, 56.11; H, 5.49; N, 10.86.



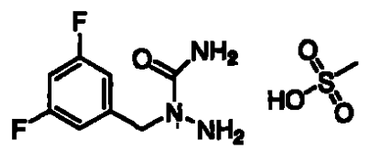
2-(3,5-Difluorophenylmethyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester To substrate imine (7.00 g, 27.3 mmol) and 5% Pt/C (5.05 g) was added tetrahydrofuran (70 mL)

and the resulting suspension hydrogenated at rt and 50 psi. After 4 h, an additional charge of 5 % Pt/C (5.00 g) was added and hydrogenation continued for 12 h. The contents were filtered and concentrated to an oil, then reconstituted in THF (70 mL) along with 5 % Pt/C (5.00 g) and hydrogenation continued for 60 h at rt and 50 psi. The contents were then filtered and concentrated. SiO_2 gel chromatography (20% ethyl acetate in hexanes) gave the title compound as an oil (4.96 g, 19.2 mmol, 70%). ^1H NMR (DMSO-d_6) δ 8.28 (br s, 1 H), 7.03 (m, 3 H), 5.03 (br s, 1 H), 3.88 (s, 2 H), 1.35 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 162.9 (dd, J = 243.6, 12.4 Hz), 144.9 (t, J = 9.6 Hz), 111.5 (d, J = 23.0 Hz), 102.5 (t, J = 25.9 Hz), 79.0, 53.9, 28.8; IR ($CHCl_3$) 3444, 2982, 2933, 1712, 1628, 1597 cm^{-1}; HRMS calcd for $C_{12}H_{16}F_2N_2O_2$ $(M + H)^+$: 259.1258. Found: 259.1252.

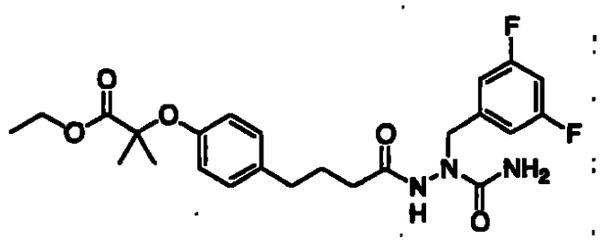


2-(Aminocarbonyl)-2-(3,5-Difluorophenylmethyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester To substrate difluorobenzyl hydrazine (2.5649 g, 9.93 mmol) in isopropanol (20 mL) at rt was added trimethylsilyl isocyanate (1.808 g, 15.7 mmol) in one portion. The reaction was stirred at rt for 36 h, then concentrated to a solid. Recrystallization (1:1 ethyl acetate:hexanes) followed by dilution with hexanes (100 mL) to facilitate stirring gave the title compound as a solid (2.84 g, 9.43 mmol, 95%): mp 128.7-129.9 °C; ^1H NMR (DMSO-d_6, 60 °C) δ8.86 (br s, 1 H), 6.97 (m, 3 H), 6.00 (s, 2 H), 4.52 (s, 2 H), 1.36 (s, 9 H); ^{13}C NMR (DMSO-d_6,) δ 162.7 (dd, J = 245, 13 Hz), 159.5, 155.1, 143.7 (t, J = 9 Hz), 111.4 (d, J = 23 Hz), 102.8 (t, J = 26 Hz), 80.4, 51.4, 28.6; IR (KBr mull) 3540, 3227, 3004, 2988, 1744, 1682 cm^{-1}. Anal. Calcd.

for $C_{13}H_{17}F_2N_3O_3$: C, 51.82; H, 5.69; N, 13.95. Found: C, 51.59; H, 5.61; N, 13.81.

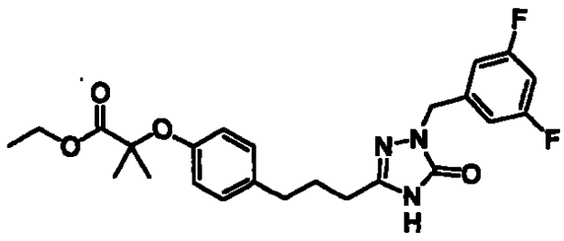


1-(3,5-Difluorophenylmethyl)hydrazinecarboxamide methanesulfonate To substrate Boc semicarbazide (1.81 g, 6.00 mmol) in tetrahydrofuran (25 mL) at rt was added methanesulfonic acid (0.725 g, 6.3 mmol, 1.05 equiv) in one portion. The reaction was stirred at rt for 24 h, then heated to reflux for 22 h. The reaction mixture was cooled to rt, filtered and the filter cake rinsed with dichloromethane. The solids were dried in vacuo overnight at 60 °C to afford title compound as a solid (1.32 g, 4.44 mmol, 74%): mp 138.4 - 139.5 °C (dec); ^{1}H NMR (DMSO-d_6, 60 °C) δ7.94 (br s, 4 H), 7.10 (m, 1 H), 6.98 (m, 2 H), 4.70, 4.06 (s, s, 2 H total, pair of rotamers), 2.48, 2.41 (s, s, 3 H total, pair of rotamers); ^{13}C NMR (DMSO-d_6,) δ 163.6 (dd, J = 246, 13 Hz), 158.0, 140.9, 111.6 (dd, J = 20, 6 Hz), 104.0 (t, J = 26 Hz), 52.1; IR (KBr mull) 3411, 3281, 3211, 1706, 1685, 1457, 1209 cm^{-1}. HRMS calcd. for $C_8H_9F_2N_3O$ (M + H)$^+$: 202.0792. Found: 202.0797.



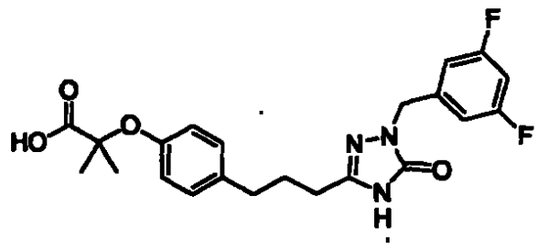
1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3,5-difluorophenyl-methyl)semicarbazide To 4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyric acid (1.0072 g, 3.42 mmol) in ethyl acetate (10 mL) at rt was added DMF (1

pipette drop), followed by oxalyl chloride (0.728 g, 5.73 mmol) dropwise over 5 min. The resulting solution was stirred for 30 min at rt, then concentrated to an oil. The oil was twice reconstituted into toluene (20 mL) and concentrated to an oil, then dissolved in ethyl acetate (3 mL). 1-(3,5-Difluorophenylmethyl)hydrazine carboxamide methanesulfonate (1.025 g, 3.45 mmol) was suspended in ethyl acetate (10 mL) at 0 °C, and pyridine (0.65 mL, 636 mg, 8.04 mmol) was added. The solution of acid chloride in ethyl acetate was then added dropwise over 15 min, and the resulting mixture stirred for 30 min at 0 °C. The mixture was then diluted with ethyl acetate and washed with 1 N HCl (2X) followed by sat'd aq. NaCl. It was then dried ($MgSO_4$), filtered and concentrated to an oil, which was chromatographed on silica gel (ethyl acetate) to afford the title compound as a solid (1.1436 g, 70%): mp 108.1 - 109.4 °C; ^1H NMR (DMSO-d_6, 60 °C) δ 9.73 (s, 1 H), 7.00 (m, 5 H), 6.70 (d, 2 H, J = 6.5 Hz), 6.03 (s, 2 H), 4.54 (br s, 2 H), 4.15 (q, 2 H, J = 7 Hz), 2.45 (m, 2 H), 2.09 (m, 2 H), 1.74 (m, 2 H), 1.48 (s, 6 H), 1.17 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 172.0, 162.5 (dd, J = 244, 13 Hz), 159.2, 153.8, 144.1, 135.8, 129.7, 119.4, 111.3 (d, J = 25 Hz), 102.8 (t, J = 26 Hz), 79.2, 51.1, 47.3, 34.3, 33.1, 27.0, 25.7, 14.6; IR (KBr) 3456, 3324, 1726, 1643, 1509, 1445 cm^{-1}; Anal. Calcd. for $C_{24}H_{29}N_3O_5F_2$: C, 60.37; H, 6.12; N, 8.80; F, 7.96. Found: C, 60.48; H, 6.28; N, 8.67; F, 7.75.



2-(4-{3-[1-(3,5-Difluorobenzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid, ethyl ester To substrate 1-[4-[4-(1-Ethoxycarbonyl-1-

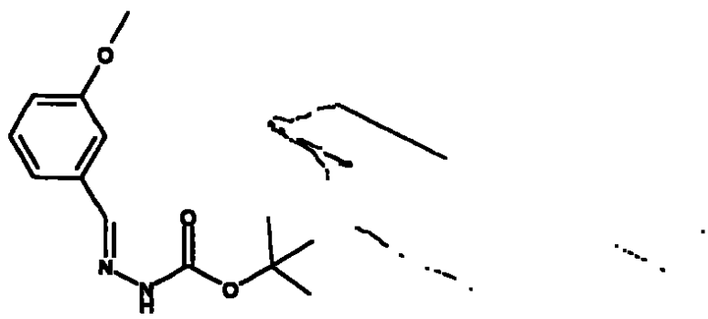
methylethoxy)phenyl]butyryl]-2-(3,4-dichlororophenylmethyl)-4-(*n*-propyl)semicarb-azide (1.06 g, 2.26 mmol) and camphorsulfonic acid (0.5283 g, 2.27 mmol) was added ethyl acetate (12 mL) and the resulting solution heated to reflux for 22 h. The solution was diluted with ethyl acetate, then washed with sat'd aq. $NaHCO_3$ followed by sat'd aq. NaCl. It was then dried ($MgSO_4$), filtered and concentrated to an oil, which was chromatographed on silica gel (1:1 ethyl acetate:hexanes) to afford the title compound as an il (0.3836 g, 37%): ^1H NMR (DMSO-d_6) δ 11.54 (s, 1 H), 7.13 (t, 1 H, *J* = 9.3 Hz), 7.04 (d, 2 H, *J* = 8.5 Hz), 6.91 (d, 2 H, *J* = 6.5 Hz), 6.68 (d, 2 H, *J* = 8.5 Hz), 4.81 (s, 2 H), 4.13 (q, 2 H, *J* = 7.0 Hz), 2.49 (t, 2 H, *J* = 7.5 Hz), 2.38 (t, 2 H, *J* = 7.5 Hz), 1.81 (m, 2 H), 1.47 (s, 6 H), 1.14 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 162.6 (dd, *J* = 245, 13 Hz), 155.0, 153.8, 147.3, 142.9 (d, *J* = 9 Hz), 135.5, 129.8, 119.5, 111.1 (t, *J* = 26, 6 Hz), 103.5 (t, *J* = 26 Hz), 79.2, 61.6, 47.1, 34.0, 28.3, 26.2, 25.7; IR ($CHCl_3$) 3004, 1727, 1695, 1601, 1509, 1464 cm^{-1}; Anal. Calcd. for $C_{24}H_{27}F_2N_3O_4$: C, 62.74; H, 5.92; N, 9.14. Found: C, 62.65; H, 5.99; N, 8.98.



2-(4-{3-[1-(3,5-Difluorobenzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid

To substrate triazolone ethyl ester (0.2971 g, 0.647 mmol) in methanol (3 mL) at rt was added 1 N NaOH (2 mL, 2.0 mmol) and the resulting mixture stirred at rt for 16 h. The mixture was then acidified by addition of 1 N HCl and concentrated to an oil, which was partitioned between ethyl acetate (35 mL) and water (25 mL). The layers were

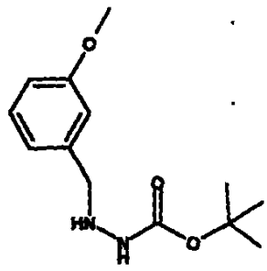
separated and the organic phase washed with sat'd aq. NaCl, then dried ($MgSO_4$), filtered and concentrated to afford the title compound as an oil (0.2643 g, 95 %): ^1H NMR (DMSO-d_6, 60 °C) δ 12.96 (br s, 1 H), 11.54 (s, 1 H), 7.13 (t, 1 H, J = 9.5 Hz), 7.04 (d, 2 H, J = 8 Hz), 6.91 (d, 2 H, J = 7 Hz), 6.72 (d, 2 H, J = 8 Hz), 4.81 (s, 2 H), 2.49 (t, 2 H, J = 7 Hz), 2.38 (t, 2 H, J = 7 Hz), 1.82 (m, 2 H), 1.46 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 175.8, 163.0 (dd, J = 245, 13 Hz), 155.0, 154.1, 147.3, 142.9, 135.0, 129.7, 119.2, 111.1 (m), 103.5 (t, J = 26 Hz), 78.9, 47.1, 34.0, 28.3, 26.2, 25.7; IR ($CHCl_3$) 3096, 3005, 2865, 1708, 1601, 1509, 1465, 1158, 1121 cm^{-1}; Anal. Calcd. for $C_{22}H_{23}F_2N_3O_4$: C, 61.25; H, 5.37; N, 9.74. Found: C, 61.21, H, 5.46; N, 9.48.



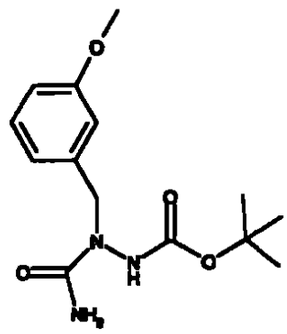
Example 124

(3-Methoxyphenyl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of *t*-butyl carbazate (5.59 g, 42.3 mmol) in ethyl acetate (15 mL) was added with stirring *m*-anisaldehyde (5.17 mL, 5.76 g, 42.3 mmol). Hexanes (70 mL) was added slowly and crystallization occurred. The resulting slurry was stirred at rt for 45 min and then cooled to 0 °C. The slurry was stirred at 0 °C for 60 min, then filtered and rinsed with cold hexanes (20 mL), and dried in vacuo at 40 °C to afford the title compound as

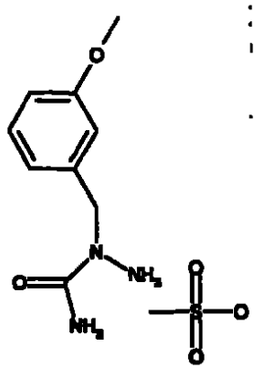
a solid (9.68 g, 91.4%): mp 135.6-137.4 °C; ^{1}H NMR (DMSO-d_6) δ 10.93 (s, 1H), 7.29 (t, 1 H, J = 8 Hz), 7.14 (d, 2 H, J = 7 Hz), 6.92 (q, 1 H, J = 7 Hz), 3.75 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 160.2, 153.1, 143.7, 136.8, 130.5, 120.0, 116.2, 111.3, 80.1, 55.7, 28.7; IR (KBr mull) 3360, 3010, 2982, 2838, 1510, 1487 cm^{-1}. A portion was recrystallized from ethyl acetate and submitted for elemental analysis. Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.34.; H, 7.46; N, 11.19.



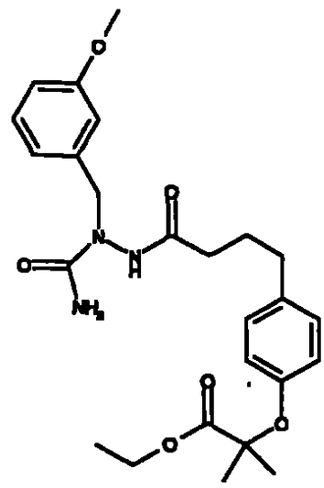
(3-Methoxybenzyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester (3-Methoxyphenyl)methylenehydrazinecarboxilic acid, 1,1-dimethylethyl ester (7.03 g, 28.1 mmol) and Pt/C (5%, 5.07 g) were slurried in THF (80 mL) and hydrogenated at rt and 50 psig for 8 hr. The slurry was then filtered through celite and concentrated in vacuo at 50 °C to aff rd the title compound as oil (6.68 g, 94.0%): ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1H), 7.19 (t, 1 H, J = 8 Hz), 6.85 (d, 1 H, J = 7 Hz), 6.77 (d, 1 H, J = 7 Hz), 3.84 (s, 2 H), 3.72 (s, 3 H), 1.37 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 159.9, 157.1, 141.1, 129.7, 121.1, 114.1, 113.1, 78.9, 55.5, 54.9, 28.9; IR ($CHCl_3$) 3008, 2982, 2935, 1712 cm^{-1}; Exact Mass: Calcd. for $C_{13}H_{20}N_2O_3Na$: 275.1372, Found: 275.1381.



3-(Aminocarbonyl)-2-(3-methoxyphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (3-Methoxybenzyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester (6.30 g, 25.0 mmol) was dissolved in isopropyl alcohol (65 mL). Trimethylsilyl isocyanate (4.73 g, 34.9 mmol) was added in one portion via syringe and the solution was allowed to stir at rt for 7 h. The slurry was cooled to 0 °C, filtered, and the solids rinsed with cold isopropanol. The solids were dried in vacuo at 40 °C to afford the title compound as a white solid (4.71 g, 63.9%). The filtrate was concentrated and purified by column chromatography (SiO_2, EtOAc) to afford additional compound (0.91 g, 12.3%). These two portions were combined to yield 5.82 g (76.2%) of the title compound: mp 136.3-138.5°C; ^1H NMR (DMSO-d_6, 60 °C) δ 8.70 (s, 1H), 7.20 (t, 1 H, J = 8 Hz), 6.80 (m, 3 H), 5.90 (s, 2 H), 4.50 (s, 2 H), 3.74 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 159.9, 159.6, 155.0, 140.2, 129.8, 120.9, 114.0, 113.2, 80.2, 55.6, 51.1, 28.7; IR ($CHCl_3$) 3003, 2984, 2938, 1745, 1680 cm^{-1}; Anal. Calcd. for $C_{14}H_{21}N_3O_4$: C, 56.94; H, 7.17; N, 14.23. Found: C, 56.54; H, 7.17; N, 13.98.

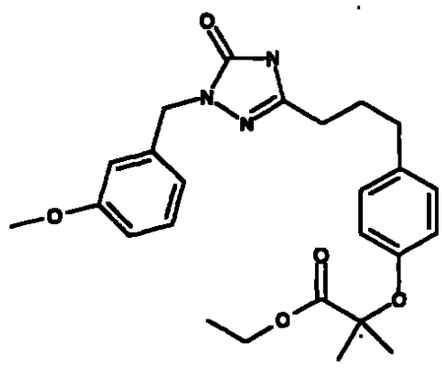


1-(3-Methoxyphenylmethyl)hydrazine carboxamide methanesulfonate 3-(Amino-carbonyl)-2-(3-methoxyphenylmethyl)hydrazine carboxylic acid, 1,1-dimethyl-ethyl ester (5.30 g, 17.9 mmol) was dissolved in dichloromethane (60 mL). Methanesulfonic acid (1.93 g, 19.9 mmol) was added in one portion and the solution was allowed to stir at rt overnight. The resulting slurry was cooled to 0 °C, filtered, and the solids rinsed with cold dichloromethane. The solids were dried in vacuo at 40 °C to afford the title compound as a white solid (5.05 g, 96.6%): mp 130.3-132.1 °C; ^{1}H NMR (DMSO-d_6) δ 9.7 (broad s, 3 H), 7.30 (t, 1 H, J = 8 Hz), 7.05 (broad s, 2 H), 6.88 (s, 3 H), 4.69 (s, 2 H), 3.74 (s, 3 H), 3.34 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 160.1, 158.2, 137.3, 130.5, 120.7, 114.3, 114.0, 55.7, 52.7, 40.4; IR (KBr mull) 3186, 2939, 1719, 1707, 1168 cm^{-1}; Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 41.23.; H, 5.88; N, 14.42. Found: C, 40.86.; H, 5.92; N, 14.61.



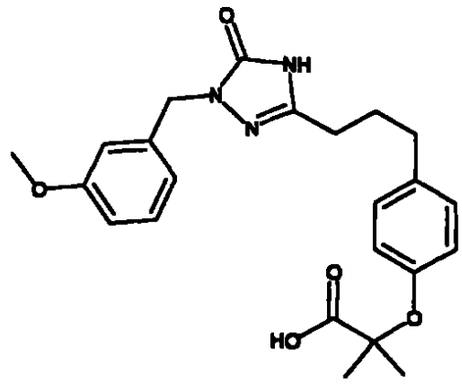
1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3-methoxyphenyl-methyl)semicarbazide 4-[4-(1-Ethoxycarbonyl-1-methyl-ethoxy)-phenyl] butyric acid (4.86 g, 16.5 mmol) was dissolved in ethyl acetate (40 mL). Oxalyl chloride (2.43 g, 19.14 mmol) was added to this solution dropwise in the presence of a catalytic amount of *N,N*-dimethylformamide (100 mg, 1.37 mmol). Completion of acid chloride formation was verified by HPLC. This solution was then added dropwise to a suspension of 1-(3-methoxyphenylmethyl)hydrazine carboxamide methanesulfonate (4.80 g, 16.5 mmol) and pyridine (1.30 g, 16.5 mmol) in ethyl acetate (55 mL) at 0 °C. After stirring at 0 °C for 6 h, an additional charge of pyridine was added (1.30 g, 16.5 mmol) and the solution was stirred at 0 °C for 1 h. The solution was warmed to rt and washed with 1N HCl (2 x 80 mL) and 5% aq. $NaHCO_3$ (2 x 80 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to a waxy solid. The solids were recrystallized from a mixture of toluene (17 mL) and heptane (7 mL) at 60 °C, cooled to 0 °C and filtered. The solids were dried in vacuo at 40 °C to afford the title compound as a white solid (5.05 g, 65%): mp 91.9 - 93.4 °C; ^1H NMR (DMSO-d_6, 60°C) δ 9.60 (s, 1 H), 7.19 (t, 1 H, *J* = 8 Hz), 7.00 (d, 2 H), 6.80 (m, 3 H), 6.71 (d, 2 H, *J* = 8 Hz), 5.92 (s, 2 H), 4.52 (s, 2 H), 4.15 (q, *J* = 7 Hz), 3.71 (s, 3 H),

2.45 (t, 2 H, J = 7 Hz), 2.07 (t, 2 H, J = 7 Hz), 1.73 (quint, 2 H, J = 7 Hz), 1.48 (s, 6 H), 1.17 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 171.9, 159.9, 159.3, 153.7, 140.5, 135.9, 129.9, 129.7, 120.9, 119.4, 114.1, 113.1, 79.2, 61.6, 55.5, 50.9, 34.3, 33.4, 27.2, 25.7, 14.6; IR (KBr mull) 3450, 3320, 3275, 3202, 2997, 2940, 1730, 1646, 1511 cm^{-1}; Anal. Calcd. for $C_{25}H_{33}N_3O_6$: C, 63.68; H, 7.05; N, 8.91. Found: C, 63.49; H, 7.02; N, 8.99.



2-(4-{3-[1-(3-Methoxybenzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester 1-[4-[4-(1-Ethoxycarbonyl-1-methyl-ethoxy)phenyl]butyryl]-2-(3-methoxyphenylmethyl)semicarbazide (4.08 g, 8.65 mmol) was dissolved in ethyl acetate (7.5 mL). Camphorsulfonic acid (2.21 g, 9.51 mmol) was added in one portion and the solution was heated to reflux overnight. The solution was cooled to rt and washed with sat'd aq. $NaHCO_3$ (2 x 40 mL) followed by 1N HCl (2 x 40 mL). The organic was concentrated to an oil, which was redissolved in ethyl acetate (40 mL). Amberlyst-15 resin (4.41 g) was added and the mixture was heated to 50 °C and stirred for 4 h. The mixture was then cooled to rt, filtered, concentrated, and

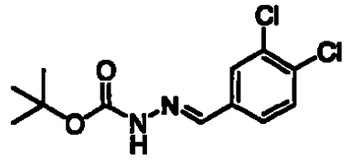
purified by column chromatography (SiO_2, 9:1 ethyl acetate:hexanes) to afford the title compound as an oil (1.93 g, 49.2%). ^1H NMR (DMSO-d_6) δ 11.47 (s, 1 H), 7.22 (t, 1 H, J = 8 Hz), 7.04 (d, 2 H, J = 8 Hz), 6.82 (d, 1 H, J = 2 Hz), 6.76 (m, 2 H), 6.68 (d, 2 H, J = 2 Hz), 4.73 (s, 2 H), 4.13 (q, 2 H, J = 7 Hz), 3.69 (s, 3 H), 2.48 (t, 2 H, J = 8 Hz), 2.36 (t, 2 H, J = 8 Hz), 1.80 (quint, 2 H, J = 7 Hz), 1.47 (s, 6 H), 1.14 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 160.0, 155.0, 153.8, 146.7, 139.8, 135.5, 130.2, 129.8, 120.1, 119.5, 113.8, 113.2, 79.2, 61.6, 55.6, 47.8, 34.0, 28.4, 26.2, 25.7, 14.6; IR ($CHCl_3$) 2940, 1692, 1508, 1467 cm^{-1}; Anal. Calcd. for $C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.26. Found: C, 66.29; H, 6.75; N, 9.19.



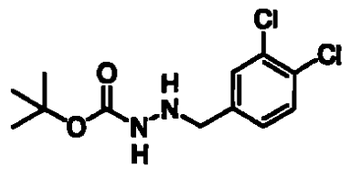
2-(4-{3-[1-(3-Methoxy-benzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid 2-(4-{3-[1-(3-Methoxy-benzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester (1.55 g, 3.42 mmol) was dissolved in a mixture of ethanol (7.5 mL) and water (7.5 mL). Solid sodium hydroxide (0.36 g, 8.73 mmol) was added in one portion and the solution was warmed to 70 °C and stirred for 1 h. The solution was cooled to rt and the pH adjusted to 7 with 6N HCl. The solution was concentrated to an oil, which was partitioned between 1N HCl (10 mL) and ethyl acetate (15 mL). The aqueous layer was then reextracted with ethyl acetate (15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo at 50 °C to afford the title compound as an oil (1.41 g, 97.0%). ^{1}H NMR (DMSO-d_6) δ 13.0 (broad s, 1 H), 11.47 (s, 1 H), 7.23 (t, 1 H, J = 8 Hz), 7.03 (d, 2 H, J = 8 Hz), 6.82 (d, 1 H, J = 2 Hz), 6.75 (m, 5 H), 4.73 (s, 2 H), 3.70 (s, 3 H), 3.35 (broad s, 1 H), 2.48 (t, 2 H, J = 8 Hz), 2.36 (t, 2 H, J = 8 Hz), 1.80 (quint, 2 H, J = 7 Hz), 1.46 (s, 6 H); ^{13}C NMR (DMSO-d_6, 20°C) δ 175.8, 160.0, 155.0, 154.1, 146.8, 139.8, 135.0, 130.3, 129.7, 120.1, 119.1, 113.8, 113.2, 78.9, 55.6,

47.8, 40.6, 40.5, 34.0, 28.4, 27.5, 26.2, 25.7; IR ($CHCl_3$) 1707, 1603, 1509, 1159 cm^{-1}; Anal. Calcd. for $C_{23}H_{27}N_3O_5$: C, 64.93; H, 6.40; N, 9.88. Found: C, 65.02; H, 6.65; N, 9.57.

Example 125

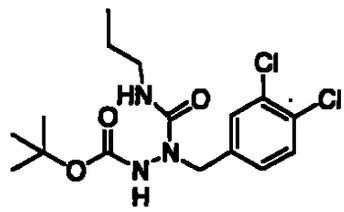


(3, 4-Dichlorophenyl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of *t*-butyl carbazate (4.99 g, 37.76 mmol) in ethyl acetate (10 mL) was added with vigorous stirring a solution of 3,4-dichlorobenzaldehyde (6.77 g, 38.6 mmol) in ethyl acetate (10 mL) followed by hexanes (40 mL). Crystallization occurred and the resulting slurry was stirred at rt for 15 min, then cooled to 0 °C. and held at that temperature for 45 min. The solids were filtered, rinsed with cold hexanes and dried in vacuo at 60 °C to afford the title compound as a solid (10.10 g, 92.4%): mp 173.8-174.4 °C (dec); ^1H NMR (DMSO-d_6) δ 11.16 (br s, 1 H), 7.79 (s, 1 H), 7.62 (d, 1 H, J = 1.8 Hz), 7.57 (d, 1 H, J = 8.5 Hz), 7.55 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 152.9, 141.1, 136.1, 132.3, 132.1, 131.6, 128.6, 127.0, 80.4, 28.7; IR (KBr mull) 3358, 3010, 2983, 1736, 1508, 1475 cm^{-1}. A portion was recrystallized (ethyl acetate) for analysis. Anal. Calcd. for $C_{12}H_{14}Cl_2N_2O_2$: C, 49.84; H, 4.88; Cl, 24.52; N, 9.69. Found: C, 49.59; H, 4.71; Cl, 24.43; N, 9.57.

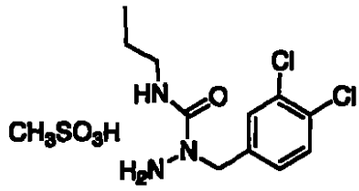


2-(3,4-Dichlorophenylmethyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester To substrate imine (2.90 g, 10.03

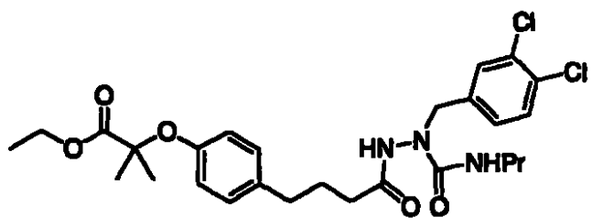
mmol) and 5% Pt/S/C (4.31 g of 55% wet catalyst, 1.94 g) was added tetrahydrofuran (30 mL) and the resulting slurry hydrogenated at 50 psi hydrogen at rt for 16 h. The slurry was filtered and the filtrate concentrated to an oil, which was chromatographed on silica gel (gradient of hexanes to 15% ethyl acetate in hexanes) to afford the title compound as an oil (2.56 g, 8.79 mmol, 88%): ^{1}H NMR (DMSO-d_6, 60 °C) δ 8.05 (br s, 1 H), 7.56 (s, 1 H), 7.52 (dd, 1 H, J = 7.5, 1.5 Hz), 7.27 (d, 1 H, J = 7.5 Hz), 3.87 (s, 2 H), 1.36 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 157.0, 141.0, 131.4, 130.8, 129.8, 129.3, 79.1, 53.6, 28.8; IR ($CHCl_3$) 3443, 2983, 1713, 1472, 1455, 1369 cm^{-1}; Anal. Calcd. for $C_{12}H_{16}Cl_2N_2O_2$: C, 49.50; H, 5.54; N, 9.62. Found: C, 49.82; H, 5.39; N, 9.50.



2-(Propylaminocarbonyl)-2-(3,4-dichlorophenylmethyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester To substrate hydrazide (2.30 g, 7.90 mmol) in isopropanol (25 mL) at rt was added propyl isocyanate (0.89 mL, 0.808 g, 9.50 mmol). After stirring for 30 min, the solution was concentrated to an oil, and chromatographed on silica gel (40% ethyl acetate in hexanes) to afford the title compound as an oil (2.63 g, 88%): ^{1}H NMR (DMSO-d_6, 60 °C) δ 8.72 (br s, 1 H), 7.52 (dd, 1 H, J = 8.0, 2.0 Hz), 7.48 (s, 1 H), 7.24 (d, 1 H, J = 8.0 Hz), 6.39 (br s, 1 H), 4.50 (br s, 2 H), 3.13 (m, 2 H), 1.41 (m, 2 H), 1.35 (s, 9 H), 0.82 (m, 3 H); ^{13}C NMR (DMSO-d_6) δ 158.4, 155.1, 140.1, 131.3, 130.9, 130.1, 129.3, 80.4, 51.2, 28.6, 23.7, 11.8; IR ($CHCl_3$) 3454, 3007, 2971, 2936, 2876, 1743, 1671, 1524 cm^{-1}; Anal. Calcd. for $C_{16}H_{23}Cl_2N_3O_3$: C, 51.07; H, 6.16; N, 11.17. Found: C, 51.01, H, 6.09; N, 11.15.

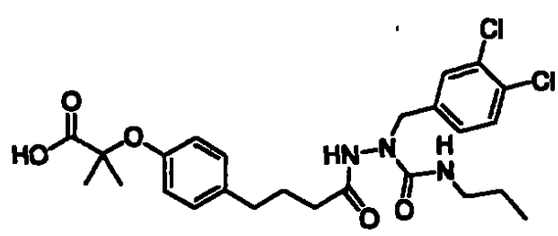


N-Propyl-1-(3,4-dichlorophenylmethyl)hydrazinecarboxamide methanesulfonate To substrate BOC semicarbazide (2.15 g, 5.71 mmol) in dichloromethane (20 mL) at rt was added methanesulfonic acid (0.39 mL, 0.578 g, 6.01 mmol) in one portion. The resulting solution was stirred at rt for 16 h, then heated to reflux for 16 h. The solution was cooled and concentrated to a foam, which was triturated with t-butyl methyl ether to afford the title compound as a solid (2.03 g, 5.53 mmol, 95%). A portion was recrystallized (ethyl acetate/ethanol) for analysis: mp 134.6 - 135.5 °C; ^{1}H NMR (DMSO-d_6, 60 °C) δ 8.35 (br 2, 4 H), 7.60 (d, 1 H, J = 8.5 Hz), 7.51 (d, 1 H, J = 2.0 Hz), 7.27 (dd, 1 H, J = 8.5, 2.0 Hz), 4.66 (s, 2 H), 3.06 (t, 2 H, J = 7.0 Hz), 2.42 (s, 3 H), 1.45 (m, 2 H), 0.83 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 157.6, 137.4, 131.8, 131.4, 131.2, 130.8, 129.1, 52.0, 42.7, 40.4, 23.3, 11.9; IR (KBr mull) 3385, 2958, 2933, 2874, 1687, 1525, 1189 cm^{-1}; Anal. Calcd. f r $C_{11}H_{15}Cl_2N_3O \cdot CH_4O_3S$: C, 38.72; H, 5.14; N, 11.29. Found: C, 38.76; H, 5.14; N, 11.26.

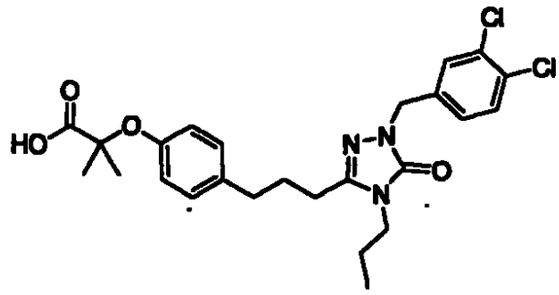


1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3,4-dichlorophenyl-methyl)-4-(propyl)semicarbazide To 4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]-butyric acid (1.005 g, 3.41 mmol) in ethyl acetate (10 mL) at rt was added DMF (1 pipette drop), followed by oxalyl chloride (0.4 mL, 0.582

g, 4.58 mmol) dropwise over 3 min. The resulting solution was stirred for 30 min at rt, then concentrated to an oil. The oil was twice reconstituted into toluene (20 mL) and concentrated to an oil, then dissolved in ethyl acetate (3 mL). *N*-Propyl-1-(3,4-dichlorophenylmethyl)hydrazine methane-sulfonate (1.1458 g, 3.08 mmol) was suspended in ethyl acetate (10 mL) at 0 °C, and pyridine (0.65 mL, 636 mg, 8.04 mmol) was added. The solution of acid chloride in ethyl acetate was then added dropwise over 2 min, and the resulting mixture stirred for 15 min at 0 °C. The mixture was then diluted with ethyl acetate and washed with 1 N HCl (2X) followed by sat'd aq. NaCl. It was then dried ($MgSO_4$), filtered and concentrated to an oil, which was chromatographed on silica gel (3:2 ethyl acetate:hexanes) to afford the title compound as an oil (1.4397 g, 85%): ^{1}H NMR (DMSO-d_6, 60 °C) δ 9.61 (s, 1 H), 7.50 (d, 1 H, *J* = 8 Hz), 7.47 (d, 1 H, *J* = 2 Hz), 7.23 (dd, 1 H, *J* = 8, 2 Hz), 7.01 (d, 2 H, *J* = 8.5 Hz), 6.71 (d, 2 H, *J* = 8.5 Hz), 6.41 (br m, 1 H), 4.53 (br s, 2 H), 4.15 (q, 2 H, *J* = 7 Hz), 3.00 (m, 2 H), 2.43 (m, 2 H), 2.09 (t, 2 H, *J* = 7 Hz), 1.74 (m, 2 H), 1.48 (s, 6 H), 1.40 (m, 2 H), 0.81 (t, 3 H, *J* = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 172.1, 158.1, 153.8, 140.4, 135.8, 131.4, 130.9, 130.6, 130.1, 129.7, 129.1, 119.5, 79.2, 61.6, 50.9, 42.3, 34.4, 33.5, 27.1, 25.7, 23.7, 14.6, 11.9; IR ($CHCl_3$) 3457, 3008, 2876, 1727, 1673, 1509 cm^{-1}; Anal. Calcd. for $C_{27}H_{35}Cl_2N_3O_5$: C, 58.70; H, 6.39; N, 7.61. Found: C, 58.60; H, 6.49; N, 7.67.

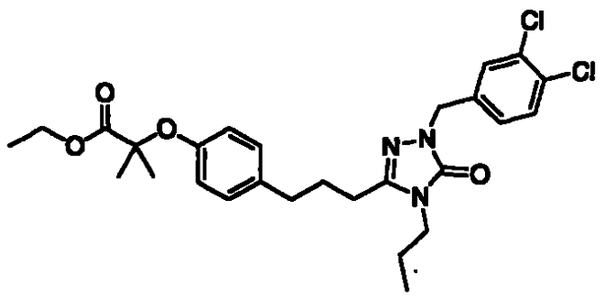


1-[4-[4-(1-Carboxy-1-methylethoxy)phenyl]butyryl]-2-(3,4-dichlorophenylmethyl)-4-(propyl)semicarbazide To substrate 1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)-phenyl]butyryl]-2-(3,4-dichlorophenylmethyl)-4-(propyl)semicarbazide (0.609 g, 1.10 mmol) in methanol (5 mL) at rt was added 1 N NaOH (2.0 mL, 2.0 mmol) and the resulting solution stirred for 16 h. The solution was then concentrated to an oil, and partitioned between ethyl acetate and 1 N HCl. The organic phase was then washed with sat'd aq. NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound as an amorphous solid (0.5563 g, 1.06 mmol, 96%): ^1H NMR (DMSO-d_6, 60 °C) δ 9.61 (s, 1 H), 7.50 (d, 1 H, J = 8 Hz), 7.47 (d, 1 H, J = 1.5 Hz), 7.23 (dd, 1 H, J = 8, 1.5 Hz), 7.01 (d, 2 H, J = 8.5 Hz), 6.75 d, 2 H, J = 8.5 Hz), 6.40 (br m, 1 H), 4.53 (br s, 2 H), 2.99 (q, 2 H, J = 6.5 Hz), 2.46 (t, 2 H, J = 7.5 Hz), 2.09 (t, 2 H, J = 7.5 Hz), 1.74 (m, 2 H), 1.47 (s, 6 H), 1.40 (q, 2 H, J = 7.5 Hz), 0.81 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 175.8, 172.1, 158.1, 154.1, 140.4, 135.3, 131.5, 130.9, 130.6, 130.1, 129.6, 129.1, 119.1, 78.9, 50.9, 42.3, 40.7, 34.4, 33.5, 27.1, 25.7, 23.7, 11.9; IR ($CHCl_3$) 3379, 3291, 2960, 2915, 1719, 1671, 1618, 1542, 1508 cm^{-1}; Anal. Calcd. for $C_{25}H_{31}Cl_2N_3O_5$: C, 57.26; H, 5.96; N, 8.01. Found: C, 57.15; H, 5.89; N, 7.94.



2-(4-{3-[1-(3,4-Dichlorobenzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triaz 1-3-yl]-propyl}-phenoxy)-2-methylpropionic acid To substrate 1-[4-[4-(1-Carboxy-1-methylethoxy)-

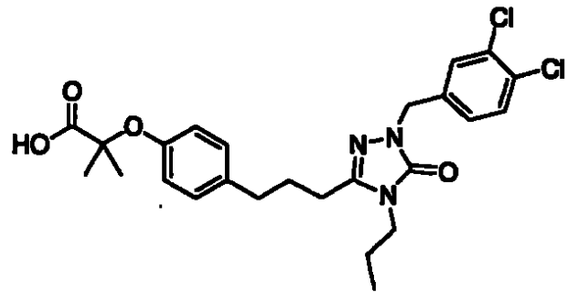
phenyl]butyryl]-2-(3,4-dichlorophenylmethyl)-4-(propyl)semicarbazide (0.3658 g, 0.697 mmol) and camphorsulfonic acid (0.1658 g, 0.714 mmol) was added toluene (10 mL) and the resulting solution heated to 90 °C for 1 h. The solution was concentrated to an oil, and chromatographed on silica gel (7:3 ethyl acetate:hexanes) to afford title compound as an oil (0.2397 g, 0.473 mmol, 68%): ^{1}H NMR (DMSO-d_6) δ 12.95 (br s, 1 H), 7.58 (d, 2 H, J = 8 Hz), 7.46 (d, 1 H, J = 1.5 Hz), 7.19 (dd, 1 H, J = 8, 1.5 Hz), 7.03 (d, 2 H, J = 8.5 Hz), 6.72 (d, 2 H, J = 8.5 Hz), 4.85 (s, 2 H), 3.47 (t, 2 H, J = 7 Hz), 2.54 (t, 2 H, J = 7.5 Hz), 1.83 (m, 2 H), 1.52 (q, 2 H, J = 7 Hz), 1.45 (s, 6 H), 0.79 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 175.8, 154.1, 147.3, 139.2, 135.2, 131.7, 131.5, 130.8, 130.1, 129.7, 128.4, 119.3, 79.0, 47.3, 42.9, 34.0, 27.8, 25.7, 24.8, 22.5, 11.5; IR ($CHCl_3$) 3028, 3005, 2939, 2878, 1696, 1574, 1509, 1472 cm^{-1}; Anal. Calcd. for $C_{25}H_{29}Cl_2N_3O_4$: C, 59.29; H, 5.77; N, 8.30. Found: C, 59.33; H, 5.63; N, 8.10.



2-(4-{3-[1-(3,4-Dichlorobenzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid, ethyl ester To substrate 1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3,4-dichlorophenylmethyl)-4-(propyl)semicarbazide (0.4976 g, 0.901 mmol) and camphorsulfonic acid (0.2078 g, 0.895 mmol) was added ethyl acetate (10 mL) and the resulting solution heated to reflux for 12 h. The solution was diluted with ethyl acetate, then washed with sat'd aq. $NaHCO_3$ followed by sat'd aq. NaCl. It was then dried ($MgSO_4$), filtered and concentrated to afford

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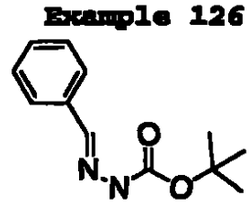
the title compound as an oil (0.4532 g (0.848 mmol, 94%): ^{1}H NMR (DMSO-d_6) δ 7.59 (d, 1 H, J = 8.5 Hz), 7.47 (d, 1 H, J = 2 Hz), 7.19 (dd, 1 H, J = 8.5, 2 Hz), 7.03 (d, 2 H, J = 8.5 Hz), 6.69 (d, 2H, J = 8.5 Hz), 4.85 (s, 2 H), 4.13 (q, 2 H, J = 7 Hz), 3.48 (t, 2 H, J = 8 Hz), 2.55 (t, 2 H, J = 7 Hz), 1.83 (m, 2 H), 1.52 (q, 2 H, J = 7 Hz), 1,47 (s, 6 H), 1.14 (t, 3 H, J = 7 Hz), 0.79 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 154.1, 153.8, 147.3, 139.2, 135.6, 131.7, 131.5, 130.8, 130.1, 129.8, 128.4, 119.6, 79.3, 61.6, 47.3, 42.9, 34.0, 27.7, 25.7, 24.7, 22.4, 14.6, 11.5; IR ($CHCl_3$) 3003, 2939, 1728, 1696, 1509 cm^{-1}; HRMS calcd. for $C_{27}H_{34}Cl_2N_3O_4$ $(M + H)^+$: 524.1926. Found: 534.1935



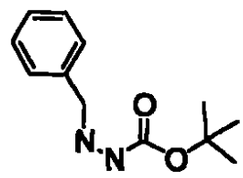
2-(4-{3-[1-(3,4-Dichlorobenzyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid

To substrate triazolone ethyl ester (0.3879 g, 0.726 mmol) in methanol (5 mL) at rt was added sodium hydroxide (2.0 mL of 2.0 M solution, 2.0 mmol) and the resulting mixture stirred at rt for 16 h. The mixture was then concentrated to an oil and partitioned between ethyl acetate and 1 N HCl. The organic phase was washed with sat'd aq. NaCl, dried ($MgSO_4$), filtered and concentrated to afford the title compound (0.336 g, 0.646 mmol, 89%) as an oil.

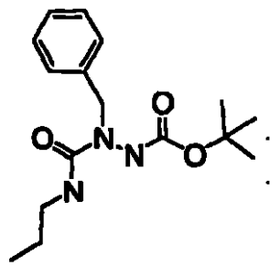
Example 126



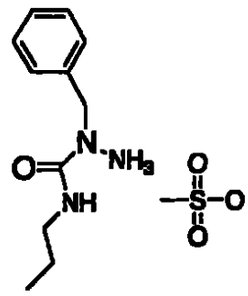
Phenylmethylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of *t*-butyl carbazate (5.62 g, 42.5 mmol) in ethyl acetate (15 mL) was added with stirring benzaldehyde (4.51 g, 42.5 mmol). Crystallization occurred and the resulting slurry was stirred at rt for 45 min. Hexanes (70 mL) was added and the slurry was cooled to 0 °C. The slurry was stirred at 0 °C for 60 min, then filtered and rinsed with cold hexanes (20mL) and dried in vacuo at 40 °C to afford the title compound as a solid (8.34 g, 89.0%): mp 184.1 - 184.9 °C; ^{1}H NMR (DMSO-d_6) δ 10.91 (s, 1 H), 7.99 (s, 1 H), 7.58 (d, 2 H, *J* = 3 Hz), 7.39 (m, 3 H), 1.45 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 153.0, 143.8, 135.3, 130.0, 129.4, 127.2, 80.1, 28.8; IR (KBr mull) 2983, 1735, 1511, 1157 cm^{-1}; A portion was recrystallized (ethyl acetate) for analysis. Anal. Calcd. For $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.16; H, 7.43; N, 12.62.



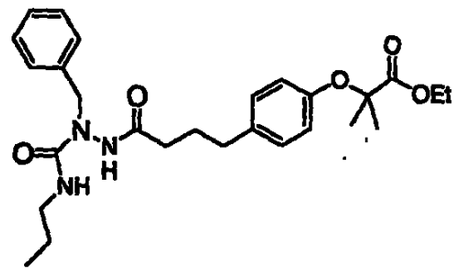
Phenylmethylhydrazinecarboxylic acid, 1,1-dimethylethyl ester Phenylmethylene-hydrazinecarboxylic acid, 1,1-dimethylethyl ester (7.00 g, 31.8 mmol) and 5% Pt/C (5.32 g) were slurried in THF (70 mL) and stirred and hydrogenated (50 psig) at rt for 3 hr. The slurry was then filtered through celite to remove the catalyst and concentrated in vacuo at 50 °C to afford the title compound as a clear oil (6.36 g, 90.0%): ^{1}H NMR (DMSO-d_6) δ 8.23 (s, 1 H), 7.29 (m, 4 H), 7.20 (m, 1 H), 4.62 (br s, 1 H), 3.85 (s, 2 H), 1.37 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 157.1, 139.4, 129.1, 128.7, 127.4, 79.0, 55.1, 28.9; IR ($CHCl_3$) 2982, 1712, 1454, 1273, 1159 cm^{-1}; Exact Mass Calcd for $C_{12}H_{21}N_2O_2$: 245.1266. Found: 245.1273.



2-(Propylaminocarbonyl)-2-(phenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester To a solution of phenylmethylhydrazinecarboxylic acid, 1,1-dimethylethyl ester (2.54 g, 11.4 mmol) in isopropanol (25 mL) was added propyl isocyanate (1.51 g, 17.6 mmol) and the solution was stirred at rt for 1 h. The solution was concentrated to a white solid. This solid was dissolved in ethyl acetate (25 mL) and washed with water (25 mL) and 10% aq. NaCl (25 mL), dried ($MgSO_4$), filtered and concentrated to an off-white solid. It was then recrystallized (2:3 ethyl acetate:hexanes) and dried in vacuo to afford the title compound as a white solid (2.53 g, 72.1%): mp 122.8 - 124.5 °C; ^1H NMR (DMSO-d_6, 60°C) δ 8.58 (s, 1 H), 7.28 (m, 2 H), 7.23 (m, 3 H), 6.26 (s, 1 H), 4.53 (s, 2 H), 3.02 (q, 2 H, J = 7 Hz), 1.41 (quint, 2 H, J = 7 Hz), 1.35 (s, 9 H), 0.83 (t, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 158.6, 155.0, 138.7, 128.9, 128.8, 127.6, 80.2, 51.5, 42.3, 28.6, 23.7, 11.8 ; IR ($CHCl_3$) 3007, 1745, 1665, 1523 cm^{-1}. Anal. Calcd. For $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.28.; H, 8.14; N, 13.51.

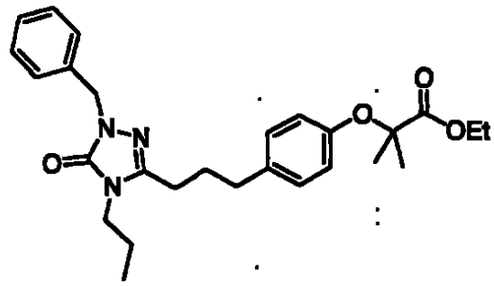


N-Propyl-1-phenylmethylhydrazine carboxamide methanesulfonate 2-(Propylaminocarbonyl)-2-(phenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (2.33 g, 7.58 mmol) was dissolved in dichloromethan (25 mL). Methanesulfonic acid (615 µL, 9.48 mmol) was added in one portion and the solution was allowed to stir at rt overnight. The solution was heated to reflux for 8 h, then concentrated to afford the title compound as a crude white solid (2.47g, 107%): mp 78.1 - 82.9 °C; ^{1}H NMR (DMSO-d_6) δ 9.7 (br s, 3 H), 7.61 (br s, 1 H), 7.38 (t, 1 H, J = 8 Hz), 7.32 (m, 4 H), 4.74 (s, 2 H), 3.07 (t, 2 H, J = 8 Hz), 2.38 (s, 3 H), 1.43, (quint, 2 H, J = 8 Hz), 0.81 (t, 3 H, J = 8 Hz); ^{13}C NMR (DMSO-d_6) δ 157.5, 135.6, 129.3, 128.7, 128.6, 52.8, 42.7, 40.3, 23.3, 11.9; IR ($CHCl_3$) 3009, 1691, 1543, 1196 cm^{-1}; Exact Mass Calcd. For $C_{11}H_{17}N_3O$: 208.1450. Found: 208.1462.

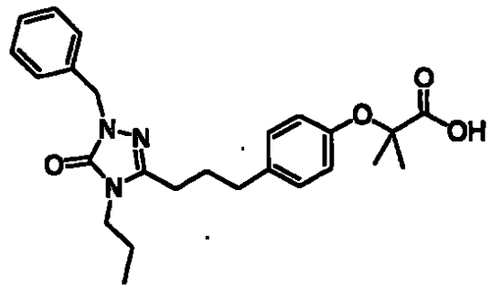


1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-phenylmethyl-4-(propyl)semicarbazide 4-[4-(1-Ethoxycarbonyl-1-methyl-ethoxy)-phenyl] butyric acid (1.50 g, 5.04 mmol) was dissolved in ethyl acetate (10 mL). Oxalyl chloride (524 µL, 6.01 mmol) was added to this solution dropwise in the presence of a catalytic amount of *N,N*-dimethylformamide (30.1 µL, 0.41 mmol). Completion of acid chloride formation was verified by HPLC. This solution was then concentrated to remove residual oxalyl chloride and the resulting oil was redissolved in ethyl acetate (10 mL). This solution was then added dropwise to a suspension of *N*-propyl-1-phenylmethylhydrazine carboxamide methanesulfonate (1.52 g, 5.01 mmol) and pyridine (970 µL, 12.6 mmol) in ethyl acetate (15 mL) at 0 °C. After stirring at 0 °C for 1 h, the solution was warmed to rt and washed with 1N HCl (2 x 20 mL) and 5% aq. $NaHCO_3$ (2 x 20 mL) followed by sat'd aq. NaCl (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to a yellow oil. The oil was purified by column chromatography (SiO_2, 1:1 ethyl acetate:hexanes) to afford the title compound as a clear oil (1.42 g, 59%): ^1H NMR (DMSO-d_6, 60 °C) δ 9.51 (s, 1 H), 7.20 (m, 5 H), 7.01 (d, 2 H, *J* = 8 Hz), 6.71 (t, 1 H, *J* = 7 Hz), 4.55 (s, 2 H), 4.17 (q, *J* = 7 Hz), 3.00 (q, 2 H, *J* = 7 Hz), 2.45 (t, 2 H, *J* = 2 Hz), 2.07 (t, 2 H, *J* = 2 Hz), 1.73 (quint, 2 H, *J* = 7 Hz), 1.48 (s, 6 H), 1.40 (q, 2 H, *J* = 7 Hz), 1.17 (t, 3 H, *J* = 7 Hz), 0.81 (t, 3 H, *J* = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0,

172.0, 158.2, 153.8, 139.0, 135.8, 129.7, 128.84, 128.79, 127.6, 119.4, 79.2, 61.6, 51.3, 42.3, 34.3, 33.4, 27.1, 25.7, 23.7, 14.6, 11.9 ; IR ($CHCl_3$) 3009, 1726, 1672, 1143 cm^{-1}; Anal. Calcd. For $C_{27}H_{37}N_3O_5$: C, 67.05; H, 7.71; N, 8.69. Found: C, 66.65.; H, 7.63; N, 8.57.



2-{4-[3-(1-Phenylmethyl-5-oxo-4-propyl-4,5-dihydro-1H-[1,2,4]triazol-3-yl)-propyl]-phenoxy}-2-methylpropionic acid ethyl ester 1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-phenylmethyl-4-(propyl)semicarbazide (1.26 g, 2.61 mmol) was dissolved in ethyl acetate (15 mL). Camphorsulfonic acid (670 mg, 2.88 mmol) was added in one portion and the solution was heated to reflux for 1 h. The solution was cooled to rt and washed with sat'd aq. NaHCO3 (2 x 10 mL) followed by 1N HCl (2 x 10 mL). The organic phase was dried (MgSO4) and concentrated to a clear, colorless oil. The material was purified by plug silica gel filtration (gradient dichloromethane to ethyl acetate) to afford the title compound as a clear, colorless oil (0.86 g, 71 %). 1H NMR (DMSO-d6) □ 7.30 (t, 3 H, *J* = 7 Hz), 7.24 (d, 1 H, *J* = 7 Hz), 7.20 (d, 2 H, *J* = 7 Hz), 7.04 (d, 2 H, *J* = 8 Hz), 6.69 (d, 2 H, *J* = 8 Hz), 4.13 (q, 2 H, *J* = 7 Hz), 3.47 (t, 2 H, *J* = 7 Hz), 2.55 (t, 2 H, *J* = 7 Hz), 2.48 (t, 2 H, *J* = 7 Hz), 1.83 (quint, 2 H, *J* = 7 Hz), 1.52, (m, 2 H), 1.47 (s, 6 H), 1.14 (t, 3 H, *J* = 7 Hz), 0.79 (t, 3 H, *J* = 7 Hz); 13C NMR (DMSO-d6) □ 174.0, 154.1, 153.8, 146.9, 138.1, 135.6, 129.8, 129.1, 128.0, 119.6, 79.3, 61.6, 48.5, 42.8, 34.0, 27.8, 25.7, 24.8, 22.5, 14.5, 11.5; IR (CHCl3) 2878, 1692, 1509, 1143 cm-1; Anal. Calcd. F r C27H35N3O4: C, 69.65; H, 7.58; N, 9.03. Found: C, 69.28; H, 7.96; N, 8.84.



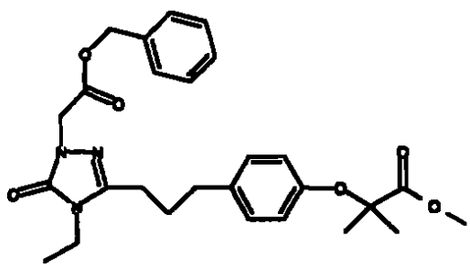
2-(4-{3-[1-(Phenylmethyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid

2-(4-{3-[1-(Phenylmethyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid ethyl ester (557 mg, 1.20 mmol) was dissolved in ethanol (5 mL) and 1N aq. NaOH (3.6 mL, 3.6 mmol) was added in one portion and the solution was stirred at room temperature for 16 h. The solution was then concentrated to a hazy colorless oil. This oil was diluted with water (5 mL) and washed with t-butyl methyl ether (5 mL). The pH of the aqueous layer was adjusted to < 1 with conc. HCl and the aqueous was extracted with ethyl acetate (10 mL, then 5 mL). This solution was washed with 1 N aqueous HCl (5 mL) and sat'd aq. NaCl (5 mL), dried ($MgSO_4$), and concentrated in vacuo to afford the title compound as a clear colorless oil (442 mg, 84.5%). ^1H NMR (DMSO-d_6) δ 12.9 (br s, 1 H), 7.30 (t, 2 H, J = 7 Hz), 7.25 (d, 1 H, J = 7 Hz), 7.20 (d, 2 H, J = 7 Hz), 7.04 (d, 2 H J = 8 Hz), 6.72 (d, 2 H, J = 8 Hz), 4.83 (s, 2 H), 3.47 (t, 2 H, J = 7 Hz), 2.54 (t, 2 H, J = 8 Hz), 2.49 (t, 2 H, J = 8 Hz), 1.83 (quint, 2 H, J = 7 Hz), 1.53, (m, 2 H), 1.46 (s, 6 H), 0.80 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 175.8, 154.1, 146.0, 138.1, 135.2, 129.7, 129.2, 128.0, 119.3, 79.0, 48.5, 42.8, 34.0, 27.9, 25.7, 24.8, 22.5, 11.5; IR ($CHCl_3$) 2938, 1509, 1468, 1233, 1155 cm^{-1}; Anal. Calcd.

For $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.24; H, 6.95; N, 9.40.

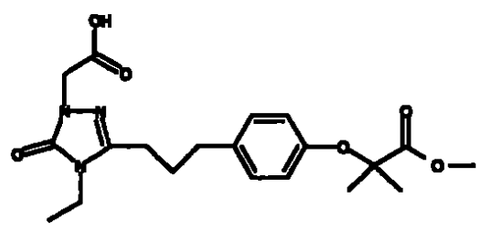
Example 127:

Step A:



The N-4 ethyl triazolinone (1 g, 0.003 mol) was combined with benzyl bromoacetate (0.089 ml, 0.0056 mol) and powdered K_2CO_3 (1.99 g, 0.014 mol) in DMF (28 ml) and stirred at 67°C overnight. Ether was added to the reaction mixture and the solution was extracted with water. Purification by flash chromatography (2:1 hexanes: ethyl acetate) gave the desired amide.
$C_{27}H_{33}N_3O_6$ (MW = 495.65); mass spectroscopy (MH^+) = 496.2

Step B:



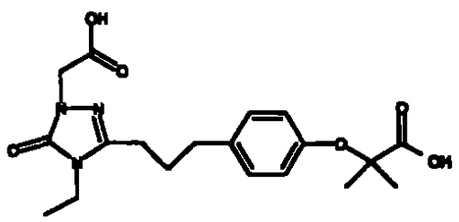
The amide from **Step A** (1.28 g, 0.0026 mol) was dissolved in ethyl acetate (20 ml) and purged with nitrogen. Palladium catalyst (0.128g, 10%) was added t the solution. The reaction mixture was purged again. Hydrogen gas was

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202

released across the system and the reaction was stirred overnight. The reaction mixture was filtered and the filtrate was concentrated. The resulting residue was carried forth without further purification.

$C_{20}H_{27}N_3O_6$ (MW = 405.45); mass spectroscopy (MH^+) = 406.3

Step C:

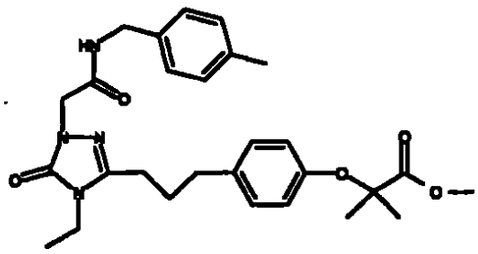


The ester from **Step B** (0.200 g, 0.00049 mol) was dissolved in ethanol (6 ml) and treated with 2N NaOH (3 ml). The solution was refluxed for one hour. Water was added to the mixture and the layer was extracted with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 then concentrated to yield the desired product as a white foam.

$C_{19}H_{25}N_3O_6$ (MW = 391.43); mass spectroscopy (MH^+) = 392.3

Example 128

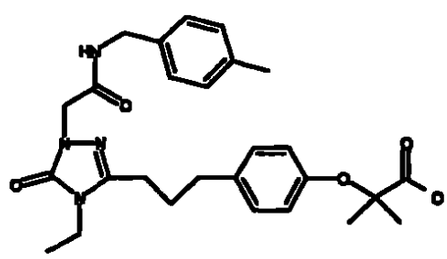
Step A:



A THF solution of the acid described in Example 127 , Step B (0.190 g, 0.00047 mol) was treated with EDC (0.134 g, 0.0007 mol) and HOAt (0.064 g, 0.0047 mol). An equivalent of 4-methyl benzyl amine (0.060 ml, 0.00047 mol) was added and the reaction was stirred overnight. The solvent was concentrated and the residue was redissolved in methylene chloride and extracted with water. Purification by flash chromatography (100 % ethyl acetate) gave the desired amide.

$C_{28}H_{36}N_4O_5$ (MW = 508.62); mass spectroscopy (MH^+) = 509.4

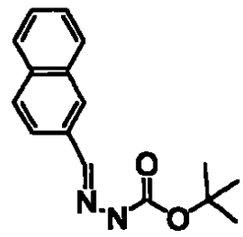
Step B:



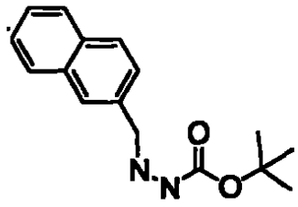
The amide from Step A (0.150 g, 0.00029 mol) was dissolved in dioxane (3 ml) and water (3 ml) then treated with LiOH (0.007 g, 0.00029 mol). The reaction was stirred for two hours. Water was added to the mixture and the layer

was extracted with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 then concentrated to yield the desired product as a white foam. $C_{27}H_{34}N_4O_5$ (MW = 494.60); mass spectroscopy (MH^+) = 495.4

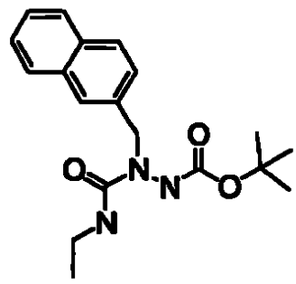
Example 129



(Naphthalen-2-yl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of *t*-butyl carbazate (7.59 g, 57.4 mmol) in ethyl acetate (22 mL) was added with stirring 2-napthaldehyde (8.98 g, 57.5 mmol). This clear yellow solution was stirred at rt for 15 min. Hexanes (105 mL) was added dropwise and solids precipitated from solution. The slurry was cooled to 0 °C, the solids were then filtered and rinsed with cold hexanes (20 mL). A second crop of solids was obtained from the filtrate, filtered and combined with the first crop. The combined solids were recrystallized (EtOAc) and filtered. A second crop was collected by concentrating the filtrate to half its original volume and filtering the resulting solids at 0°C. The two crops of solids were combined and dried in vacuo at 40 °C to afford the title compound as a solid (13.17 g, 85.0%): mp 182.1-190 °C (dec.); ^1H NMR (DMSO-d_6) δ 11.04 (s, 1H), 8.17 (s, 1 H), 7.99 (s, 1H), 7.93-7.86 (m, 4H), 7.52-7.49 (m, 2H), 1.47 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 153.1, 143.9, 134.1, 133.6, 133.1, 129.1, 128.9, 128.5, 128.4, 127.5, 127.3, 123.1, 80.1, 28.8; IR ($CHCl_3$) 3061, 3010, 2982, 1733, 1505, 1369 cm^{-1}; Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.95; H, 6.89; N, 10.31.



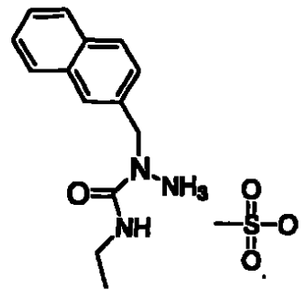
(Naphthalen-2-yl)methylhydrazinecarboxylic acid, 1,1-dimethylethyl ester (Naphthalen-2-yl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester (7.08 g, 26.2 mmol) and 5 % Pt/C (7.11 g) were slurried in THF (70 mL) and hydrogenated at 50 psig at rt for 4 hr. A second charge of 5% Pt/C (1.78g) was added and hydrogenation continued for 16 h. The slurry was then filtered through celite to remove the catalyst and concentrated in vacuo at 50 °C to afford the title compound as a clear oil (7.01 g, 98.3%): ^{1}H NMR (DMSO-d_6) δ 8.27 (s, 1 H), 7.83 (m, 4 H), 7.48 (m, 3 H), 6.97 (m, 1 H), 4.88 (s, 1 H), 4.04 (s, 2 H), 1.37 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 137.1, 133.6, 132.9, 128.2, 128.1, 127.7, 127.3, 126.6, 126.4, 126.2, 79.0, 55.1, 28.9, 23.5; IR ($CHCl_3$) 3445, 1711, 1454, 1393, 1331 cm^{-1}; Exact Mass Calcd for $C_{16}H_{20}N_2O_2$: 295.1422. Found: 295.1414.



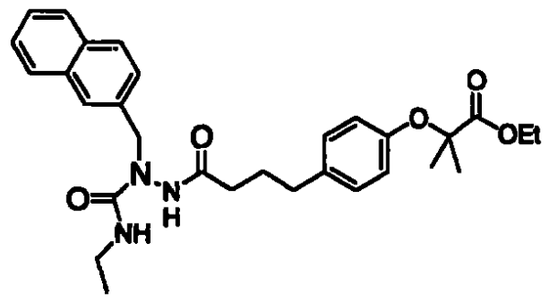
2-(Ethylaminocarbonyl)-2-(Naphthalen-2-yl)methylhydrazine carboxylic acid, 1,1-dimethylethyl ester (Naphthalen-2-yl)methyl-hydrazinecarboxylic acid, 1,1-dimethylethyl ester (2.84 g, 10.4 mmol) was dissolved in isopropanol (30 mL).

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3006

Ethyl isocyanate (1.23 mL, 15.6 mmol) was added in one portion and the solution was stirred at rt for 1 h, then concentrated to a yellow oil. Column chomatography (SiO_2, 2:3 EtOAc: hexanes) afforded the title compound as a clear, colorless oil (2.66 g, 55%): ^1H NMR (DMSO-d_6, 60°C) δ 8.60 (s, 1 H), 7.8 (m, 3 H), 7.72, (s, 1 H), 7.4 (m, 3 H), 6.37 (s, 1 H), 4.71 (s, 2 H), 3.11 (quint, 2 H, J = 6 Hz), 1.32 (s, 9 H), 1.04 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 158.6, 155.0, 136.2, 133.5, 133.0, 129.3, 128.2, 128.1, 127.5, 126.7, 126.3, 60.4, 35.4, 28.6, 16.3, 14.7; IR ($CHCl_3$) 3453, 2983, 1664, 1370, 1156 cm^{-1}; Exact Mass Calcd for $C_{19}H_{25}N_3O_3$: 366.1794. Found: 366.1797.

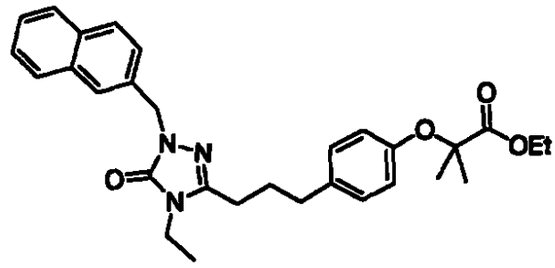


N-Ethyl-2-(naphthalen-2-yl)methylhydrazine carboxamide methanesulfonate 2-(Ethylaminocarbonyl)-2-(naphthalen-2-yl)methylhydrazine carboxylic acid, 1,1-dimethylethyl ester (2.52 g, 7.34 mmol) was dissolved in dichloromethane (25 mL). Methanesulfonic acid (524 µL, 8.07 mmol) was added in one portion and the solution was stirred at rt overnight. The solution was then heated to reflux for 8 h, then concentrated to afford the title compound as a white amorphous solid (2.49g, 96 %): m.p. 46.2 - 48.1 °C; ^1H NMR (DMSO-d_6) δ 9.7 (br s, 3 H), 7.9 (m, 3 H), 7.82, s, 1H, 7.61 (br s, 1 H), 7.52 (m, 2 H,), 7.44 (d, 1 H, J = 7 Hz), 3.18 (quint, 2 H, J = 8 Hz), 2.38 (s, 3 H), 1.07 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 157.5, 133.4, 133.3, 133.1, 129.0, 128.5, 128.3, 127.7, 127.1, 126.9, 126.7, 53.2, 40.4, 35.9, 15.8; IR ($CHCl_3$) 3415, 2939, 1543, 1191, 1043 cm^{-1}; Exact Mass Calcd. for $C_{14}H_{17}N_3O$: 244.1450. Found: 244.1460.



1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(naphthalen-2-yl)methyl-4-(propyl)semicarbazide 4-[4-(1-Ethoxycarbonyl-1-methyl-ethoxy)-phenyl] butyric acid (1.35 g, 4.59 mmol) was dissolved in ethyl acetate (10 mL). Oxalyl chloride (425 µL, 4.86 mmol) was added to this solution dropwise in the presence of a catalytic amount of *N,N*-dimethylformamide (25 µL, 0.34 mmol). Completion of acid chloride formation was verified by HPLC. This solution was then concentrated to remove residual oxalyl chloride and the resulting oil dissolved in ethyl acetate (10 mL). This solution was then added dropwise to a suspension of *N*-ethyl-2-(naphthalen-2-yl)methylhydrazine carboxamide methanesulfonate (1.50 g, 4.42 mmol) and pyridine (895 µL, 11.1 mmol) in ethyl acetate (15 mL) at 0 °C. After stirring at 0 °C for 4 h, the solution was warmed to rt and washed with 1N HCl (2 x 25 mL) and 5% aq. $NaHCO_3$ (2 x 25 mL) followed by sat'd aq. NaCl (25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to a yellow oil, which was purified by column chromatography (SiO_2, 7:3 ethyl acetate: hexanes) to afford the title compound as an oil (1.59 g, 69%): ^1H NMR (DMSO-d_6, 60°C) □ 9.51 (*s*, 1 H), 7.85 (m, 3 H), 7.70 (*s*, 1 H), 7.42 (m, 3 H), 6.94 (d, 2 H, *J* = 7 Hz), 6.67 (d, 2 H, *J* = 7 Hz), 6.38 (*s*, 1 H), 4.72 (*s*, 2 H), 4.16 (q, *J* = 7 Hz), 3.08 (t, 2 H, *J* = 7 Hz), 2.41 (t, 2 H, *J* = 8 Hz), 2.07 (t, 2 H, *J* = 8 Hz), 1.72 (quint, 2 H, *J* = 7 Hz), 1.47 (*s*, 6 H), 1.17 (t, 3 H, *J* = 7 Hz), 1.01 (t, 3 H, *J* = 7 Hz); ^{13}C NMR (DMSO-d_6) □ 174.0, 172.1, 158.2, 153.7, 136.4, 135.8, 133.5, 133.0, 129.7, 128.4, 128.2, 128.1, 127.4, 126.7, 126.3, 119.4, 79.2, 61.6, 51.3, 35.4, 34.3, 33.5, 27.2, 25.7, 16.3, 14.6; IR ($CHCl_3$) 3454, 2938, 1727,

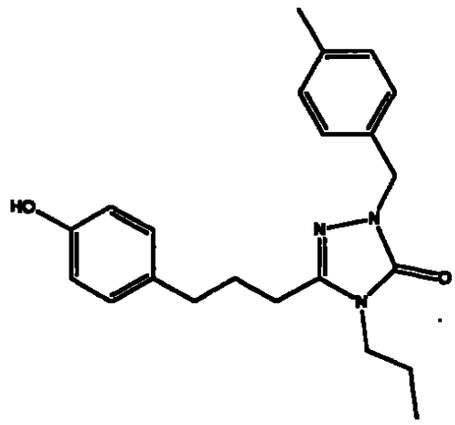
1670, 1509, 1233, 1142 cm^{-1}; Anal. Calcd. for $C_{30}H_{37}N_3O_5$: C, 69.34 ; H, 7.18; N, 8.09. Found: C, 69.19; H, 7.49; N, 7.93.



2-{4-[3-(4-Ethyl-1-(naphthalen-2-yl)methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl)-propyl]-phenoxy}-2-methylpropionic acid ethyl ester 1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(naphthalen-2-yl)methyl-4-(propyl)semicarbazide (1.30 g, 2.51 mmol) was dissolved in ethyl acetate (15 mL). Camphorsulfonic acid (0.645 g, 2.78 mmol) was added in one portion and the solution was heated to reflux for 4 h. The solution was cooled to rt and washed with sat'd aq. $NaHCO_3$ (2 x 20 mL) followed by 1N HCl (2 x 20 mL). The organic was dried ($MgSO_4$) and concentrated to afford the title compound as a clear, colorless oil (1.23 g, 98 %). ^1H NMR (DMSO-d_6) □ 7.85 (t, 3 H, J = 8 Hz), 7.73 (s, 1 H), 7.48 (quint, 2 H, J = 4 Hz), 7.38 (d, 1 H, J = 8 Hz), 7.02 (d, 2 H, J = 8 Hz), 6.66 (d, 2 H, J = 8 Hz), 4.99 (s, 2 H), 4.13 (q, 2 H, J = 7 Hz), 3.57 (q, 2 H, J = 8 Hz), 2.53 (m, 4 H), 1.82 (quint, 2 H, J = 7 Hz), 1.46 (s, 6 H), 1.13 (m, 6 H); ^{13}C NMR (DMSO-d_6) □ 174.0, 154.0, 146.7, 135.6, 135.5, 133.5, 132.9, 129.7, 128.9, 128.3, 128.2, 127.0, 126.8, 126.4, 119.5, 79.2, 61.6, 48.7, 36.4, 34.0, 27.9, 25.7, 24.8, 14.9, 14.5; IR ($CHCl_3$) 2940, 1729, 1693, 1509, 1233, 1179, 1142 cm^{-1}; Anal. Calcd. for $C_{30}H_{35}N_3O_4$: C, 71.83; H, 7.03; N, 8.38. Found: C, 71.64; H, 7.12; N, 8.19.

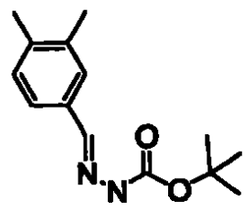
2-{4-[3-(4-Ethyl-1-(naphthalen-2-yl)methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl)-propyl]-phenoxy}-2-methylpropionic acid 2-{4-[3-(4-Ethyl-1-(naphthalen-2-yl)-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl)-propyl]-phenoxy}-2-methylpropionic acid ethyl ester (725 mg, 1.45 mmol) was dissolved in ethanol (10 mL) and 1N NaOH (4.3 mL, 4.3 mmol) was added in one portion and the solution was stirred at room temperature for 1 h. The solution was then concentrated to an oil, which was washed with t-butyl methyl ether (5 mL). The pH of the aqueous phase was adjusted to < 1 with conc. HCl, and extracted with ethyl acetate (2 x 10 mL). The combined extracts dried ($MgSO_4$), filtered and concentrated to afford the title compound as a clear yellow oil (0.570 g, 83%). ^1H NMR (DMSO-d_6) δ 12.9 (br s, 1 H), 7.86 (t, 2 H, J = 8 Hz), 7.73 (s, 1 H), 7.48 (quint, 2 H, J = 4 Hz), 7.38 (d, 1 H), 7.01 (d, 2 H, J = 7 Hz), 6.69 (d, 2 H, J = 7 Hz), 4.99 (s, 2 H), 3.57 (quint, 2 H, J = 7 Hz), 2.52 (t, 2 H, J = 8 Hz), 1.82 (quint, 2 H, J = 7 Hz), 1.45 (s, 6 H), 1.12 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 175.8, 154.1, 154.0, 146.8, 135.6, 135.2, 133.5, 132.9, 129.7, 128.9, 128.3, 128.2, 127.0, 126.8, 126.7, 126.4, 119.2, 79.0, 48.7, 36.4, 34.0, 27.9, 25.7, 24.8, 14.9; IR ($CHCl_3$) 2940, 1693, 1509, 1469, 1156 cm^{-1}; Exact Mass Calcd. for $C_{28}H_{31}N_3O_4$: 474.2393. Found: 474.2393.

Example 130



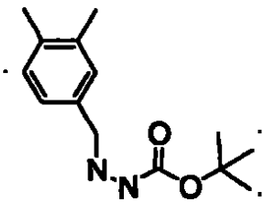
5-[3-(4-hydroxy-phenyl)-propyl]-2-(4-methyl-benzyl)-4-propyl-2,4-dihydro-[1,2,4]-triazol-3-one 1-[(4-Methoxyphenyl)butyryl]-2-(4-methylphenylmethyl)-4-propyl)semi-carbazide (0.312 g, 0.785 mmol) and excess pyridine hydrochloride were melted together with stirring at 180 °C for 1 h. After cooling to room temperature, the contents were diluted with ethyl acetate (25 mL) and 5 N HCl (25 mL). The organic layer was washed with additional 5 N HCl (25 mL) followed by sat'd aq. $NaHCO_3$ (2 x 25 mL). The organic layer was then washed with sat'd aq. NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated to afford the title compound as a yellow oil (0.201 g, 0.55 mmol, 70%). Spectral data in accord with previous example. Exact Mass Calc'd. for $C_{22}H_{28}N_3O_3$ $(M + H)^+$: 366.2182. Found: 366.2192.

Example 131

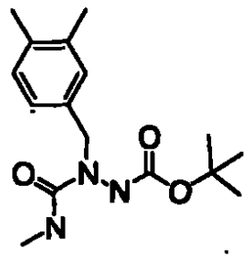


(3,4-dimethylphenyl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of *t*-butyl carbazate (5.06 g, 38.3 mmol) in ethyl acetate (15 mL) was added with stirring 3,4-dimethylbenzaldehyde (5.20 mL, 5.26 g, 39.2

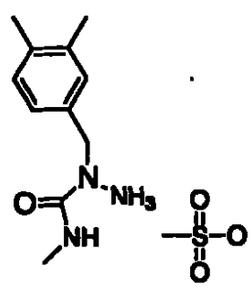
mmol). Crystallization occurred and the resulting slurry was stirred at rt for 45 min. Hexanes (70 mL) was added and the slurry was cooled to 0 °C. The slurry was stirred at 0 °C for 60 min, then filtered and rinsed with cold hexanes (20mL), and dried in vacuo at 40 °C to afford the title compound as a solid (8.76 g, 92.1%): mp 167.7 - 168.6 °C ^{1}H NMR (DMSO-d_6) δ 10.82 (s, 1H), 7.92 (s, 1 H), 7.36 (s, 1 H), 7.28 (d, 2 H, J = 3 Hz), 7.14 (d, 2 H, J = 3 Hz), 2.206 (s, 3 H), 2.20 (s, 3 H) 1.44 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 153.0, 144.1, 138.5, 137.3, 132.9, 130.5, 128.1, 124.8, 79.9, 28.8, 19.99, 19.97; IR (KBr mull) 3361, 3009, 2981, 2981, 1513, 1495 cm^{-1}. A portion was further purified by recrystallization from ethyl acetate for analysis. Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.51; H, 8.07; N, 11.22.



(3,4-dimethylbenzyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester (3,4-dimethylphenyl) methylenehydrazinecarboxilic acid, 1,1-dimethylethyl ester (7.02 g, 28.3 mmol) and 5% Pt/C (5.04g) were slurried in THF (70 mL) and hydrogenated at 50 psi at rt for 4 hr. The slurry was then filtered through celite and concentrated in vacuo at 50 °C to afford the title compound as a clear oil (6.74 g, 95.2%): ^{1}H NMR (DMSO-d_6, 20°C) δ 8.20 (s, 1H), 7.06 (s, 1 H), 7.01 (dd, 2 H, J = 8, 2 Hz), 4.56 (s, 1 H), 3.77 (s, 2 H), 2.18 (s, 6 H), 1.38 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 157.1, 136.5, 136.3, 135.2, 130.4, 129.8, 126.5, 78.9, 54.9, 28.9, 20.0, 19.7; IR ($CHCl_3$) 2982, 1712, 1453, 1369 cm^{-1}; Exact Mass Calcd. for $C_{14}H_{22}N_2O_2$: 251.1759. Found: 251.1757.

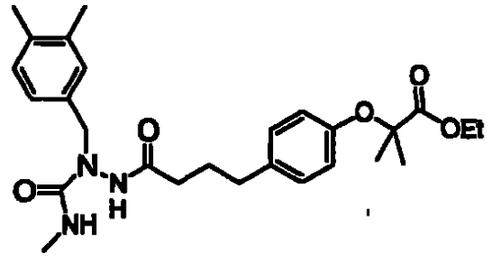


2-(Methylaminocarbonyl)-2-(3,4-dimethylphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (3,4-Dimethylphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (2.51 g, 10.0 mmol) was dissolved in isopropanol (25 mL). Methyl isocyanate (1.0 mL, 16.7 mmol) was added in one portion via syringe and the solution was allowed to stir at ambient temperature for 1 h. The solution was concentrated to afford the title compound as a white solid (3.30 g of 87% potency material by ^{1}H-NMR, 2.86g, 93%): mp 99.7 - 104.9 °C; ^{1}H NMR (DMSO-d_6, 60°C) δ 8.45 (s, 1H), 7.03 (d, 1 H, J = 8 Hz), 6.99 (s, 1 H), 6.93 (d, 1 H), 6.26 (s, 1 H), 4.45 (s, 2 H), 2.60 (d, 3 H, J = 7 Hz), 2.18 (s, 6 H), 1.35 (s, 9 H); ^{13}C NMR (DMSO-d_6, 20°C) δ 159.0, 155.0, 136.3, 135.7, 135.3, 130.3, 129.9, 126.6, 80.1, 50.8, 28.7, 27.7, 20.1, 19.7; IR ($CHCl_3$) 3466, 1681, 1528, 1247, 1155 cm^{-1}. A portion was recrystallized for elemental analysis: Anal. Calcd. for $C_{16}H_{25}N_3O_3$: C, 62.52.; H, 8.20; N, 13.67. Found: C, 62.87; H, 8.15; N, 13.59.



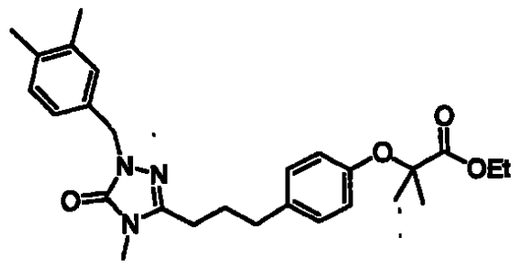
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***N*-Methyl-1-(3,4-dimethylphenylmethyl)hydrazine carboxamide methanesulfonate** 2-(Methylaminocarbonyl)-2-(3,4-dimethylphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (2.52 g, 8.20 mmol) was dissolved in dichloromethane (25 mL). Methanesulfonic acid (717 µL, 11.04 mmol) was added in one portion and the solution was allowed to stir at rt for 4 h. An additional charge of methanesulfonic acid (132 µL, 2.0 mmol) was added and the solution stirred at rt for 12 h. The resulting slurry was cooled to 0 °C, filtered, and the solids rinsed with cold dichloromethane. The solids were dried in vacuo at 40 °C overnight to afford a white solid (1.44 g). The filtrate was concentrated and purified by recrystallization (ethyl acetate) to afford an additional amount of white solid (0.73g). The two crops were combined and homogenized to afford the title compound as a white solid (2.17g, 87%): m.p. 124.3 - 125.6 °C; ^{1}H NMR (DMSO-d_6) δ 9.4 (broad s, 3 H), 7.45 (broad s, 1 H), 7.10 (d, 1 H, *J* = 8 Hz), 7.05 (s, 1 H), 7.00 (d, 1 H, *J* = 8 Hz), 4.61 (s, 2 H), 2.67 (s, 3 H), 2.36 (s, 3 H), 2.19 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 158.2, 137.0, 136.7, 132.8, 130.4, 129.9, 126.2, 52.7, 40.4, 27.7, 20.2, 19.7; IR ($CHCl_3$) 3004, 2946, 1693, 1505, 1171 cm^{-1}; Anal. Calcd. for $C_{12}H_{21}N_3O_5$: C, 47.51.; H, 6.98; N, 13.85. Found: C, 47.30; H, 7.01; N, 13.51.

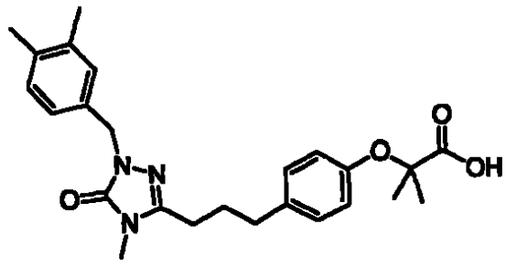


1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3,4-dimethylphenyl-methyl)-4-methylsemicarbazide 4-[4-(1-Ethoxycarbonyl-1-methyl-ethoxy)-phenyl] butyric acid (1.46 g, 4.96 mmol) was dissolved in ethyl acetate (10 mL).

Oxalyl chloride (474 µL, 5.46 mmol) was added to this solution dropwise in the presence of a catalytic amount of *N,N*-dimethylformamide (30.6 µL, 0.39 mmol). Completion of acid chloride formation was verified by HPLC. This solution was then added dropwise to a suspension of *N*-Methyl-1-(3,4-dimethylphenylmethyl)hydrazine carboxamide methanesulfonate (1.50 g, 4.95 mmol) and pyridine (1.00 mL, 12.9 mmol) in ethyl acetate (15 mL) at 0 °C. After stirring at 0 °C for 6 h, the solution was warmed to rt and washed with 1N HCl (2 x 20 mL), 5% aq. $NaHCO_3$ (2 x 20 mL) and sat'd aq. NaCl. The organic layer was dried ($MgSO_4$), filtered and concentrated to a yellow oil. The oil was purified by column chromatography (SiO_2, 9:1 ethyl acetate:hexanes), to afford the title compound as a clear oil (1.48 g, 62%): ^1H NMR (DMSO-d_6, 60°C) δ 9.42 (s, 1 H), 6.97 (m, 5 H), 6.71 (d, 2 H, *J* = 8 Hz), 6.23 (s, 1 H), 4.46 (s, 2 H), 4.15 (q, *J* = 7 Hz), 2.59 (s, 3 H), 2.43 (t, 2 H, *J* = 8 Hz), 2.15 (s, 6 H), 2.06 (t, 2 H, *J* = 8 Hz), 1.70 (quint, 2 H, *J* = 7 Hz), 1.48 (s, 6 H), 1.17 (t, 3 H, *J* = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 172.0, 158.7, 153.8, 136.4, 136.0, 135.9, 135.4, 130.2, 129.9, 129.7, 126.5, 119.5, 79.2, 61.6, 50.6, 34.4, 33.5, 27.6, 27.2, 25.7, 20.0, 19.7, 14.6; IR ($CHCl_3$) 3009, 1669, 1509, 1142 cm^{-1}; Exact Mass Calcd. for $C_{27}H_{38}N_3O_5$: 484.2811. Found: 484.2822.



2-(4-{3-[1-(3,4-Dimethylphenylmethyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester 1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(3,4-dimethylphenylmethyl)-4-methylsemicarbazide (1.20 g, 2.47 mmol) was dissolved in ethyl acetate (10 mL). Camphorsulfonic acid (0.64 g, 2.72 mmol) was added in one portion and the solution was heated to reflux for 1 h. The solution was cooled to rt and washed with sat'd aq. $NaHCO_3$ (2 x 8 mL) followed by 1N HCl (2 x 8 mL). The organic phase was dried ($MgSO_4$) and concentrated to afford the title compound as a clear, colorless oil (1.08 g, 94%). ^1H NMR (DMSO-d_6) δ 7.04 (m, 3 H), 7.03 (s, 1 H), 6.93 (d, 1 H, J = 2 Hz), 6.68 (d, 2 H, J = 7 Hz), 4.72 (s, 2 H), 4.13 (q, 2 H, J = 7 Hz), 3.08 (s, 3 H), 2.53 (t, 2 H, J = 8 Hz), 2.47 (t, 2 H, J = 8 Hz), 1.80 (quint, 2 H, J = 7 Hz), 1.47 (s, 6 H), 1.14 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 154.1, 147.1, 136.8, 135.9, 135.6, 135.3, 130.1, 129.8, 129.4, 125.7, 119.5, 79.2, 61.6, 48.4, 34.1, 27.7, 27.6, 25.7, 25.0, 20.0, 19.7, 14.6; IR ($CHCl_3$) 2941, 1729, 1509, 1238, 1143 cm^{-1}; Anal. Calcd. for $C_{27}H_{35}N_3O_4$: C, 69.65; H, 7.58; N, 9.03. Found: C, 69.25; H, 7.47; N, 8.88.

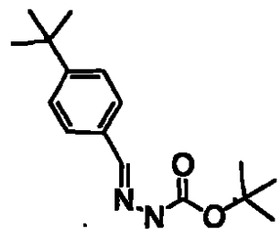


2-(4-{3-[1-(3,4-Dimethylphenylmethyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid

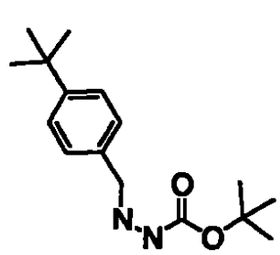
2-(4-{3-[1-(3,4-Dimethylphenylmethyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methylpropionic acid ethyl ester (916 mg, 1.97 mmol) was dissolved in ethanol (10 mL) and 2N NaOH (3.0 mL, 6.0 mmol) was added in one portion. The solution was stirred at room temperature for one hour, then concentrated to a hazy colorless oil. This oil was partitioned between 1N HCl (10 mL) and ethyl acetate (10 mL). The aqueous layer was then reextracted with ethyl acetate (10 mL). Solids precipitated from this solution on stirring. The slurry was cooled to 0°C, filtered and dried in vacuo at 50 °C overnight to afford the title compound as a white solid (695 mg, 80%): mp 145.8 - 149.6 °C; ^{1}H-NMR (DMSO-d_6) δ 12.98 (s, 1H), 7.05 (dd, 3 H, J = 8.5, 3.0 Hz), 7.00 (s, 1 H), 6.93 (d, 1 H, J = 7.5 Hz), 6.73 (d, 2 H, J = 8.5 Hz), 4.73 (s, 2 H), 2.52 (t, 2 H, J = 7.5 Hz), 2.47 (t, 2 H, J = 7.5 Hz), 2.14 (s, 6 H), 1.80 (quint, 2 H, J = 7.5 Hz), 1.46 (s, 6 H); ^{13}C NMR (DMSO-d_6, 20°C) δ 175.8, 154.1, 154.0, 147.1, 136.8, 135.9, 135.3, 135.2, 130.1, 129.7, 129.4, 125.7, 119.2, 78.9, 48.4, 34.1, 27.7, 27.6, 25.7, 25.1, 20.0, 19.7; IR ($CHCl_3$) 2936, 2490, 1730, 1658, 1510, 1148 cm^{-1}; Anal. Calcd. for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.60. Found: C, 68.23; H, 7.01; N, 9.44.

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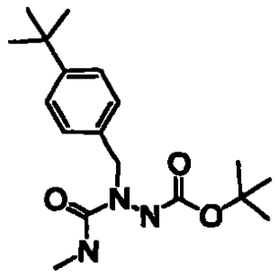
Example 132



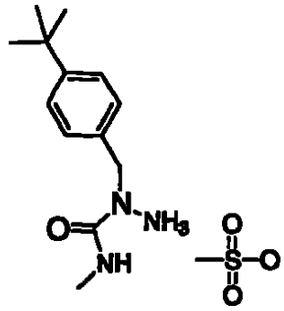
(4-t-Butyl)methylenehydrazinecarboxylic acid, 1,1-dimethylethyl ester To a solution of t-butyl carbazate (5.02 g, 37.9 mmol) in ethyl acetate (15 mL) was added with stirring 4-t-butylbenzaldehyde (6.40 mL, 6.21 g, 37.9 mmol). Crystallization occurred and the resulting slurry was stirred at rt for 15 min. Hexanes (30 mL) was added and the slurry was cooled to 0 °C. The slurry was stirred at 0 °C for 30 min, filtered and rinsed with cold hexanes (20mL), then dried in vacuo at 40 °C to afford the title compound as a solid (9.27 g, 88.3%): mp 173.7 - 175.7 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 10.85 (s, 1 H), 7.96 (s, 1 H), 7.63 (s, 1 H), 7.50 (d, 2 H, J = 3 Hz), 7.40 (d, 2 H, J = 3 Hz), 1.45 (s, 9 H), 1.25 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 152.7, 143.8, 132.6, 127.0, 126.2, 80.0, 39.7, 35.2, 31.7, 28.8; IR (KBr mull) 3361, 3010, 2968, 1514, 1500 cm^{-1}; A portion was recrystallized (ethyl acetate) for analysis. Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.13. Found: C, 69.20; H, 8.85; N, 10.09.



(4-t-Butylbenzyl)hydrazinecarboxylic acid, 1,1-dimethylethyl ester (4-*t*-Butylphenyl) methylenehydrazinecarboxilic acid, 1,1-dimethylethyl ester (7.05 g, 25.5 mmol) and 5 % Pt/C (5.01g) were slurried in THF (70 mL) and hydrogenated at 50 psig at rt for 3 hr. The slurry was then filtered through celite to remove the catalyst and concentrated in vacuo at 50 °C to afford the title compound as a clear oil (6.79 g, 95.6%): ^{1}H NMR (DMSO-d_6, 60°C) δ 7.30 (m, 2 H), 7.23 (m, 2 H), 4.44 (s, 1 H), 3.82 (s, 1 H), 1.38 (s, 9 H), 1.27 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 157.1, 149.8, 136.3, 128.9, 125.5, 78.9, 54.7, 34.8, 31.9, 28.9; IR ($CHCl_3$) 3008, 2967, 2869, 1712 cm^{-1}; Anal. Calcd. for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.83; H, 9.21; N, 9.98.



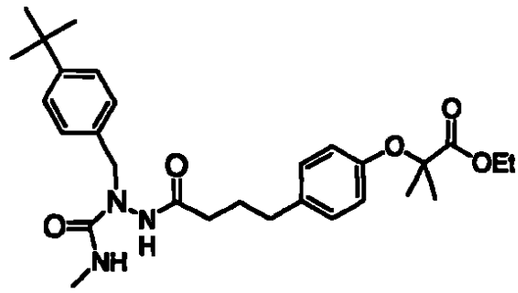
2-(Methylaminocarbonyl)-2-(4-t-butylphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (4-*t*-Butylbenzyl) hydrazinecarboxilic acid, 1,1-dimethylethyl ester (2.54 g, 9.12 mmol) was dissolved in isopropanol (25 mL). Methyl isocyanate (0.83 g, 14.11 mmol) was added in one portion via syringe and the solution was allowed to stir at rt for 1 h. The solution was concentrated to afford the title compound as a waxy white solid (3.22 g of 89% potency material by ^{1}H-NMR, 2.87g, 93.7%): mp 124.1 - 128.6 °C; ^{1}H NMR (DMSO-d_6, 60°C) δ 8.54 (br s, 1 H), 7.30 (d, 2 H, *J* = 2 Hz), 7.16 (d, 2 H, *J* = 2 Hz), 6.28 (s, 1 H), 4.48 (s, 2 H), 2.59 (d, 3 H,



J = 2 Hz), 1.31 (s, 9 H), 1.26 (s, 9 H); ^{13}C NMR (DMSO-d_6, 60°C) δ 159.1, 155.0, 149.9, 135.5, 128.9, 125.5, 80.1, 50.9, 34.8, 31.9, 28.7, 27.7; IR ($CHCl_3$) 3005, 2968, 2938, 1666 cm^{-1}. A portion of this material was recrystallized (toluene) for analysis. Anal. Calcd. for $C_{18}H_{29}N_3O_3$: C, 64.45; H, 8.71; N, 12.53. Found: C, 63.91; H, 8.51; N, 12.44.

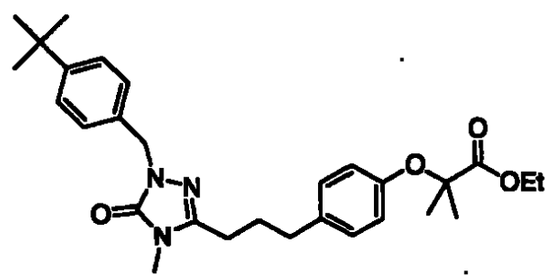
***N*-Methyl-1-(4-t-butylphenylmethyl)hydrazine carboxamide methanesulfonate** 3-(Methylaminocarbonyl)-2-(4-t-butylphenylmethyl)hydrazine carboxylic acid, 1,1-dimethylethyl ester (2.56 g, 7.90 mmol) was dissolved in dichloromethane (25 mL). Methanesulfonic acid (641 µL, 9.88 mmol) was added in one portion and the solution was stirred at rt overnight. The resulting slurry was cooled to 0 °C, filtered, and the solids rinsed with cold dichloromethane. The solids were dried in vacuo at 40 °C to afford the title compound as a white solid (2.10 g, 80.1%): mp 96.8 - 97.4 °C; ^{1}H NMR (DMSO-d_6) δ 9.7 (br s, 3 H), 7.5 (br s, 1 H), 7.39 (d, 2 H, *J* = 3 Hz), 7.20 (d, 2 H, *J* = 3 Hz), 4.65 (s, 2 H), 2.67 (s, 3 H), 2.35 (s, 3 H), 1.26 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 158.2, 151.1, 132.7, 128.4, 126.1, 52.6, 40.4, 34.9, 31.8, 27.7; IR (KBr mull) 2967, 1690, 1550, 1188, 1076 cm^{-1}; Exact Mass Calcd. for $C_{13}H_{22}N_3O$: 236.1763. Found: 236.1758.

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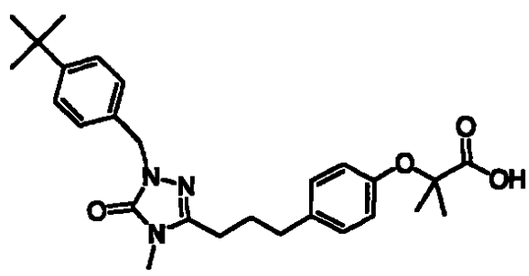
1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(4-*t*-butylphenyl-methyl)-4-methylsemicarbazide 4-[4-(1-Ethoxycarbonyl-1-methyl-ethoxy)-phenyl] butyric acid (0.89 g, 3.02 mmol) was dissolved in ethyl acetate (10 mL). Oxalyl chloride (316 µL, 3.62 mmol) was added to this solution dropwise in the presence of a catalytic amount of *N,N*-dimethylformamide (17 µL, 0.24 mmol). Completion of acid chloride formation was verified by HPLC. The solution was then concentrated to remove excess oxalyl chloride and then redissolved in ethyl acetate (7 mL). This solution was then added dropwise to a suspension of *N*-Methyl-1-(4-t-butylphenylmethyl)hydrazine carboxamide methanesulfonate (1.02 g, 3.07 mmol) and pyridine (256 µL, 6.14 mmol) in ethyl acetate (10 mL) at 0 °C. After stirring at 0 °C for 3 h, an additional charge of pyridine (256 µL, 6.14 mmol) was added and the solution was stirred at 0°C for 1 h. The solution was warmed to rt and washed with 1N HCl (2 x 10 mL) and then with 5% aq. $NaHCO_3$ (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to an orange oil. Column chromatography (SiO_2, ethyl acetate) afforded the title compound as a clear oil (1.06 g, 68%): ^1H NMR (DMSO-d_6, 60°C) δ 9.50 (s, 1 H), 7.29 (d, 2 H, *J* = 8 Hz), 7.16 (d, 2 H, *J* = 8 Hz), 7.01 (d, 2 H, *J* = 8 Hz), 6.71 (d, 2

H, J = 8 Hz), 6.27 (br s, 1 H), 4.52 (br s, 2 H), 4.15 (q, J = 7 Hz), 2.58 (d, 3 H, J = 4 Hz), 2.44 (t, 2 H, J = 7 Hz), 2.07 (t, 2 H, J = 7 Hz), 1.72 (quint, 2 H, J = 7 Hz), 1.48 (s, 6 H), 1.25 (s, 9 H), (1.17 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 172.0, 158.7, 153.8, 149.9, 135.9, 129.7, 128.7, 125.6, 119.5, 79.2, 61.6, 50.8, 34.8, 34.4, 33.4, 31.8, 27.7, 27.1, 25.7, 14.6.; IR ($CHCl_3$) 3009, 2966, 1671, 1509, 1211 cm^{-1}; Anal. Calcd. for $C_{29}H_{41}N_3O_5$: C, 68.08; H, 8.08; N, 8.21. Found: C, 67.70; H, 7.86; N, 8.11.



2-(4-{3-[1-(4-t-Butylphenylmethyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester 1-[4-[4-(1-Ethoxycarbonyl-1-methylethoxy)phenyl]butyryl]-2-(4-t-butyl phenylmethyl)-4-methylsemicarbazide (0.93 g, 1.82 mmol) was dissolved in ethyl acetate (10 mL). Camphorsulfonic acid (0.46 g, 1.98 mmol) was added in one portion and the solution was heated to reflux and stirred for 1 h. The solution was cooled to rt and washed with sat'd aq. $NaHCO_3$ (2 x 8 mL), 1N HCl (2 x 8 mL) and sat'd aq. NaCl (8 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated to afford the title compound as clear, colorless oil (0.84 g, 93.6%): ^{1}H NMR (DMSO-d_6) δ 7.30 (d, 2 H, J = 8 Hz), 7.15 (d, 2 H, J = 8 Hz), 7.05 (d, 2 H, J = 8 Hz), 6.68 (d, 2 H, J = 8 Hz), 4.77 (s, 2 H), 4.13 (q, 2 H, J = 7 Hz), 3.69 (s, 3 H), 2.53 (t, 2 H, J = 8 Hz), 2.47 (t, 2 H, J = 8 Hz), 1.81 (quint, 2 H, J =

7 Hz), 1.47 (s, 6 H), 1.22 (s, 9 H), 1.14 (t, 3 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 174.0, 154.1, 153.8, 150.4, 147.1, 135.6, 135.0, 129.8, 128.0, 125.9, 119.5, 79.2, 61.6, 48.3, 34.9, 34.1, 31.8, 27.7, 27.6, 25.7, 25.1, 14.6; IR ($CHCl_3$) 2967, 1695, 1509, 1475, 1232 cm^{-1}; Anal. Calcd. for $C_{29}H_{39}N_3O_4$: C, 70.56.; H, 7.96; N, 8.51. Found: C, 70.28; H, 7.85; N, 8.43.

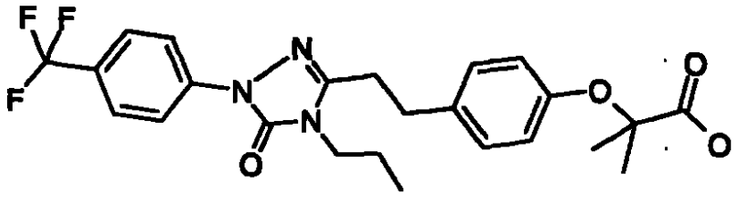


2-(4-{3-[1-(4-t-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid 2-(4-{3-[1-(4-*t*-Butylbenzyl)-4-methyl-5-oxo-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid ethyl ester (0.69 g, 1.39 mmol) was dissolved in ethanol (4 mL), 1 N NaOH (4.75 mL) was added in one portion and the solution was stirred at ambient temperature overnight. The solution was concentrated to a hazy, colorless oil. This oil was partitioned between 1N HCl (5 mL) and ethyl acetate (5 mL). The aqueous layer was then reextracted with ethyl acetate (5 mL) and the organic layers combined, dried ($MgSO_4$), filtered and concentrated in vacuo at 50 °C to afford the title compound as a clear oil (0.56 g, 86 %): ^{1}H NMR (DMSO-d_6) δ 12.9 (br s, 1 H), 7.31 (d, 2 H, J = 6 Hz), 7.14 (d, 2 H, J = 8 Hz), 7.05 (d, 2 H, J = 7 Hz), 6.73 (d, 2 H, J = 2 Hz), 4.77 (s, 2 H), 3.09 (s, 3 H), 2.53

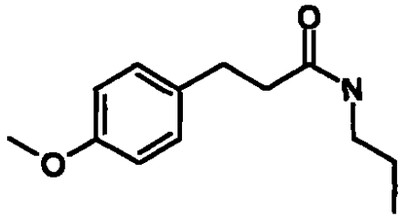
(t, 2 H, J = 8 Hz), 2.49 (t, 2 H, J = 8 Hz), 1.81 (quint, 2 H, J = 7 Hz), 1.46 (s, 6 H), 1.22 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 175.8, 154.14, 154.10, 150.5, 147.2, 135.2, 135.0, 129.7, 128.0, 125.9, 119.2, 79.0, 48.3, 34.9, 34.1, 31.8, 27.7, 27.6, 25.7, 25.1; IR ($CHCl_3$) 2966, 1695, 1509, 1235 cm^{-1}; Anal. Calcd. for $C_{27}H35N_3O4$: C, 69.65; H, 7.58; N, 9.02. Found: C, 69.30; H, 7.30; N, 8.96.

Example 133

2-Methyl-2-(4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-propionic acid



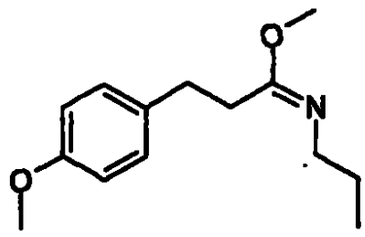
Step A: Preparation of 3-(4-Methoxy-phenyl)-N-propyl-propionamide



To a solution of 3-(4-methoxyphenyl)propionic acid (8.0 g, 44.4 mmol), propylamine hydrochloride (4.24 g, 44.4 mmol), 4-dimethylaminopyridine (0.65 g, 5.33 mmol) and triethylamine (6.9 mL, 48.96 mmol) in methylene chloride (70 mL) was added 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochl ride (10.21 g, 53.28 mmol). The

reaction mixture was stirred overnight at ambient temperature followed by dilution with methylene chloride. The mixture was washed with 1N hydrochloric acid, 2N sodium hydroxide, water, brine and dried. Evaporation of the solvent yielded the pure product (10.36 g; 95.4%): ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.76 (brs, 1 H), 7.10 (d, 2 H, J = 8.8 Hz), 6.79 (d, 2 H, J = 8.0 Hz), 3.68 (s, 3 H), 2.95 (q, 2 H, J = 5.6 Hz). 2.71 (t, 2 H, J = 7.6 Hz), 2.28 (t, 2H, J = 7.2 Hz), 1.34 (m, 2 H), 0.77 (t, 3 H, J = 7.2 Hz); ESMS *m/z* (relative intensity) 222.2 ($M + H^+$, 100).

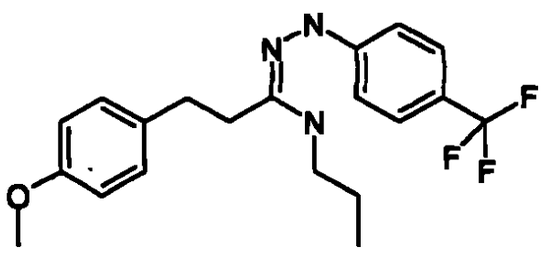
Step B: Preparation of 3-(4-Methoxyphenyl)-N-propyl-propionimidic acid methyl ester



To a solution of 3-(4-Methoxy-phenyl)-N-propyl-propionamide (3.0 g, 13.57 mmol in methylene chloride (15 mL) was added trimethyloxonium tetrafluoroborate (2.0 g, 13.57 mmol) and the reaction mixture stirred overnight at ambient temperature. HPLC and TLC analysis indicated the presence of starting material. More trimethyloxonium tetrafluoroborate (0.25 g) was added and the reaction mixture was allowed to stir for 2.5 h and quenched with cold saturated aqueous potassium carbonate solution. The mixtur was extracted ethyl acetate. The combined organic extracts were washed with water, brine, dried and evaporated t

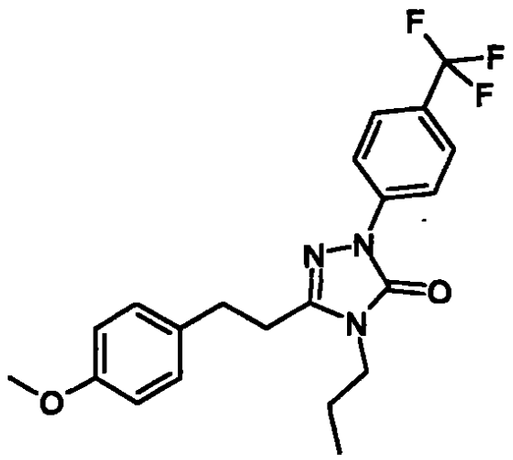
dryness to afford the pure product (3.0 g, 93.8%): ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.10 (d, 2 H), 6.80 (d, 2 H, J = 8.4 Hz), 3.78 (s, 3 H), 3.61 (s, 3 H), 3.08 (t, 2 H, J = 7.6 Hz), 2.70 (m, 2 H), 2.48 (m, 2 H), 1.45 (m, 2 H), 0.86 (t, 3 H, J = 7.6 Hz); ESMS *m/z* (relative intensity) 236.1 (M + H^+, 100).

Step C: Preparation of



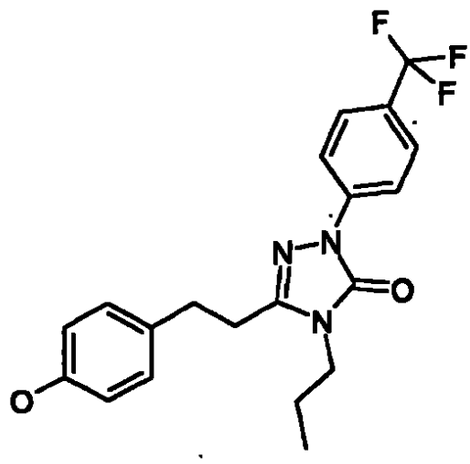
To a solution of 3-(4-Methoxyphenyl)-N-propyl-propionimidic acid methyl ester (3.0 g, 12.77 mmol) in methylene chloride (10 mL) was added 4-trifluoromethylphenylhydrazine (2.25 g, 12.77 mmol) in methylene chloride (10 mL) and the reaction mixture is stirred overnight at 45°C. HPLC and TLC analysis revealed the presence of considerable starting material. The reaction mixture was refluxed overnight with no appreciable change. The reaction solvent was evaporated and replaced with 1,2-dichloroethane (20 mL). The reaction mixture was stirred at 84°C over 72 hr. The reaction mixture was quenched with water, extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried and evaporated to dryness to afford the crude product (5.3 g) which was carried on to the next step without further purification: ESMS *m/z* (relative intensity) 378.0 (M - H^+, 50).

Step D: Preparation of 5-[2-(4-Methoxyphenyl)ethyl]-4-propyl-2-(4-trifluoromethylphenyl)-2,4-dihydro-[1,2,4]triazol-3-one



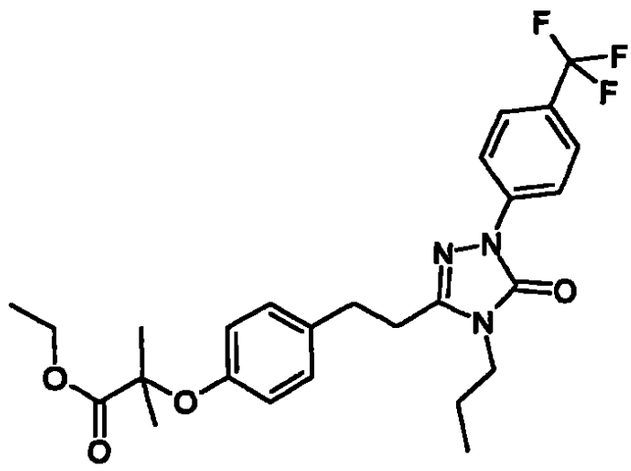
To a solution of the crude hydrazine intermediate from step C (5.3 g) in anhydrous THF (25 mL) was added carbonyldiimidazole (2.5 g, 15.38 mmol) and the reaction mixture is stirred overnight at ambient temperature. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (gradient of ethyl acetate in hexanes) yielding the title compound (1.52 g,). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.18 (d, 2 H, J = 8.0 Hz), 7.65 (d, 2H, J = 8.0 Hz), 7.18 (d, 2 H, J = 7.8 Hz), 7.83 (d, 2 H, 8.0 Hz), 3.80 (s, 3 H), 3.55 (t, 2 H, J = 8.0 Hz), 3.08 (t, 2 H, J = 8.0 Hz), 2.82 (m, 2 H), 1.65 (m, 2 H), 0.96 (s, 3 H); ESMS *m/z* (relative intensity) 406.2 ($M + H^+$, 100).

Step E: Preparation of 5-[2-(4-Hydroxyphenyl)ethyl]-4-propyl-2-(4-trifluoromethylphenyl)-2,4-dihydro-[1,2,4]triazol-3-one



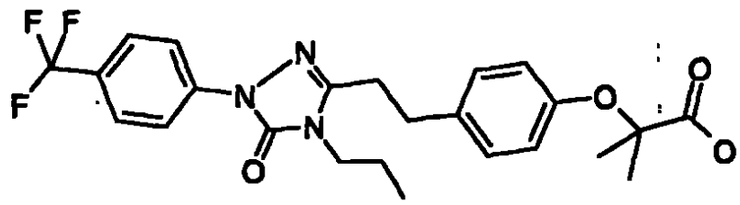
To a solution of 5-[2-(4-Methoxyphenyl)ethyl]-4-propyl-2-(4-trifluoromethylphenyl)-2,4-dihydro-[1,2,4]triazol-3-one (1.52 g, 3.75 mmol) in methylene chloride (36 mL) at -78°C was added boron tribromide (0.75 mL) and allowed to warm to ambient temperature. After 2 h, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried and evaporated to dryness to yield the product (1.35 g, 92.5%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.13 (d, 2 H, J = 8.8 Hz), 7.81 (d, 2H, J = 8.8 Hz), 7.09 (d, 2 H, J = 8.4 Hz), 6.66 (m, 2 H), 3.56 (t, 2 H), 2.89 (m, 4 H), 1.58 (m, 2 H), 0.84 (m, 3 H); ESMS *m/z* (relative intensity) 392.2 ($M + H^+$, 100), 390.1 ($M - H^+$, 100).

Step F: Preparation of 2-Methyl-2-(4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-propionic acid ethyl ester



To a mixture of 5-[2-(4-Hydroxyphenyl)ethyl]-4-propyl-2-(4-trifluoromethylphenyl)-2,4-dihydro-[1,2,4]triazol-3-one (0.10 g, 0.26 mmol) and cesium carbonate (0.16 g, 0.49 mmol) in anhydrous DMF (2.5 mL) was added ethyl 2-bromoisobutyrate (81.1 mg, 60.6 □L, 0.42 mmol). The reaction mixture was heated to 75°C overnight. More ethyl 2-bromoisobutyrate (30.3 □L) was added and the mixture was stirred at 110°C overnight and ambient temperature over the weekend. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with 5% aqueous lithium chloride solution, water, brine, dried and evaporated. Chromatotron chromatography (gradient of ethyl acetate in hexanes) gave the pure compound (94 mg, 70.7 %): ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.14 (m, 2 H), 7.65 (m, 2 H,), 7.10 (m, 2 H), 6.80 (m, 2 H), 4.23 (m, 2 H), 3.53 (m, 2 H), 3.05 (m, 2 H), 2.83 (m, 2 H), 1.70 (m, 2 H), 1.57 (s, 6 H), 1.26 (m, 6 H); ESMS *m/z* (relative intensity) 506.1 ($M + H^+$, 100).

Step G: 2-Methyl-2-(4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-propionic acid

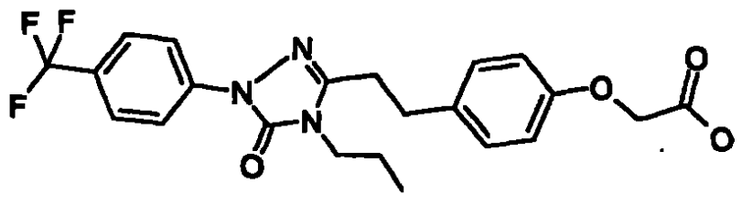


2-Methyl-2-(4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-propionic acid ethyl ester (94 mg, 0.19 mmol) and a 2N solution of sodium hydroxide (2.3 mL) in ethanol (5 mL) was heated to 80°C for 35 min. The solvent was evaporated, water added and the solution made acidic with concentrated hydrochloric acid (pH 0-1), extracted with ether. The combined organic extracts were washed with water, brine, dried and evaporated to dryness to afford the pure compound (82mg, 92.3%): ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.06 (d, 2 H, J = 8.3 Hz), 7.59 (d, 2 H, J = 8.3 Hz), 7.09 (d, 2 H, 6.4 Hz), 6.83 (d, 2 H, J = 8.3 Hz), 3.45 (t, 2 H, J = 7.4 Hz), 3.02 (d, 2 H, J = 7.3 Hz), 2.79 (m, 2 H), 1.60 (m, 2 H), 1.52 (s, 6 H), 0.87 (t, 3 H, J = 7.8 Hz); ESMS *m/z* (relative intensity) 476.1 ($M - H^+$, 50).

The following compounds were made in substantially similar method:

Example 134

(4-{2-[5-Oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-acetic acid

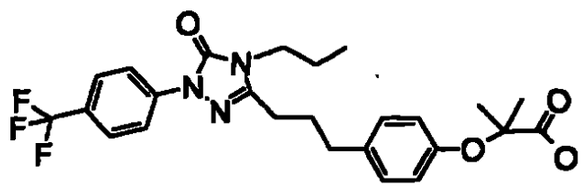


^{1}HNMR (400 MHz, $CDCl_3$) δ 8.08 (d, 2 H, J = 8.3 Hz), 7.60 (d, 2 H, J = 8.3 Hz), 7.12 (d, 2 H, J = 8.8 Hz), 6.82 (d, 2 H, 8.8 Hz), 4.60 (s, 2 H) 3.48 (t, 2 H, J = 7.4 Hz), 3.03 (d, 2

H, J = 7.4 Hz), 2.80 (t, 2 H, J = 7.4 Hz), 1.60 (m, 2 H), 0.88 (t, 3 H, J = 7.3 Hz); ESMS *m/z* (relative intensity) 450.2 ($M + H^+$, 80).

Example 135

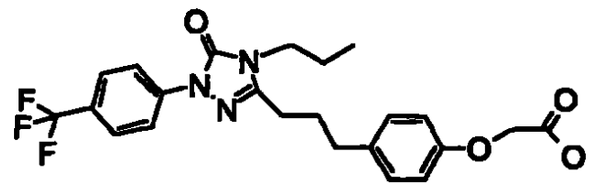
2-Methyl-2-(4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid



^{1}HNMR (400 MHz, $CDCl_3$) δ 8.12 (d, 2 H, J = 8.8 Hz), 7.80 (d, 2 H, J = 8.81 Hz), 7.12 (d, 2 H, J = 8.31 Hz), 6.74 (d, 2 H, 8.8 Hz), 3.56 (m, 2 H), 2.64 (m, 4 H), 1.96 (m, 2 H), 1.60 (m, 2H), 1.45 (s, 6 H), 0.85 (t, 3 H, J = 7.33 Hz); ESMS *m/z* 492.15 ($M + H^+$).

Example 136

(4-{2-[5-Oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-acetic acid

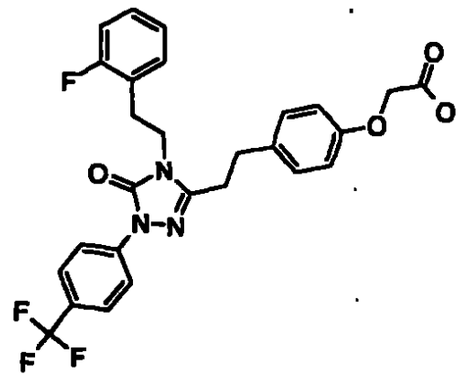


^{1}HNMR (400 MHz, $CDCl_3$) δ 8.12 (d, 2 H, J = 8.8 Hz), 7.80 (d, 2 H, J = 8.8 Hz), 7.14 (d, 2 H, J = 8.31 Hz), 6.82 (d, 2 H, 8.32 Hz), 4.60 (s, 2 H), 3.56 (t, 2 H, J = 7.33 Hz), 2.64 (m, 4 H), 1.96 (m, 2 H), 1.60 (m, 2 H), 0.85 (t, 3 H, J = 7.34 Hz); ESMS m/z 464.14 ($M + H^+$).

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Example 137

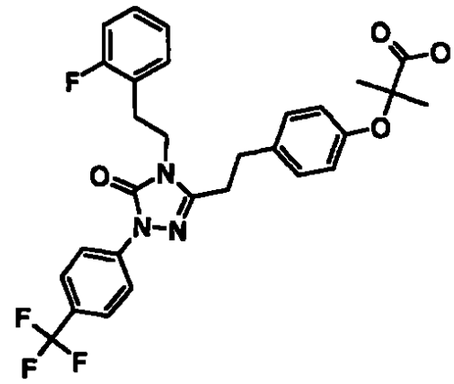
(4-{2-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-acetic acid



^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.48 - 2.52 (m, 2H), 2.75 - 2.79 (m, 2H), 2.96 (m, 2H), 3.85 (m, 2H), 4.44 (s, 2H), 6.78 (d, *J* = 7.82 Hz, 2H), 7.06 - 7.14 (m, 4H), 7.24 - 7.28 (m, 2H), 7.80 (d, *J* = 8.32 Hz, 2H), 8.10 (d, *J* = 8.32 Hz, 2H); MS (ES, m/z):$C_{27}H_{23}F_4N_3O_4$: 529.99(M^++1), 528.01(M^+-1).

Example 138

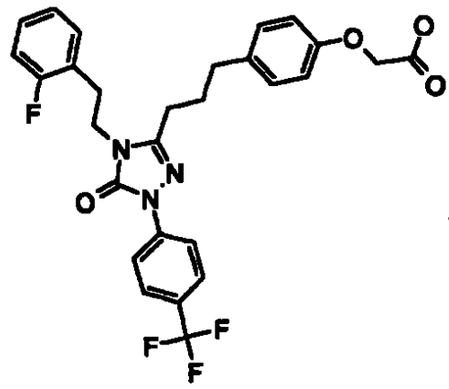
2-(4-{2-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-2-methyl-propionic acid



^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.54 (s, 6H), 2.62 (t, J = 7.33 Hz, 2H), 2.87 (t, J = 7.34 Hz, 2H), 3.05 (m, 2H), 3.93 (m, 2H), 6.82 (d, J = 8.32 Hz, 2H), 7.15 - 7.23 (m, 4H), 7.33 - 7.37 (m, 2H), 7.89 (d, J = 8.32 Hz, 2H), 8.18 (d, J = 8.31 Hz, 2H); MS (ES, m/z):$C_{29}H_{27}F_4N_3O_4$: 558.05(M^++1), 556.07(M^+-1).

Example 139

(4-{3-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-acetic acid

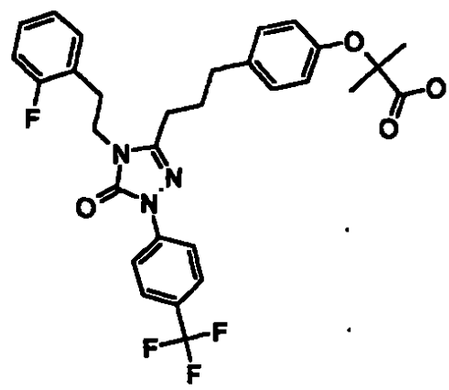


^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.76 - 1.80 (m, 2H), 2.23 (t, J = 7.82 Hz, 2H), 2.51 (t, J = 7.34 Hz, 2H), 2.97 (t, J = 6.85

Hz, 2H), 3.83 (t, J = 6.85 Hz, 2H), 4.61 (s, 2H), 6.81 (d, J = 8.80 Hz, 2H), 7.07 - 7.13 (m, 4H), 7.22 - 7.26 (m, 2H), 7.80 (d, J = 8.80 Hz, 2H), 8.10 (d, J = 8.82 Hz, 2H); MS (ES, m/z):$C_{28}H_{25}F_4N_3O_4$: 544.24(M^++1), 542.21(M^+-1).

Example 140

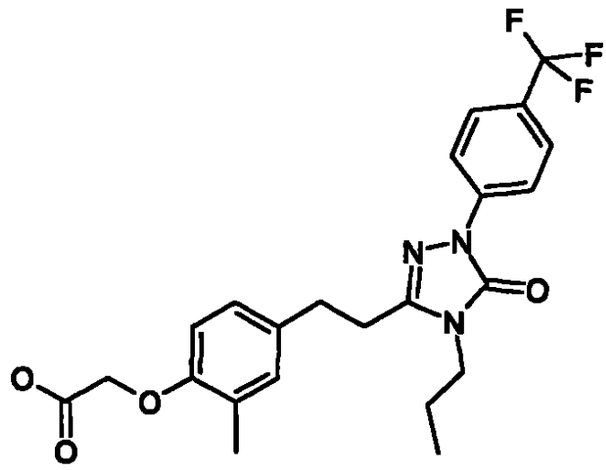
2-(4-{3-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-2-methyl-propionic acid



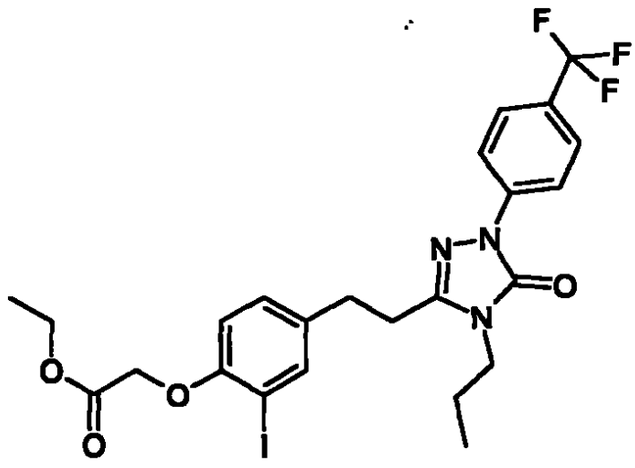
^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.46 (s, 6H), 1.78 (m, 2H), 2.24(t, J = 7.83 Hz, 2H), 2.51 (t, J = 7.82 Hz, 2H), 2.97 (t, J = 6.36 Hz, 2H), 3.83 (t, J = 6.80 Hz, 2H), 6.74 (d, J = 8.32 Hz, 2H), 7.05 - 7.11 (m, 4H), 7.24 (m, 2H), 7.79 (d, J = 8.80 Hz, 2H), 8.10 (d, J = 8.32 Hz, 2H); MS (ES, m/z):$C_{30}H_{29}F_4N_3O_4$: 572.20(M^++1), 570.30(M^+-1).

Example 141

2-methyl-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)acetic acid



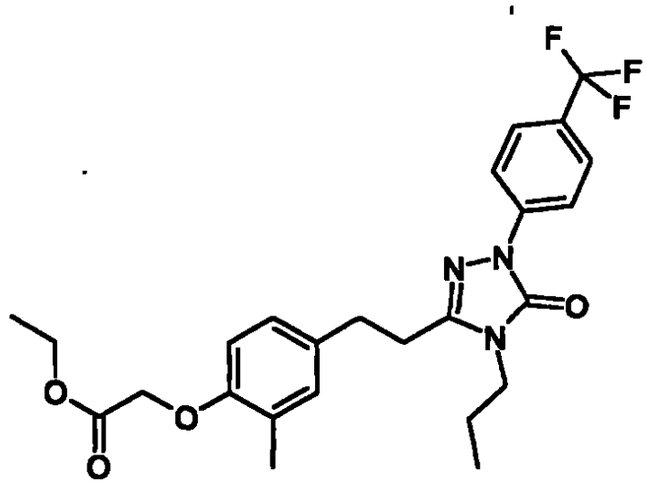
Step A: Preparation of (2-Iodo-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-acetic acid ethyl ester



A mixture of (4-{2-[5-Oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)acetic acid ethyl ester (180 mg, 0.38 mmol), iodine (105 mg, 0.42 mmol), silver sulfate (131 mg, 0.42 mmol) and

ethanol were stirred at room temperature. After 3.5 h, more iodine (86 mg) and
silver sulfate (106 mg) were added and stirred for another 0.5 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried and evaporated to dryness to afford the product (217 mg, 95%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.15 (d, 2 H, J = 8.4 Hz), 7.73 (s, 1 H), 7.67 (d, 2 H, J = 8.4 Hz), 7.18 (m, 1 H), 6.67 (d, 1H, J = 8.0 Hz), 4.66 (s, 2 H), 4.26 (q, 2 H, J = 7.6 Hz), 3.68 (t, 2 H, J = 7.3 Hz), 3.05 (t, 2 H, J = 7.4 Hz), 2.82 (t, 2H, J = 7.3 Hz), 1.7 (m, 2H), 1.29 (t, 3 H, J = 7.6 Hz), 0.96 (t, 3 H, J = 7.6 Hz); ESMS *m/z* (relative intensity) 604.2 (M + H^+, 100).

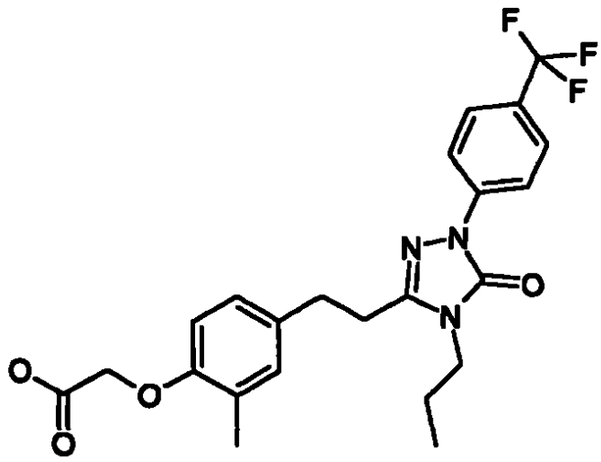
Step B: Preparation of 2-methyl-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)acetic acid ethyl ester



A mixture of 2-iodo-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)acetic acid (182 mg, 0.3 mmol), methylboronic

acid (53.9 mg, 0.9 mmol) and cesium fluoride (136.7 mg, 0.9 mmol) in dioxane (3 mL) was degassed and filled with nitrogen for three times, then [1,1'bis(diephenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1:1) (36 mg, 0.04 mmol) was added and the reaction mixture was heated to 80°C. After 4h, reaction mixture was filtered through celite and evaporated. Flash chromatography on silica gel(gradient of ethyl acetate in hexanes) yielded the pure compound (73 mg, 49.3%): ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.16 (d, 2 H, J = 8.4 Hz), 7.66 (d, 2 H, J = 8.8 Hz), 7.05 (s, 1 H), 7.00 (m, 1 H), 6.64 (d, 1 H, J = 8.0 Hz), 4.62 (s, 2 H), 4.25 (m, 2 H), 3.56 (t, 2 H, J = 8.0 Hz), 3.02 (t, 2 H, J = 8.4 Hz), 2.83 (t, 2H, J = 8.4 Hz), 2.29 (s, 3 H), 1.7 (m, 2H), 1.29 (t, 3 H, J = 6.8 Hz), 0.95 (t, 3 H, J = 7.2 Hz); ESMS *m/z* (relative intensity) 492.2 ($M + H^+$, 75).

Step C: Preparation of 2-methyl-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)acetic acid

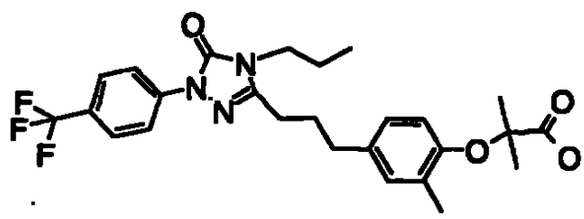


A mixture of 2-methyl-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)acetic acid ethyl ester (70 mg, 0.14 mmol) and a 2N solution of sodium hydroxide (1.6 mL) in ethanol (3.3 mL) was heated to 75°C for 45 min. The solvent was evaporated, water added and the solution made acidic with concentrated hydrochloric acid (pH 0-1), extracted with ether. The combined organic extracts were washed with water, brine, dried and evaporated to dryness to afford the pure compound (60 mg, 96.4%): ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.09 (d, 2 H, J = 8.8 Hz), 7.60 (d, 2 H, J = 8.8 Hz), 6.99 (s, 1 H), 6.94 (m, 1 H), 6.60 (d, 1 H, 8.4 Hz), 4.61 (s, 2 H), 3.48 (t, 2 H, J = 8.0 Hz), 2.98 (t, 2 H, J = 8.4 Hz), 2.76 (t, 2 H, J = 7.2 Hz), 2.21 (s. 3 H), 1.62 (m, 2 H), 0.88 (t, 3 H, J = 7.6 Hz); ESMS *m/z* (relative intensity) 464.2 ($M + H^+$, 40), 462.1 ($M - H^+$, 100).

The following compounds were made in a substantially similar method:

Example 142

2-Methyl-2-(2-methyl-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-phenoxy)-propionic acid

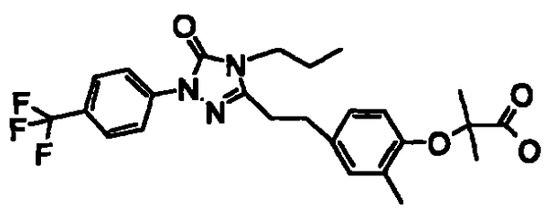


HNMR (400 MHz, $CDCl_3$) □ 8.15 (m, 2 H), 7.80 (m, 2 H), 6.99 (s, 1 H), 6.94 (m, 1 H), 6.62(m, 1 H), 3.56 (m, 2H), 2.62

(m, 4 H), 2.10 (s, 3 H), 1.98 (m, 2 H), 1.60 (m, 2 H), 1.45 (s, 6 H), 0.85 (m, 3 H); ESMS *m/z* 506.3 ($M + H^+$)

Example 143

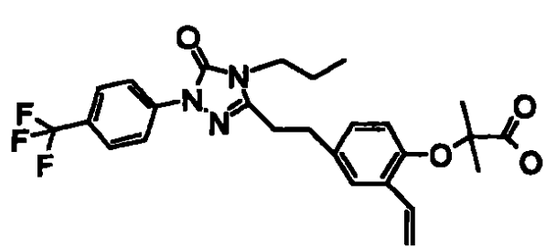
2-Methyl-2-(2-methyl-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-propionic acid



HNMR (400 MHz, $CDCl_3$) □ 8.13 (d, 2 H, *J* = 8.8 Hz), 7.82 (d, 2 H, *J* = 9.3 Hz), 7.1 (m, 1 H), 7.0 (m, 1 H), 6.62(m, 1 H), 3.58 (m, 2H), 2.91 (s, 4 H), 2.12 (s, 3 H), 1.59 (m, 2 H), 1.46 (s, 6 H), 0.85 (m, 3 H); ESMS *m/z* 492.3 ($M + H^+$)

Example 144

2-Methyl-2-(2-vinyl-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)-propionic acid

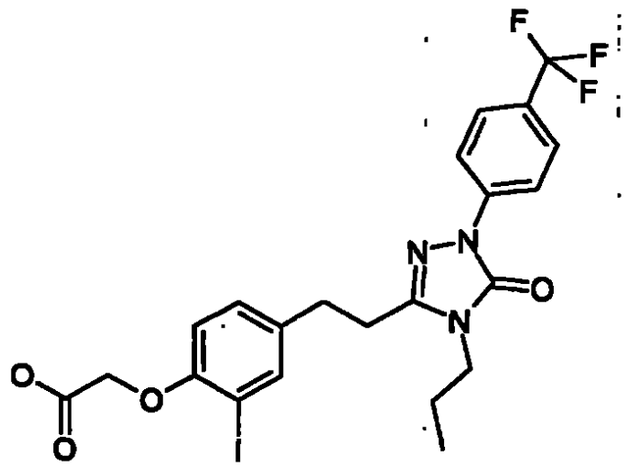


HNMR (400 MHz, $CDCl_3$) □ 8.13 (d, 2 H, *J* = 8.32 Hz), 7.81 (d, 2 H, *J* = 8.8 Hz), 7.51 (d, 1 H, *J* = 2.44 Hz), 7.13 (m, 1 H), 6.96 (m, 1 H), 6.69 (m, 1H), 5.78 (m, 1H), 5.23(m, 1H), 3.58 (t, 2H, *J* = 7.34 Hz), 2.96 (m, 4 H), 1.60 (m, 2H), 1.46 (s, 6 H), 0.84 (t, 3 H, *J* = 7.3 Hz); ESMS *m/z* 504.03 ($M + H^+$)

336

Example 145

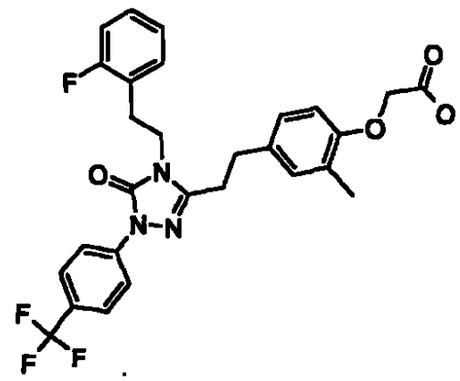
(2-Iodo-4-{2-[5-oxo-4-propyl-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-phenoxy)acetic acid



^{1}HNMR (400 MHz, $CDCl_3$) □ 8.08 (d, 2 H, J = 8.4 Hz), 7.69 (s, 1 H), 7.61 (d, 2 H, J = 8.8 Hz), 7.11 (d, 1 H, J = 8.4 Hz), 6.65 (d, 1 H, 8.0 Hz), 4.63 (s, 2 H), 3.51 (t, 2 H, J = 7.6 Hz), 3.01 (t, 2 H, J = 7.6 Hz), 2.77 (t, 2 H, J = 7.2 Hz), 1.63 (m, 2 H), 0.89 (t, 3 H, J = 7.2 Hz); ESMS *m/z* (relative intensity) 576.0 ($M + H^+$, 100), 574.0 ($M - H^+$, 100).

Example 146

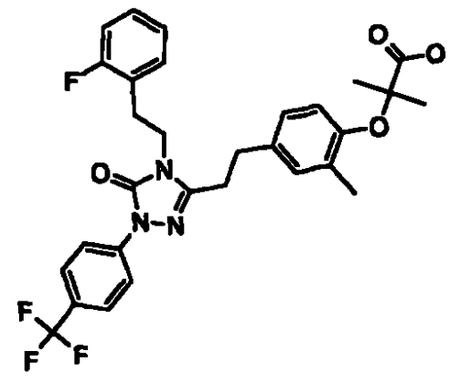
(4-{2-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-2-methyl-phenoxy)-acetic acid



^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.15 (s, 3H), 2.47 - 2.51 (m, 2H), 2.75 (t, J = 7.34 Hz, 2H), 2.97 (t, J = 6.36 Hz, 2H), 3.85 (t, J = 6.36 Hz, 2H), 4.63 (s, 2H), 6.70 (d, J = 8.32 Hz, 1H), 6.91 - 6.96 (m, 2H), 7.08 - 7.14 (m, 2H), 7.24 - 7.29 (m, 2H), 7.81 (d, J = 8.31 Hz, 2H), 8.10 (d, J = 8.31 Hz, 2H); MS (ES, m/z):$C_{28}H_{25}F_4N_3O_4$: 544.01(M^++1), 542.05(M^+-1).

Example 147

2-(4-{2-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-ethyl}-2-methyl-phenoxy)-2-methyl-propionic acid

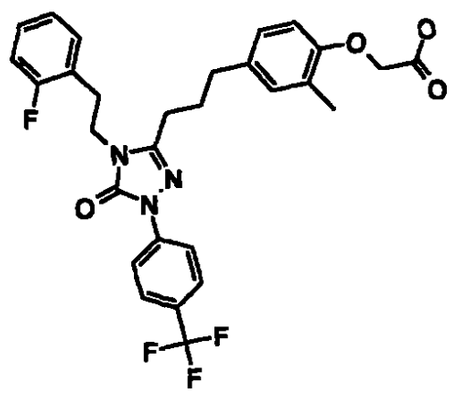


^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.46 (s, 6H), 2.12 (s, 3H), 2.50 - 2.52 (m, 2H), 2.74 (t, J = 7.83 Hz, 2H), 2.96 (t, J = 6.85 Hz, 2H), 3.84 (t, J = 6.85 Hz, 2H), 6.59 (d, J = 7.83 Hz,

1H), 6.88 (d, J = 8.31 Hz, 1H), 6.97 (s, 1H), 7.10 - 7.12 (m, 2H), 7.25 - 7.29 (m, 2H), 7.81 (d, J = 8.30 Hz, 2H), 8.10 (d, J = 8.30 Hz, 2H); MS (ES, m/z):$C_{30}H_{29}F_4N_3O_4$: 571.97(M^++1), 570.00(M^+-1).

Example 148

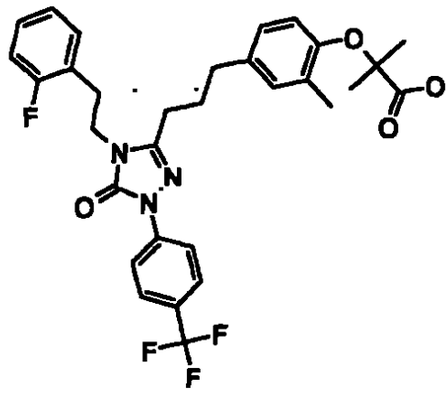
(4-{3-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-2-methyl-phenoxy)-acetic acid



^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.76 - 1.80 (m, 2H), 2.15 (s, 3H), 2.23 (t, J = 7.82 Hz, 2H), 2.45 - 2.48 (m, 2H), 2.96 (t, J = 6.36 Hz, 2H), 3.83 (t, J = 6.85 Hz, 2H), 4.63 (s, 2H), 6.70 (d, J = 8.32 Hz, 1H), 6.90 (d, J = 7.83 Hz, 1H), 6.95 (s, 1H), 7.07 - 7.12 (m, 2H), 7.22 (m, 2H), 7.80 (d, J = 8.80 Hz, 2H), 8.10 (d, J = 8.32 Hz, 2H); MS (ES, m/z):$C_{29}H_{27}F_4N_3O_4$: 558.23(M^++1), 556.23(M^+-1).

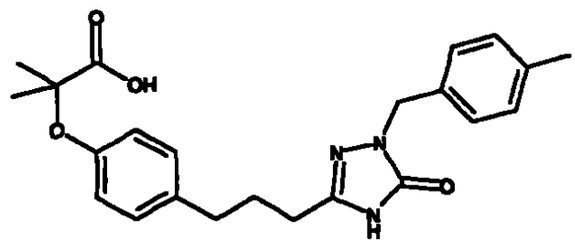
Example 149

2-(4-{3-[4-[2-(2-Fluoro-phenyl)-ethyl]-5-oxo-1-(4-trifluoromethyl-phenyl)-4,5-dihydro-1H-[1,2,4]triazol-3-yl]-propyl}-2-methyl-phenoxy)-2-methyl-propionic acid



^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.46 (s, 6H), 1.76 - 1.80 (m, 2H), 2.11 (s, 3H), 2.23 (t, J = 7.82 Hz, 2H), 2.45 (t, J = 7.82 Hz, 2H), 2.96 (t, J = 6.36 Hz, 2H), 3.83 (t, J = 6.85 Hz, 2H), 6.60 (d, J = 8.31 Hz, 1H), 6.86 (dd, J_1 = 8.31 Hz, J_2 = 1.96 Hz, 1H), 6.96 (d, J = 1.96 Hz, 1H), 7.07 - 7.11 (m, 2H), 7.21 - 7.26 (m, 2H), 7.79 (d, J = 8.80 Hz, 2H), 8.10 (d, J = 8.80 Hz, 2H); MS (ES, m/z):$C_{31}H_{31}F_4N_3O_4$: 586.2(M^++1), 584.2(M^+-1).

Example 150



Preparation of Form IV Polymorph

Title compound (5.75 g) is combined with ethyl acetate (30 mL) and heated to reflux as a slurry. Additional ethyl acetate (19 mL) is added and solution at reflux is obtained. The solution is cooled and crystallization occurs. The slurry is cooled to 0 °C and held at that temperature for 1

hr, then filtered and the filter cake rinsed with cold ethyl acetate. The crystals obtained are dried in vacuo at 60 °C overnight to afford the title compound as the desired form IV polymorph: 5.45 g, 94.5%. mp: 129.4-130.3 °C.

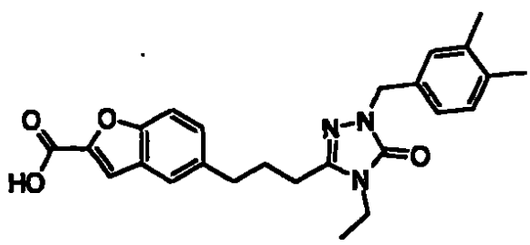
Form IV

Angle 2-Theta °	d value Angstrom	Intensity %
6.863	12.87	4.7
7.933	11.135	25.7
13.225	6.689	49.9
13.746	6.437	12.5
15.023	5.893	1.2
15.97	5.545	33.9
16.669	5.314	4.3
17.005	5.21	3.1
17.327	5.114	23.1
17.925	4.944	12
19.598	4.526	30.5
20.132	4.407	2
20.453	4.339	3.2
20.764	4.274	100
21.714	4.089	2
21.954	4.045	2.2
22.736	3.908	2.4
24.055	3.697	32.5
24.538	3.625	3.2
24.803	3.587	5.5
25.498	3.491	5
26.667	3.34	7.4
27.83	3.203	3.4
28.333	3.147	1.6
28.739	3.104	6.5

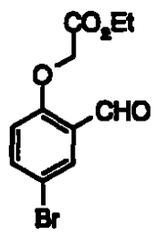
29.503	3.025	0.8
30.193	2.9575	4.2
30.552	2.9236	1.4
30.894	2.8921	0.8
32.905	2.7197	1.1
33.296	2.6887	1
34.198	2.6198	2.7

Example 151

Preparation of



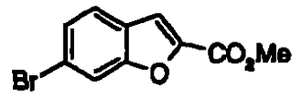
Step A: Preparation of



To a solution of 5-bromo salicylaldehyde (3.15 g, 15.6 mmol) in DMF (10 mL) at room temperature was added K_2CO_3 (5.0 g, 36.2 mmol) and ethyl bromoacetate (2.6 mL, 23.4 mmol). The mixture was stirred at room temperature for one hour. The mixture was diluted with diethyl ether (20 mL) and 1N HCl was added until pH 3-4. The organic layer was separated and washed with water and brine. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to give the titled compound.

$C_{11}H_{11}BrO_4$. (MW: 287.11); MS:m/z (M^+ + 1) 288.1.

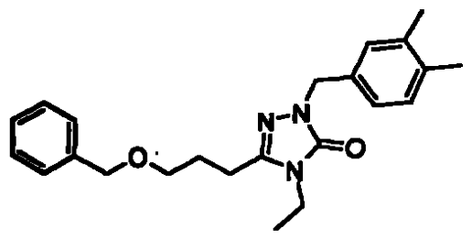
Step B: Preparation of



To a solution of MeONa (prepared from 88 mg of Na (3.8 mmol) in 10 mL of MeOH) was added a solution of the **Step A** product in methanol (1 mL) at room temperature. The mixture was refluxed for 10 minutes in a preheated bath at 80°C. Then, the reaction mixture was allowed to cool to room temperature and the titled compound precipitate from the solution as a white solid. The solid was filtered off and dry under vacuum.

$C_{10}H_7BrO_3$ (MW: 255.07); MS:m/z (M^+ + 1) 256.

Step C: Preparation of



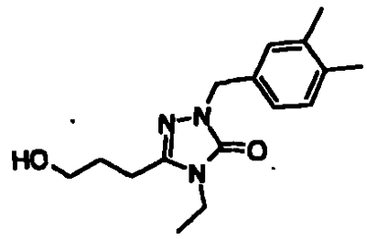
To a solution of the product prepared as in **Example 38, Step D** (11.3 g, 0.0436 mol) in methyl ethyl ketone (300 mL), was added 3,4-dimethylbenzyl chloride (16.0 mL, 0.1089 mol) followed by potassium carbonate powder (30.1 g, 0.1382 mol).The resulting mixture was stirred at 80-85°C under a drying tube for 48 hours. The reaction mixture was cooled to room temperature and then partitioned between ethyl acetate (300 mL) and NH_4Cl saturated aqueous solution (300 mL). The aqueous layer was extracted with ethyl acetate (200 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50% ethyl

343
376

acetate in hexane to give the titled compound as colorless oil.

$C_{23}H_{29}N_3O_2$ (MW = 379.51); MS: m/z (M^+ + 1) = 380.2

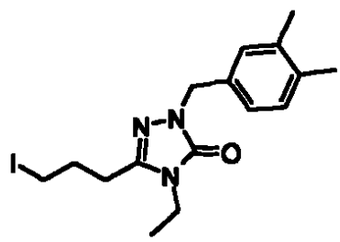
Step D: Preparation of



To a solution of the **Step C** product (16.0 g, 0.0421 mol) in ethanol (400 mL) at room temperature, palladium, 10% on activated carbon (4.2 g) was added. Mixture was stirred under hydrogen atmosphere (balloon) for 3 hours and then filtered through a plug of celite. Evaporation of the solvent gave the titled compound that was used in **Step E** without further purification.

$C_{16}H_{23}N_3O_2$ (MW = 289.38); MS: m/z (M^+ + 1) = 290.2

Step E: Preparation of

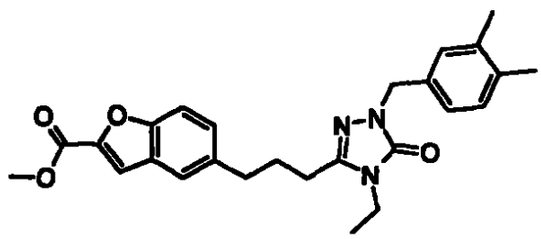


To a solution of triphenylphosphine (8.1 g, 31.0 mmol) and imidazole (2.1 g, 31.0 mmol) in a 3:1 mixture of Et_2O-CH_3CN (160 mL) at 0°C under nitrogen atmosphere, iodine (7.8 g, 31.0 mmol) was added in small portions with vigorous stirring. The resulting mixture was warmed at r om

temperature and stirred for 30 minutes. Then, mixture was cooled to 0°C and a solution of the **Step D** product (6.0 g, 20.7 mmol) in a 1:1 mixture of Et_2O-CH_3CN (40 mL) was added. Reaction was stirred at 0°C for 15 min and at room temperature for 30 minutes and then poured onto 0.5N HCl (200 mL). The aqueous layer was extracted twice with a 1:1 mixture of Et_2O-hexanes (300 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50% ethyl acetate in hexane to give the titled compound as yellow oil.

$C_{16}H_{22}IN_3O$ (MW = 399.28); MS: m/z (M^+ + 1) = 400.2

Step F: Preparation of

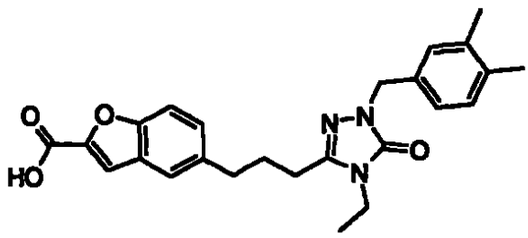


To a stirred slurry of zinc dust (0.968 g, 14.7 mmol) in anhydrous THF (5 mL) under nitrogen atmosphere at 60°C was added 1,2-dibromoethane (63 µL, 0.7 mmol). After 15 minutes of vigorous stirring, the slurry was allowed to cool to room temperature and chlorotrimethylsilane (78 µL, 0.6 mmol) was added. Mixture was stirred for 30 minutes and then a solution of the **Step E** product (0.98 g, 2.46 mmol) in anhydrous THF (5 mL) was added dropwise. Mixture was reheated to 60°C and then stirred for 10 minutes. A solution f the **Step B** (0.210 g, 0.82 mmol), $Pd(dba)_2$ (0.0237 g, 0.04 mmol) and tri-o-tolylphosphine (0.025 g, 0.082 mmol) in anhydrous THF (2.5 mL) was added and the r sulting solution

maintained at 60°C for 2 h. Reaction was then cooled at room temperature and poured onto a 1:1 mixture of AcOEt and 0.5N HCl (40 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic layers were washed with 0.5N HCl (20 mL), dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50 % ethyl acetate in hexane to give the titled compound as colorless oil.

$C_{26}H_{29}N_3O_4$ (MW = 447.54); MS: m/z (M^+ + 1) = 448.2.

Step G: Preparation of

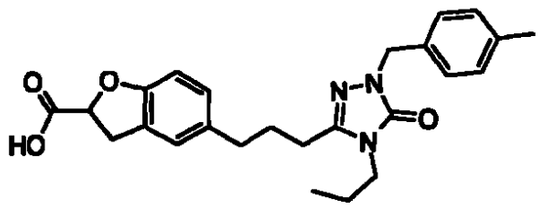


To a solution of **Step F** product (0.235 g, 0.52 mmol) in THF (10.5 mL) at room temperature a 1N solution of LiOH (4.2 mL, 4.2 mmol) was added. The mixture was stirred overnight, and then layers were separated. The aqueous layer was washed with diethyl ether (3 x 10 mL), and cooled to 0°C. After the pH was adjusted to 1-2 by addition of 1N HCl, the aqueous layer was extracted with AcOEt (2 x 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to dryness to give the titled compound.

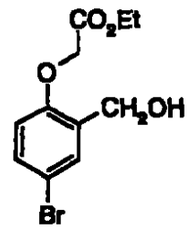
$C_{25}H_{27}N_3O_4$ (MW = 433.51); MS: m/z (M^+ + 1) = 434.2.

Example 152

Preparation of



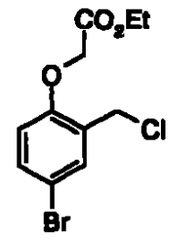
Step A: Preparation of



To a solution **Step A** Example 151 product (2.5 g, 8.7 mmol) in EtOH(10 mL) at 0°C was added in one portion $NaBH_4$ (0.394 g, 10.4 mmol). The mixture was stirred for 90 min allowing the temperature to rise. Then acetone (1 mL) was added and the solvent was removed under vacuum. The oil obtained was disolved in CH_2Cl_2 (20 mL) and washed with Brine (20 mL). The layers were separated and the organic one was dried over Na_2SO_4 and filtered. Evaporation of solvent yielded the titled compound in pure form.

$C_{11}H_{11}BrO_4$. (MW: 289.11); MS:m/z (M^+ + 1) 290.1.

Step B: Preparation of

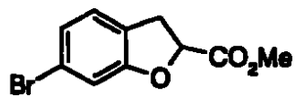


To a solution $SOCl_2$ (0.7 mL, 10.3 mmol) and Pyridine (3 drops) in CH_2Cl_2 (10 mL) at room temperature was added dropwise a solution of **Step A** product (2.5 g, 8.6 mmol) in

CH_2Cl_2 (5 mL). The reaction mixture was heated at 50°C for 2 h, then allowed to cool and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The organics were joined, dried over Na_2SO_4 and filtered. Evaporation of solvent yielded the titled compound in pure form.

$C_{11}H_{12}BrClO_3$. (MW: 307.57); MS:m/z (M^+ + 1) 307.0.

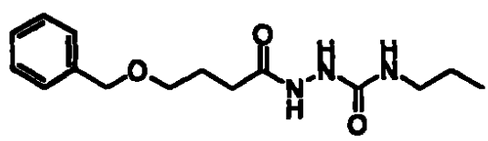
Step C: Preparation of



To a solution of **Step B** product (1.83 g, 5.9 mmol) in *N*-methyl-2-pyrrolidinone (6 mL) at 0°C under N_2 atmosphere was added in one portion NaH (60% mineral oil, 0.283 g, 7 mmol). The reaction mixture was stirred at room temperature for a day, then some drops of MeOH were added. The mixture was diluted in AcOEt (20 mL) and HCl 10% (20 mL). The layers were separated and the organic layer was wased with HCl 10% (2x20 mL), and finally witn Brine (20 mL). The organic layer was dried over Na_2SO_4 and filtered. Evaporation of solvent yield the titled compound.

$C_{10}H_9BrO_3$ (MW: 257.09); MS:m/z (M^+ + 1) 257.0.

Step D: Preparation of



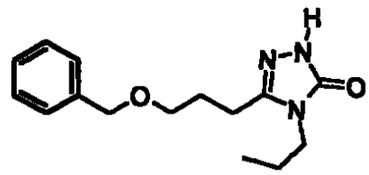
To a solution of the **Example 38, Step B** product (82.2 g, 0.423 mol) in THF (400mL), was added a solution of propyl isocyanate (Aldrich, 47.6 mL, 0.508 mol) in THF (400 mL) dropwise and the mixture was stirred at room temperature for

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an hour. Evaporation of solvent gave the titled compound as an off-white powder that was used in step E without further purification.

$C_{15}H_{23}N_3O_3$ (MW = 293.37); MS: m/z (M^+ + 1) = 294.2

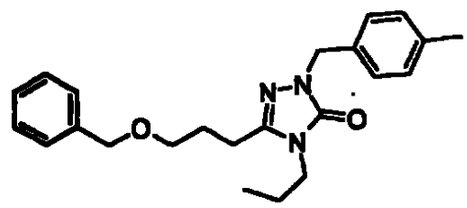
Step E: Preparation of



A suspension of the Step D product (124.0 g, 0.423 mol) in a solution of KOH (28.5 g, 0.508 mol) in water (570 mL) (1.2 eq of 5%KOH aqueous solution) was heated at 110°C for 1 hour (as soon as the temperature is increased, suspension disappear). At that time, TLC showed no starting material remained and reaction was cooled to room temperature. Then, pH was adjusted to pH=6-7 by addition of 1N HCl , and extracted with AcOEt (3x500 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give the titled compound as white solid.

$C_{15}H_{21}N_3O_2$ (MW = 275.35); MS: m/z (M^+ + 1) = 276.2

Step F: Preparation of

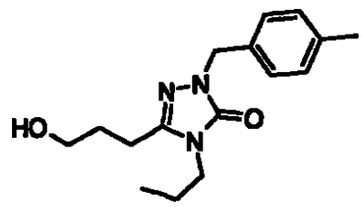


To a solution of the Step E product (11.5 g, 0.0418 mol) in methyl ethyl ketone (300 mL), was added 4-methylbenzyl bromide (11.6 g, 0.0616 mol) followed by potassium carbonate powder (28.9 g, 0.209 mol).The resulting mixture was stirred at 80-85°C under a drying tube for 24 hours. The reaction mixture was cooled t room temperature and then partitioned

between ethyl acetate (300 mL) and NH_4Cl saturated aqueous solution (300 mL). The aqueous layer was extracted with ethyl acetate (200 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50% ethyl acetate in hexane to give the titled compound as colorless oil.

$C_{23}H_{29}N_3O_2$ (MW = 379.51); MS: m/z (M^+ + 1) = 380.2

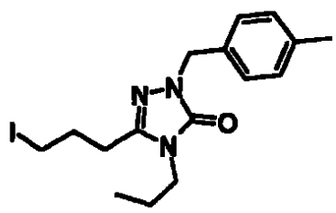
Step G: Preparation of



To a solution of the **Step F** product (10.0 g, 0.0263 mol) in ethanol (500 mL) at room temperature, palladium, 10% on activated carbon (2.6 g) was added. Mixture was stirred under hydrogen atmosphere (balloon) for 3 hours and then filtered through a plug of celite. Evaporation of the solvent gave the titled compound as white solid that was used in **Step H** without further purification.

$C_{16}H_{23}N_3O_2$ (MW = 289.38); MS: m/z (M^+ + 1) = 290.2

Step H: Preparation of

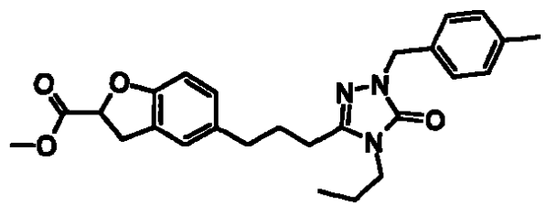


To a solution of triphenylphosphine (10.3 g, 39.4 mmol) and imidazole (2.7 g, 39.4 mmol) in a 3:1 mixture of Et_2O-CH_3CN

(200 mL) at 0°C under nitrogen atmosphere, iodine (10.0 g, 39.4 mmol) was added in small portions with vigorous stirring. The resulting mixture was warmed at room temperature and stirred for 1 hour. Then, mixture was cooled to 0°C and a solution of the **Step G** product (7.6 g, 26.3 mmol) in a 1:1 mixture of Et_2O-CH_3CN (50 mL) was added. Reaction was stirred at 0°C for 15 min and at room temperature for 1 hour and then poured onto 0.5N HCl (100 mL). The aqueous layer was extracted twice with a 1:1 mixture of Et_2O-hexanes (200 mL) and the combined organic phase dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50% ethyl acetate in hexane to give the titled compound as yellow oil.

$C_{16}H_{22}IN_3O$ (MW = 399.28); MS: m/z (M^+ + 1) = 400.2

Step I: Preparation of

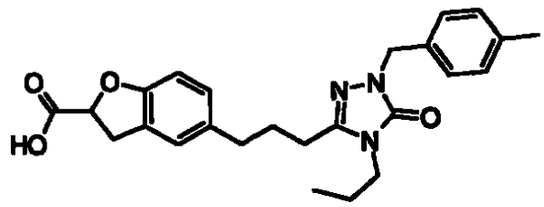


To a stirred slurry of zinc dust (0.411 g, 6.3 mmol) in anhydrous THF (1.5 mL) under nitrogen atmosphere at 60°C was added 1,2-dibromoethane (27 µL, 0.31 mmol). After 15 minutes of vigorous stirring, the slurry was allowed to cool to room temperature and chlorotrimethylsilane (33 µL, 0.26 mmol) was added. Mixture was stirred for 30 minutes and then a solution of the **Step H** product (0.42 g, 1.05 mmol) in anhydrous THF (1.5 mL) was added dropwise. Mixture was reheated to 60°C and then stirred for 10 minutes. A solution of **Step C** product (0.285 g, 1.05 mmol), $Pd(dba)_2$ (0.030 g, 0.052 mmol) and tri-o-tolylphosphine (0.032 g, 0.105 mmol) in anhydrous THF (2.5 mL) was added and the resulting solution maintained at 60°C for 2 h. Reaction was then

cooled at room temperature and poured onto a 1:1 mixture of AcOEt and 0.5N HCl (50 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with 0.5N HCl (25 mL), dried over Na_2SO_4 and filtered. Evaporation of solvent gave a crude product, which was purified on a silica gel column eluting with 50 % ethyl acetate in hexane to give the titled compound as colorless oil.

$C_{26}H_{31}N_3O_4$ (MW = 449.55); MS: m/z (M^+ + 1) = 450.2.

Step J: Preparation of

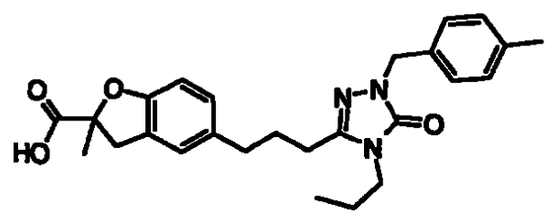


To a solution of **Step I** product (0.05 g, 0.11 mmol) in THF (2.5 mL) at room temperature a 1N solution of NaOH (2.5 mL, 2.5 mmol) was added. The mixture was stirred for two days and then layers were separated. The aqueous layer was washed with diethyl ether (4 x 5 mL), and cooled to 0°C. After the pH was adjusted to 1-2 by addition of 1N HCl, the aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to dryness to give the titled compound.

$C_{25}H_{29}N_3O_4$ (MW = 435.53); MS: m/z (M^+ + 1) = 435.2.

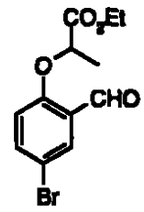
Example 153

Preparation of



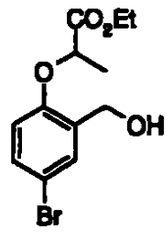
352

Step A: Preparation of



To a solution of 5-bromo salicylaldehyde (2.6g, 13 mmol) in DMF (10 mL) at room temperature was added K_2CO_3 (5.5 g, 39 mmol) and ethyl 2-bromopropionate (2.6 mL, 19.5 mmol). The mixture was stirred at room temperature for two hours. The solid was filtered off and the filtrate was washed with 1N HCl (10 mL) and H_2O (10 mL). The organic layer was dried over Na_2SO_4 and filtered. Evaporation of solvent gave a solid which was suspended in hexane (30 mL) and filtered yielding the titled compound in pure form. $C_{12}H_{13}BrO_4$. (MW: 301.14); MS:m/z (M^+ + 1) 302.2.

Step B: Preparation of

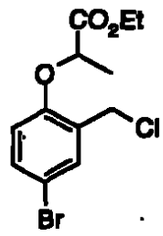


To a solution **Step A** product (1.5 g, 4.98 mmol) in EtOH(25 mL) at 0°C was added in one portion $NaBH_4$ (0.206 g, 5.47 mmol). The mixture was stirred for 30 min allowing the temperature to rise. Then acetone (1 mL) was added and the solvent was removed under vacuum. The oil obtained was disolved in CH_2Cl_2 (20 mL) and washed with Brine (20 mL). The layers were separated and the organic one was dried over

Na_2SO_4 and filtered. Evaporation of solvent yielded the titled compound in pure form.

$C_{12}H_{15}BrO_4$. (MW: 303.14); MS:m/z (M^+ + 1) 304.2.

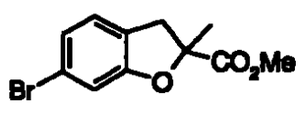
Step C: Preparation of



To a solution $SOCl_2$ (0.43 mL, 5.97 mmol) and Pyridine (2 drops) in CH_2Cl_2 (5 mL) at room temperature was added dropwise a solution of **Step B** product (1.3 g, 4.38 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was heated at 50°C for 90 min, then allowed to cool and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The organics were joined, dried over Na_2SO_4 and filtered. Evaporation of solvent yielded the titled compound in pure form.

$C_{12}H_{14}BrClO_3$. (MW: 321.60); MS:m/z (M^+ + 1) 321.0.

Step D: Preparation of

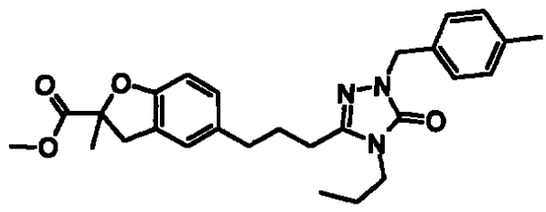


To a solution of **Step C** product (1.3 g, 4 mmol) in *N*-methyl-2-pyrrolidinone (4 mL) at 0°C under N_2 atmosphere was added in one portion NaH (60% mineral oil, 0.194 g, 4.85 mmol). The reaction mixture was stirred at room temperature for a day, then some drops of MeOH were added. The mixture was diluted in AcOEt (20 mL) and HCl 10% (20 mL). The layers

were separated and the organic layer was wased with HCl 10% (2x20 mL), and finally witn Brine (20 mL). The organic layer was dried over Na_2SO_4 and filtered. Evaporation of solvent yield the titled compound.

$C_{11}H_{11}BrO_3$ (MW: 271.11); MS:m/z (M^+ + 1) 271.0.

Step E: Preparation of

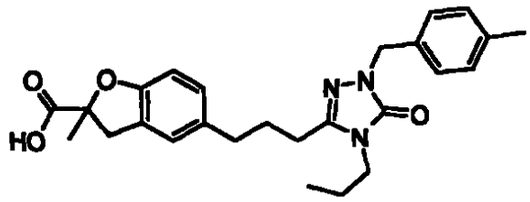


To a stirred slurry of zinc dust (0.411 g, 6.3 mmol) in anhydrous THF (1.5 mL) under nitrogen atmosphere at 60°C was added 1,2-dibromoethane (27 □L, 0.31 mmol). After 15 minutes of vigorous stirring, the slurry was allowed to cool to room temperature and chlorotrimethylsilane (33 µL, 0.26 mmol) was added. Mixture was stirred for 30 minutes and then a solution of the **Example 152, Step H** product (0.42 g, 1.05 mmol) in anhydrous THF (1.5 mL) was added dropwise. Mixture was reheated to 60°C and then stirred for 10 minutes. A solution of **Step D** product (0.271 g, 1.0 mmol), $Pd(dba)_2$ (0.030 g, 0.052 mmol) and tri-o-tolylphosphine (0.032 g, 0.105 mmol) in anhydrous THF (2.5 mL) was added and the resulting solution maintained at 60°C for 2 h. Reaction was then cooled at room temperature and poured onto a 1:1 mixture of AcOEt and 0.5N HCl (50 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with 0.5N HCl (25 mL), dried over Na_2SO_4 and filtered. Evaporation of s lvent gave a crude product, which was

purified on a silica gel column eluting with 50 % ethyl acetate in hexane to give the titled compound as colorless oil.

$C_{27}H_{33}N_3O_4$ (MW = 463.58); MS: m/z (M^+ + 1) = 464.2.

Step F: Preparation of

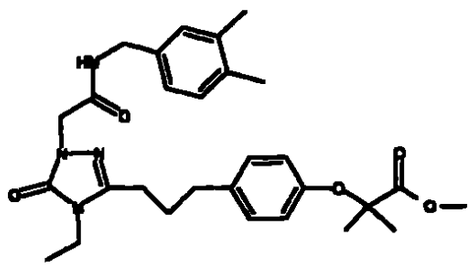


To a solution of **Step D** product (0.05g, 0.10 mmol) in THF (2 mL) at room temperature a 1N solution of NaOH (2mL, 2 mmol) was added. The mixture was stirred for three days, and then layers were separated. The aqueous layer was washed with diethyl ether (3 x 10 mL), and cooled to 0°C. After the pH was adjusted to 1-2 by addition of 1N HCl, the aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to dryness to give the titled compound.

$C_{26}H_{31}N_3O_4$ (MW = 449.55); MS: m/z (M^+ + 1) = 450.2.

Example 154

Step A:

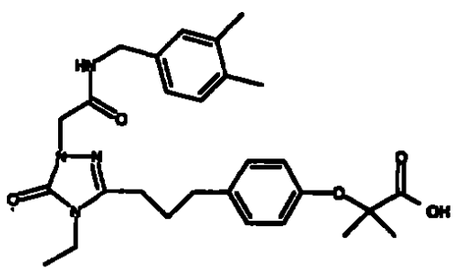


A THF solution of the acid described in Example

127. Step B (0.300 g, 0.0007 mol) was treated with EDC (0.212 g, 0.0011mol) and HOAt (0.095 g, 0.0007 mol). An equivalent 3, 4 dimethyl benzyl amine (0.10 ml, 0.0007 mol) was added and the reaction was stirred overnight. The solvent was concentrated and the residue was redissolved in methylene chloride and extracted with water. Purification by flash chromatography (100 % ethyl acetate) gave the desired amide.

$C_{29}H_{38}N_4O_5$ (MW = 522.65); mass spectroscopy (MH^+) = 523.3

Step B:

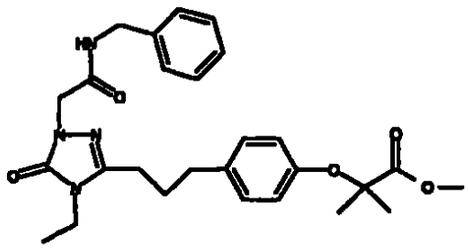


The amide from Step A (0.260 g, 0.0005 mol) was dissolved in dioxane (3 ml) and water (3 ml) then treated with LiOH (0.012 g, 0.0005 mol). The reaction was stirred for two hours. Water was added to the mixture and the layer was extracted with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 then concentrated to yield the desired product as a white foam.

$C_{28}H_{36}N_4O_5$ (MW = 508.62); mass spectroscopy (MH^+) = 509.4

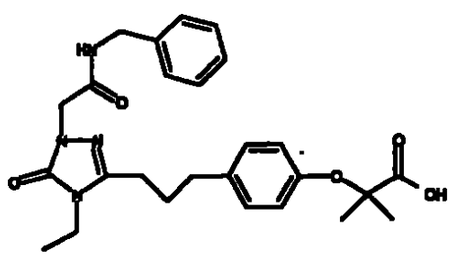
Example 155

Step A:



A THF solution of the acid described in Example 127 , Step B (0.300 g, 0.0007 mol) was treated with EDC (0.212 g, 0.0011 mol) and HOAt (0.095 g, 0.0007 mol). An equivalent of benzyl amine (0.076 ml, 0.0007 mol) was added and the reaction was stirred overnight. The solvent was concentrated and the residue was redissolved in methylene chloride and extracted with water. Purification by flash chromatography (100 % ethyl acetate) gave the desired amide. $C_{27}H_{34}N_4O_5$ (MW = 494.60); mass spectroscopy (MH^+) = 495.2

Step B:



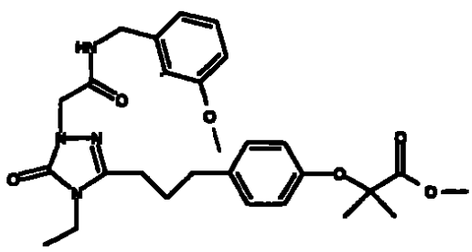
The amide from Step A (0.176 g, 0.00035 mol) was dissolved in dioxane (3 ml) and water (3 ml) then treated with LiOH

(0.0085 g, 0.00035 mol). The reaction was stirred for two hours. Water was added to the mixture and the layer was extracted with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 then concentrated t yield the desired product as a white foam.

$C_{26}H_{32}N_4O_5$ (MW = 480.57); mass spectroscopy (MH^+) = 481.4

Example 156

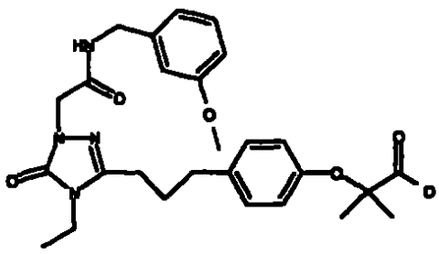
Step A:



A THF solution of the acid described in Example 127 , Step B (0.300 g, 0.0007 mol) was treated with EDC (0.212 g, 0.0011 mol) and HOAt (0.095 g, 0.0007 mol). An equivalent of 3-methoxy benzyl amine (0.090 ml, 0.0007 mol) was added and the reaction was stirred overnight. The solvent was concentrated and the residue was redissolved in methylene chloride and extracted with water. Purification by flash chromatography (100 % ethyl acetate) gave the desired amide.

$C_{28}H_{36}N_4O_6$ (MW = 524.62); mass spectroscopy (MH^+) = 525.3

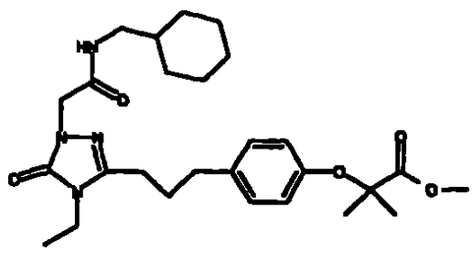
Step B:



The amide from Step A (0.260 g, 0.00049 mol) was dissolved in dioxane (3 ml) and water (3 ml) then treated with LiOH (0.012 g, 0.00049 mol). The reaction was stirred for two hours. Water was added to the mixture and the layer was extracted with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 then concentrated to yield the desired product as a white foam.
$C_{27}H_{34}N_4O_6$ (MW = 510.59); mass spectroscopy (MH^+) = 511.3

Example 157

Step A:

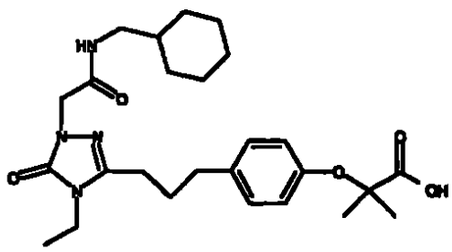


A THF solution of the acid described in Example 127 , Step B (0.300 g, 0.0007 mol) was treated with EDC (0.212 g, 0.0011 mol) and HOAt (0.095 g, 0.0007 mol). An equivalent of 3-methoxy benzyl amine (0.091 ml, 0.0007 mol) was added and the reaction was stirred overnight. The solvent was c ncentrated and the residue was redissolved in

methylene chloride and extracted with water. Purification by flash chromatography (100 % ethyl acetate) gave the desired amide.

$C_{27}H_{40}N_4O_5$ (MW = 500.6); mass spectroscopy (MH^+) = 501.4

Step B:



The amide from Step A (0.290 g, 0.00058 mol) was dissolved in dioxane (3 ml) and water (3 ml) then treated with LiOH (0.013 g, 0.00058 mol). The reaction was stirred for two hours. Water was added to the mixture and the layer was extracted with ether. The aqueous layer was acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 then concentrated to yield the desired product as a white solid.

$C_{26}H_{38}N_4O_5$ (MW = 486.62); mass spectroscopy (MH^+) = 487.4

Biological Assays

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPARα receptors were determined by the procedures detailed below. DNA-dependent binding (ABCD binding) was carried out using SPA technology with PPAR receptors. Tritium-labeled PPARα agonists were used as radioligands for generating displacement curves and IC_{50} values with compounds of the

invention. Cotransfection assays were carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs were constitutively expressed using plasmids containing the CMV promoter. For PPARα, interference by endogenous PPARγ in CV-1 cells was an issue. In order to eliminate such interference, a GAL4 chimeric system was used in which the DNA binding domain of the transfected PPAR was replaced by that of GAL4, and the GAL4 response element was utilized in place of the AOX PPRE. Cotransfection efficacy was determined relative to PPARα agonist reference molecules. Efficacies were determined by computer fit to a concentration-response curve, or in some cases at a single high concentration of agonist (10 μM).

These studies were carried out to evaluate the ability of compounds of the invention to bind to and/or activate various nuclear transcription factors, particularly huPPARα ("hu" indicates "human"). These studies provide in vitro data concerning efficacy and selectivity of compounds of the invention. Furthermore, binding and cotransfection data for compounds of the invention were compared with corresponding data for marketed compounds that act on huPPARα.

The binding and cotransfection efficacy values found, for compounds of the invention and compounds of this invention which are useful for modulating a PPAR alpha receptor, were $\leq$ 100 nM and $\geq$ 50%, respectively.

Evaluation of Triglyceride Reduction and HDL Cholesterol Elevation in HuapoAI Transgenic Mice

Seventeen different series of studies were performed to evaluate the effect of compounds of the present invention upon HDL and triglyceride levels in human apoAI mice. For

each compound tested, seven to eight week old male mice, transgenic for human apoAI (C57BL/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME) were acclimated in individual cages for two weeks with standard chow diet (Purina 5001) and water provided ad libitum. After the acclimation, mice and chow were weighed and assigned to test groups (n = 5) with randomization by body weight. Mice were dosed daily by oral gavage for 8 days using a 29 gauge, 1-1/2 inch curved feeding needle (Popper & Sons). The vehicle for the controls, test compounds and the positive control (fenofibrate 100mg/kg) was 1% carboxymethylcellulose (w/v) with 0.25% tween 80 (w/v). All mice were dosed daily between 6 and 8 a.m. with a dosing volume of 0.2ml. Prior to termination, animals and diets were weighed and body weight change and food consumption were calculated. Three hours after last dose, mice were euthanized with CO2 and blood was removed (0.5-1.0 ml) by cardiac puncture. After sacrifice, the liver, heart, and epididymal fat pad were excised and weighed, Blood was permitted to clot and serum was separated from the blood by centrifugation.

Cholesterol and triglycerides were measured colorimetrically using commercially prepared reagents (for example, as available from Sigma #339-1000 and Roche #450061 for triglycerides and cholesterol, respectively). The procedures were modified from published work (McGowan M. W. et al., Clin Chem 29:538-542,1983; Allain C. C. et al., Clin Chem 20:470-475,1974. Commercially available standards for triglycerides and total cholesterol, respectively, commercial quality control plasma, and samples were measured in duplicate using 200 µl of reagent. An additional aliquot of sample, added to a well containing 200 µl water, provided a blank for each specimen. Plates were incubated at room

temperature on a plate shaker and absorbance was read at 500 nm and 540 nm for total cholesterol and triglycerides, respectively. Values for the positive control were always within the expected range and the coefficient of variation for samples was below 10%. All samples from an experiment were assayed at the same time to minimize inter-assay variability.

Serum lipoproteins were separated and cholesterol quantitated by fast protein liquid chromatography (FPLC) coupled to an in line detection system. Samples were applied to a Superose 6 HR size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16ml/min mixed with the column effluent through a T-connection and the mixture passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37 C water bath. The colored product produced in the presence of cholesterol was monitored in the flow strem at 505 nm and the analog voltage from the monitor was converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration was plotted vs time and the area under the curve corresponding to the elution of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) was calculated using Perkin Elmer Turbochrome software. The results of these studies are provided in the following tables for triglyceride and HDL cholesterol levels. Note that the superscripted numbers in the following tables refer to the study numbers. Further, the values, determined in each study, for triglyceride levels in the control mice and for HDL cholesterol levels in

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fenofibrate-treated mice are also provided in the following tables.

Triglyceride Serum Levels in Mice Dosed with a Compound of the Invention was Compared to Mice Receiving the Vehicle to identify compounds which could be particularly useful for lowering triglycerides. Generally, triglyceride decreases of greater than or equal to 30% (thirty percent) compared to control following a 30 mg/kg dose suggests a compound that can be especially useful for lowering triglyceride levels.

The percent increase of HDLc serum levels in mice receiving a compound of the invention was compared to mice receiving vehicle to identify compounds of the invention that could be particularly useful for elevating HDL levels. Generally, and increase of greater than or equal to 25% (twenty five percent) increase in HDLc level following a 30 mg/kg dose suggests a compound that can be especially useful for elevating HDLc levels.

It may be particularly desirable to select compounds of this invention that both lower triglyceride levels and increase HDLc levels. However, compounds that either lower triglyceride levels or increase HDLc levels may be desirable as well.

Evaluation of Glucose Levels in db/db Mice

The effects, upon plasma glucose of administering various dose levels of five different compounds of the present invention and the PPAR gamma agonist rosiglitazone (BRL49653) or the PPAR alpha agonist fenofibrate, and the control, to male db/db mice, were studied.

Five week old male diabetic (db/db) mice [for example, C57Bl/Ks/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor,

ME] or lean littermates were housed 6 per cage with food and water available at all times. After an acclimation period of 2 weeks, animals were individually identified by ear notches, weighed, and bled via the tail vein for determination of initial glucose levels. Blood was collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube. Sample was discharged into a heparinized microtainer with gel separator and retained on ice. Plasma was obtained after centrifugation at 4°C and glucose measured immediately. Remaining plasma was frozen until the completion of the experiment, when glucose and triglycerides were assayed in all samples. Animals were grouped based on initial glucose levels and body weights. Beginning the following morning, mice were dosed daily by oral gavage for 7 days. Treatments were test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice were weighed and bled (tail vein) 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals were bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 were assayed for glucose. After the 24 hour bleed, animals were weighed and dosed for the final time. Three hours after dosing on day 8, animals were anesthetized by inhalation of isoflurane and blood obtained via cardiac puncture (0.5-0.7 ml). Whole blood was transferred to serum separator tubes, chilled on ice and permitted to clot. Serum was obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation,

the liver, heart and epididymal fat pads were excised and weighed.

Glucose was measured colorimetrically using commercially purchased reagents. According to the manufacturers, the procedures were modified from published work (McGowan, M. W., Artiss, J. D., Strandbergh, D. R. & Zak, B. Clin Chem, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte, coupled with a color reaction first described by Trinder (Trinder, P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays were further modified in our laboratory for use in a 96 well format. The commercially available standard for glucose, commercially available quality control plasma, and samples (2 or 5 µl/well) were measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates were incubated at room temperature for 18 minutes for glucose on a plate shaker (DPC Micormix 5) and absorbance read at 500 nm on a plate reader. Sample absorbances were compared to a standard curve (100-800 for glucose). Values for the quality control sample were always within the expected range and the coefficient of variation for samples was below 10%. All samples from an experiment were assayed at the same time to minimize inter-assay variability.

The results of the study, suggest compounds of the present invention that significantly reduced db/db mouse

plasma glucose levels while resulting in body weight gains that were less than those observed for rosiglitazone.

Evaluation of the Effects of Compounds of the Present Invention upon A^y Mice Body Weight, Fat Mass, Glucose and Insulin Levels

Female A^y Mice

Female A^y mice were singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty weeks of age the mice were randomly assigned to vehicle control and treated groups based on body weight and body fat content as assessed by DEXA scanning (N=6). Mice were then dosed via oral gavage with either vehicle or a Compound of this invention (50 mg/kg) one hour after the initiation of the light cycle (for example, about 7 A.M.) for 18 days. Body weights were measured daily throughout the study. On day 14 mice were maintained in individual metabolic chambers for indirect calorimetry assessment of energy expenditure and fuel utilization. On day 18 mice were again subjected to DEXA scanning for post treatment measurement of body composition.

The results of p.o. dosing of compound for 18 days on body weight, fat mass, and lean mass were evaluated and suggest which compounds of this invention can be especially useful for maintaining desirable weight and/or promoting desired lean to fat mass.

Indirect calorimetry measurements revealed a significant reduction in respiratory quotient (RQ) in treated animals during the dark cycle [0.864 $\pm$ 0.013 (Control) vs. 0.803 $\pm$ 0.007 (Treated); $p < 0.001$]. This

reduction in RQ is indicative of an increased utilization of fat during the animals' active (dark) cycle. Additionally, treated animals displayed significantly higher rates of energy expenditure than control animals (17.40 ± 0.49 vs. 13.62 ± 0.26 kcal/kg/hr, respectively).

Male KK/A^y Mice

Male KK/A^y mice were singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty-two weeks of age the mice were randomly assigned to vehicle control and treated groups based on plasma glucose levels. Mice were then dosed via oral gavage with either vehicle or a Compound of this invention (30 mg/kg) one hour after the initiation of the light cycle (7 A.M.) for 14 days. Plasma glucose, triglyceride, and insulin levels were assessed on day 14.

The results of p.o. dosing of compound for 14 days on plasma glucose, triglycerides, and insulin are evaluated to identify compounds of this invention which may be especially desired.

Method to Elucidate the LDL-cholesterol Total-cholesterol and Triglyceride Lowering Effect of Compound 5(8)

Male Syrian hamsters (Harlan Sprague Dawley) weighing 80-120 g were placed on a high-fat cholesterol-rich diet for two to three weeks prior to use. Feed and water were provided ad libitum throughout the course of the experiment. Under these conditions, hamsters became hypercholesterolemic showing plasma cholesterol levels between 180-280 mg/dl. (Hamsters fed with normal chow had a total plasma ch lesterol level between 100-150 mg/dl.) Hamsters with

high plasma cholesterol (180 mg/dl and above) were randomized into treatment groups based on their total cholesterol level using the GroupOptimizeV211.xls program.

A Compound of this invention was dissolved in an aqueous vehicle (containing CMC with Tween 80) such that each hamster received once a day approx. 1 ml of the solution by garvage at doses 3 and 30 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) was given as a known alpha-agonist control at a dose of 200 mg/kg, and the blank control was vehicle alone. Dosing was performed daily in the early morning for 14 days.

Quantification of Plasma Lipids :

On the last day of the test, hamsters were bled (400 ul) from the suborbital sinus while under isoflurane anesthesia 2 h after dosing. Blood samples were collected into heparinized microfuge tubes chilled in ice bath. Plasma samples were separated from the blood cells by brief centrifugation. Total cholesterol and triglycerides were determined by means of enzymatic assays carried out automatically in the Monarch equipment (Instrumentation Laboratory) following the manufacturer's precedure. Plasma lipoproteins (VLDL, LDL and HDL) were resolved by injecting 25 ul of the pooled plasma samples into an FPLC system eluted with phosphate buffered saline at 0.5 ml/min through a Superose 6 HR 10/30 column (Pharmacia) maintained room temp. Detection and characterization of the isolated plasma lipids were accomplished by postcolumn incubation of the effluent with a Cholesterol/HP reagent (for example, Roche Lab System; infused at 0.12 ml/min) in a knitted reaction coil maintained at 37°C. The intensity of the color formed

was proportional to the cholesterol concentration and was measured photometrically at 505 nm.

The effect of administration of a Compound of this invention for 14 days is studied for the percent reduction in LDL level with reference to the vehicle group. The LDL-lowering efficacy for certain compounds of this invention is markedly more potent than that of fenofibrate. Compounds of this invention that decrease LDL greater than or equal to 30% (thirty percent) compared to vehicle can be especially desired.

The total-cholesterol and triglyceride lowering effects of a Compound of this invention was also studied. The data for reduction in total cholesterol and triglyceride levels after treatment with a compound of this invention for 14 days was compared to the vehicle to suggest compounds that can be particularly desired. The known control fenofibrate did not show significant efficacy under the same experimental conditions.

Method to Elucidate the Fibrinogen-Lowering Effect of PPAR Modulators

Zucker Fatty Rat Model:

The life phase of the study on fibrinogen-lowering effect of compounds of this invention was part of the life phase procedures for the antidiabetic studies of the same compounds. On the last (14th) day of the treatment period, with the animals placed under surgical anesthesia, ~ 3ml of blood is collected, by cardiac puncture, into a syringe containing citrate buffer. The blood sample is chilled and centrifuged at 4°C to isolate the plasma that was stored at -70 °C prior t fibrinogen assay.

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Quantification of Rat Plasma Fibrinogen:

Rat plasma fibrinogen levels were quantified by using a commercial assay system consists of a coagulation instrument following the manufacturer's protocol. In essence, 100 ul of plasma was sampled from each specimen and a 1/20 dilution is prepared with buffer. The diluted plasma is incubated at 37°C for 240 seconds. Fifty microliters of clotting reagent thrombin solution (provided by the instrument's manufacturer in a standard concentration) is then added. The instrument monitored the clotting time, a function of fibrinogen concentration quantified with reference to standard samples.

Results :

Compounds of this invention are capable of lowering fibrinogen level in vivo. Compounds that lower fibrinogen level greater than vehicle can be especially desired.

Cholesterol and triglyceride lowering effects of compounds of this invention were also produced in Zucker rats.

Method to Elucidate the Anti-body Weight Gain and Anti-appetite Effects of Compounds of this invention

Fourteen-Day Study in Zucker Fatty Rat[1] or ZDF Rat[2] Models :

Male Zucker Fatty rats, non-diabetic (Charles River Laboratories, Wilmington, MA) or male ZDF rats (Genetic Models, Inc, Indianapolis, IN) of comparable age and weight were acclimated for 1 week prior to treatment. Rats were on normal chow and water was provided ad libitum throughout the course of the experiment.

α-agonists were dissolved in an aqueous vehicle such that each rat received once a day approximately 1 ml of the solution by garvage at doses 0.1, 0.3, 1 and 3 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) a known alpha-agonist given at doses of 300 mg/kg, as well as the vehicle were controls. Dosing was performed daily in the early morning for 14 days. Over the course of the experiment, body weight and food consumption were monitored.

Using this assay, compounds of this invention were found to result in significant weight reduction.

EQUIVALENTS:

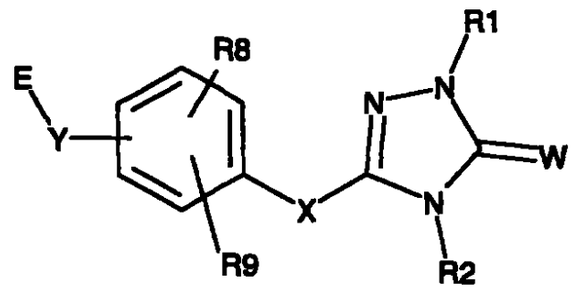
While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

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CLAIMS

What is claimed is:

1. A compound represented by the following structural Formula I:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and $-CH_2-C(O)-R17-R18$, wherein R17 is O or NH and R18 is optionally substituted benzyl;

(b) W is O or S;

(c) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(d) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(e) Y is C, O, S, NH or a single bond; and

(f) E is selected from the group consisting of hydrogen, C(R3)(R4)A, A, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is an functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted substituted arylmethyl and optionally substituted C1-C4alkyl;

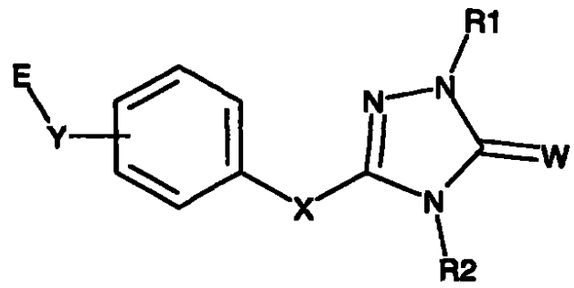
(g) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(h) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl,

substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

(i) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl.

2. A compound as Claimed by Claim 1 represented by the following structural Formula I':



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-2}-alkyl, heteroaryl-C_{0-2}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl or phenyl;

(b) W is O or S;

(c) R2 is H or a substituted or unsubstituted group selected from C_1-C_6 alkyl and C_3-C_6 cycloalkyl;

(d) X is a C_2-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(e) Y is C, O, S, NH or a single bond; and

(f) E is $(CH_2)_n$ COOH or C(R3)(R4)A, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is an acidic functional group such as carboxyl, carboxamide substituted or

unsubstituted sulfonamide, or substituted or unsubstituted tetrazole,

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl.

3. A compound as claimed by any one of Claims 1 or 2 wherein W is O.

4. A compound as claimed by any one of Claims 1, 2 or 3 wherein E is A.

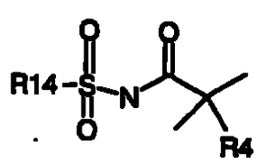
5. A compound as claimed by any one of Claims 1, 2, 3 or 4 wherein A is COOH.

6. A compound as claimed by any one of Claims 1, 2, 3, 4 or 5 wherein Y is O.

7. A compound as claimed by any one of Claims 1, 2, 3, 4 or 5 wherein Y is C.

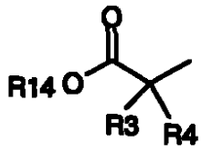
8. A compound of Claim 7 wherein E is selected from the group consisting of aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxyalkyl, aminoaryl, and aminoC_{1-4}alkyl.

9. A compound as claimed by any one of Claims 1, 2, 3, 6, or 7 wherein E is a group of the formula:



, wherein R14 is selected from the group consisting of CF_3, substituted or unsubstituted phenyl, substut d or unsubstituted aryl-C_{0-4}-alkyl, and C_{1-6}-alkyl.

10. A compound as claimed by any one of Claims 1, 2, 3, 6, or 7 wherein E is a group of the formula:



wherein R14 is selected from the group consisting of CF_3, substituted or unsubstituted phenyl, substuted or unsubstituted aryl-C_{0-4}-alkyl, and C_{1-6}-alkyl.

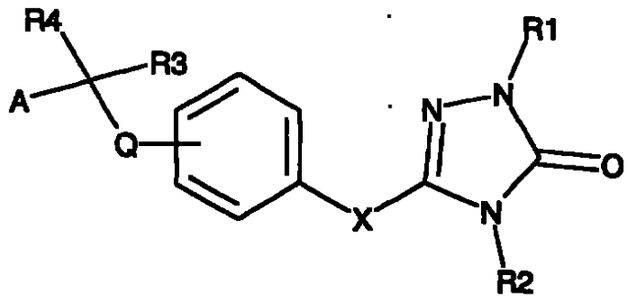
11. A compound as claimed by any one of Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 wherein X is optionally substituted C_2-C_5 alkylene.

12. A compound as claimed by any one of Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 wherein X is propylene.

13. A compound of Claim 1 which is Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl-.

14. A compound of Claim 13 which is Crystalline Propanoic Acid, 2-[4-[3-[2,5-dihydro-1-[(4-methylphenyl)methyl]-5-oxo-1*H*-1,2,4-triazol-3-yl]propyl]phenoxy]-2-methyl- having an X-ray diffraction pattern which comprises at least one of the following peaks: 13.2 +/- 0.2, 15.9 +/- 0.2, 20.7 +/- 0.2, and 24.1 +/- 0.2 in 2θ when obtained from a copper radiation source.

15. A compound as claimed by any one of Claims 1, 2, 5, 11 or 12 that is represented by the following structural formula:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and $-CH_2$-C(O)-R17-R18, wherein R17 is O or NH and R18 is optionally substituted benzyl;

(b) R2 is H or a substituted or unsubstituted group selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and heteroaryl;

(c) X is a C_2-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Q is C, O or S;

(e) A is a functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(f) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy; and

(g) R4 is H, hal , a substituted or unsubstituted

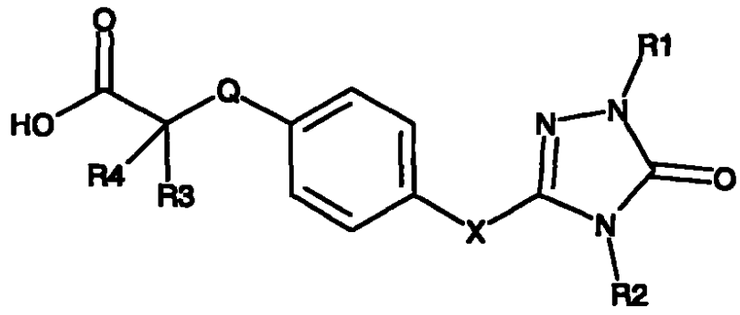
group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl.

16. A compound as claimed by Claim 15 wherein A is COOH.

17. A compound as claimed by any one of Claims 15, or 16 wherein R3 is methyl.

18. A compound as claimed by any one of Claims 15, 16 or 17 wherein R4 is methyl.

19. A compound as claimed by any one of Claims 1, 2, 11 or 12 that is represented by the following structural formula:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and $-CH_2-C(O)-R17-R18$, wherein R17 is O or NH and R18 is optionally substituted benzyl;

(b) R2 is H or a substituted or unsubstituted group selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and heteroaryl;

(c) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Q is C, O or S;

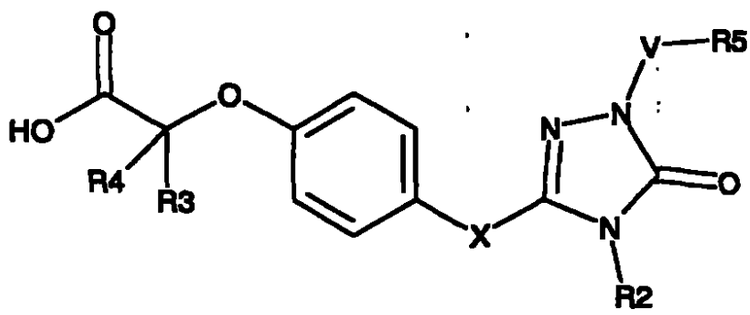
(e) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy; and

(f) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl.

20. A compound as claimed by any one of Claims 1-12, 15, 16, 17, 18, or 19 wherein R1 selected from the group consisting of a substituted or unsubstituted C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl.

21. A compound as claimed by any one of Claims 1-12, 15, 16, 17, 18, 19 or 20 wherein R1 is substituted aryl.

22. A compound as claimed by any one of Claims 1, 2, 11, or 12 that is represented by the following structural formula:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R2 is H or a substituted or unsubstituted group selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and heteroaryl;

(b) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

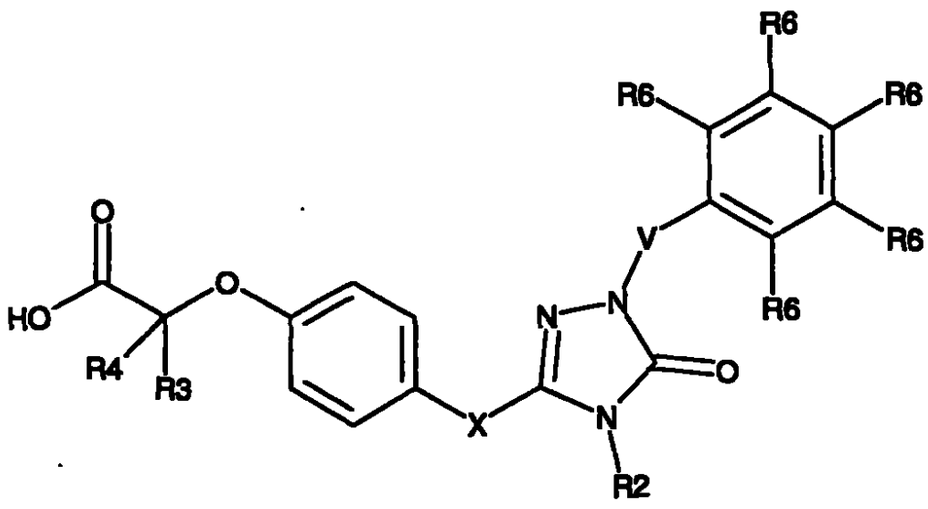
(c) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy;

(d) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(e) V is a bond or a unsubstituted or substituted C1-C3 alkylene group; and

(f) R5 is substituted or unsubstituted group selected from aryl, heteroaryl and cycloalkyl groups.

23. A compound as claimed by any one of Claims 1, 2, 11 or 12 that is represented by the following structural formula:



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and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R2 is H or a substituted or unsubstituted group selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and heteroaryl (delete heteroaryl);

(b) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(c) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy;

(d) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(e) V is a bond or a unsubstituted or substituted C1-C3 alkylene group; and

(f) R6 is H, OH, C1-C5 alkyl, alkoxy, halo, haloalkyl, haloalkoxy, nitro, phenyl, aryloxy, SO2R7, SR7, cyano, benzyloxy, phenoxy, alkylcarboxamido or COOH wherein R7 is an alkyl or a haloalkyl.

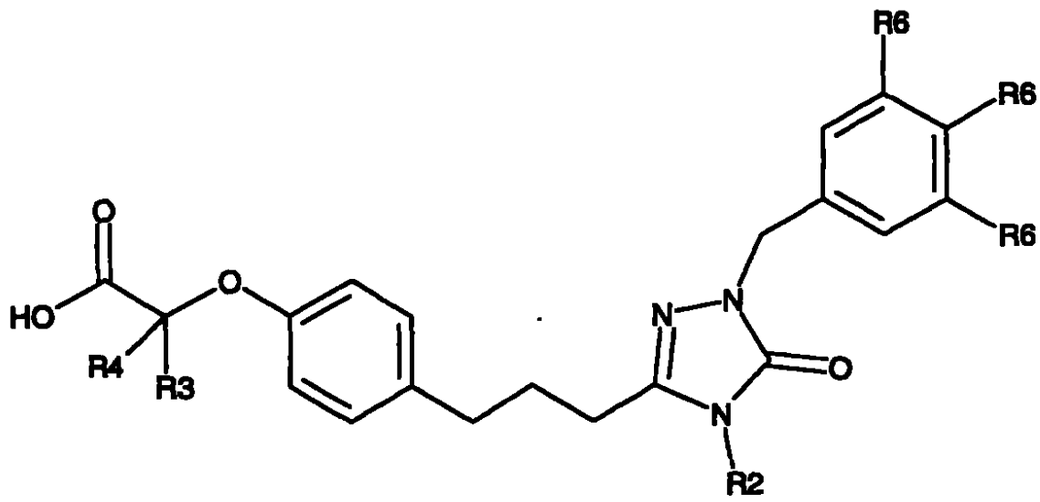
24. A compound of Claim 23 wherein V is methylene.

25. A compound as claimed by any one of Claims 23 or 24 wherein X is propylene.

26. A compound as claimed by any one of Claims 23, 24 or 25 wherein R3 is methyl.

27. A compound as claimed by any one of Claims 23, 24, 25 or 26 wherein R4 is methyl.

28. A compound as claimed by any one of Claims 1 or 2 that is represented by the following structural formula:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R2 is H or a substituted or unsubstituted group selected from C_1-C_6 alkyl, C_3-C_6 cycloalkyl and heteroaryl (delete heteroaryl);

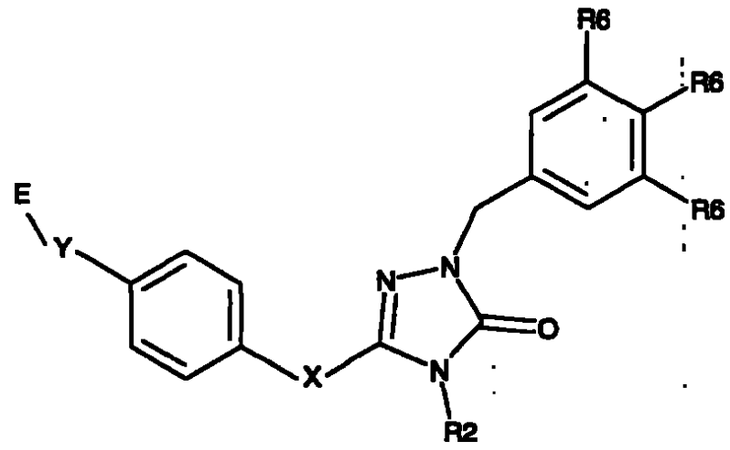
(b) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy;

(c) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl; and

(d) R6 is independently selected from the group consisting of H, OH, C1-C5 alkyl, alkoxy, halo, haloalkyl, haloalkoxy, nitro, phenyl, aryloxy, SO2R7, SR7, cyano, benzyloxy, phenoxy,

alkylcarboxamido or COOH wherein R7 is an alkyl or a haloalkyl.

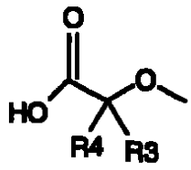
29. A compound as claimed by any one of Claims 1, 2, or 4-28, that is represented by the following structure:



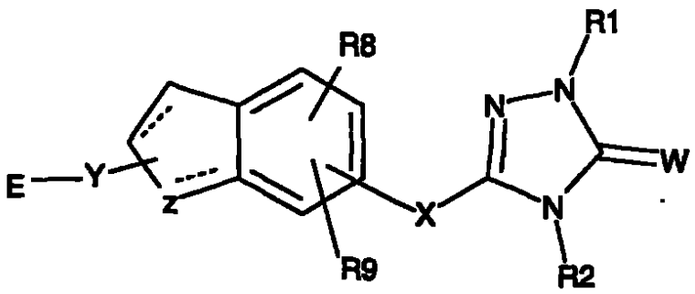
wherein R6 is independently selected from the group consisting of H, OH, C_1-C_5 alkyl, alkoxy, halo, haloalkyl, haloalkoxy, nitro, phenyl, aryloxy, SO2R7, SR7, cyano, benzyloxy, phenoxy, alkylcarboxamido or COOH wherein R7 is an alkyl or a haloalkyl.

30. A compound as claimed by any one of Claims 1, 2, or 4-29 wherein there are two R6 substituents independently selected from the group consisting of hydrogen, C_1-C_5 alkyl, Cl, F, OCH_3, CF_3, and SCF_3.

31. A compound as claimed by any one of Claims 1, 2, or 4-30 wherein EY is



32. A compound represented by the following structural formula:



and pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(b) R1 is selected from the group consisting of hydrogen, substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and $-CH_2-C(O)-R17-R18$, wherein R17 is O or NH and R18 is optionally substituted benzyl;

(b) W is O or S;

(c) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(f) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(g) Y is C, O, S, NH or a single bond; and

(f) E is selected from the group consisting of hydrogen, C(R3)(R4)A, A, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_1-

$_4$alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC$_{1-4}$alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is a functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted arylmethyl and optionally substituted C1-C4 alkyl;

(g) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

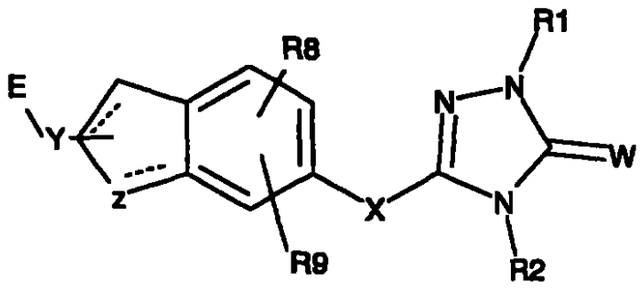
(h) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10;

(i) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl;

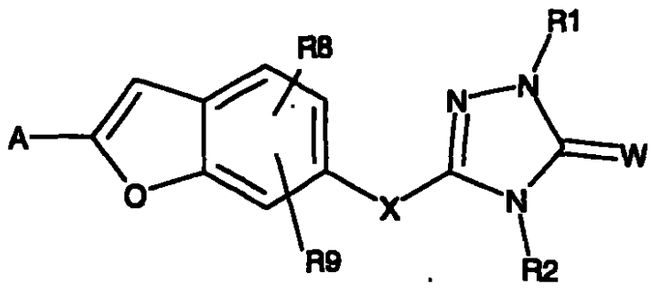
(j) Z is C_0-C_3 alkylene, O, S, N, O-(C_0-C_2 alkylene), S-(C_0-C_2 alkylene), and N-(C_0-C_2 alkylene); and

(k) --- is an optional bond to form a double bond.

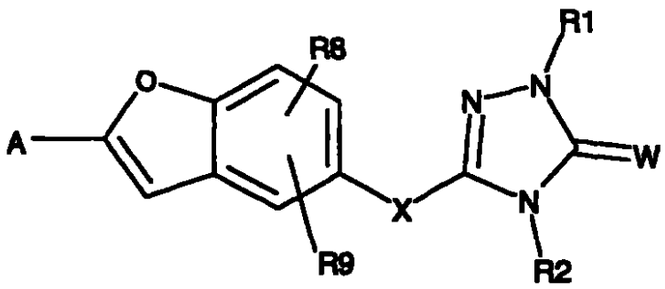
33. A compound of Claim 32 having the formula:



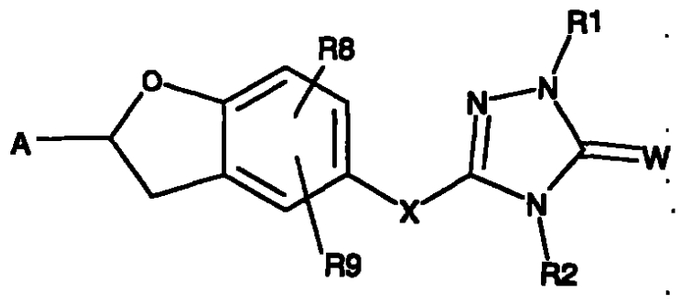
34. A compound of Claim 32 or 33 represented by the structural formula:



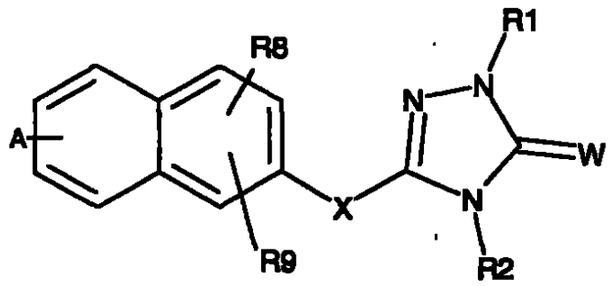
35. A compound of Claim 32 represented by the structural formula:



36. A compound of Claim 32 or 33 represented by the following structure:



37. A compound of Claim 32 or 33 represented by the following structure:



38. A compound as claimed by any one of Claims 32, 33, 34, 35, 36, or 37 wherein A is COOH.

39. A compound as claimed by any one of Claims 32, 33, 34, 35, 36, 37, or 38 wherein W is O.

40. A compound as claimed by any one of Claims 32, 33, 34, 35, 36, 37, 38, or 39 wherein R2 is C_1-C_4 alkyl.

41. A compound as claimed by any one of Claims 32, 33, 34, 35, 36, 37, 38, 39, or 40, wherein X is C_2-C_3 alkylene.

42. A compound as claimed by any one of Claims 32, 33, 34, 35, 36, 37, 38, 39, 40, or 41 wherein R1 is optionally substituted phenyl or benzyl.

43. A compound as claimed by any one of Claims 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, or 42, wherein R1 is a substituted or unsubstituted group selected from the group consisting of C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl and phenyl.

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44. A compound as claimed by any one of Claims 1-43 wherein said compound is radiolabeled.

45. A compound as claimed by any one of Claims 1-44 wherein said compound is tritiated.

46. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and at least one compound as claimed by any one of Claims 1-45, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

47. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

48. The method of Claim 47, wherein the peroxisome proliferator activated receptor is an α receptor.

49. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

50. A method of preventing diabetes mellitus in a mammal, comprising the step of administering to the mammal an effective amount of at least one compound of Claims 1-43, r a pharmaceutically acceptable salt, solvate or hydrate thereof.

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51. The method of any one of Claims 49 or 50 wherein the compound lowers blood glucose levels.

52. A method of treating cardiovascular disease in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

53. A method of preventing cardiovascular disease in a mammal, comprising the step of administering to the mammal an effective amount of at least one compound of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

54. The method of any one of Claims 52 or 53 wherein the compound lowers triglycerides in the mammal.

55. The method of any one of Claims 52, 53, or 54 wherein the compound lowers low density lipoproteins in the mammal.

56. The method of Claims 52, 53 or 54 wherein the compound increases high density lipoproteins in a mammal.

57. A method of treating Syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

58. A method of preventing Syndrome X in a mammal,

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comprising the step of administering to the mammal an effective amount of at least one compound of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

59. The method of Claim 58 wherein the compound lowers blood glucose levels.

60. The method of any one of Claims 58 or 59 wherein the compound lowers serum concentration of triglycerides in the mammal.

61. The method of any one of Claims 58, 59 or 60 wherein the compound lowers serum concentration of low density lipoproteins in the mammal.

62. The method of any one of Claims 58, 59, 60 or 61 wherein the compound increases serum concentration of high density lipoproteins in a mammal.

63. A method of treating obesity in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

64. A method of preventing obesity in a mammal, comprising the step of administering to the mammal an effective amount of at least one compound of Claims 1-43, or a pharmaceutically acceptable salt, solvate or hydrate thereof.

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65. The method of any one of Claims 47-64 wherein the mammal is a human.

66. A compound for use in therapy for a disorder modulated by a peroxisome proliferator activated receptor, wherein the compound, or pharmaceutically acceptable salt, solvate or hydrate thereof, is a compound of Claims 1-43.

67. Use of a compound for the manufacture of a medicament for the treatment of a condition modulated by a peroxisome proliferator activated receptor, wherein the compound, or pharmaceutically acceptable salt, solvate or hydrate thereof, is a compound of Claims 1-43.

68. All methods disclosed herein of preparing the compounds represented by Structural Formula I.

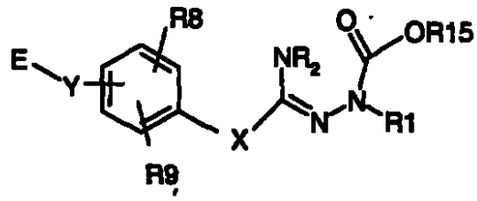
69. A process for preparing a triazolone from an acyl semicarbazide comprising contacting said acyl semicarbazide with an acid.

70. A process as claimed by Claim 69 wherein the acid is a sulfonic acid.

71. A process as claimed by Claim 69 wherein the acid is pyridinium hydrochloride.

72. A process as claimed by any one of Claims 69, 70, or 71 wherein the triazalone is represented by Formula I.

73. A compound of the formula:



wherein

(a) R1 is hydrogen or is selected from the group consisting of a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl;

(b) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(c) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Y is C, O, S, NH or a single bond; and

(e) E is selected from the group consisting of hydrogen, $(CH_2)_n$ COOR19, C(R3)(R4)A, substituted or unsubstituted selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl,and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is a functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or

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unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4alkyl and optionally substituted arylmethyl;

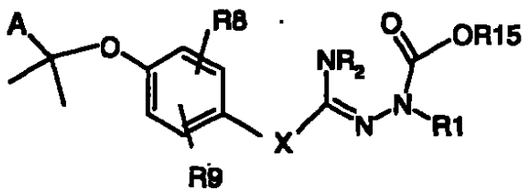
(f) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(g) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

(h) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl; and

(i) R15 is selected from the group consisting of hydrogen and an optionally substituted substituent selected from the group consisting of C_1-C_4 alkyl, aryl, and benzyl.

74. A compound of Claim 73 having the formula:



75. A compound as claimed by any one of Claims 73 and 74 wherein X is C_2-C_5 alkylene.

76. A compound as claimed by any one of Claims 73, 74, or 75 wherein A is selected from the group consisting of COOH, and C_1-C_3alkylnitrile.

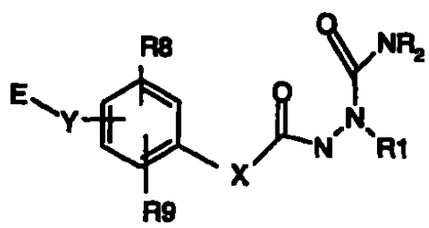
77. A compound as claimed by any one of Claims 73, 74, 75, or 76 wherein R2 is C_1-C_4 alkyl.

78. A compound as claimed by any one of Claims 73, 74, 75, 76 or 77, wherein X is C_2-C_3 alkylene.

79. A compound as claimed by any one of Claims 73, 74, 75, 76, 77, or 78 wherein R1 is optionally substituted phenyl or benzyl.

80. A compound as claimed by any one of Claims 73, 74, 75, 76, 77, 78, or 79 wherein R1 is a substituted or unsubstituted group selected from the group consisting of C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl and phenyl.

81. A compound of the formula:



wherein

(a) R1 is hydrogen or is selected from the group consisting of a substituted or unsubstituted group

selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl;

(b) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(c) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Y is C, O, S, NH or a single bond; and

(e) E is selected from the group consisting of hydrogen, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C(R3)(R4)A, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is an acidic functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstituted sulfonamide, substituted or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5

alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4alkyl and optionally substituted arylmethyl;

(f) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(g) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

(h) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl.

82. A compound as claimed by Claim 81 wherein X is C_2-C_5 alkylene.

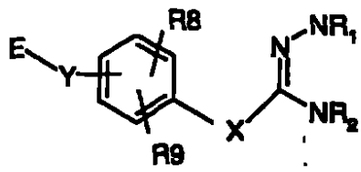
83. A compound as claimed by any one of Claims 81 or 82wherein A is selected from the group consisting of COOH, and C_1-C_3alkylnitrile.

84. A compound as claimed by any one of Claims 81, 82, or 83 wherein R2 is C_1-C_4 alkyl.

85. A compound as claimed by any one of Claims 81, 82, 83, or 84, wherein X is C_2-C_3 alkylene.

86. A compound as claimed by any one of Claims 81, 82, 83, 84, or 85 wherein R1 is optionally substituted phenyl or benzyl.

87. A compound f the formula:



wherein

(a) R1 is hydrogen or is selected from the group consisting of a substituted or unsubstituted group selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl;

(b) R2 is H or a substituted or unsubstituted group selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, sulfonamide, amide, OR10 and C_3-C_6 cycloalkyl;

(c) X is an optionally substituted C_1-C_5 alkylene linker wherein one carbon atom of the linker may be replaced with O, NH or S;

(d) Y is C, O, S, NH or a single bond; and

(e) E is selected from the group consisting of hydrogen, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOR19, C(R3)(R4)A, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl, and wherein

(i) n is 0, 1, 2 or 3,

(ii) A is an acidic functional group selected from the group consisting of carboxyl, C_1-C_3alkylnitrile, carboxamide, substituted or unsubstitut d sulfonamide, substituted

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or unsubstituted acylsulfonamide and substituted or unsubstituted tetrazole;

(iii) R3 is H, saturated or unsaturated C_1-C_5 alkyl, C_1-C_5 alkoxy, and

(iv) R4 is H, halo, a substituted or unsubstituted group selected from C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl and phenyl, or R3 and R4 are combined to form a C_3-C_4 cycloalkyl;

(v) R19 is selected from the group consisting of hydrogen, optionally substituted C1-C4 alkyl and optionally substituted arylmethyl;

(f) R8 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(g) R9 is independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, substituted or unsubstituted aryl, substituted or unsubstituted aryl-C_1-C_4 alkyl, substituted or unsubstituted heteroaryl, C_1-C_6 allyl, and OR10; and

(h) R10 is independently selected from the group consisting of hydrogen and C_1-C_4 alkyl.

88. A compound as claimed by Claim 87 wherein X is C_2-C_5 alkylene.

89. A compound as claimed by any one of Claims 87 or 88 wherein A is selected from the group consisting of COOH, and C_1-C_3alkylnitrile.

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90. A compound as claimed by any one of Claims 87, 88, or 89 wherein R2 is C_1-C_4 alkyl.

91. A compound as claimed by any one of Claims 87, 88, 89, or 90, wherein X is C_2-C_3 alkylene.

92. A compound as claimed by any one of Claims 87, 88, 89, 90, or 91 wherein R1 is optionally substituted phenyl or benzyl.

93. A compound as claimed by any one of Claims 1, 3, 6, 7, 11, 12, 29, 30, 32, 33, 73, 81, 84, 85, 86, 87, 88, 91, 91, or 92 wherein E is selected from the group consisting of hydrogen, C(R3)(R4)A, substituted or unsubstituted selected from the group consisting of $(CH_2)_n$ COOH, C_1-C_6 alkyl, C_1-C_6 allyl, aryl-C_{0-4}-alkyl, thio-C_{1-4}-alkyl, thioaryl, C_{1-4}alkoxyaryl, C_{1-4}alkoxy C_{1-4}alkyl, aminoaryl, and aminoC_{1-4}alkyl.

94. A compound as disclosed by any one of the examples herein.

AGONISTAS DEL RECEPTOR ALFA ACTIVADO DEL PROLIFERADOR DE PEROXISOMAS

ANTECEDENTES DE LA INVENCIÓN

Los receptores activados del proliferador de peroxisomas (PPARs) son miembros de la superfamilia de receptores de hormonas nucleares, que son factores de transcripción activados por ligandos que regulan la expresión génica. Se han descubierto diversos tipos de PPARs, entre los que se incluyen PPARα, NUC1, PPARγ y PPARδ.

Los subtipos de receptor PPARα se activan mediante ácidos grasos de cadena media y larga. Están implicados en la estimulación de la beta-oxidación de los ácidos grasos y en la actividad de los fibratos, lo cual produce una reducción sustancial de triglicéridos en plasma y modera la reducción de colesterol en lipoproteínas de baja densidad (LDL).

Los receptores PPARα, PPARγ y PPARδ están implicados en diabetes mellitus, enfermedades cardiovasculares, obesidad, síndrome X y enfermedades gastrointestinales, como por ejemplo, enfermedad del intestino inflamado. El síndrome X es la combinación de los síntomas que incluyen hiperinsulemia combinada con hipertensión, elevado peso corporal, elevado nivel de triglicéridos y elevado nivel

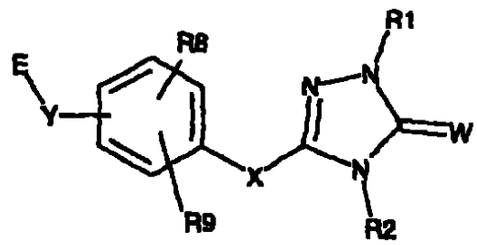
de LDL.

El tratamiento habitual con agonistas de PPAR para el síndrome X se refiere al uso de tiazolidindionas (TZDs) u otros potenciadores de la sensibilidad a insulina (ISEs). Las TZD son una clase de agonistas de PPAR gamma que se ha demostrado que aumentan la sensibilidad de las células sensibles a insulina. El aumentar la sensibilidad a insulina en lugar de la cantidad de insulina en sangre reduce la probabilidad de coma hipoglucémico. Sin embargo, las TZD y los ISE ejercen, típicamente, poco efecto a la hora de prevenir la parte cardiovascular del síndrome X pues su administración no da como resultado una disminución de los triglicéridos y las LDL en colesterol mientras que aumenta las HDL en colesterol. Además, los efectos secundarios asociados habitualmente con el tratamiento con TZD incluye una ganancia de peso significativa y, en el caso de troglitazona, provoca toxicidad en el hígado. Por tanto, existe la necesidad de nuevos agentes farmacéuticos para el tratamiento o prevención de enfermedades cardiovasculares, particularmente las asociadas con el síndrome X, que prevengan o minimicen la ganancia de peso y, más preferiblemente, que mejoren la sensibilidad a insulina.

SUMARIO DE LA INVENCIÓN

La presente invención se refiere a compuestos representados por la siguiente Fórmula Estructural

Fórmula I



y las sales, solvatos e hidratos farmacéuticamente aceptables de los mismos, en la que:

(a) R1 se selecciona del grupo constituido por hidrógeno, un grupo, sustituido o insustituido, seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cicloalquilaril C_3-C_6-alquilo C_0-C_2, y $-CH_2-C(O)-R17-R18$, en la que R17 es O o NH y R18 es bencilo opcionalmente sustituido;

(b) W es O o S;

(c) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(d) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(e) Y es C, O, S, NH o un enlace sencillo; y

(f) E se selecciona del grupo constituido por hidrógeno, C(R3)(R4)A, A, sustituido o insustituido, seleccionado del grupo constituido por $(CH_2)_n$COOR19, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6,

arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

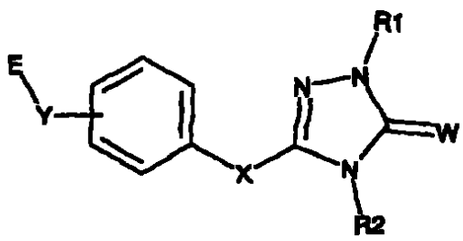
(v) R19 se selecciona del grupo constituido por hidrógeno, alquilo C_1-C_4 opcionalmente sustituido y arilmetilo opcionalmente sustituido;

(g) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

(h) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

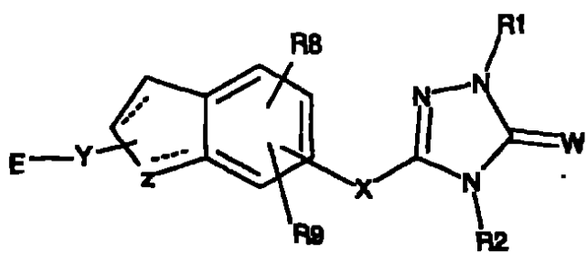
(i) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4,

Una realización adicional es un compuesto de Fórmula Estructural I' y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo:



En la Fórmula Estructural I', R1 es R1 es un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_2, heteroarilalquilo C_0-C_2, cicloalquilaril C_3-C_6-alquilo C_0-C_2 o fenilo; W es O o S; R2 es H o un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_6, y cicloalquilo C_3-C_6; X es un alquileno C_2-C_5 de unión en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S; Y es C, O, S, NH o un enlace sencillo; Además, E es $(CH_2)_nCOOH$ o C(R3)(R4)A, en la que n es 0, 1, 2 o 3, o C(R3)(R4)A, en la que A es un grupo funcional ácido, como por ejemplo carboxilo, carboxamida, sulfonamida sustituida o insustituida, o tetrazol sustituido o insustituido; R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5. Adicionalmente, R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4.

Otra realización de la presente invención es un compuesto representado por la siguiente Fórmula Estructural:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R1 se selecciona del grupo constituido por hidrógeno, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cicloalquilarilo C_3-C_6-alquilo C_0-C_2, y $-CH_2-C(O)-R17-R18$, en la que R17 es O o NH y R18 es un bencilo opcionalmente sustituido;

(b) W es O o S;

(c) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(d) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(e) Y es C, O, S, NH o un enlace sencillo; y

(f) E se selecciona del grupo constituido por hidrógeno, C(R3)(R4)A, A, un grupo sustituido o insustituido constituido por $(CH_2)_nCOOR19$,

alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, arilmetilo opcionalmente sustituido y alquilo C_1-C_4 opcionalmente sustituido;

(g) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, y halo;

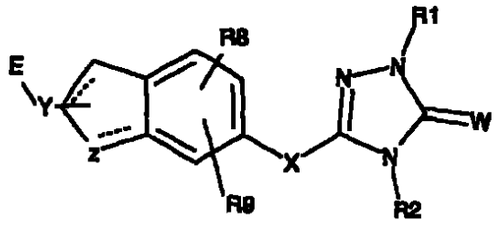
(h) R9 se selecciona independientemente el grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6 y OR10;

(i) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4;

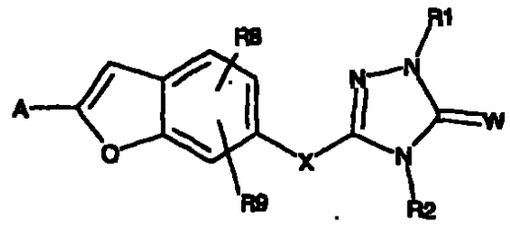
(j) Z es alquileno C_0-C_3, O, S, N, O-(alquileno C_0-C_2), S-(alquileno C_0-C_2) y N-(alquileno C_0-C_2); y

(k) - - - es un enlace opcional para formar un doble enlace.

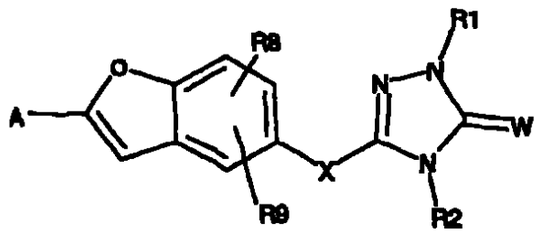
Otra realización reivindicada en la presente invención es un compuesto de fórmula:



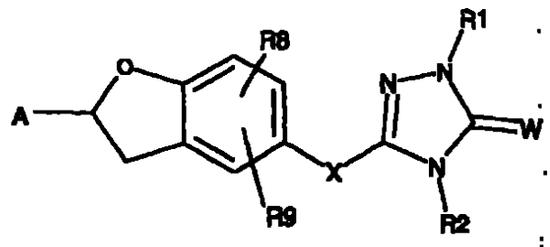
Otra realización de esta invención es un compuesto de la siguiente fórmula, que puede ser preferido:



En otra realización de la presente invención, los compuestos representados por la siguiente estructura pueden ser preferidos:

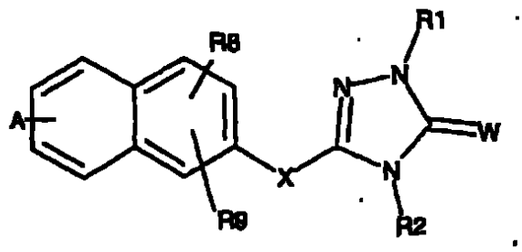


En otra realización de esta invención, un compuesto de la siguiente Fórmula Estructural puede ser preferido:



Otro compuesto reivindicado en la presente invención

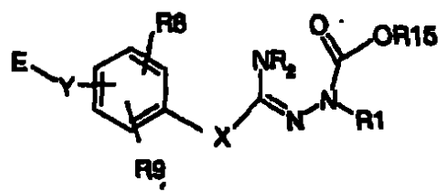
que puede ser preferido se muestra en la siguiente estructura:



En otro aspecto de esta invención, un compuesto reivindicado en la presente memoria descriptiva está radiomarcado.

La presente invención proporciona, adicionalmente, un procedimiento de preparación de una triazolona a partir de una semicarbazida de acilo que comprende poner en contacto dicha semicarbazida de acilo con un ácido. Los ácidos preferidos para dicho procedimiento son ácido sulfónico y clorhidrato de piridinio. Es una realización preferida de esta invención cuando el triazol preparado mediante dicho procedimiento es un compuesto de Fórmula I.

Otra realización de la presente invención es un compuesto de fórmula



en la que:

(a) R1 es hidrógeno o se selecciona del grupo constituido por un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4 y cicloalquilaril C_3-C_6-alquilo C_0-C_2;

(b) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(c) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(d) Y es C, O, S, NH o un enlace sencillo; y

(e) E se selecciona del grupo constituido por hidrógeno, $(CH_2)_nCOOR19$, C(R3)(R4)A, A, sustituido o insustituido, seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-

alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, alquilo C_1-C_4 opcionalmente sustituido y arilmetilo opcionalmente sustituido;

(f) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

(g) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4,

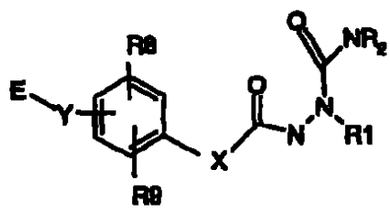
alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

(h) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4; y

(i) R15 se selecciona del grupo constituido por hidrógeno y un sustituyente opcionalmente sustituido seleccionado del grupo constituido por alquilo C_1-C_4, arilo y bencilo.

Dichos compuestos son particularmente útiles como intermedios para la preparación de los compuestos reivindicados en la presente memoria descriptiva.

Otra realización de la presente invención es un compuesto de fórmula:



en la que

(a) R1 es hidrógeno o se selecciona del grupo constituido por un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_8, arilalquilo C_0-C_4,

heteroarilalquilo C_0-C_4 y cicloalquilaril C_3-C_6-alquilo C_0-C_2;

(b) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(c) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(d) Y es C, O, S, NH o un enlace sencillo; y

(e) E se selecciona del grupo constituido por hidrógeno, o se selecciona del grupo constituido por $(CH_2)_nCOOR19$, C(R3)(R4)A, sustituido o insustituido, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo ácido funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida,

acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, alquilo C_1-C_4 opcionalmente sustituido y arilmetilo opcionalmente sustituido;

(f) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

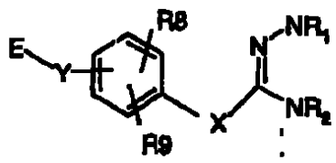
(g) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

(h) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4.

Dichos compuestos son particularmente útiles

como intermedios para la preparación de compuestos de fórmula I.

Otra realización de la invención reivindicada en la presente memoria descriptiva en un compuesto de fórmula:



en la que

(a) R1 es hidrógeno o se selecciona del grupo constituido por un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4 y cicloalquilaril C_3-C_6-alquilo C_0-C_2;

(b) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(c) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(d) Y es C, O, S, NH o un enlace sencillo; y

(e) E se selecciona del grupo constituido por hidrógeno, o se selecciona del grupo constituido por $(CH_2)_nCOOR19$, C(R3)(R4)A, sustituido o insustituido, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo ácido funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, alquilo C_1-C_4 opcionalmente

sustituido y arilmetilo opcionalmente sustituido;

(f) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

(g) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

(h) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4. Dichos compuestos son especialmente útiles como intermedios para la fabricación de compuestos de fórmula I.

Para compuestos de Fórmula Estructural I, es preferible que E sea C(R3)(R4)A. Es más preferible que A sea un grupo carboxilo. Es incluso más preferible que E sea C(R3)(R4)COOH y R3 sea H o CH_3.

La presente invención proporciona también ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico cristalino, compuesto de fórmula I o una sal, solvato, hidrato o

profármaco del mismo.

En una realización, la presente invención se refiere también a composiciones farmacéuticas que comprenden, al menos un compuesto de la presente invención, o una sal, solvato, hidrato o profármaco farmacéuticamente aceptable del mismo, y un vehículo farmacéuticamente aceptable.

En otra realización, la presente invención se refiere a un procedimiento de modulación de un receptor PPAR alfa poniendo en contacto el receptor con al menos un compuesto representado por la Fórmula Estructural I y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo.

En otra realización, la presente invención se refiere a un procedimiento de fabricación de un compuesto representado por la Fórmula Estructural I.

Se cree que los compuestos de la presente invención y las sales, solvatos e hidratos farmacéuticamente aceptables de los mismos son eficaces a la hora de tratar y prevenir el síndrome X, la diabetes de tipo II, la hiperglucemia, la hiperlipidemia, la obesidad, la coagulopatía, la hipertensión, la aterosclerosis y otros trastornos relacionados con el síndrome X y con enfermedades cardiovasculares. Además, los compuestos presentan menos efectos secundarios que los compuestos usados normalmente para tratar estas afecciones. Además,

los compuestos de esta invención pueden ser útiles para disminuir el fibrinógeno, aumentar los niveles de HDL, tratar enfermedades renales, controlar el peso ideal, tratar enfermedades de desmielinización, tratar ciertas infecciones víricas y tratar enfermedades del hígado.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Los términos usados para describir la presente invención tienen los siguientes significados en la presente memoria descriptiva.

Según se usa en la presente memoria descriptiva, los grupos alquilo incluyen hidrocarburos de cadena lineal o ramificada, que están completamente saturados.

Según se usa en la presente memoria descriptiva, un alquileno de unión es un grupo hidrocarburo C_1-C_5, de cadena lineal o ramificada, opcionalmente insaturado.

Los grupos cicloalquilo, según se usan en la presente memoria descriptiva, incluyen hidrocarburos cíclicos, que están parcial o completamente saturados.

Según se usa en la presente memoria descriptiva, los grupos arilo incluyen sistemas carbocíclicos de anillo aromático (por ejemplo, fenilo), condensados con sistemas policíclicos de anillo aromático (por ejemplo, naftilo y antracenilo) y sistemas de anillo aromático fundidos con sistemas carbocíclicos de anillo no aromático (por

ejemplo, 1, 2, 3, 4-tetrahidronaftilo y benzodioxinaftilo).

Un grupo heterocíclico, según se usa en la presente memoria descriptiva, es un sistema de anillo que tiene al menos un heteroátomo como nitrógeno, azufre u oxígeno. Los grupos heterocíclicos incluyen benzofuranilo, benzotiazolilo, benzotienilo, isoquinolilo, isoxazolilo, morfolino, oxadiazolilo, piridilo, pirimidinilo, pirrolilo, quinolilo, tetrahidropiranilo y tienilo.

Ejemplos de sustituyentes R1, R5, E, R4, R19 y R9 adecuados, cuando dichos R1, E, R4, R5, R19 o R9 son uno o más seleccionados independientemente del grupo constituido por alquilo C_1-C_8, arilo, $(CH_2)_nCOOR19$, alilo C_1-C_6, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, heterocíclico, -CH_2-C(O)-R17-R18, cicloalquilaril C_1-C_6-alquilo C_0-C_2 y cicloalquilo; los grupos sustituidos adecuados incluyen, por ejemplo, alquilo C_1-C_5, alcoxi C_1-C_5, haloalquilo C_1-C_5, haloalcoxi C_1-C_5, nitro, ciano, CHO, hidroxilo, ácido alcanoico C_1-C_4, fenilo, ariloxi, SO2R7, SR7, benciloxi, alquilcarboxamido o COOH. R7 es un alquilo o haloalquilo. Cuando R1, R5, E, R4, R19 o R9 están sustituidos, es preferible que haya de 1 a 3 sustituciones en dichos grupos R1, R5, E, R4, R19 o R9.

Ejemplos de sustituyentes adecuados para un "alquileno C_2-C_5 de unión opcionalmente sustituido" incluyen uno o más seleccionados independientemente del grupo constituido por alquilo C_1-C_6, oxo, arilalquilo C_0-C_3 sustituido o insustituido, alcoxi C_1-C_3, hidroxi, cicloalquilo C_3-C_6 y halo. Cuando el alquileno de unión está sustituido, es preferible que haya de una a tres sustituciones independientes.

Ejemplos de sustituyentes adecuados para alquileno C_1-C_3 sustituido incluyen uno o más seleccionados independientemente entre alquilo C_1-C_6, oxo, arilalquilo C_0-C_3, alcoxi C_1-C_3, hidroxi y halo. Cuando el alquileno está sustituido es preferible que haya de 1 a 3 sustituciones independientes.

Los sustituyentes adecuados para los grupos R2 sustituidos, siendo R2 alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, sulfonamida, amida, OR10 o cicloalquilo C_3-C_6, incluyen, por ejemplo, uno o más seleccionados independientemente del grupo constituido por OH, alcoxi, haloalquilo, amino, COOH, heteroaril-O-, heteroaril-C(O)-, alquil-O-, alquil-C(O)-, cicloalquilo C_3-C_6, aril-O-, aril-C(O)-, heteroarilo, arilo, heterocicloalquilo, heterocicloalquil-O- y heterocicloalquil-C(O)-. Cuando R2 está sustituido, es preferible que haya de 1 a 3 sustituciones independientes en el grupo R2.

Ejemplos de sustituyentes adecuados para los grupos A, siendo A sulfonamida, incluyen uno o más seleccionado independientemente entre alquilo C_1-C_4, haloalquilo C_1-C_4, heteroarilo sustituido o insustituido o arilo sustituido o insustituido. Cuando el grupo A está sustituido, es preferible que haya de 1 a 3 sustituciones independientes en el grupo A.

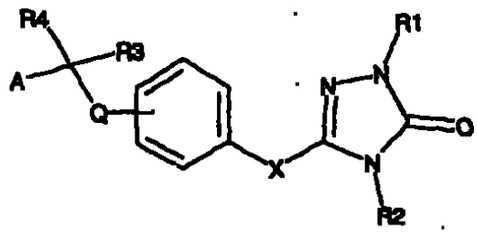
Ejemplos de sustituyentes adecuados para los grupos A, siendo A acilsulfonamida y tetrazol, incluyen, por ejemplo, uno o más seleccionados independientemente entre alquilo C_1-C_4, haloalquilo C_1-C_4, heteroarilo sustituido o insustituido o arilo sustituido o insustituido.

Los sustituyentes adecuados para R4, siendo R4 alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_1-C_6, arilalquilo C_0-C_4 o fenilo, incluyen, por ejemplo, fenilo, alcoxi C_1-C_4, hidroxi y alcoxi. Cuando R4 está sustituido, es preferible que tenga de 1 a 4 sustituciones independientes en el grupo R4.

Preferiblemente, para los compuestos de la presente invención, representados por la Fórmula Estructural I, y con sus composiciones farmacéuticas respectivas, W es un oxígeno.

Más preferiblemente, los compuestos de la presente invención, y con sus composiciones farmacéuticas

respectivas, tienen una estructura representada por la Fórmula Estructural II:

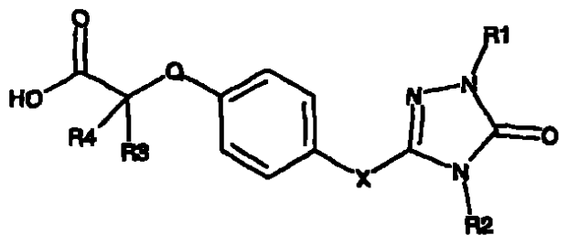


Fórmula Estructural II

En la Fórmula Estructural II, R1, R2, X, R3, R4 y A son tal y como se han definido para la Fórmula Estructural I. Q es C, O o S.

Para los compuestos de Fórmula Estructural I, es preferible que R3 sea H o CH_3.

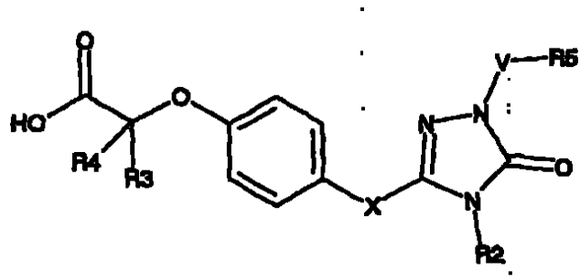
Los compuestos que pueden ser especialmente preferidos son los compuestos de fórmula III, y con sus composiciones farmacéuticas respectivas. Dichos compuestos tienen una estructura representada por la Fórmula Estructural III:



Fórmula Estructural III

En la Fórmula Estructural III, R1, R2, X, Q, R3 y R4 son tal y como se han definido para las Fórmulas Estructurales I y II.

Otra realización preferida son los compuestos de la presente invención que tienen fórmula IV, y sus composiciones farmacéuticas respectivas, que tienen una estructura representada por la Fórmula Estructural IV

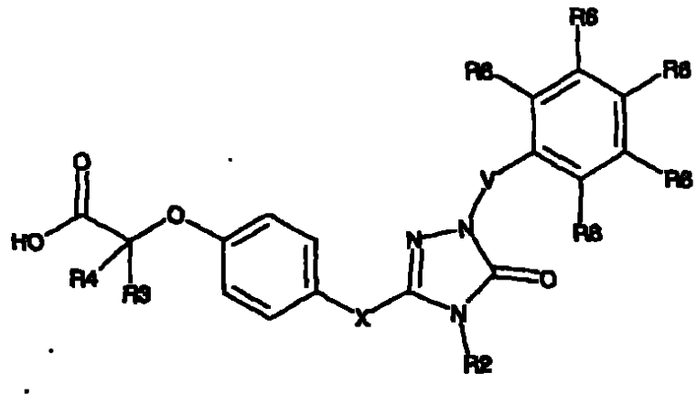


Fórmula Estructural IV

En la Fórmula Estructural IV, R2, X, R3 y R4 son tal y como se han definido para las Fórmulas Estructurales I y II. V es un enlace, un alquileno C_1-C_3 sustituido o insustituido con un grupo oxo o alquilo. R5 es un grupo sustituido o insustituido seleccionado entre grupos arilo, heteroarilo y cicloalquilo.

Otra realización preferida son los compuestos de la presente invención, con sus composiciones farmacéuticas

respectivas, que tienen una estructura representada por la Fórmula Estructural V.



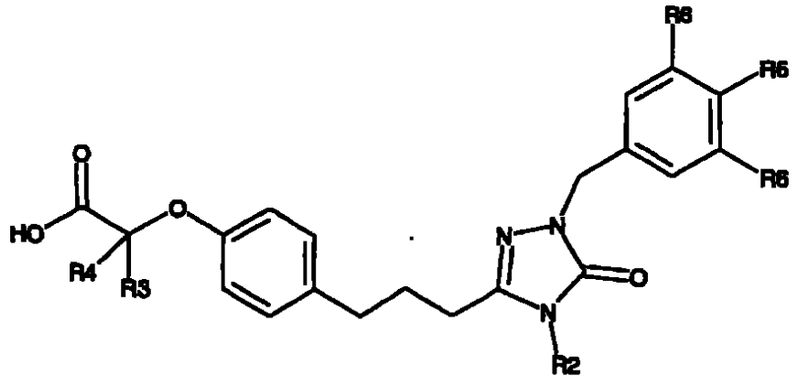
Fórmula Estructural V

En la Fórmula Estructural V, R2, X, R3, R4 y V son tal y como se han definido para las Fórmulas Estructurales I, II y IV. R6 es H, OH, alquilo C_1-C_5, alcoxi, halo, haloalquilo, haloalcoxi, nitro, fenilo, ariloxi, SO2R7, SR7, ciano, benciloxi, fenoxi, alquilcarboxamido o COOH. R7 es un alquilo o haloalquilo.

Para los compuestos de la presente invención y sus composiciones farmacéuticas respectivas que tengan una estructura representada por la Fórmula Estructural V, es preferible que V sea metileno. Es más preferible que V sea metileno y X propileno. Es incluso más preferible que V sea metileno, X propileno, R3 metilo y R4 metilo.

Otra realización preferida son los compuestos de la

presente invención, y con sus composiciones farmacéuticas respectivas, que tienen una estructura representada por la Fórmula Estructural VI.



Fórmula Estructural VI

En la Fórmula Estructural VI, R2, R3, R4 y R6 son tal y como se han definido para las Fórmulas Estructurales I, II, IV y V. Para los compuestos de Fórmula Estructural VI, es preferible que cada grupo R6 sea H o metilo, independientemente.

La presente invención proporciona también un ácido propanoico cristalino deseado, ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico.

Los compuestos de Fórmula Estructural I pueden contener uno o más centros quirales, y pueden existir en diferentes formas ópticamente activas. Cuando los

compuestos de Fórmula Estructural I contienen un centro quiral, los compuestos existen en dos formas enantioméricas y la presente invención incluye ambos enantiómeros y mezclas de enantiómeros, como por ejemplo mezclas racémicas. Los enantiómeros se pueden resolver mediante procedimientos conocidos para los expertos en la técnica, por ejemplo por formación de sales diasteroisoméricas que se pueden separar, por ejemplo, por cristalización; por formación de derivados o complejos diasteroisoméricos que se pueden separar, por ejemplo, por cristalización, cromatografía gas-líquida o líquida; por reacción selectiva de un enantiómero con un reactivo específico del enantiómero, por ejemplo por esterificación enzimática; o por cromatografía gas-líquida o líquida en una atmósfera quiral, por ejemplo en un soporte quiral por ejemplo sílice que tenga unido un ligando quiral o en presencia de un disolvente quiral. Debe entenderse que cuando el enantiómero deseado se convierte en otra entidad química mediante los procedimientos de separación descritos anteriormente, es necesaria otra etapa más para liberar la forma enantiomérica deseada. De manera alternativa, se pueden sintetizar los enantiómeros específicos mediante síntesis asimétrica usando reactivos, sustratos, catalizadores o disolventes ópticamente activos, o convirtiendo un enantiómero en el otro mediante

transformación asimétrica.

Cuando un compuesto representado por la Fórmula Estructural I tiene más de un sustituyente quiral, puede existir en sus formas diastereoisoméricas. Los pares diastereoisoméricos se pueden separar mediante procedimientos conocidos para los expertos en la técnica, por ejemplo por cromatografía o cristalización y entonces los enantiómeros individuales de cada par se pueden separar como se ha descrito anteriormente. La presente invención incluye cada diastereosiómero de los compuestos de Fórmula Estructural I y las mezclas de los mismos.

Ciertos compuestos de Fórmula Estructural I pueden existir en diferentes formas conformacionales estables que se pueden separar. La asimetría torsional debida a la rotación restringida alrededor de un enlace sencillo asimétrico, por ejemplo debido a impedimentos estéricos o deformación del anillo, puede permitir la separación de los diferentes confórmeros. La presente invención incluye cada isómero conformacional de los compuestos de Fórmula Estructural I y las mezclas de los mismos.

Ciertos compuestos de Fórmula Estructural I pueden existir en forma zwitteriónica y la presente invención incluye cada forma zwitteriónica de los compuestos de Fórmula Estructural I y las mezclas de las mismas.

Ciertos compuestos de Fórmula Estructural I y sus

sales pueden existir también en forma de solvatos, por ejemplo hidratos, y la presente invención incluye cada solvato y las mezclas de los mismos.

El término "sal farmacéuticamente aceptable" se refiere a sales de los compuestos de Fórmula Estructural I que son sustancialmente inocuos para mamíferos. Las sales farmacéuticamente aceptables típicas incluyen las sales preparadas por reacción de los compuestos de la presente invención con un ácido orgánico o mineral o con una base orgánica o inorgánica. Dichas sales se conocen como sales de adición de base, respectivamente. Debe reconocerse que el contraión particular que forma parte de cualquier sal de esta invención no tienen una naturaleza crítica, siempre y cuando la sal en su conjunto sea farmacéuticamente aceptable y siempre y cuando el contraión no aporte cualidades indeseables a la sal en su conjunto.

Gracias a este resto ácido, un compuesto de Fórmula Estructural I forma sales con bases farmacéuticamente aceptables. Algunos ejemplos de sales de adición de base incluyen sales metálicas como las de aluminio; sales de metales alcalinos como las de litio, sodio o potasio y sales de metales alcalinotérreos como las de calcio y magnesio; y las sales de amonio o amonio sustituido. Ejemplos de sales de amonio sustituido incluyen, por

ejemplo, las que tienen alquilaminas inferiores como por ejemplo trimetilamina, trietilamina; hidroxialquilaminas como por ejemplo 2-hidroxietilamina, bis-(2-hidroxietil)-amina o tri-(2-hidroxietil)-amina, cicloalquilaminas como por ejemplo biciclohexilamina o dibencilpiperidina, N-benzil-β-fenetilamina, dehidroabietilamina, N,N'-bisdehidro-abietilamina, glucamina, N-metilglucamina; bases de tipo piridina como por ejemplo piridina, colidina, quinina o quinolina; y sales de aminoácidos básicos como por ejemplo lisina y arginina.

Ejemplos de bases inorgánicas incluyen, sin limitación, hidróxido sódico, hidróxido potásico, carbonato potásico, carbonato sódico, bicarbonato sódico, bicarbonato potásico, hidróxido cálcico, carbonato cálcico y similares.

Los compuestos de Fórmula Estructural I que está sustituidos con un grupo básico, pueden existir como sales con ácidos farmacéuticamente aceptables. La presente invención incluye dichas sales. Ejemplos de dichas sales incluyen, clorhidratos, bromhidradros, sulfatos, metanosulfonatos, nitratos, maleatos, acetatos, citratos, fumaratos, tartratos [por ejemplo, (+)-tartratos, (-)-tartratos o mezclas de los mismos, incluyendo mezclas racémicas], succinatos, benzoatos y sales con aminoácidos como por ejemplo ácido glutámico.

Estas sales se pueden preparar mediante procedimientos conocidos para los expertos en la técnica.

Ciertos compuestos de Fórmula Estructural I y sus sales pueden existir también en forma de solvatos, por ejemplo hidratos, y la presente invención incluye cada solvato y mezclas de los mismos.

Los materiales poco cristalinos y/o amorfos son menos deseables, típicamente, que los materiales muy cristalinos para el procesado de las formulaciones. Los compuestos amorfos son menos estables química y físicamente y tienden a adsorber cantidades significativas de agua. La adsorción de agua por un material amorfo en una cápsula de gelatina, por ejemplo, puede causar que la cápsula se contraiga o deforme según se transfiere la humedad de la cápsula al componente amorfo. Además, los compuestos amorfos tienen tendencia a precipitar en las disoluciones que los contienen. Si un fármaco amorfo precipita en una disolución de administración, pueden verse afectadas negativamente las propiedades de disolución y biodisponibilidad del fármaco.

Además, no es deseable formular, en general, compuestos farmacéuticos que contengan cantidades sustanciales de un disolvente orgánico (por ejemplo, acetato de etilo) debido a la toxicidad potencial del disolvente para el receptor del fármaco y a los cambios de

potencia del compuesto farmacéutico en función del disolvente. Además, desde el punto de vista de la fabricación, también es menos deseable, en general, preparar materiales no cristalinos cuando dicha preparación implica la recogida del producto final por filtración. Dichas filtraciones son más difíciles de llevar a cabo, en general, cuando el material a recoger no es cristalino. Además, también es menos deseable, en general, desde el punto de vista de la fabricación, formular compuestos farmacéuticos que contengan cantidades sustanciales de agua (hidratos) porque el nivel de hidratación suele ser, típicamente, función de la humedad relativa a la que el compuesto farmacéutico se produce y almacena. En otras palabras, la variabilidad de potencia es más problemática, típicamente, para un hidrato que para la forma anhidra correspondiente.

Los profármacos son compuestos de la presente invención, que tienen grupos que se pueden escindir por vía química o metabólica y que se convierten, por solvólisis o en condiciones fisiológicas, en los compuestos de la invención, que son farmacéuticamente activos *in vivo*. Los profármacos incluyen derivados ácidos bien conocidos para los expertos en la técnica, como por ejemplo, ésteres preparados por reacción del compuesto ácido inicial con un alcohol adecuado, o amidas preparadas

por reacción del compuesto ácido inicial con una amina adecuada. Los profármacos preferidos son ésteres alifáticos o aromáticos sencillos provenientes de grupos ácidos colgantes sobre los compuestos de esta invención. En algunos casos, es deseable preparar profármacos de tipo doble éster como por ejemplo ésteres de (aciloxi)alquilo o ésteres de ((alcoxicarbonil)oxi)alquilo. Los ésteres particularmente preferidos como profármacos son los de metilo, etilo, propilo, isopropilo, n-butilo, isobutilo, terc-butilo, morfolinoetilo y N,N'-dietilglicolamido.

Los profármacos de éster de metilo se pueden preparar por reacción de la forma ácida de un compuesto de fórmula I en un medio como metanol con un catalizador de esterificación ácida o básica (por ejemplo, NaOH, H_2SO_4). Los profármacos de éster de etilo se preparan de manera similar usando etanol en lugar de metanol.

Los profármacos de éster de morfoliniletilo se pueden preparar por reacción de la sal de sodio de un compuesto de Fórmula Estructural I (en un medio de dimetilformamida, por ejemplo) clorhidrato de 4-(2-cloroetil)morfina (disponible en Aldrich Chemical Co., Milwaukee, Wisconsin, USA, Item N° C4, 220-3).

Caracterización de la forma cristalina del ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-

triazol-3-il]propil]fenoxi]-2-metil-propanoico

Se utilizan calorimetría de exploración diferencial, análisis termogravimétricos (DSC/TGA), adsorción/desorción de humedad y difracción de polvo con rayos X (XRD) para caracterizar el ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico. TGA es una medida de la pérdida de peso inducida térmicamente del material en función de la temperatura. Se usa habitualmente para estudiar los procesos de desolvatación y para la determinación cuantitativa del contenido total de volátiles en un sólido. DSC es una técnica que se usa habitualmente para detectar el polimorfismo de compuestos porque la(s) temperatura(s) a las que se produce el cambio físico en un material suele ser característica de dicho material. Las isotermas de adsorción de humedad proporcionan la evaluación del grado de hidroscopicidad asociado con un material dado y la caracterización de hidratos y no hidratos. Por último, XDR es una técnica que detecta grandes órdenes de magnitud en un material cristalino.

El polimorfo termodinámicamente favorable del ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico cristalino se caracteriza usando un difractómetro Siemens

D5000 equipado con una fuente de radiación CuKα (λ=1,54056 Ansgstroms) y un detector de estado sólido.

En la técnica cristalográfica se sabe que, para una forma cristalina dada, las intensidades relativas de los picos de difracción pueden variar debido a la orientación preferente resultante de factores como la morfología y el hábito cristalinos. En los lugares donde estén presentes los efectos de la orientación preferente se alteran las intensidades de los picos, pero las posiciones características de los picos del polimorfo no varían. Véase, por ejemplo, The United States Pharmacopeia n° 23, National Formulary n° 18, páginas 1843-1844, 1995. Además, en la técnica cristalográfica se sabe que, para una forma cristalina dada, las posiciones angulares del pico pueden variar ligeramente. Por ejemplo, las posiciones del pico pueden variar debido a la variación de la temperatura a la que se analiza la muestra, al desplazamiento de la muestra o a la presencia o ausencia de un patrón interno. En el presente caso, una variabilidad del pico de $\pm$ 0,2 en 2θ tiene en cuenta estas variaciones potenciales sin obstaculizar la identificación inequívoca de una forma cristalina deseada.

Un procedimiento bien conocido y aceptado para buscar formas cristalinas en la bibliografía es el procedimiento "Fink". El procedimiento Fink usa las cuatro líneas más

intensas para la búsqueda inicial seguidas de las cuatro líneas más intensas siguientes. Según el procedimiento Fink, basado en intensidades de pico y en posiciones de pico, la forma cristalina deseada del ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico se puede identificar por la presencia de picos a 13,2 +/- 0,2, 15,9 +/- 0,2, 20,7 +/- 0,2 y 24,1 +/- 0,2 en 2θ, cuando el patrón se obtiene a partir de una fuente de radiación de cobre. La presencia de la forma de ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico cristalino deseada se puede verificar también mediante los picos a 7,9 +/- 0,2, 17,37 +/- 0,2 y 19,5 +/- 0,2 en 2θ, cuando el patrón se obtiene a partir de una fuente de radiación de cobre.

El término "ingrediente activo" se refiere a compuestos descritos generalmente por la Fórmula Estructural I así como las sales, solvatos y profármacos de dichos compuestos.

El término "farmacéuticamente aceptable" significa que el vehículo, diluyente, excipiente y sal debe ser compatible con los otros ingredientes de la composición, y no debe ser perjudicial para el receptor de la misma. Las composiciones farmacéuticas de la presente invención se preparan mediante procedimiento conocidos en la técnica

usando ingredientes conocidos y fácilmente disponibles.

El término "prevención" se refiere a la reducción de la probabilidad de que el receptor sufra o desarrolle cualquiera de las afecciones patológicas descritas en la presente memoria.

El término "tratamiento" se refiere a la mediación de una enfermedad o afección y prevenir o mitigar su progresión posterior o mejorar los síntomas asociados con la enfermedad o afección.

El término "cantidad farmacéuticamente eficaz" significa que la cantidad de un compuesto, o de su sal, solvato, hidrato o profármaco, obtendrá la respuesta biológica o médica de un tejido, sistema o mamífero. Dicha cantidad se puede administrar profilácticamente a un paciente que se cree que es susceptible de desarrollar una enfermedad o afección. Cuando dicha cantidad se administra profilácticamente a un paciente, puede ser eficaz también para prevenir o atenuar la severidad de la afección mediada. Se pretende que dicha cantidad incluya una cantidad suficiente para modular un receptor de PPAR alfa o para prevenir o mediar una enfermedad o afección. Las afecciones prevenidas o tratadas mediante receptores de PPARα incluyen diabetes mellitus, enfermedades cardiovasculares, síndrome X, obesidad y enfermedades gastrointestinales.

Un "mamífero" es un individuo que es miembro de la clase taxonómica Mamíferos. La clase Mamíferos incluye humanos, monos, chimpancés, gorilas, ganado vacuno, cerdos, caballos, ovejas, perros, gatos, ratones y ratas.

Es preferible la administración a humanos. Los compuestos y composiciones de la presente invención son útiles para el tratamiento y/o profilaxis de enfermedades cardiovasculares, para aumentar los niveles de HDL de colesterol en suero, para disminuir los niveles de triglicéridos en suero y para disminuir los niveles de LDL de colesterol en suero. Un nivel elevado de triglicéridos y LDL y un nivel bajo de HDL son factores de riesgo para el desarrollo de enfermedades coronarias, ictus y otros trastornos y enfermedades del sistema circulatorio.

Los compuestos y composiciones de la presente invención también son útiles para tratar y/o prevenir la obesidad.

Además, estos compuestos y composiciones son útiles para el tratamiento y/o profilaxis de la diabetes mellitus no dependiente de insulina (NIDDM) con ganancia de peso reducida o inexistente de los pacientes. Además, los compuestos y composiciones de la presente invención son útiles para tratar o prevenir trastornos agudos o transitorios en la sensibilidad a insulina, como por ejemplo la que ocurre después de una operación quirúrgica,

trauma, infarto de miocardio y similares. El médico experto en la técnica sabe identificar los seres humanos que se beneficiarán de la administración de los compuestos y composiciones de la presente invención.

La presente invención proporciona también un procedimiento para el tratamiento y/o profilaxis de la hiperglucemia en un mamífero humano o no humano que comprende administrar una cantidad eficaz inocua de un compuesto de fórmula general (I), o una forma tautomérica del mismo y/o una sal farmacéuticamente aceptable del mismo y/o un solvato farmacéuticamente aceptable del mismo a un mamífero hiperglucémico humano o no humano que lo necesite.

Son útiles como sustancias terapéuticas en la prevención o tratamiento del síndrome X, la diabetes mellitus y las enfermedades y trastornos endocrinos y cardiovasculares relacionados en seres humanos o animales.

La invención se refiere también al uso de un compuesto de fórmula I según se ha descrito anteriormente, para la fabricación de un medicamento para tratar una afección mediada por PPARα.

Se puede usar una cantidad terapéuticamente eficaz de un compuesto de fórmula estructural I para la preparación de un medicamento útil para tratar el síndrome X, la diabetes, la obesidad, para disminuir los niveles de

triglicéridos, disminuir los niveles de LDL en suero, aumentar el nivel en plasma de lipoproteína de alta densidad y para tratar, prevenir o reducir el riesgo de desarrollar aterosclerosis y para prevenir o reducir el riesgo de tener una primera o posterior enfermedad aterosclerótica en mamíferos, particularmente en seres humanos. En general, una cantidad terapéuticamente eficaz de un compuesto de la presente invención reduce, típicamente, los niveles de triglicéridos en el suero de un paciente en aproximadamente un 20% o más, y aumenta los niveles de HDL en suero en un paciente. Preferiblemente, los niveles de HDL aumentan aproximadamente un 30% o más. Además, una cantidad terapéuticamente eficaz de un compuesto, usada para prevenir o tratar NIDDM, reduce típicamente los niveles de glucosa en suero, o más específicamente HbA1c, de un paciente en aproximadamente un 0,7% o más.

Ventajosamente, las composiciones que contienen el compuesto de fórmula estructural I o las sales del mismo se pueden proporcionar en forma de dosificaciones unitarias, preferiblemente cada unidad de dosificación contiene de aproximadamente 1 a aproximadamente 500 mg, aunque fácilmente se entiende que la cantidad de compuesto o compuestos de fórmula estructural I que se debe

administrar realmente la determinará el médico, según las circunstancias relevantes.

Según se usa en la presente memoria descriptiva el síndrome X incluye el síndrome prediabético de resistencia a insulina y las complicaciones resultantes del mismo, la resistencia a insulina, la diabetes no dependiente de insulina, la dislipidemia, la obesidad por hiperglucemia, la coagulopatía, la hipertensión y otras complicaciones asociadas con la diabetes. Los procedimientos y tratamientos mencionados en la presente memoria descriptiva incluyen los anteriores y engloban el tratamiento y/o profilaxis de cualquiera de los siguientes o cualquier combinación de los siguientes: síndrome prediabético de resistencia a insulina, las complicaciones resultantes del mismo, la resistencia a insulina, la diabetes tipo II o no dependiente de insulina, la dislipidemia, la hiperglucemia, la obesidad y las complicaciones asociadas con la diabetes incluyendo enfermedades cardiovasculares, especialmente aterosclerosis.

Las composiciones se formulan y administran del mismo modo general detallado en la presente memoria descriptiva. Los compuestos de la presente invención se pueden usar eficazmente en solitario o combinados con uno o más agentes activos dependiendo de la terapia diana

pretendida. La terapia combinada incluye la administración de una composición de una sola dosis farmacéutica que contiene un compuesto de fórmula estructural I y uno o más agentes activos, así como la administración de un compuesto de fórmula estructural I y cada agente activo en su propia formulación de dosificación farmacéutica separada. Por ejemplo, se puede administrar al paciente un compuesto de fórmula estructural I o un secretogogo de insulina como por ejemplo inhibidores de biguanidas, tiazolidindionas, sulfonilureas, insulina o α-glucosidosa junto con una composición de una sola dosificación oral como por ejemplo un comprimido o cápsula o cada agente se administra en formulaciones de dosificación oral por separado. Cuando se usan formulaciones de dosificación por separado, se puede administrar un compuesto de fórmula estructural I y uno o más agentes activos adicionales esencialmente al mismo tiempo, es decir, de manera concurrente, o en tiempos escalonados por separado, es decir, secuencialmente; se entiende que la terapia combinatoria incluye todos estos regímenes.

Un ejemplo de tratamiento combinatorio o prevención de aterosclerosis puede ser en el que se administra un compuesto de fórmula estructural I o sales del mismo combinado con uno o más de los siguientes agentes activos: agentes antihiperlipidémicos; agentes que aumentan HDL en

plasma; agentes antihipercolesterolémicos; fibratos, vitaminas, aspirina y similares. Como se ha indicado anteriormente, los compuestos de fórmula estructural I se pueden administrar combinados con más de un agente activo adicional.

Otro ejemplo de terapia combinatoria puede observarse al tratar la diabetes y los trastornos relacionados cuando los compuestos de fórmula estructural I y las sales de los mismos se pueden usar eficazmente combinados con, por ejemplo, inhibidores de sulfonilureas, biguanidas, tiazolidindionas, α-glucosidasa, otros secretogogos de insulina, insulina, así como los agentes activos discutidos anteriormente para el tratamiento de la aterosclerosis.

Los compuestos de la presente invención, y las sales, solvatos e hidratos farmacéuticamente aceptables de los mismos, tienen propiedades farmacológicas valorables y se pueden usar en composiciones farmacéuticas que contienen una cantidad terapéuticamente eficaz de un compuesto de la presente invención, o sales, ésteres o profármacos farmacéuticamente aceptables de los mismos, combinados con uno o más excipientes farmacéuticamente aceptables. Los excipientes son sustancias inertes como por ejemplo, sin limitación, vehículos, diluyentes, cargas, aromatizantes, edulcorantes, lubricantes, solubilizantes, agentes de

suspensión, humectantes, aglutinantes, desintegrantes, material encapsulante y otros adyuvantes convencionales. La formulación apropiada depende de la vía de administración elegida. Las composiciones farmacéuticas contienen, típicamente, de aproximadamente 1 a aproximadamente 99% en peso del ingrediente activo que es un compuesto de la presente invención.

Preferiblemente, la formulación farmacéutica es una forma de dosificación unitaria. Una "forma de dosificación unitaria" es una unidad físicamente discreta que contiene una dosis unitaria, adecuada para administración en sujetos humanos u otros mamíferos. Por ejemplo, una forma de dosificación unitaria puede ser una cápsula o un comprimido, o un número de cápsulas o comprimidos. Una "dosis unitaria" es una cantidad predeterminada del compuesto activo de la presente invención, calculada para producir el efecto terapéutico deseado, asociado con uno o más excipientes farmacéuticamente aceptables. La cantidad de ingrediente activo en una dosis unitaria se puede variar o ajustar entre aproximadamente 0,1 y aproximadamente 1000 miligramos o más según el tratamiento particular implicado.

El régimen de dosificación de los compuestos de la presente invención lo selecciona un experto en la técnica médica o veterinaria, teniendo en cuenta una variedad de

factores, incluyendo, sin limitación, la especie, la edad, el peso, el sexo y el estado médico del receptor, la severidad del estado a tratar, la vía de administración, el nivel de función metabólica y excretora del receptor, la forma de dosificación empleada, el compuesto particular y la sal del mismo empleados y similares.

Preferiblemente, los compuestos de la presente invención se administran en una sola dosis diaria, o la dosis diaria total se puede administrar en dosis divididas, dos, tres o más veces al día. Cuando la administración es por vía transdérmica, la administración, por supuesto, es continua.

Las vías de administración de las composiciones farmacéuticas de la presente invención incluyen, por ejemplo, administración oral, gotas para los ojos, rectal, transmucosa, tópica o intestinal; administración parenteral (bolus o infusión), incluyendo inyecciones intramusculares, subcutáneas e intramedulares así como inyecciones intratecales, intraventricular directa, intravenosa, intraperitoneal, intranasal o intraocular. Los compuestos de la invención se pueden administrar también en un sistema diana de administración de fármaco, como por ejemplo en un liposoma revestido con anticuerpos específicos de las células del endotelio.

Para administración oral de un paciente a tratar, los compuestos se pueden formular fácilmente combinando los compuestos activos con vehículos farmacéuticamente aceptables bien conocidos en la técnica. Dichos vehículos permiten que los compuestos de la invención se formulen como comprimidos, píldoras, polvos, saquitos, gránulos, grageas, cápsulas, líquidos, elixires, tintes, geles, emulsiones, siropes, pastas, suspensiones y similares, para ingestión oral. Las preparaciones farmacéuticas para uso oral se pueden obtener combinando el compuesto activo con un excipiente sólido, opcionalmente moliendo la mezcla resultante, y procesando la mezcla de gránulos después de añadir los compuestos auxiliares adecuados, si se desea, para obtener los núcleos de los comprimidos o grageas.

Para administración oral en forma de comprimido o cápsula, el ingrediente activo se puede combinar con un vehículo oral inocuo farmacéuticamente aceptable, como por ejemplo, sin limitación, lactosa, almidón, sacarosa, glucosa, metilcelulosa, carbonato de calcio, fosfato de calcio, sulfato de calcio, carbonato de sodio, manitol, sorbitol y similares; junto con, opcionalmente, desintegrantes, como por ejemplo, sin limitación, polivinilpirrolidona reticulada, maíz, almidón, metilcelulosa, agar, bentonita, goma xantano, ácido algínico o una sal del mismo como por ejemplo alginato

sódico y similares; y, opcionalmente, aglutinantes, por ejemplo, sin limitación, gelatina, goma arábiga, azúcares naturales, beta-lactosa, edulcorantes de maíz, gomas naturales y sintéticas, goma arábiga, tragacanto, alginato sódico, carboximetilcelulosa, polietilenglicol, ceras y similares y, opcionalmente, lubricantes, por ejemplo, sin limitación, estearato de magnesio, estearato de sodio, ácido esteárico, oleato de sodio, benzoato de sodio, acetato de sodio, cloruro de sodio, talco y similares. Cuando la forma de dosificación unitaria es una cápsula, puede contener, además de los materiales anteriores, un vehículo líquido como por ejemplo un aceite graso.

Las formulaciones en forma sólida incluyen polvos, comprimidos y cápsulas. Un vehículo sólido puede ser una o más sustancias que pueden actuar también como aromatizantes, lubricantes, solubilizantes, agentes de suspensión, aglutinantes, desintegrantes de comprimidos y material de encapsulación.

En los polvos, el vehículo es un sólido finamente dividido que está mezclado con el ingrediente activo finamente dividido. En los comprimidos, el ingrediente activo está mezclado con un vehículo que tiene las propiedades de aglutinamiento necesarias y las proporciones adecuadas y compactado en la forma y tamaño deseados.

Pueden estar presentes otros materiales diversos como revestimientos para modificar la forma física de la unidad de dosificación. Por ejemplo, los comprimidos pueden estar revestidos con una goma laca, un azúcar o ambos. Un jarabe o elixir puede contener, además del ingrediente activo, sacarosa como edulcorante, metilo y poliparabenos como conservantes, un tinte y un aromatizante como por ejemplo aroma de cereza o naranja.

Las formulaciones líquidas estériles, incluyen suspensiones, emulsiones, jarabes y elixires. El ingrediente activo se puede disolver o suspender en un vehículo farmacéuticamente aceptable, como por ejemplo agua estéril, un disolvente orgánico estéril o una mezcla de ambos agua estéril y un disolvente orgánico estéril.

El ingrediente activo se puede disolver también en un disolvente orgánico adecuado, por ejemplo, propilenglicol acuoso. Se pueden fabricar otras composiciones dispersando el ingrediente activo finamente dividido en almidón acuoso o en una disolución de carboximetilcelulosa de sodio o en un aceite adecuado.

Los núcleos de las grageas están provistos de los revestimientos adecuados. Para este propósito, se pueden usar disoluciones concentradas de azúcar, que opcionalmente pueden contener goma arábiga, talco, polivinilpirrolidona, gel carbopol, polietilenglicol y/o

dióxido de titanio, disoluciones de laca y disolventes orgánicos adecuados o mezclas de disolventes. Se pueden añadir tintes o pigmentos a los revestimientos de los comprimidos o grageas para identificación o para caracterizar diferentes combinaciones de dosis del compuesto activo.

Las preparaciones farmacéuticas que se pueden usar oralmente incluyen cápsulas de ajuste suave de gelatina, así como cápsulas blandas sellada de gelatina y un plastificante, como por ejemplo glicerol o sorbitol. Las cápsulas de ajuste suave pueden contener los ingredientes activos mezclados con una carga como lactosa, aglutinantes como almidones y/o lubricantes como talco o estearato de magnesio y, opcionalmente, estabilizantes. En las cápsulas blandas, los compuestos activos se pueden disolver o suspender en los líquidos adecuados, como por ejemplo aceites grasos, parafinas líquidas o polietilenglicoles líquidos. Además, se pueden añadir estabilizantes.

Todas las formulaciones para administración oral deben estar en dosificaciones adecuadas para dicha administración. Las composiciones particularmente adecuadas para administración oral son las formas de dosificación unitaria como por ejemplo comprimidos y cápsulas.

Para administración parenteral, los compuestos de la presente invención o las sales de los mismos, se pueden combinar con medios acuosos estériles u orgánicos para formar disoluciones o suspensiones inyectables. Las formulaciones para inyección se pueden presentar en formas de dosificación unitarias, como por ejemplo ampollas o en recipientes multidosis, con un conservante añadido. Las composiciones pueden tomar la forma de suspensiones, disoluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes formuladores como por ejemplo agentes de suspensión, estabilización y/o dispersión. Las formas farmacéuticas adecuadas para uso inyectable incluyen disoluciones o dispersiones acuosas estériles y polvos estériles para la preparación extemporánea de disoluciones inyectables estériles. En todos los casos, la forma debe ser estéril y debe mantenerse fluida mientras se pueda inyectar. Debe ser estable en las condiciones de fabricación y almacenamiento y se debe prevenir cualquier tipo de contaminación. El vehículo puede ser un disolvente o un medio de dispersión que contienen, por ejemplo, agua, preferiblemente en tampones fisiológicamente compatibles como por ejemplo disolución de Hank, disolución de Ringer o tampón salino fisiológico, etanol, poliol (por ejemplo, glicerol, propilenglicol y polietilenglicol líquido), propilenglicol y polietilenglicol líquido), mezclas

adecuadas de los mismos y aceites vegetales. En las condiciones habituales de almacenamiento y utilización, estas preparaciones contienen un conservante para evitar el crecimiento de microorganismos.

Las disoluciones inyectables preparadas de esta manera se pueden administrar después intravenosa, intraperitoneal, subcutánea o intramuscularmente, siendo la vía intramuscular la preferida en seres humanos.

Para administración transmucosa, en la formulación se usan penetradores de barrera apropiados para que se pueda permear dicha formulación. Dichos penetradores son conocidos, en general, en la técnica. Los compuestos activos se pueden administrar intranasalmente como, por ejemplo, gotas líquidas o pulverizadores.

Para administración bucal, las composiciones se pueden tomar en forma de comprimidos o pastillas formuladas de manera convencional.

Para administración por inhalación, los compuestos para usar según la presente invención se administran convenientemente en forma de inhalador en polvo seco o como presentación de pulverizador en aerosol en envases presurizados o un nebulizador usando el propulsor adecuado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas adecuado. En el caso de un aerosol

presurizado, la unidad de dosificación se puede proporcionar proveyendo una válvula para administrar una cantidad medida. Las cápsulas y cartuchos de gelatina para usar en un inhalador o insuflador se pueden formular de manera que contienen una mezcla en polvo del compuesto y una base de polvo adecuada como por ejemplo lactosa o almidón.

Las composiciones farmacéuticas de la presente invención se pueden fabricar de manera conocida, por ejemplo, mediante procedimientos de mezcla, disolución, granulación, fabricación de grageas, levigación, emulsión, encapsulación, oclusión o liofilización.

Para fabricar las composiciones de la presente invención, el ingrediente activo se mezcla, en general, con un vehículo o se diluye con un vehículo o se engloba en un vehículo que puede estar en forma de cápsula, saquito, papel u otro tipo de contenedor. Cuando el vehículo sirve como diluyente, puede ser un material sólido, sólido liofilizado o pasta, semisólido o líquido que actúa como vehículo o puede estar en forma de comprimidos, píldoras, polvos, pastillas, elixires, suspensiones, emulsiones, disoluciones, jarabes, aerosoles (en un medio sólido o líquido) o pomada, que contiene, por ejemplo, hasta un 10% en peso del compuesto activo. Los

compuestos de la presente invención se formulan, preferiblemente, antes de su administración.

Las siguientes formulaciones farmacéuticas 1 a 8 solo son ilustrativas y no se pretende que limiten de modo alguno el alcance de la invención. "Ingrediente Activo" se refiere a un compuesto según la fórmula estructural I o las sales del mismo.

Formulación 1

Las cápsulas duras de gelatina se preparan usando los siguientes ingredientes:

	Cantidad (mg/cápsula)
Ingrediente activo	250
Almidón, secado	200
Estearato de magnesio	100
Total	460 mg

Formulación 2

Un comprimido se prepara usando los siguientes ingredientes:

	Cantidad (mg/comprimido)
Ingrediente activo	250
Celulosa microcristalina	400
Dióxido de silicio, pirógeno	10
Ácido esteárico	5
Total	665 mg

Los componentes se mezclan y comprimen para formar los comprimidos, pesando cada uno de ellos 665 mg.

Formulación 3

Una disolución en aerosol se prepara usando los siguientes ingredientes:

	Peso
Ingrediente activo	0,25
Etanol	25,75
Propulsor 22 (clorodifluorometano)	74,00
Total	100,00 mg

El ingrediente activo se mezcla con etanol y la mezcla se añade a un parte del propulsor 22 se enfría a 30°C y se

transfiere a un dispositivo de llenado. Después, se alimenta la cantidad requerida a un depósito de acero inoxidable y se diluye con lo que queda del propulsor. Después, las unidades de válvula se ajustan al depósito.

Formulación 4

Los comprimidos, cada uno de 60 mg del ingrediente activo, se preparan de la siguiente manera:

Ingrediente activo	60 mg
Almidón	45 mg
Celulosa microcristalina	35 mg
Polivinilpirrolidona (disolución al 10% en agua)	4 mg
Carboximetilo sódico de almidón	4,5 mg
Estearato de magnesio	0,5 mg
Talco	1 mg
Total	150 mg

El ingrediente activo, el almidón y la celulosa se hacen pasar a través de un tamiz U.S. de malla N° 45 y se mezclan vigorosamente. La disolución acuosa que contiene polivinilpirrolidona se mezcla con el polvo resultante y, después, la mezcla se hace pasar a través de un tamiz U.S. de malla N° 14. Los gránulos producidos de esta manera se secan a 50°C y se hacen pasar a través de un tamiz U.S. de malla N° 18. El carboximetilo sódico de almidón, el

estearato de magnesio y el talco se hacen pasar previamente a través de un tamiz U.S. de malla N° 60. y después se añaden a los gránulos, y después de la mezcla éstos se comprimen en un aparato al efecto dando comprimidos que pesan 150 mg cada uno.

Formulación 5

Las cápsulas, cada una de 80 mg de ingrediente activo, se preparan de la siguiente manera:

Ingrediente activo	80 mg
Almidón	59 mg
Celulosa microcristalina	59 mg
Estearato de magnesio	2 mg
Talco	2 mg
Total	200 mg

Se mezclan el ingrediente activo, la celulosa, el almidón y el estearato de magnesio, se hacen pasar a través de un tamiz U.S. de malla N° 45 y se utilizan para rellenar cápsulas duras de gelatina en cantidades de 200 mg.

Formulación 6

Los supositorios, cada uno de 225 del ingrediente activo, se preparan de la siguiente manera:

Ingrediente activo	225 mg
Glicéridos saturados de ácido graso	2.000 mg
Total	2.225 mg

El ingrediente activo se hace pasar a través de un tamiz U.S. de malla N° 60 y se suspende en los glicéridos saturados de ácido graso fundidos previamente usando el calor mínimo necesario. Después, la mezcla se vierte en un molde de supositorio de capacidad nominal 2 g y se deja enfriar.

Formulación 7

Las suspensiones, cada una de 50 mg de ingrediente activo por cada 5 ml de dosis, se preparan de la siguiente manera:

Ingrediente activo	50 mg
Carboximetilcelulosa de sodio	50 mg
Jarabe	1,25 ml
Disolución de ácido benzoico	0,10 ml
Aroma	c.s.
Color	c.s.
Agua purificada hasta el total	5 ml

El ingrediente activo se hace pasar a través de un tamiz U.S. de malla N° 45 y se mezcla con la carboximetilcelulosa de sodio y el jarabe para formar una pasta suave. La disolución de ácido benzoico, aroma y color se diluye con una parte del agua y se añade, con agitación. Después, se añade suficiente agua para producir el volumen requerido.

Formulación 8

Una formulación intravenosa se puede preparar de la siguiente manera:

Ingrediente activo	100 mg
Solución salina isotónica	1.000 ml

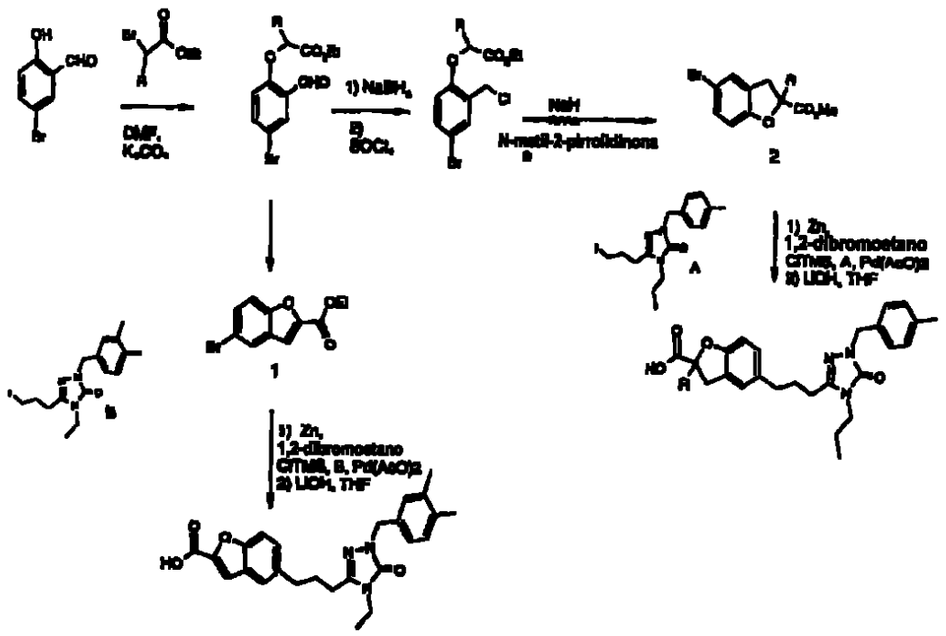
La disolución de los materiales anteriores se administra, generalmente, por vía intravenosa a un sujeto a una velocidad de 1 ml por minuto.

En otra realización de los compuestos de la presente invención, el compuesto se radiomarca, como por ejemplo con carbono-14, o se tritia. Dichos compuestos radiomarcados o tritiados son útiles como patrones de referencia para ensayos in vitro para identificar nuevos agosnistas de PPARα.

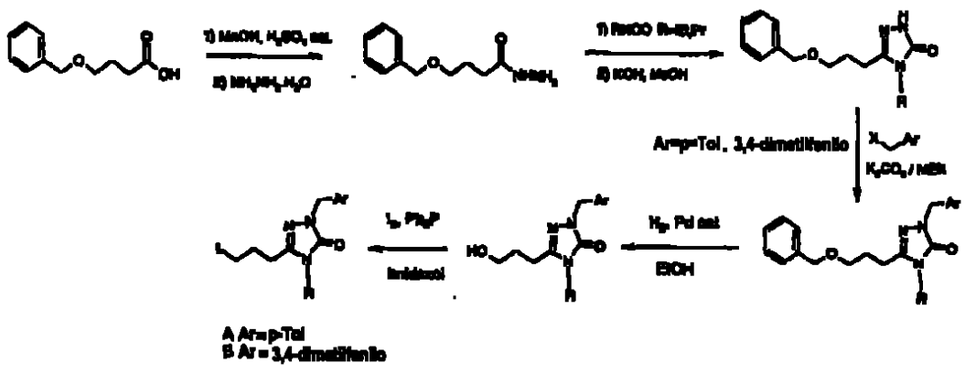
SÍNTESIS

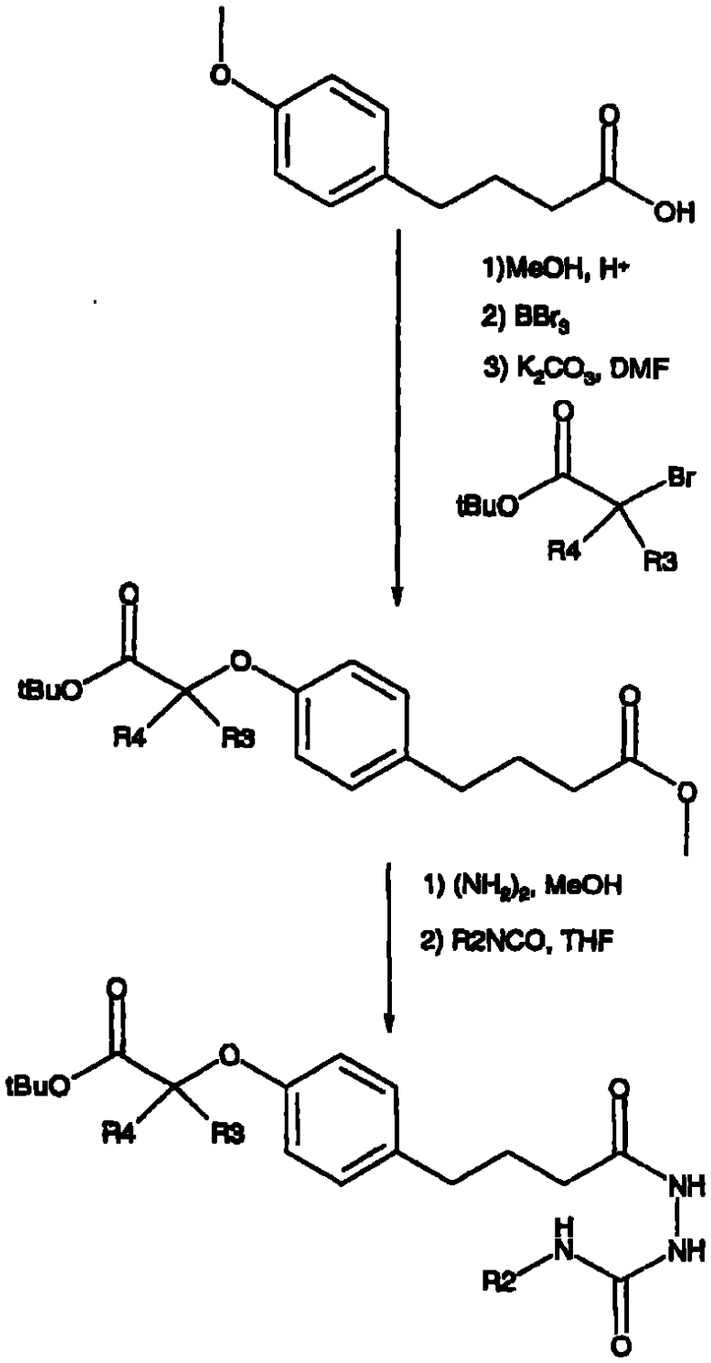
Los compuestos de la presente invención se han formado de la manera específica descrita en los ejemplos. Además, la mayoría de compuestos se han preparado más generalmente según lo mostrado en el siguiente esquema. Los procedimientos de síntesis alternativos pueden ser eficaces también y conocidos para los expertos en la técnica.

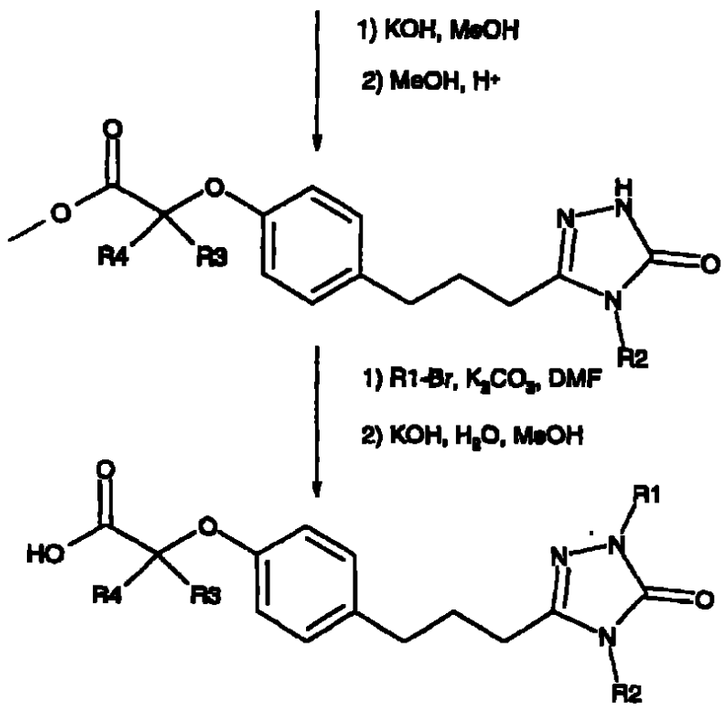
Ciertos compuestos de esta invención se han preparado como se muestra en el esquema 1. Los intermedios 1, 2 se han obtenido de aldehído a partir p-bromo salicilo y alfa-bromo ésteres disponibles en el mercado. Los intermedios A y B se han obtenido siguiendo la secuencia de reacción mostrada en el esquema 2. Los compuestos finales se han obtenido mediante una reacción de acoplamiento con catalizador de paladio entre 1 y 2 con A o B, seguida de hidrólisis básica del éster al ácido.



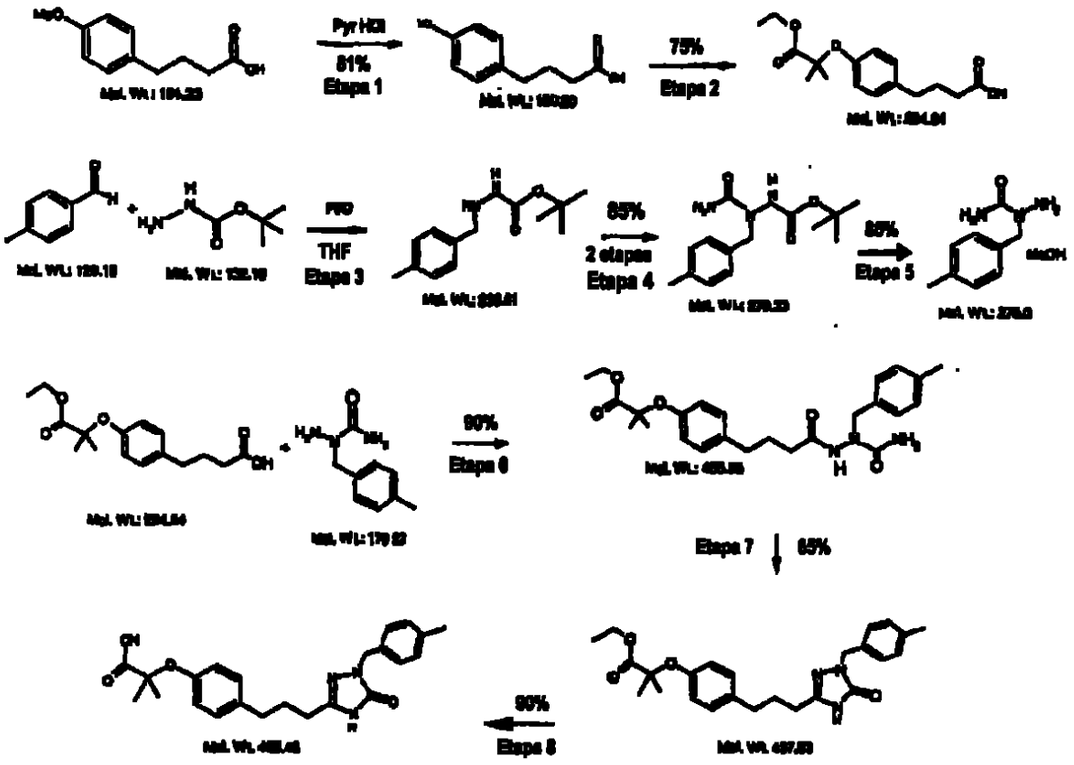
Esquema 2




O
OH
1)MeOH, H+
2) BBr3
3) K2CO3, DMF
O
tBuO
Br
R4
R3
tBuO
O
R4
R3
O
O
1) (NH2)2, MeOH
2) R2NCO, THF
tBuO
O
R4
R3
O
NH
H
N
NH
R2
O


1) KOH, MeOH
2) MeOH, H+
1) R1-Br, K2CO3, DMF
2) KOH, H2O, MeOH

Agonista de PPAR alfa 518674 DSR 10-00



Los ejemplos proporcionados en este documento son ilustrativos de la invención y no pretenden limitar el alcance de la invención reivindicada en forma alguna.

EJEMPLIFICACIÓN

Análisis Instrumental

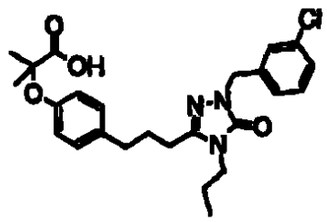
Los espectros infrarrojos se registraron en un espectrómetro Perkin Elmer 781. Los espectros de ^{1}H RMN se registraron en un espectrómetro Varian 400 MHz a temperatura ambiente. Los datos se proporcionan como se indica a continuación: los desplazamientos químicos en ppm a partir del patrón interno tetrametilsilano en la escala δ, multiplicidad (a = ancho, s = singlete, d = doblete, t = triplete, c = cuadruplete, qn = quintuplete y m = multiplete), integración, constante de acoplamiento (Hz) y asignación. La ^{13}C RMN se registró en un espectrómetro Varian de 400 MHz a temperatura ambiente. Los desplazamientos químicos se presentan en ppm a partir de tetrametilsilano en la escala δ, empleando la resonancia del disolvente como patrón interno ($CDCl_3$ a 77,0 ppm y DMSO-d_6 a 39,5 ppm). Los análisis de combustión se realizaron por Eli Lilly & Company Microanalytical Laboratory. Los espectros de masas de alta resolución se obtuvieron en espectrómetros VG ZAB 3F o VG 70 SE. La cromatografía de capa fina analítica se realizó sobre placas 60-F de gel de sílice de 0,25 mm de reactivo de EM. La visualización se realizó con

luz UV.

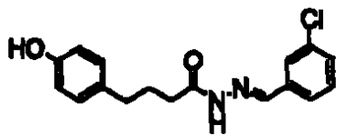
Compuestos Ejemplificados

Ejemplo 1

El compuesto 1, mostrado más adelante, se preparó de acuerdo a las Etapas indicadas a continuación:

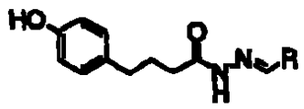


Etapa A: Preparación de



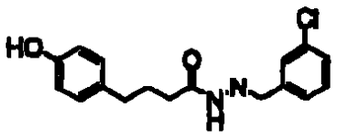
A una suspensión de 4-(4-hidroxifenil)butirilhidrazida (0,5 g, 2,58 mmol) en isopropanol (5 ml) se le añadió 3-cloro-benzaldehído (Aldrich, 420 mg, 3 mmol), seguido de ácido toluenosulfónico (25 mg). La mezcla de reacción se agitó a temperatura ambiente durante 20 horas. Un sólido separado, que se había filtrado, se lavó con isopropanol (0,25 ml) y se secó, dando el producto en forma de un sólido. MS: m/z (M^+ +1): 317.

Otros compuestos, mostrados más adelante, se prepararon sustituyendo el 3-cloro-benzaldehído por el benzaldehído apropiado.



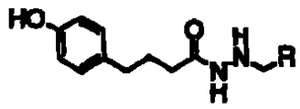
R	MS: m/z (M^+ + 1)
3-Metilfenilo	297
Fenilo	283
2,4-Difluorofenilo	319
2-Metilfenilo	297
3-Metoxifenilo	313

Etapa B: Preparación de:



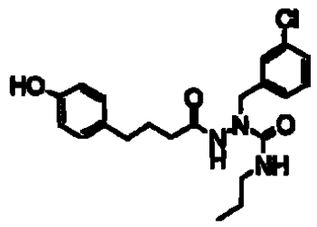
A una solución del producto de la Etapa A (650 mg, 2,05 mmol Ejemplo 1) en una mezcla de 5 ml de isopropanol, tetrahidrofurano y ácido acético (1:1:0,3) se le añadió cianoborohidruro sódico (1,25 g, 20 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 30 h. La mezcla de reacción de diluyó con acetato de etilo (50 ml) y se lavó con agua (2 x 75 ml). La fase orgánica se secó (Na_2SO_4) y se concentró a sequedad, dando el producto en forma de un jarabe. MS: m/z (M^+ + 1): 319.

También se prepararon otros compuestos, mostrados a continuación:



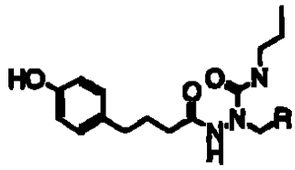
R	MS: m/z (M^+ + 1)
3-Metilfenilo	299
Fenilo	285
2,4-Difluorofenilo	321
2-Metilfenilo	299
3-Metoxifenilo	315

Etapa C: Preparación de:



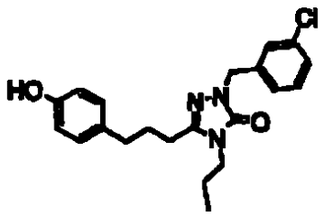
A una solución del producto de la Etapa B (400 mg, 1,26 mmol) en THF anhidro (5 ml) se le añadió isocianato de n-propilo (213 mg, 2,52 mmol). La mezcla de reacción se agitó durante 16 horas. A la mezcla de reacción se le añadió metanol (1 ml) y se continuó agitando durante 30 min más. El disolvente se retiró sobre un evaporador rotatorio, dando el producto en forma de un residuo oleoso. MS: m/z (M^+ + 1): 404

También se prepararon otros compuestos, mostrados a continuación:



R	MS: m/z (M^+ + 1)
3-Metilfenilo	384
Fenilo	370
2,4-Difluorofenilo	406
2-Metilfenilo	384
3-Metoxifenilo	400

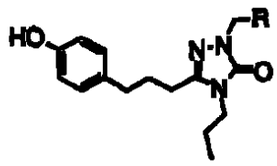
Etapa D: Preparación de 2-(3-clorobencil)-5-(3-(4-hidroxifenil)propil)-4-n-propiltriazolin-3H-3-ona



Se disolvió el producto de la Etapa C, [carbazato de 1-(4-(4-hidroxifenil))butiril-2-(3-clorobencil)-4-n-propilo] (200 mg), en metanol (20 ml). A esta solución se le añadió hidróxido potásico sólido (0,50 g) y la mezcla de reacción se calentó a reflujo durante 24 horas con agitación. La mezcla de reacción se concentró hasta un pequeño volumen (5 ml) y se diluyó con agua (50 ml) y después, la capa acuosa se acidificó con ácido clorhídrico 5 N (pH ~ 2). La capa acuosa se extrajo con acetato de etilo

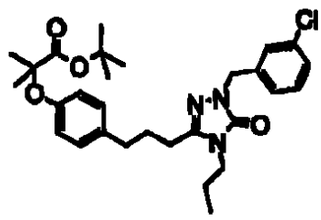
(2 x 50 ml), la capa orgánica se secó (Na_2SO_4) y el disolvente se retiró sobre un evaporador rotatorio, dando el producto en forma de un residuo oleoso. MS: m/z (M^+ + 1): 386

También se prepararon otros compuestos, mostrados a continuación:



R	MS: m/z (M^+ + 1)
3-Metilfenilo	366
Fenilo	352
2,4-Difluorofenilo	388
2-Metilfenilo	366
3-Metoxifenilo	382

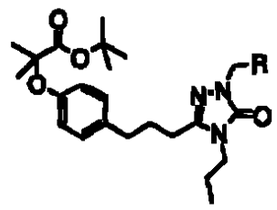
Etapa E: Preparación de:



A una solución del producto de la Etapa D, [2-(3-clorobencil)-5-(3-(4-hidroxifenil)propil)-4-n-propiltriazolin-3H-3-ona] (0,17 g, 0,45 mmol), en DMF anhidro (5 ml) se le añadió bromoisobutirato de *terc*-butilo

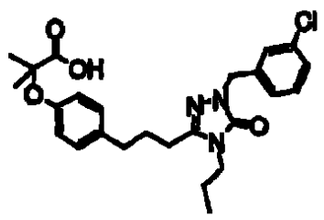
(0,70 g, 3,14 mmol) seguido de K_2CO_3 (1,0 g, en polvo). La mezcla de reacción se agitó a 50°C durante 64 horas. La mezcla de reacción se diluyó con agua (30 ml) y se extrajo con acetato de etilo (2 x 25 ml). La capa de acetato de etilo se secó (Na_2SO_4) y se concentró sobre un evaporador rotatorio para dar un residuo oleoso, que se purificó adicionalmente en una columna sobre gel de sílice (1 cm x 7 in.), eluyendo con una mezcla de acetato de etilo-hexano (20-30% v/v), dando el producto en forma de un aceite. MS: m/z (M^+ + 1); 530.

También se prepararon otros compuestos, mostrados a continuación:



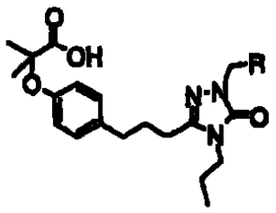
R	MS: m/z (M^+ + 1)
3-Metilfenilo	466
Fenilo	452
2,4-Difluorofenilo	530
2-Metilfenilo	466
3-Metoxifenilo	

Etapa F: Preparación de:



El producto de la Etapa E (180 mg) se trató con una mezcla de ácido trifluoroacético y diclorometano (10 ml, 50% v/v) con agitación durante 3 horas. El disolvente se retiró sobre un evaporador rotatorio y el residuo se secó a alto vacío, dando el compuesto del título en forma de un aceite. MS: m/z (M^+ + 1): 472,9.

También se prepararon otros compuestos, mostrados a continuación:

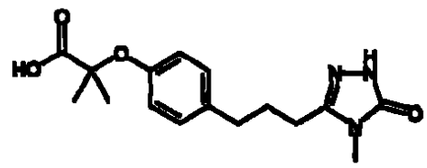


Ejemplo Número	R	MS: m/z (M^+ + 1)
1(2)	3-Metilfenilo	452
1(3)	Fenilo	438
1(4)	2,4-Difluorofenilo	473
1(5)	2-Metilfenilo	452
1(6)	3-Metoxifenilo	468

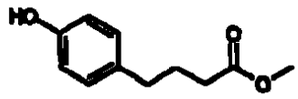
Ejemplo 2

Compuesto 2(1)

El compuesto mostrado a continuación se preparó como se indica más adelante:

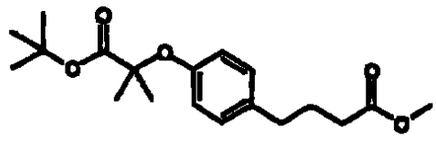


Etapa A: Preparación de:



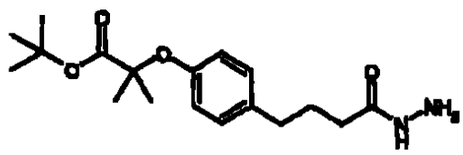
A una solución enfriada (0°C) de tribromuro de boro (50 g, 200 mmol) en CH_2Cl_2 (50 ml) se le añadió gota a gota durante una hora una solución de 4-(4-metoxifenil)butirato de metilo (15,5 g, 74,4 mmol) en CH_2Cl_2 (100 ml). Después de agitar durante una hora más a 0°C, la mezcla de reacción se trató con 1:1 CH_3OH:CH_2Cl_2 (120 ml) con refrigeración y agitación durante una noche a temperatura ambiente. La concentración de la mezcla dio un aceite que se repartió entre acetato de etilo (150 ml) y agua (150 ml). La capa acuosa se extrajo con acetato de etilo (2 x 50 ml) y los extractos orgánicos combinados se lavaron con agua (50 ml) y salmuera (50 ml), se secaron (Na_2SO_4) y después se concentraron, dando el fenol deseado en forma de un aceite. $C_{12}H_{14}O_3$ (PM = 194,23); MS: m/z (M^+ + 1) = 195

Etapa B: Preparación de:



El fenol de la Etapa A (18,6 g, 96 mmol) se disolvió en DMF (300 ml) y se trató con 2-bromoisobutirato de t-butilo (50 ml, 288 mmol), K_2CO_3 en polvo (53,0 g, 384 mmol) y $MgSO_4$ (1,6 g, 95 mmol) y la mezcla resultante se calentó a 75°C durante una noche. Después de la refrigeración a temperatura ambiente, la mezcla de reacción se decantó en HCl acuoso 1 N (300 ml) y se extrajo con éter dietílico (3 x 150 ml). Los sólidos restantes de la decantación se lavaron varias veces con éter dietílico. Los extractos de éter dietílico y los lavados se combinaron con HCl acuoso 1 N (150 ml), se secaron (Na_2SO_4) y se concentraron para dar un aceite oscuro. La purificación por cromatografía ultrarrápida (elución en gradiente, hexanos a 95:5 de hexanos:acetato de etilo), dio el éter deseado en forma de un aceite. $C_{19}H_{28}O_5$ (PM = 336,43):MS: m/z (M^+ + 1) = 337

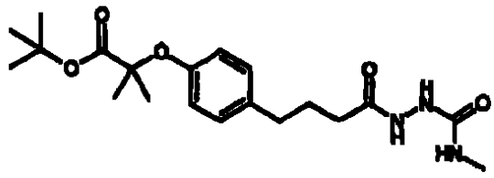
Etapa C: Preparación de:



Una solución del éter de la Etapa B (21,8 g, 64 mmol) en metanol (250 ml) se trató con hidrato de hidrazina (32,0

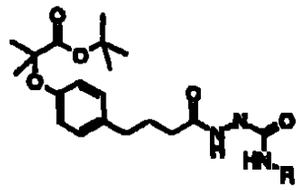
g, 650 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se concentró y el residuo se repartió entre acetato de etilo (250 ml) y agua (100 ml). La capa acuosa se extrajo con acetato de etilo (2 x 100 ml) y los extractos orgánicos combinados se lavaron con salmuera (100 ml), se secaron (Na_2SO_4) y se concentraron, dando la acilhidrazida deseada en forma de un aceite. $C_{18}H_{28}N_2O_4$ (PM = 336,43); MS: m/z (M^+ + 1) = 337

Etapa D: Preparación de:



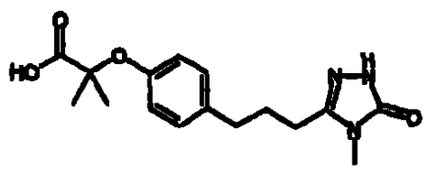
A una solución de la acilhidrazida de la Etapa C (6,6 g, 19,6 mmol) en THF anhidro (150 ml) se le añadió isocianato de metilo (1,51 ml, 25,5 mmol) en una porción. La mezcla de reacción se agitó durante una noche a temperatura ambiente y después se concentró, dando el semicarbazato de acilo deseado en forma de un aceite. $C_{20}H_{31}N_3O_5$ (PM = 393,49); MS: m/z (M^+ + 1) = 394

Los compuestos mostrados a continuación también se prepararon sustituyendo el isocianato de metilo por un isocianato de alquilo o isocianato de arilo apropiado.



R	MS: m/z (M^+ + 1)
Etilo	408
n-Propilo	422
n-Butilo	436
n-Pentilo	450
n-Hexilo	464
2,4-Dimetoxibencilo	530
2,4,6-Trimetoxibencilo	664
Alilo	

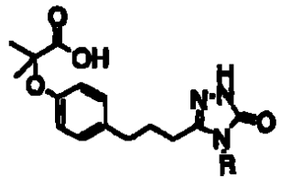
Etapa E: Preparación de:



A una solución de la acilsemicarbazida de la Etapa D en metanol (175 ml) se le añadió hidróxido potásico sólido (13 g, 231 mmol) y la mezcla de reacción se calentó a reflujo durante 48 horas. Después de la refrigeración a temperatura ambiente, la mezcla de reacción se diluyó con agua (50 ml) y cloruro de metileno (200 ml) y después se

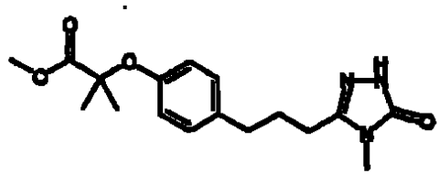
acidificó a pH 2 con ácido clorhídrico 5 N. La capa acuosa se extrajo con cloruro de metileno (2 x 40 ml). Los extractos orgánicos combinados se lavaron con agua (75 ml) y salmuera (75 ml), se secaron (Na_2SO_4) y se concentraron, dando la triazolinona deseada en forma de un aceite. $C_{16}H_{21}N_3O_4$ (PM = 319,36): MS: m/z (M^+ + 1) = 320.

Los compuestos presentados a continuación también se prepararon por este procedimiento de ciclación



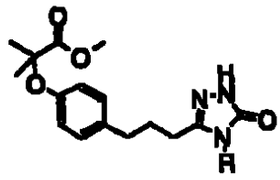
R	MS: m/z (M^+ + 1)
Etilo	334
n-Propilo	348
n-Butilo	362
n-Pentilo	376
n-Hexilo	390
2,4-Dimetoxibencilo	456
2,4,6-Trimetoxibencilo	590
Alilo	

Etapa F: Preparación de:



A una solución de la triazolinona de la Etapa E en metanol (150 ml) se le añadió ácido sulfúrico concentrado (1 ml) y la mezcla de reacción se agitó a temperatura ambiente durante 18 horas. Después de la concentración para retirar el metanol, el aceite se disolvió en acetato de etilo (125 ml), se lavó con agua (50 ml), $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml). La capa orgánica se secó (Na_2SO_4) y se concentró, dando el éster metílico en forma de un sólido. $C_{17}H_{23}N_3O_4$ (PM = 333,39); MS: m/z (M^+ + 1) = 334.

Los compuestos presentados a continuación también se prepararon por esterificación de Fisher de los ácidos carboxílicos anteriores.

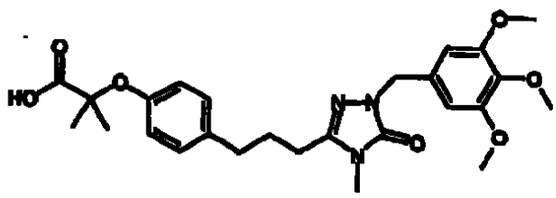


Ejemplo Número	R	MS: m/z (M^+ + 1)
2(2)	Etilo	438
2(3)	n-Propilo	362
2(4)	n-Butilo	376

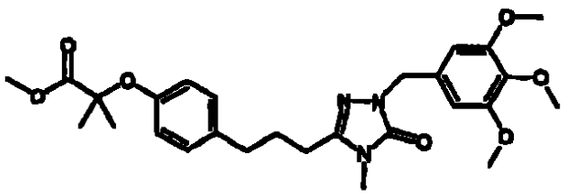
2(5)	n-Pentilo	390
2(6)	n-Hexilo	404
2(7)	2,4-Dimetoxibencilo	470
2(8)	2,4,6-Trimetoxibencilo	604
2(9)	Alilo	

Ejemplo 3

Compuesto 3(1)



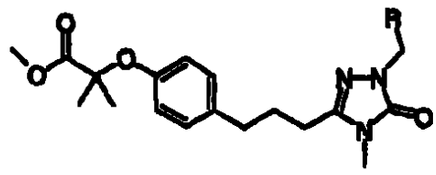
Etapa A: Preparación de:



A una solución del éster metílico, específicamente el compuesto 2(1) (100 mg, 0,29 mmol), en DMF (2 ml) se le añadió cloruro de 3,4,5-trimetoxibencilo (129 mg, 0,6 mmol) y carbonato potásico en polvo (350 mg, 2,53 mmol) y la mezcla resultante se calentó a 45°C durante 24 horas. Después de enfriar a temperatura ambiente, la mezcla de

reacción de diluyó con agua (10 ml) y se extrajo con acetato de etilo (3 x 3 ml). Los extractos orgánicos combinados se concentraron al vacío para dar un aceite que se purificó por cromatografía ultrarrápida (elución en gradiente, 1:4 de acetato de etilo:hexanos a 4:1 de acetato de etilo:hexanos), dando el producto deseado en forma de un aceite. $C_{27}H_{35}N_3O_7$ (PM = 513,60); MS: m/z (M^+ + 1) = 514

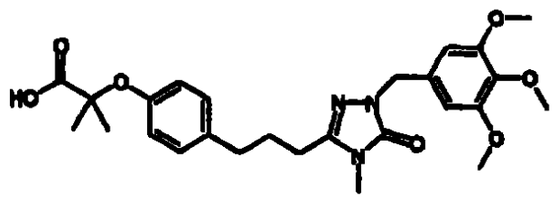
Los compuestos presentados a continuación también se prepararon por alquilación de N-metiltriazolinona usando los haluros de alquilo apropiados en lugar de cloruro de 3,4,5-trimetoxibencilo.



R	MS: m/z (M^+ + 1)
3,5-Dimetoxifenilo	484
4-Bifenilo	500
3-Clorofenilo	458
3-Cloro-4-metilfenilo	472
Bis-trifluorometilfenilo	560
3,4-Diflourofenilo	460
3-Fenoxifenilo	516
4-Isopropilfenilo	468
3-Triflourometoxifenilo	508

4-Metoxifenilo	454
4-Trifluorometoxifenilo	508
4-Metilsulfonilfenilo	502
3-(Triflourometiltio)fenilo	524
4-Etilfenilo	452
3,4-Dimetilfenilo	452
4-*terc*-Butilfenilo	480
2-Naftilo	474
3-Metilfenilo	438
Fenmetilo	438
3-(5-Cloro)benzotiofeno	515
4-Metilfenilo	438
3,5-Difluorofenilo	460
3-Trifluorofenilo	492
3,4-Diclorofenilo	493
Fenilo	424
3,5-Dimetilfenilo	452
4-Clorofenilo	458

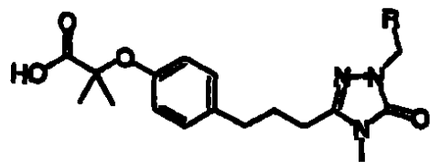
Etapa B: Preparación de:



Una solución del éster metílico de la Etapa A (125 mg, 0,24 mmol) en metanol (3 ml) se trató con NaOH acuoso 5 N

(0,30 ml) y la mezcla se agitó durante una noche a temperatura ambiente. Después de la concentración a sequedad, el residuo se disolvió en agua (5 ml), la solución se acidificó a pH 3 con ácido clorhídrico concentrado y después se extrajo en cloruro de metileno (3 x 2 ml). Los extractos orgánicos combinados se secaron por elución a través de un cartucho cargado con tierra de diatomeas y después se concentró, proporcionando el ácido carboxílico en forma de un sólido céreo. $C_{26}H_{33}N_3O_7$ (PM = 499,57); MS: m/z (M^+ + 1) = 500

Los compuestos presentados a continuación también se prepararon por hidrólisis del éster metílico apropiado presentado anteriormente.

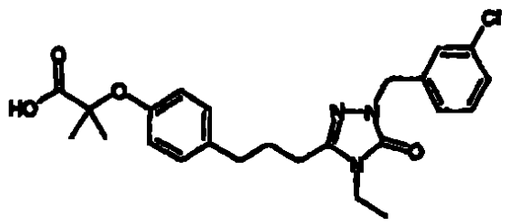


Ejemplo Número	R	MS: m/z (M^+ + 1)
3(2)	3,5-Dimetoxifenilo	470
3(3)	4-Bifenilo	486
3(4)	3-Clorofenilo	444
3(5)	3-Cloro-4-metilfenilo	458
3(6)	2,4-Diflourometilfenilo	546
3(7)	3,4-Difluorofenilo	446

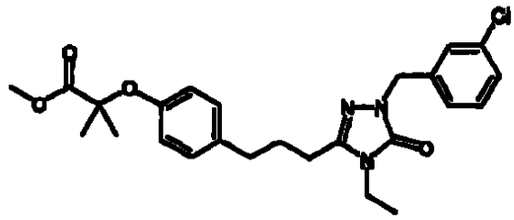
3(8)	3-Fenoxifenilo	502
3(9)	4-Isopropilfenilo	452
3(10)	3-Triflourometoxifenilo	494
3(11)	4-Metoxifenilo	440
3(12)	4-Trifluorometoxi	494
3(13)	4-Metilsulfonilfenilo	488
3(14)	3-(Trifluorometiltio)fenilo	510
3(15)	4-Etilfenilo	348
3(16)	3,4-Dimetilfenilo	438
3(17)	4-*terc*-Butilfenilo	466
3(18)	2-Naftilo	460
3(19)	3-Metilfenilo	424
3(20)	Fenmetilo	424
3(21)	3-(5-Cloro)benzotiofeno	501
3(22)	4-Metilfenilo	424
3(23)	3,5-Difluorofenilo	446
3(24)	3-Trifluorofenilo	478
3(25)	3,4-Diclorofenilo	479
3(26)	Fenilo	410
3(27)	3,5-Dimetilfenilo	438
3(28)	4-Clorofenilo	444

Ejemplo 4

Compuesto 4(1)



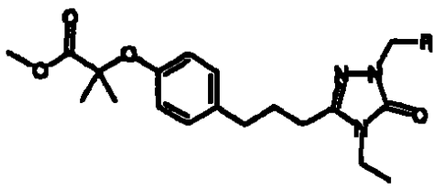
Etapa A: Preparación de:



A una solución del Compuesto 2(2) (100 mg, 0,28 mmol) en DMF (2 ml) se le añadió bromuro de m-clorobencilo (119 mg, 0,58 mmol) y carbonato potásico en polvo (350 mg, 2,53 mmol) y la mezcla resultante se calentó a 45°C durante 24 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con agua (10 ml) y se extrajo con acetato de etilo (3 x 3 ml). Los extractos orgánicos combinados se concentraron para dar un aceite que se purificó por cromatografía ultrarrápida (elución en gradiente, 1:4 de acetato de etilo:hexanos a 4:1 de acetato de etilo:hexanos), dando el producto deseado en forma de un aceite. $C_{25}H_{30}ClN_3O_4$ (PM = 471,99); MS: m/z (M^+ + 1) = 473.

Los compuestos presentados a continuación también se prepararon por alquilación del Compuesto 2(2) usando el haluro de alquilo apropiado en lugar de bromuro de m-

clorobencilo.

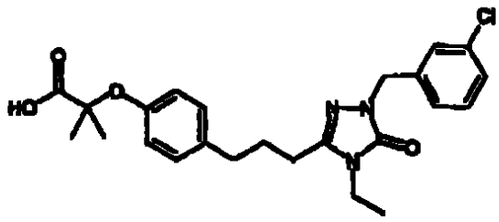


R	MS: m/z (M^+ + 1)
n-propilo	
3-clorofenilo	472
3-metilfenilo	452
fenilo	438
2,4-difluorofenilo	
3-trifluorometilfenilo	506
4-metilfenilo	452
2-metilfenilo	
3-nitrofenilo	
4-carboxifenilo	
2-feniletilo	
3,5-difluorofenilo	474
2-piridilo	
4-piridilo	
3-piridilo	
2-quinolinoílo	489
6-(4-metoxi-2-trifluorometil)quinolinoilo	
3-(5-cloro)benzo[b]tienilo	

4-*terc*-butilfenilo	494
β-naftilo	488
α-metilbencilo	
3,5-dimetilfenilo	
2,6-diclorofenilo	
3-cianofenilo	463
5-(6-cloro)piperonilo	
4-cianofenilo	463
5-piperonilo	482
3-trifluorometoxifenilo	522
bis-2,4-trifluorometilfenilo	
ciclohexilo	
4-etilfenilo	
3,4-dimetilfenilo	466
4-trifluorometiltiofenilo	
4-isopropilfenilo	480
3-metoxifenilo	466
4-trifluorometoxifenilo	522
3,4-diclorofenilo	507
4-clorofenilo	
3,4-difluorofenilo	474
4-metilsulfonilfenilo	
2-metoxifenilo	

3,5-dimetoxifenilo	498
3,4,5-trimetoxifenilo	528
4-*terc*-pentilfenilo	
2-(6-metil)naftilo	502
2-naftoílo	516
5-(*terc*-butil)1,2,4-oxadiazol-3-ilo	486
3-metil-4-metoxifenilo	482
4-benciloxifenilo	544
3-cloro-4-metilfenilo	487
3-fenoxifenilo	530
4-acetomidofenilo	495
4-trifluorometilfenilo	506
p-bifenilo	514
3,5-dimetilisoxazol-4-ilo	457

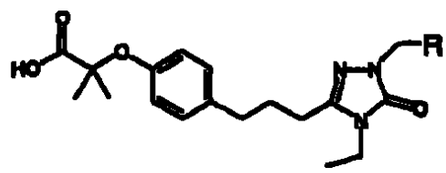
Etapa B: Preparación de:



Una solución del producto (125 mg, 0,24 mmol) de la Etapa A en metanol (3 ml) se trató con NaOH acuoso 5 N (0,30 ml) y la mezcla se agitó durante una noche a temperatura ambiente. Después de la concentración a sequedad, el residuo se disolvió en agua (5 ml), la

solución se acidificó a pH 3 con ácido clorhídrico concentrado y después se extrajo en cloruro de metileno (3 x 2 ml). Los extractos orgánicos combinados se secaron por elución a través de un cartucho cargado con tierra de diatomeas y después se concentró, proporcionando el ácido carboxílico en forma de un sólido céreo. $C_{26}H_{33}N_3O_7$ (PM = 457,96); MS: m/z (M^+ + 1) = 458.

Los compuestos presentados a continuación también se prepararon por hidrólisis del éster metílico apropiado presentado anteriormente.



Ejemplo Número	R	MS: m/z (M^+ + 1)
4(2)	n-propilo	
4(3)	3-metilfenilo	438
4(4)	fenilo	424
4(5)	2,4-difluorofenilo	
4(6)	3-trifluorometilfenilo	492
4(7)	4-metilfenilo	438
4(8)	2-metilfenilo	
4(9)	3-nitrofenilo	
4(10)	4-carboxifenilo	

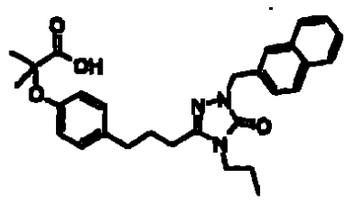
4(11)	2-feniletilo	
4(12)	3,5-difluorofenilo	460
4(13)	2-piridilo	
4(14)	4-piridilo	
4(15)	3-piridilo	
4(16)	2-quinolinoilo	475
4(17)	6-(4-metoxi-2-trifluorometil)quinolinoilo	
4(18)	3-(5-cloro)benzo[b]tiofenilo	515
4(19)	4-*terc*-butilfenilo	480
4(20)	β-naftilo	474
4(21)	α-metilbencilo	
4(22)	3,5-dimetilfenilo	
4(23)	2,6-diclorofenilo	
4(24)	3-cianofenilo	449
4(25)	5-(6-cloro)piperonilo	
4(26)	4-cianofenilo	449
4(27)	5-piperonilo	468
4(28)	3-trifluorometoxifenilo	508
4(29)	bis-2,4-trifluorometilfenilo	
4(30)	ciclohexilo	
4(31)	4-etilfenilo	

4(32)	3,4-dimetilfenilo	452
4(33)	4-trifluorometiltiofenilo	
4(34)	4-isopropilfenilo	466
4(35)	4-metoxifenilo	454
4(36)	4-trifluorometoxifenilo	508
4(37)	3,4-diclorofenilo	493
4(38)	4-clorofenilo	
4(39)	3,4-difluorofenilo	460
4(40)	4-metilsulfonilfenilo	
4(41)	2-metoxifenilo	
4(42)	3,5-dimetoxifenilo	484
4(43)	3,4,5-trimetoxifenilo	514
4(44)	4-*terc*-pentilfenilo	
4(45)	2-(6-metil)naftilo	488
4(46)	2-naftoílo	502
4(47)	5-(*terc*-butil)1,2,4-oxadiazol-3-ilo	472
4(48)	3-metil-4-metoxifenilo	468
4(49)	4-benciloxifenilo	530
4(50)	3-cloro-4-metilfenilo	473
4(51)	3-fenoxifenilo	516
4(52)	4-acetamidofenilo	481
4(53)	4-trifluorometilfenilo	492
4(54)	p-bifenilo	500

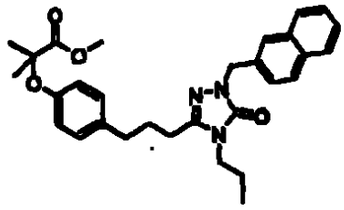
4(55)	3,5-dimetilisoxazol-4-ilo	443

Ejemplo 5

Compuesto 5(1)



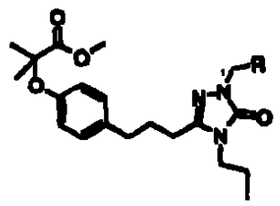
Etapa A: Preparación de



A una solución de triazolinona, Compuesto 2(3) (0,4 mmol) en DMF anhidro (2 ml), se le añadió 2-bromometil-naftaleno (0,8 mmol), seguido de K_2CO_3 anhidro (500 mg, en polvo). La reacción se agitó de 40 a 45°C durante 18 h. La mezcla de reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (3 x 20 ml). La capa orgánica combinada se secó (Na_2SO_4) y se concentró para dar un residuo oleoso. El producto bruto se purificó adicionalmente sobre una columna de sílice pre-cargada (Biotage, Quad 3), eluyendo con una mezcla de acetato de etilo-hexano, dando el producto. MS: m/z (M^+ + 1) = 502.

Los compuestos presentados a continuación también se prepararon por alquilación del Compuesto 2(3) usando los

haluros de alquilo apropiados en lugar de 2-bromometilnaftaleno.

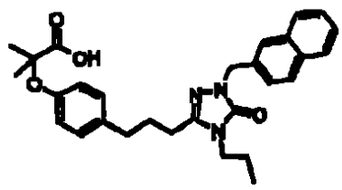


R	MS: m/z (M^+ + 1)
n-etilo	404
3-clorofenilo	486
3-metilfenilo	466
fenilo	452
2,4-difluorofenilo	488
3-trifluorometilfenilo	520
4-metilfenilo	466
2-metilfenilo	466
3-nitrofenilo	497
4-carboxifenilo	496
2-fenilmetilo	466
3,5-difluorofenilo	388
2-piridilo	443
4-piridilo	443
3-piridilo	443
2-quinolinoilo	503
6-(4-metoxi-2-	601

trifluorometil)quinolinoilo	
3-(5-cloro)benzo[b]tienilo	543
4-*terc*-butilfenilo	508
β-naftilo	502
α-metilbencilo	446
3,5-dimetilfenilo	480
2,6-diclorofenilo	521
3-cianofenilo	477
5-(6-cloro)piperonilo	531
4-cianofenilo	477
5-piperonilo	496
3-trifluorometoxifenilo	536
bis-2,4-trifluorometilfenilo	588
ciclohexilo	458
4-etilfenilo	480
3,4-dimetilfenilo	480
4-trifluorometiltiofenilo	552
4-isopropilfenilo	494
4-metoxifenilo	482
4-trifluorometoxifenilo	536
3,4-diclorofenilo	521
4-clorofenilo	486
3,4-difluorofenilo	488

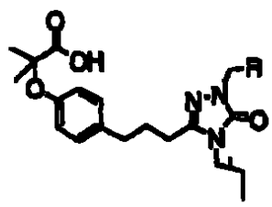
4-metilsulfonilfenilo	530
2-metoxifenilo	482
3,5-dimetoxifenilo	512
3,4,5-trimetoxifenilo	542
4-*terc*-pentilfenilo	522
2-(6-metil)naftilo	516
2-naftoílo	530
5-(*terc*-butil)1,2,4-oxadiazol-3-ilo	500

Etapa B: Preparación de:



A una solución del éster metílico de la Etapa A (150 mg) en metanol (2 ml) se le añadió una solución acuosa de KOH (2 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 h. El metanol se retiró en un evaporador rotatorio y la capa acuosa se diluyó con agua (1 ml). Ésta después, se acidificó con HCl acuoso 5 N (pH~2). La capa acuosa se extrajo con diclorometano (3 x 20 ml), se secó (Na_2SO_4) y se concentró a sequedad, dando el producto en forma de una espuma. MS: m/z (M^+ + 1) = 488.

Los compuestos presentados a continuación también se prepararon por hidrólisis del éster metílico apropiado.



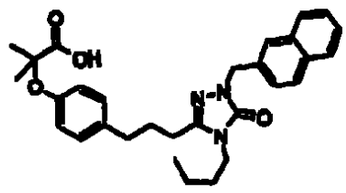
Ejemplo Número	R	MS: m/z (M^+ + 1)
5(2)	n-etilo	390
5(3)	3-clorofenilo	472
5(4)	3-metilfenilo	452
5(5)	fenilo	438
5(6)	2,4-difluorofenilo	474
5(7)	3-trifluorometilfenilo	506
5(8)	4-metilfenilo	452
5(9)	2-metilfenilo	452
5(10)	3-nitrofenilo	483
5(11)	4-carboxifenilo	482
5(12)	fenilmetilo	452
5(13)	3,5-difluorofenilo	474
5(14)	2-piridilo	439
5(15)	4-piridilo	439
5(16)	3-piridilo	439
5(17)	2-quinolinoilo	489
5(18)	6-(4-metoxi-2-trifluorometil)quinolinoilo	587

5(19)	3-(5-cloro)benzo[b]tienilo	529
5(20)	4-*terc*-butilfenilo	494
5(21)	α-metilbencilo	452
5(22)	3,5-dimetilfenilo	466
5(23)	2,6-diclorofenilo	507
5(24)	3-cianofenilo	463
5(25)	5-(6-cloro)piperonilo	517
5(26)	4-cianofenilo	463
5(27)	5-piperonilo	482
5(28)	3-trifluorometoxifenilo	522
5(29)	bis-2,4-trifluorometilfenilo	574
5(30)	ciclohexilo	444
5(31)	4-etilfenilo	466
5(32)	3,4-dimetilfenilo	466
5(33)	4-trifluorometiltiofenilo	538
5(34)	4-isopropilfenilo	480
5(35)	4-metoxifenilo	468
5(36)	4-trifluorometoxifenilo	522
5(37)	3,4-diclorofenilo	507
5(38)	4-clorofenilo	472
5(39)	3,4-difluorofenilo	474
5(40)	4-metilsulfonilfenilo	516
5(41)	2-metoxifenilo	468

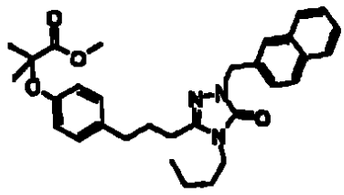
5(42)	3,5-dimetoxifenilo	498
5(43)	3,4,5-trimetoxifenilo	528
5(44)	4-*terc*-pentilfenilo	508
5(45)	2-(6-metil)naftilo	502
5(46)	2-naftoílo	516
5(47)	5-(*terc*-butil)1,2,4-oxadiazol-3-ilo	486

Ejemplo 6

Compuesto 6(1)



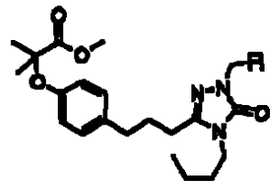
Etapa A: Preparación de:



A una solución del derivado de 4-butiltriazolinona, Compuesto 2(4) (188 mg, 0,4 mmol), en DMF anhidra (3 ml), se le añadió 2-bromoetilnaftaleno (265 mg, 1,2 mmol), seguido de K_2CO_3 (500 mg, en polvo). La reacción se agitó de 40 a 45°C durante 18 h. La mezcla de reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (3 x 20 ml). Las capas orgánicas combinadas se concentraron para dar un

residuo oleoso. El producto bruto se purificó en una columna de sílice pre-cargada (Biotag, Quad 3), eluyendo con una mezcla de acetato de etilo-hexano, dando el producto. MS: M/z (M^+ + 1) = 516.

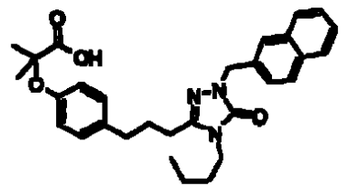
Los compuestos presentados a continuación también se prepararon por alquilación del derivado de 4-butiltriazolinona usando el haluro9 de alquilo apropiado en lugar de 2-brometilnaftaleno.



R	MS: m/z (M^+ + 1)
3-Trifluorometilfenilo	534
3-Cianofenilo	491
3,5-Bistrifluorometilfenilo	502
Fenilo	466
4-Cianofenilo	491
3,5-Dimetilfenilo	494
4-*terc*-Butilfenilo	522
4-Naftilfenilo	480
2-Bifenilo	542
3,5-Diflourofenilo	502
Piperonilo	510

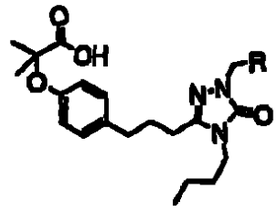
Fenilmetilo	480

Etapa B: Preparación de:



A una solución del éster de la Etapa A (150 mg) en 2 ml de metanol se le añadió una solución acuosa de NaOH 2 N. La mezcla de reacción se agitó a temperatura ambiente durante 2 h. El metanol se retiró sobre el evaporador rotatorio. La mezcla de reacción se acidificó con HCl acuoso 5 N (pH~3) y se extrajo con diclorometano (2 x 25 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró a sequedad, dando el producto en forma de un residuo oleoso. MS: m/z (M^+ + 1) = 502.

Los compuestos presentados a continuación también se prepararon por hidrólisis del éster metílico apropiado.

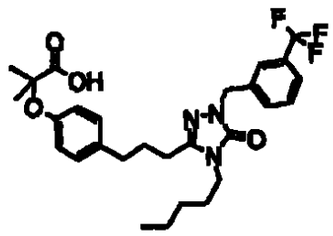


Ejemplo Número	R	MS: m/z (M^+ + 1)
6(2)	3-Trifluorometilfenilo	520
6(3)	3-Cianofenilo	477

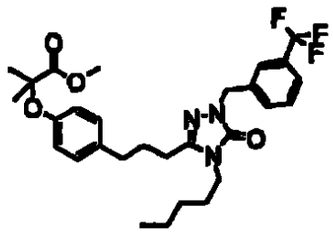
6(4)	3,5-Bistrifluorometilfenilo	588
6(5)	Fenilo	452
6(6)	4-Cianofenilo	477
6(7)	3,5-Dimetilfenilo	480
6(8)	4-*terc*-Butilfenilo	508
6(9)	4-Metilfenilo	466
6(10)	2-Bifenil	528
6(11)	3,5-Diflourofenilo	488
6(12)	Piperonilo	496
6(13)	Fenilmetilo	466

Ejemplo 7

Compuesto 7(1)



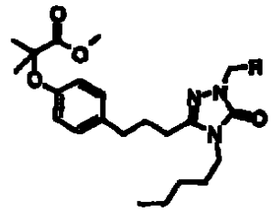
Etapa A: Preparación de



A una solución del derivado de 4-n-pentiltriazolinona, Compuesto 2(5) (150 mg, 0,39 mmol), en DMF anhidra (3 ml), se le añadió bromuro de 3-trifluorometilbencilo (286 mg,

1,2 mmol), seguido de K_2CO_3 anhidro (500 mg, en polvo). La reacción se agitó de 40 a 45°C durante 18 h. La mezcla de reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (3 x 20 ml). Las capas orgánicas combinadas se concentraron para dar un residuo oleoso. El producto bruto se purificó en una columna de sílice pre-cargada (Biotage, Quad 3), eluyendo con una mezcla de acetato de etilo-hexano, dando el producto. MS: m/z (M^+ + 1) = 548.

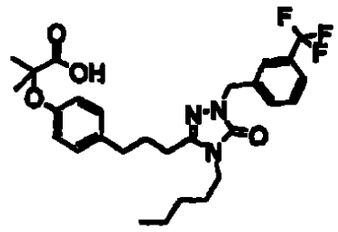
Los compuestos presentados a continuación se prepararon de la misma forma, por alquilación del derivado de 4-n-pentiltriazolinona usando el haluro de alquilo apropiado en lugar del bromuro de 3-trifluorometilbencilo.



R	MS: m/z (M^+ + 1)
3,5-bis-triflourometilfenilo	616
fenilo	480
4-cianofenilo	505
3,5-dimetilfenilo	508
4-*terc*-butilfenilo	536
4-metilfenilo	494

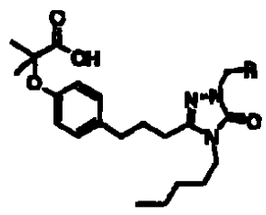
2-bifenilo	556
3,5-difluorofenilo	516
piperanilo	524
3-heptilo	502
2-naftilo	
3-cianofenilo	

Etapa B: Preparación de:



A una solución del éster de la Etapa A (170 mg) en 2 ml de metanol se le añadió una solución acuosa de NaOH 2 N (2,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. El metanol se retiró sobre el evaporador rotatorio. La mezcla de reacción se acidificó con HCl acuoso 5 N (pH~3) y se extrajo con diclorometano (2 x 25 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró a sequedad, dando el producto en forma de un residuo oleoso. MS: m/z (M^1 + 1) = 534.

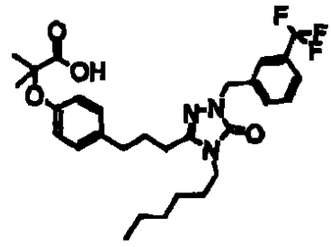
Los compuestos presentados a continuación también se prepararon por hidrólisis del éster metílico apropiado.



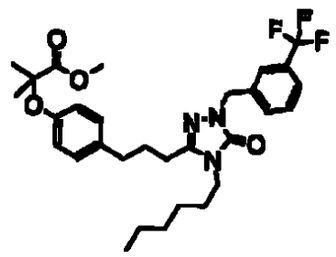
Ejemplo Número	R	MS: m/z (M^+ + 1)
7(2)	3,5-bis-triflourometilfenilo	602
7(3)	fenilo	466
7(4)	4-cianofenil	491
7(5)	3,5-dimetilfenilo	494
7(7)	4-*terc*-butilfenilo	522
7(7)	4-metilfenilo	480
7(8)	2-bifenilo	542
7(9)	3,5-difluorofenilo	502
7(10)	piperanilo	510
7(11)	3-heptilo	488
7(12)	2-naftilo	516
7(13)	3-cianofenilo	491

Ejemplo 8

Compuesto 8(1)



Etapa A: Preparación de:



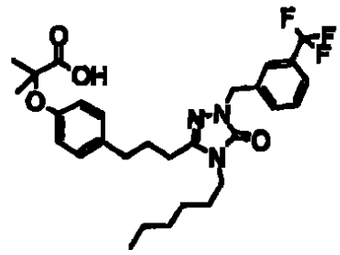
A una solución del derivado de 4-hexiltriazolinona, Compuesto 2(6) (150 mg, 0,39 mmol) y DMF anhidro (3 ml), se le añadió el bromuro 3-trifluorometilbencilo (286 mg, 1,2 mmol), seguido de K_2CO_3 anhidro (500 mg, en polvo). La reacción de agitó de 40 a 45°C durante 18 h. La mezcla de reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (3 x 20 ml). Las capas orgánicas combinadas se concentraron para dar un residuo oleoso. El producto bruto se purificó adicionalmente sobre una columna de sílice pre-cargada en sílice (Biotage, Quad 3), eluyendo con una mezcla de acetato de etilo-hexano, dando los productos en forma de aceites.

Los compuestos presentados a continuación se prepararon por alquilacion del Compuesto 2(6) y usando el haluro de alquilo apropiado en lugar del bromuro de 3-trifluoro-metilbencilo.

R	MS: m/z (M^+ + 1)
2-naftilo	
3-cianofenilo	

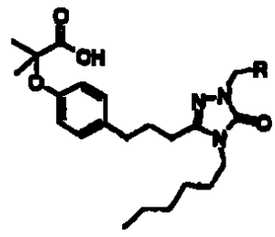
3,5-bis-trifluorometilfenilo	

Etapa B: Preparación de:



A una solución del éster de la Etapa A (204 mg) en 2 ml de metanol se le añadió una solución de NaOH 2 N (2,5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. El metanol se retiró sobre el evaporador rotatorio. La mezcla de reacción se acidificó con HCl acuoso 5 N (pH~3) y se extrajo con diclorometano (2 x 25 ml). La capa orgánica se secó sobre Na_2SO_4 y se concentró a sequedad, dando el producto en forma de un residuo oleoso. MS: m/z (M+1) 548.

Los compuestos presentados a continuación se prepararon por hidrólisis del éster metílico apropiado.

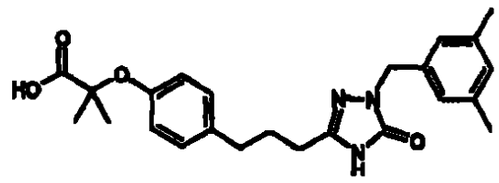


Ejemplo Número	R	MS: m/z (M^+ + 1)

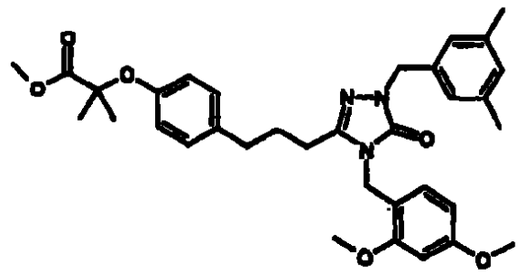
8(2)	2-naftilo	530
8(3)	3-cianofenilo	505
8(4)	3,5-bis-trifluorometilfenilo	616

Ejemplo 9

Compuesto 9(1)



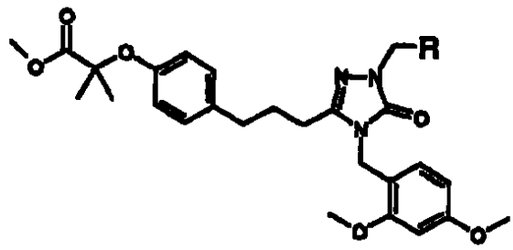
Etapa A: Preparación de:



A una solución del derivado de 4-(2,4-dimetoxibencil)-triazolina del Compuestos 2(7) (190 mg, 0,40 mmol) en DMF (2 ml) se le añadió bromuro de 3,5-dimetilbencilo (159 mg, 0,80 mmol) y carbonato potásico en polvo (350 mg, 2,53 mmol) y la mezcla resultante se calentó a 45°C durante 24 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con agua (10 ml) y se extrajo con acetato de etilo (3 x 3 ml). Los extractos orgánicos combinados se concentraron para dar un aceite que se purificó por cromatografía ultrarrápida (elución en

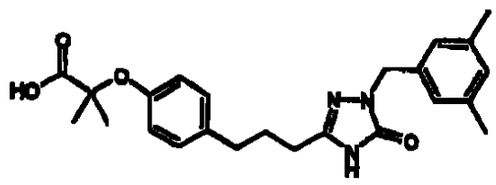
gradiente, 1:4 de acetato de etilo:hexanos a 4:1 de acetato de etilo:hexanos), dando el producto deseado en forma de un aceite. $C_{34}H_{41}N_3O_6$ (PM = 587,72): MS: m/z (M^+ + 1) = 588.

Los siguientes compuestos se prepararon utilizando el bromuro apropiado en lugar de bromuro de 3,4-dimetilbencilo, como se muestra en la tabla.



R	MS: m/z (M^+ + 1)
4-t-butilfenilo	616
3-fenoxifenilo	652
3-metilfenilo	574
3-trifluorometilfenilo	628
2-naftilo	610
3,5-dimetilfenilo	588

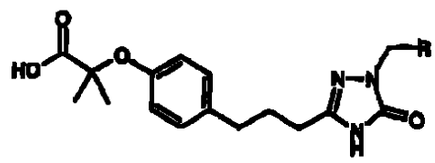
Etapa B: Preparación de:



Una solución del producto de la Etapa A (157 mg, 0,26 mmol) en bromuro de hidrógeno al 33% (en peso) en ácido

acético (3 ml) se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se trató con hielo (30 g) y la mezcla se extrajo con acetato de etilo (2 x 15 ml). Los extractos de acetato de etilo combinados se lavaron con agua y salmuera, se secaron y concentraron para dar un aceite. El aceite se disolvió en metanol (3 ml), se trató con NaOH acuoso 5 N (0,5 ml) y la solución resultante se agitó a temperatura ambiente durante 18 horas. La concentración para retirar el metanol dio un residuo que se disolvió en agua (10 ml) y la solución resultante se acidificó a pH 3 con ácido clorhídrico concentrado. La suspensión se extrajo con cloruro de metileno (3 x 4 ml). Los extractos orgánicos combinados se purificaron por HPLC de fase inversa, dando el producto deseado en forma de una espuma después de la liofilización. $C_{24}H_{29}N_3O_4$ (PM = 423,52); Espectroscopía de masas (MH^+) = 424.

Los compuestos presentados a continuación se prepararon a partir de los correspondientes ésteres de metilo.

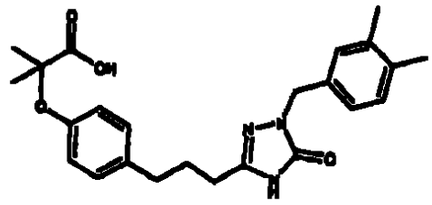


Ejemplo Número	R	MS: m/z (M^+ + 1)

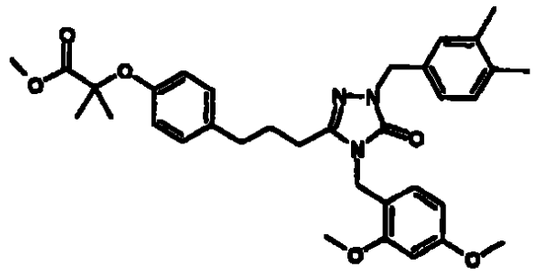
9(2)	4-t-butilfenilo	452
9(3)	3-fenoxifenilo	488
9(4)	3-metilfenilo	410
9(5)	3-trifluorometilfenilo	464
9(6)	2-naftilo	446

Ejemplo 10

Compuesto 10



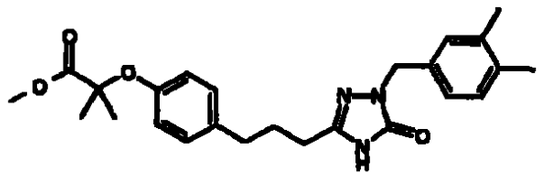
Etapa A: Preparación de:



A una solución del derivad de 4-(2,4-dimetoxibencil)-triazolinona del Compuesto 2(7) (9,0, 21,3 mmol) en DMF (25 ml), se le añadió bromuro de 3,4-dimetilbencilo (4,62 g, 25 mmol) y carbonato potásico (10 g), y la mezcla resultante se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (3 x 75 ml). Los extractos orgánicos combinados se concentraron para dar un aceite. Como

alternativa, el producto podía purificarse adicionalmente por cromatografía ultrarrápida (elución en gradiente, 1:4 de acetato de etilo:hexanos a 4:1 de acetato de etilo:hexanos), dando el producto deseado en forma de un aceite. MS: m/z (M^+ + 1)) 588.

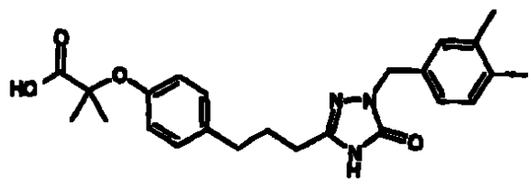
Etapa B: Preparación de:



Una solución del producto de la Etapa A (9,5 g) en bromuro de hidrógeno al 33% (en peso) en ácido acético (50 ml) se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se trató con hielo (100 g) y la mezcla se extrajo con acetato de etilo (2 x 100 ml). Los extractos del acetato de etilo combinados se lavaron con agua, salmuera, se secaron y se concentraron para dar un aceite. El aceite se disolvió en metanol (200 ml), se trató con 2 ml de H_2SO_4 concentrado y la solución resultante se agitó a temperatura ambiente durante 18 horas. La concentración para retirar el metanol dio un residuo que se disolvió en cloruro de metileno (200 ml) y se lavó con agua (2 x 100 ml), seguido de $NaHCO_3$ acuoso saturado. Los extractos orgánicos combinados se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía ultrarrápida (SiO_2, EtOAc/Hexanos), dando el producto deseado en forma de un

sólido. MS: m/z (M^+ + 1) = 438.

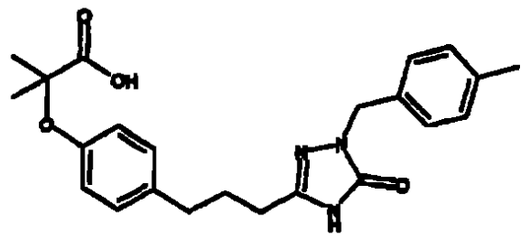
Etapa C: Preparación de:



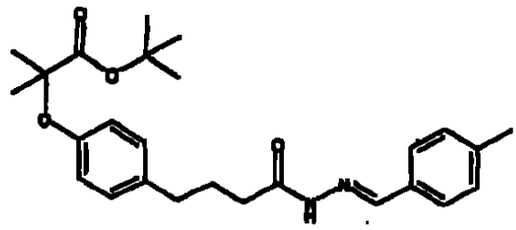
A una solución del producto de la Etapa B (150 mg) en metanol (3 ml) se le añadió NaOH 2 N (2 ml) y la mezcla se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró, se diluyó con cloruro de metileno (25 ml), se añadió agua (5 ml) y la mezcla se acidificó con HCl concentrado a pH ~ 2. Las capas se separaron, la capa acuosa se extrajo cloruro de metileno (2 x 25 ml). Los extractos orgánicos combinados se secaron (Na_2SO_4) y se concentraron, dando el producto deseado en forma de un sólido. MS: m/z (M^+ + 1) = 424.

Ejemplo 11

Compuesto 11

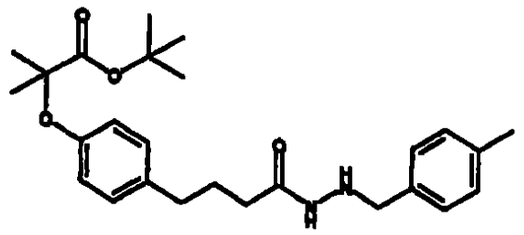


Etapa A: Preparación de:



Al producto de acilhidrazida del Ejemplo 2, Etapa C (5,4079 g, 16,07 mmol) en acetato de etilo (15 ml) se le añadió *p*-metil benzaldehído (1,90 ml, 1.936 g, 16,11 mmol) mediante una jeringa. La solución resultante se agitó a temperatura ambiente y se añadieron hexanos (30 ml). Comenzó a formarse un precipitado y la suspensión resultante se agitó durante 16 horas, después se enfrió a 0°C y se filtró. La torta de filtro se aclaró con hexanos enfriados y se secó al aire, produciendo la imina deseada (6,49 g, 92,1%) en forma de un sólido blanco. Análisis calculado para $C_{26}H_{34}N_2O_4$: C, 71,21; H, 7,81; N, 6,39; Encontrado: C, 70,90; H, 7,79; N, 6,45.

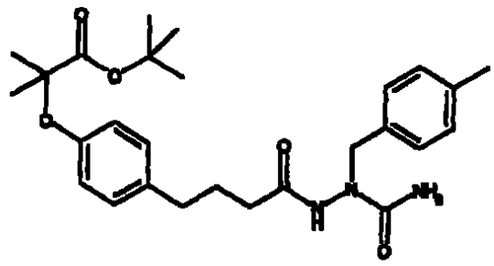
Etapa B: Preparación de:



Al producto de la Etapa A (4,0 g, 9,12 mmol) en THF (40 ml) se le añadió óxido de platino (0,2012 g) y la suspensión resultante se hidrogenó a temperatura ambiente y

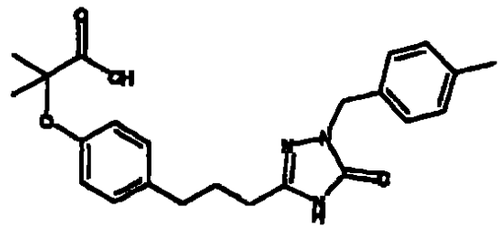
a 275,79 kPa durante 3 h. La solución se filtró, se añadió una carga más de óxido de platino (0,303 g) y la suspensión resultante se hidrogenó a temperatura ambiente y 275,79 kPa durante 16 h. La suspensión se filtró y se concentró al vacío a 60°C, produciendo la acilhidrazida deseada (3,88 g, 96,6%) en forma de un aceite viscoso. $C_{26}H_{36}N_2O_4$ (PM = 440,58); MS: m/z (M^+ + 1) = 441.

Etapa C: Preparación de:



Se combinaron la acilhidrazida de la Etapa B (287 g, 0,65 mmol, 1 equiv) e isopropanol (1,7 l) y calentaron a 50°C. Se añadió rápidamente isocianato de trimetilsililo (85%, 112 g, 0,98 mol, 1,5 equiv). La reacción se agitó durante 45 min, después se enfrió a 0°C y se agitó durante 30 min. Se recogió por filtración un sólido cristalino incoloro y se secó, proporcionando el producto de acil semicarbazida (253,7 g, 81%) $C_{27}H_{37}N_3O_5$ (PM = 483,60): MS: m/z (M^+ + 1) = 484.

Etapa D: Preparación de:

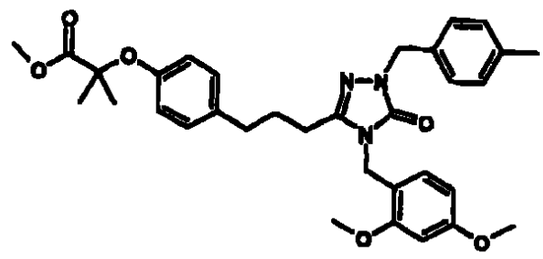


Se combinaron el producto de acil semicarbazida de la Etapa C (25,0 g, 0,0517 mol, 1,0 equiv), tolueno (250 ml) y ácido metanosulfónico (1,68 ml, 0,0258 mol, 0,5 equiv) se combinaron y la solución resultante se calentó a reflujo con destilación azeotrópica de agua durante 4 horas. La reacción se concentró al vacío y el residuo se repartió entre CH_2Cl_2 (250 ml) y agua (50 ml). Las capas se separaron y la fase orgánica se lavó con HCl 1 N (3 x 50 ml), se secó (Na_2SO_4), se filtró y la torta de filtro se lavó con CH_2Cl_2 (3 x 30 ml). El filtrado se concentró para dar una película blanca espumosa, se disolvió en CH_2Cl_2 (200 ml) y se lavó con HCl 1 N (4 x 100 ml, después 5 x 200 ml), se secó (Na_2SO_4) y concentró para dar una espuma blanca. El producto bruto se disolvió en acetato de etilo caliente (75 ml) y se sembró con el producto auténtico. La suspensión resultante se dejó en reposo a temperatura ambiente durante 1 h y después se refrigeró durante una noche. Se recogieron por filtración cristales incoloros, se lavaron con una cantidad mínima de acetato de etilo frío y se secaron, produciendo la triazolona deseada (12,5 g, 59%). $C_{23}H_{27}N_3O_4$ (PM = 409,48); MS: m/z (M^+ + 1) = 410.

Ejemplo 12

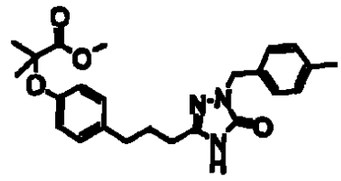
Compuesto 12(1)

Etapa A: Preparación de:



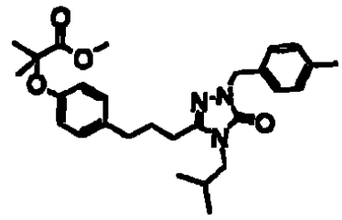
A una solución del derivado de 4-(2,4-dimetoxibencil)-triazolinona del Compuesto 2(7) (9,0, 21,3 mmol) en DMF (25 ml) se le añadió bromuro de 4-metilbencilo (4,62 g, 25 mmol), carbonato potásico en polvo (10 g) y la mezcla resultante se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se diluyó con agua (100 ml) y se extrajo con acetato de etilo (3 x 75 ml). Los extractos orgánicos combinados se concentraron para dar un aceite. Como alternativa, el producto podría purificarse por cromatografía ultrarrápida (elución en gradiente, 1:4 de acetato de etilo:hexanos a 4:1 de acetato de etilo:hexanos), dando el producto deseado en forma de un aceite. MS: m/z (M^+ + 1) = 588.

Etapa B. Preparación de:



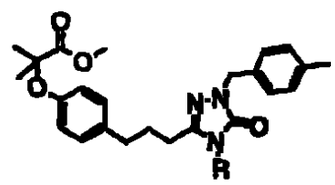
Una mezcla del derivado de 4-(2,4-dimetoxibencil)triazolinona de la Etapa A (12,6 g, 21,9 mmol) y una solución de HBr (50 ml, en ácido acético glacial al 32% p/p) se agitó a temperatura ambiente durante 24 h. A la mezcla de reacción se le añadió hielo triturado (50 g) y se eluyó con agua (100 ml). La capa acuosa se extrajo con acetato de etilo (400 ml). La capa de acetato de etilo se lavó con agua (2 x 250 ml) y salmuera (100 ml) y se secó sobre Na_2SO_4. La capa de acetato de etilo se concentró a sequedad sobre un evaporador rotatorio para dar un residuo oleoso. El residuo se recogió en metanol (300 ml). A esta solución se le añadió ácido sulfúrico concentrado (5 ml) con agitación. La mezcla de reacción se agitó a temperatura ambiente durante 18 h. El metanol se retiró hasta un pequeño volumen (25 ml) y el residuo se diluyó con acetato de etilo (200 ml), se lavó con agua (2 x 200 ml), una solución saturada de $NaHCO_3$ (2 x 100 ml) y salmuera (100 ml) y se secó sobre Na_2SO_4. La capa de acetato de etilo se concentró a sequedad para dar un residuo que se purificó sobre una columna de sílice ultrarrápida, dando el producto en forma de un residuo oleoso. MS: m/z (M+1) 424.

Etapa C: Preparación de:



A una solución del producto de la Etapa B (50 mg, 0,12 mmol) en DMF (3 ml) se le añadió yoduro de isopropilmetilo seguido de anhidro (250 mg, en polvo). La mezcla de reacción se agitó a 40-45°C durante 18 h. La mezcla de reacción se diluyó con agua (10 ml) y se extrajo con acetato de etilo (3 x 15 ml). La capa orgánica combinada se concentró a sequedad sobre un evaporador rotatorio y después a alto vacío durante 2 h. El producto bruto se cromatografió sobre una columna de sílice pre-cargada usando un sistema cromatográfico paralelo Biotage Quad3, eluyendo con una mezcla de acetato de etilo-hexano (30-40%, v/v), dando el producto en forma de un residuo oleoso. MS: m/z (M+1) 480.

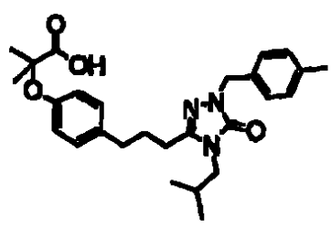
Los compuestos presentados a continuación se prepararon por alquilación del producto de la Etapa B usando el haluro de alquilo apropiado presentado en la tabla



Haluro de alquilo	R	MS: m/z (M+1)
1-Yodo-2-metilpropano	Isobutilo	480
Éter metílico de 2-bromoetilo	2-Metoxietilo	482
Éter metílico de 2-bromoetilo	2-Etoxietilo	496
1-Bromobutan-2-ona	2-Oxobutilo	494
Benzoato de 4-bromobutilo	4-Hidroxibutilo	496
Acetato de 2-bromoetilo	2-Hidroxietilo	468
	2-(N,N-Dietil)etilo	523
1-Bromo-3,3-dimetilbutan-2-ona	3,3-Dimetil-2-oxobutilo	522
Bromoetilciclopropano	Ciclopropilmetilo	478
	1-Morfolinocarbonil-2-isopropilmetilo	593
Bromopropanoato de metilo	2-Metoxicarboniletilo	510
	3-(2-Tetrahidro-	566

	piraniloxi)prop-1-ilo	
1-Bromo-3-hidroxipropano	3-Hidroxipropilo	482
Bromoacetato de metilo	2-Metoxicarbonilmetilo	496
Yoduro de isopropilo	Isopropilo	466
	Metoxietoxietilo	526
	3-Metoxi-2-hidroxipropilo	512
2-Clorometilpiridieno	2-Piridilmetilo	515
4-Clorometil piridina	4-Piridilmetilo	515
Bromuro de bencilo	Bencilo	514
	2,2,2-Trifluoroetilo	
	3,3,3-Trifluoropropilo	
	4,4,4-Trifluorobutilo	

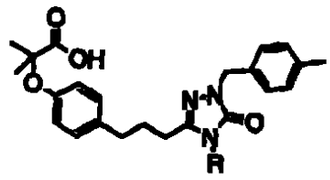
Etapa D: Preparación de:



A una solución del producto de la Etapa C (15 mg) en MeOH (1 ml) se le añadió NaOH 2 n (2 ml) y la mezcla se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se concentró, se diluyó con 15 ml de agua, se acidificó a pH ~ 2 con HCl concentrado y se extrajo con cloruro de metileno (3 x 10 ml). Las capas orgánicas combinadas se secaron (Na_2SO_4) y se concentraron para dar el

producto en forma de un aceite. MS: m/z (M+1) 466.

Los compuestos presentados a continuación se prepararon a partir de los ésteres metílicos correspondientes.

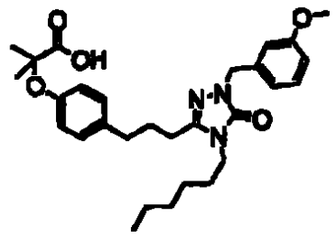


Ejemplo Número	R	MS: m/z (M^+ + 1)
12(2)	2-Metoxietilo	468
12(3)	2-Etoxietilo	482
12(4)	2-Oxobutilo	480
12(5)	4-Hidroxibutilo	482
12(6)	2-Hidroxietilo	454
12(7)	2-(N,N-Dietil)etilo	509
12(8)	3,3-Dimetil-2-oxobutilo	508
12(9)	Ciclopropilmetilo	464
12(10)	1-Morfolinocarbonil-2-metilpropilo	579
12(11)	2-carboxietilo	482
12(12)	THPéter	552
12(13)	3-Hidroxipropilo	468
12(14)	Carboximetilo	468
12(15)	Isopropilo	452

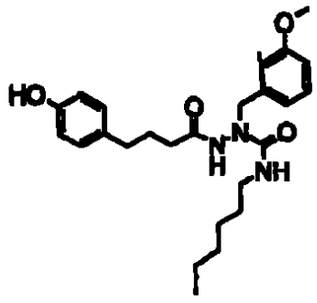
12(16)	Metoxietiloxietilo	512
12(17)	3-Metoxi-2-hidroxipropilo	498
12(18)	2-Piridilmetilo	501
12(19)	4-Piridilmetilo	501
12(20)	Bencilo	500
12(21)	2,2,2-Trifluoroetilo	492
12(22)	3,3,3-Trifluoropropilo	506
12(23)	4,4,4-Trifluorobutilo	520

Ejemplo 13

Compuesto 13



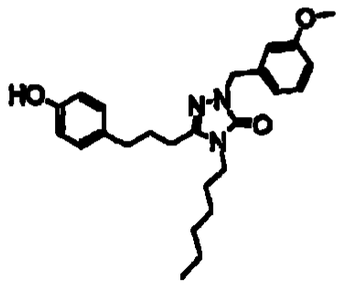
Etapa A: Preparación de



A una solución de hidrazida, específicamente el compuesto 3-metoxifenilo del Ejemplo 1, Etapa B (250 mg, 0,79 mmol) en THF anhidro (5 ml) se le añadió isocianato de n-hexilo (202 mg, 1,59 mmol). La mezcla de reacción se

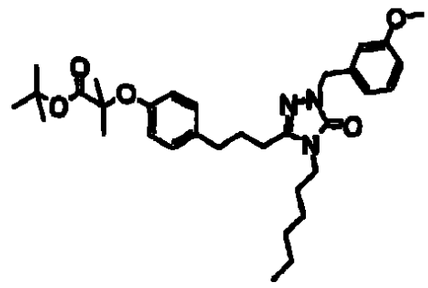
agitó a temperatura ambiente durante 18 h. A la mezcla de reacción se le añadió metanol (1 ml) y se agitó durante 30 minutos más. El disolvente se evaporó sobre un evaporador rotatorio, dando el semicarbazato. MS: m/z (M+1) 442

Etapa B: Preparación de



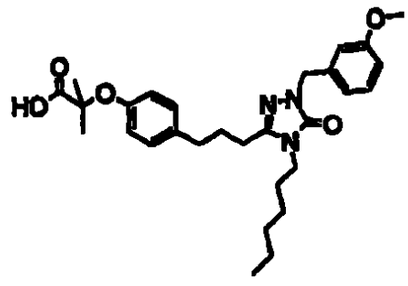
A una solución del producto de la Etapa A, en metanol (20 ml) y agua (0,5 ml) se le añadió KOH (500 mg). La mezcla de reacción se calentó a reflujo con agitación durante 48 h. La mezcla de reacción se enfrió a temperatura ambiente y se concentró sobre un evaporador rotatorio hasta un pequeño volumen (5 ml). La mezcla de reacción se diluyó con agua (30 ml) se acidificó con HCl 5 N (pH 2~3) y se extrajo con acetato de etilo (2 x 35 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron sobre un evaporador rotatorio, dando el producto en forma de un residuo oleoso incoloro. MS: m/z (M+1) 424.

Etapa C: Preparación de



A una solución del producto de la Etapa B (300 mg, 0,71 mmol) en DMF anhidro (5 ml) se le añadió bromoisobutirato de *terc*-butilo (1 g, 4,48 mmol) seguido de K_2CO_3 anhidro en polvo (20 ml). La mezcla de reacción se calentó a 50°C con agitación durante 64 h. La mezcla de reacción se diluyó con agua (30 ml) y se extrajo con acetato de etilo (2 x 30 ml). La capa de acetato de etilo combinada se secó (Na_2SO_4) y se concentró a sequedad sobre un evaporador rotatorio, dando un residuo oleoso. El producto bruto se purificó por cromatografía sobre columna de sílice ultrarrápida, eluyendo con una mezcla de acetato de etilo al 20%-hexano, dando el producto en forma de un aceite incoloro. MS: m/z (M^+ + 1) 566

Etapa D: Preparación de

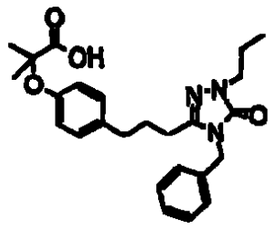


El producto de la Etapa C (225 mg) se trató con una

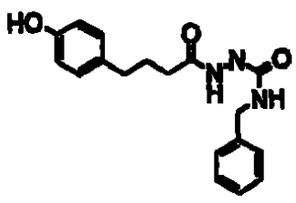
mezcla 50:50 de TFA y diclorometano (10 ml). La reacción se agitó a temperatura ambiente durante 2 h. El disolvente se retiró sobre un evaporador rotatorio y el residuo se secó a alto vacío, dando el producto en forma de un aceite incoloro MS: m/z (M+1) 510.

Ejemplo 14

Compuesto 14(1)

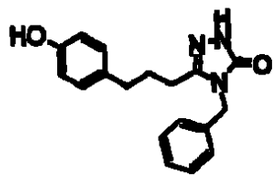


Etapa A: Preparación de



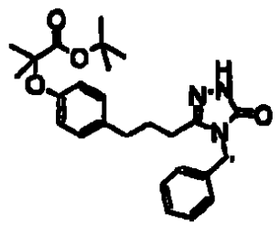
A una solución de 4-(4-hidroxifenil)butirilhidrazina (200 mg, 1,03 mmol) en THF (5 ml) se le añadió isocianato de bencilo (200 mg, 1,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 48 h. A la mezcla de reacción se le añadió metanol (1 ml) y se agitó durante 30 minutos más. El disolvente se retiró sobre un evaporador rotatorio, dando el producto en forma de un sólido blanco. MS: m/z (M+1) 328

Etapa B: Preparación de



A una solución del semicarbazato de la Etapa A (315 mg) en metanol (20 ml) se le añadió KOH sólido (1 g). La reacción se calentó a reflujo con agitación durante 20 h. La mezcla de reacción se concentró hasta un pequeño volumen (5 ml) y se acidificó con HCl 5 N a pH 3. Después se extrajo con acetato de etilo (2 x 30 ml). La capa de acetato de etilo se secó (Na_2SO_4) y se concentró a sequedad, dando el producto en forma de un sólido gomoso. MS: m/z (M+1) 310

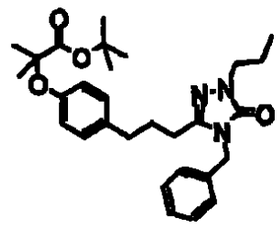
Etapa C: Preparación de



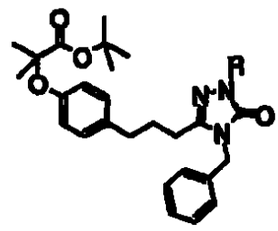
A una solución de la bencil triazolinona de la Etapa B (270 mg) en DMF (7,5 ml) se le añadió isobutirato de *terc*-butilo (1,1 g), seguido de K_2CO_3 anhidro, sólido en polvo (500 mg). La mezcla de reacción se calentó a 50°C con agitación durante 3 días. La mezcla de reacción se diluyó con agua (40 ml) y se extrajo con acetato de etilo (2 x 40 ml). La capa de acetato de etilo se secó (Na_2SO_4) y se

concentró sobre un evaporador rotatorio para dar un residuo bruto. El producto bruto se purificó sobre una columna de sílice ultrarrápida, eluyendo con acetato de etilo al 60%-hexano, dando el producto. MS: m/z (M+1) 452

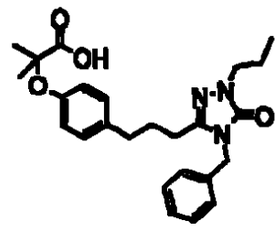
Etapa D: Preparación de



A una solución de la benciltriazolinona de la Etapa C (30 mg) en THF anhidro (1 ml) se le añadió 1-yodopropano, seguido de una solución KOH metanólico 1 M (1 ml). Inicialmente, la reacción se agitó a temperatura ambiente durante 24 h. Después, la reacción se calentó a 50°C durante 18 h. La mezcla de reacción se diluyó con agua (20 ml) y se extrajo con acetato de etilo (2 x 20 ml). La capa de acetato de etilo se secó (Na_2SO_4) y se concentró a sequedad para dar un residuo. El residuo se purificó sobre una columna de sílice ultrarrápida, eluyendo con una mezcla de acetato de etilo al 40%-hexano, dando el producto.
MS: m/z (M+1) = 494.



Etapa E: Preparación de



Se trató el éster *terc*-butílico de la Etapa D (16 mg) se trató con una mezcla al 50% de ácido trifluoroacético y diclorometano (2 ml) durante 2 h con agitación. El disolvente se retiró sobre un evaporador rotatorio y el residuo se secó a alto vacío, dando el producto en forma de un aceite.

MS: m/z (M+1) 438

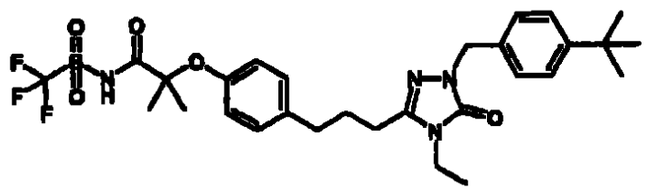
Los compuestos mostrados a continuación se sintetizaron por alquilación de benciltriazolina, usando los bromuros apropiados para dar los productos correspondientes.

Ejemplo Número	R	MS: m/z (M+1)
14 (2)	H	
14 (3)	Bencilo	

14 (4)	4-terc-butilbencilo	

Ejemplo 15

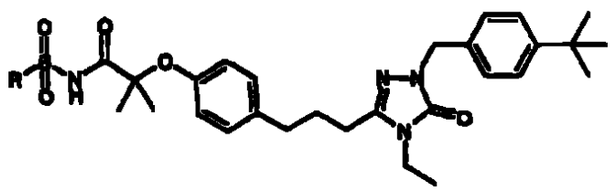
Compuesto 15 (1)



A una solución del compuesto descrito en el Ejemplo 4, Compuesto 4 (19) (120 mg, 0,25 mmol), trifluorometanosulfonamida (37 mg, 0,25 mmol) y 4-dimetilaminopiridina (31 mg, 0,25 mmol) en cloruro de metileno (2 ml) a temperatura ambiente se le añadieron *N,N*-diisopropiletilamina (65 mg, 0,50 mmol) y clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (77 mg, 0,40 mmol). Después de agitar durante 24 horas, la mezcla de reacción se concentró al vacío, dando un residuo que se repartió entre acetato de etilo y ácido clorhídrico 1 N. La capa orgánica se lavó con agua y salmuera, se secó (Na_2SO_4) y se concentró hasta un aceite que se purificó por cromatografía ultrarrápida (elución en gradiente 1:4 de acetato de etilo:hexanos a acetato de etilo al 100%), dando el producto deseado en forma de un sólido blanco.

$C_{29}H_{37}N_4O_5SF_{34}$ (PM = 610,70); espectroscopía de masas (MH^+) = 611.

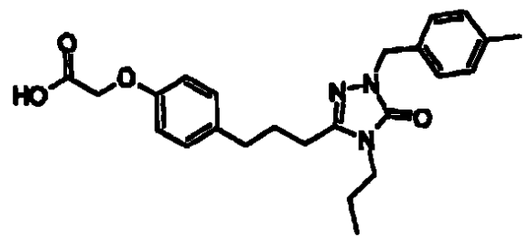
Los siguientes compuestos también se prepararon utilizando la sulfonamida apropiada (mostrada en la tabla) mediante el procedimiento del Compuesto 15 (1).



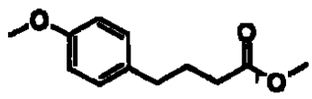
Ejemplo Número	RSO_2NH_2	R	(MH^+)
15 (2)	bencenosulfonamida	fenilo	619
15 (3)	α-toluenosulfonamida	bencilo	633
15 (4)	4-metoxibencenosulfonamida	4-metoxifenilo	649
15 (5)	naftaleno-2-sulfonamida	β-naftilo	669
15 (6)	metanosulfonamida	metilo	557
15 (7)	5-bromotiofeno-2-sulfonamida	5-bromo-2-tienilo	704
15 (8)	3-clorobencenosulfonamida	3-clorofenilo	654
15 (9)	6-etoxi-2-benzotiazolsulfonamida	6-etoxi-2-benzotiazolilo	720

Ejemplo 16

Compuesto 16

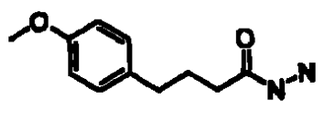


Etapa A: Preparación de 4-(4-metoxifenil)-butirato de metilo



A una solución de ácido 4-(4-metoxifenil)-butírico (25,1 g, 0,129 mol) en metanol (130 ml) se le añadió gota a gota ácido sulfúrico (concentrado, 1,0 ml) y se agitó a temperatura ambiente durante una noche en una atmósfera de nitrógeno. La mezcla de reacción se concentró en un evaporador rotatorio, el residuo después se repartió entre acetato de etilo (200 ml) y una solución acuosa saturada de bicarbonato sódico (200 ml). La fase orgánica se separó, se lavó con salmuera (3 x 200 ml), después se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio el compuesto del título en forma de un aceite (26,8 g, 99%). Masa (MH+) = 209.

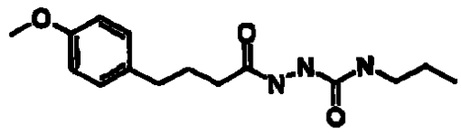
Etapa B. Preparación de



Una mezcla de 4-(4-metoxifenil)-butirato de metilo

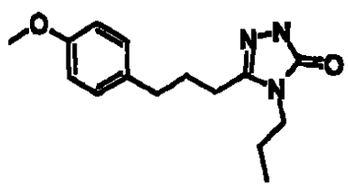
(10,4 g, 0,0500 mol) de la Etapa A e hidrato de hidrazina (25,0 g, 0,500 mol) en metanol (250 ml) se calentó a reflujo durante una hora. Después se enfrió a temperatura ambiente y se agitó durante una noche. El disolvente se evaporó y el residuo se repartió entre acetato de etilo (200 ml) y agua (200 ml). La capa orgánica se lavó con salmuera (3 x 200 ml), se secó sobre Na_2SO_4, se filtró y se concentró a sequedad, dando el compuesto del título en forma de un cristal blanco (8,79 g, 85%). Masa (MH+) = 209.

Etapa C: Preparación de



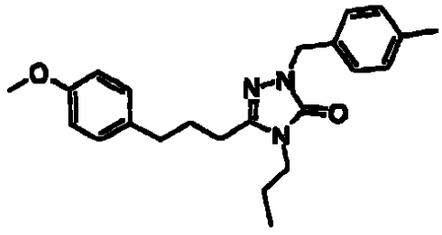
A una solución del producto de la Etapa B (8,76 g, 0,0421 mol) en THF (200 ml) se le añadió gota a gota isocianato de n-propilo (Aldrich, 4,34 ml, 0,0463 mol) y la mezcla se agitó a temperatura ambiente durante una hora. La evaporación del disolvente dio el compuesto del título en forma de un polvo blanquecino (12,4 g, 100%). Masa (MH+) = 294.

Etapa D. Preparación de



A una solución del producto de la Etapa C (12,4 g, 0,0421 mol) en metanol (200 ml) se le añadió en una porción hidróxido potásico (35,4 g, 0,632 mol). La mezcla de reacción se calentó a 70°C durante 36 horas. Después se concentró sobre un evaporador rotatorio, el residuo después se repartió entre cloruro de metileno (150 ml) y agua (150 ml) y se llevó a pH = 7 mediante HCl concentrado antes de que las dos capas se separasen. La capa acuosa se extrajo con más cloruro de metileno (150 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se filtraron. La evaporación del disolvente dio el compuesto del título en forma de un sólido blanquecino (11,2 g, 97%). Masa (MH+) = 276.

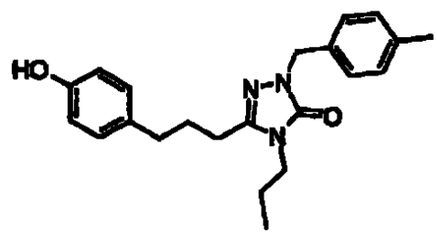
Etapa E: Preparación de



A una solución del producto de la Etapa D (5,51 g, 0,0200 mol) en DMF (100 ml) se le añadió α-bromo-p-xileno (8,30 g, 0,0440 mol) seguido de carbonato potásico en

polvo (13,8 g, 0,100 mol). Se calentó a 70°C en una atmósfera de nitrógeno durante una noche. La mezcla de reacción se repartió entre acetato de etilo (200 ml) y agua (200 ml) y la capa acuosa se extrajo una vez más con acetato de etilo (200 ml). La fase orgánica se combinó, se lavó con salmuera (4 x 200 ml), después se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio un producto bruto que se purificó sobre una columna de gel de sílice eluyendo con acetato de etilo al 20-60% en hexano, dando el compuesto del título en forma de un aceite incoloro (6,59 g, 87%). Masa (MH+) = 380.

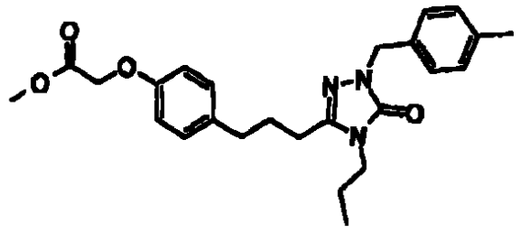
Etapa F: Preparación de



A una solución del producto de la Etapa E (6,55 g, 0,0173 mol) en DCM (100 ml) a 0°C se le añadió gota a gota una solución de BBr_3 (4,91 ml, 0,0519 ml) en cloruro de metileno (25 ml). La reacción se mantuvo a 0°C y se agitó durante una hora. Después se inactivó mediante 1:1 de MeOH/DCM (20 ml), se agitó durante una hora más a 0°C y después a temperatura ambiente durante una noche. La mezcla de reacción se lavó con agua (3 x 100 ml) y la capa orgánica se separó, se secó sobre Na_2SO_4, se filtró y se

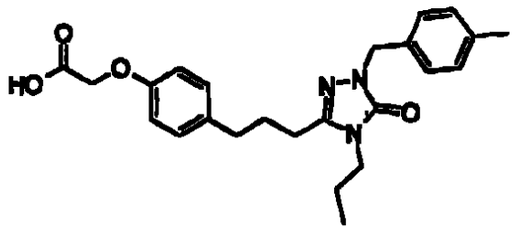
concentró hasta un aceite amarillo que se purificó por cromatografía sobre una columna de gel de sílice eluyendo con acetato de etilo al 20-60% en hexano, dando el compuesto del título en forma de un sólido blanco (2,39 g, 39%). Como alternativa, el compuesto del título puede obtenerse a -78°C en lugar de a 0°C sobre la misma escala, sólido blanco (4,89 g, 78%). Masa (MH+) = 366.

Etapa G: Preparación de



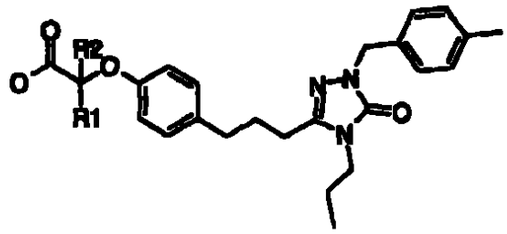
El producto de la Etapa F (0,100 g, 0,000274 mol) se disolvió en DMF (1,0 ml) y se le añadió bromoacetato de metilo (0,103 g, 0,000548 mol) seguido de carbonato potásico (0,189 g, 0,0137 mol). Después de calentar a 50°C durante el fin de semana, la reacción se diluyó con acetato de etilo (2 ml), se lavó con agua (2 ml), la capa orgánica se pasó a través de un tubo chem elut 1005 y el tubo se lavó con más acetato de etilo (50 ml). La evaporación del disolvente dio el éster metílico en forma de un aceite que se purificó sobre Biotage Quad3 (gel de sílice, acetato de etilo al 20-60% en hexano). Masa (MH+) 438.

Etapa H: Preparación de



El éster metílico obtenido de la Etapa G se trató con 1:1 de MeOH/NaOH 0,5 N (6 ml) a temperatura ambiente durante una noche y después se concentró. El residuo resultante se diluyó con agua (2 ml), se enfrió a 0°C y se acidificó a pH = 2 mediante la adición gota a gota de HCl concentrado. La suspensión acuosa se cargó sobre un tubo Chem elut 1005 y se eluyó con DCM (50 ml). La evaporación del cloruro de metileno dio el compuesto del título en forma de un aceite (0,103 g, 89%). Masa (MH+) = 424.

Los compuestos presentados a continuación se prepararon de acuerdo con el procedimiento indicado anteriormente mediante el uso del metil o etil α-sustituido-α-bromo éster apropiado en la Etapa G.

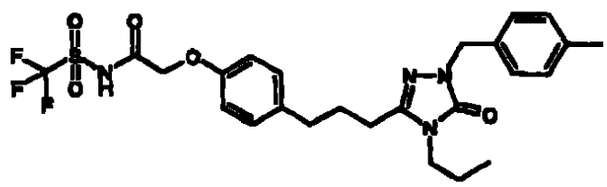


Ejemplo Número	R1	R2	MS (m/z)

16 (2)	Metilo	H	438
16 (3)	Etilo	H	452
16 (4)	Isopropilo	H	466
16 (5)	F	F	460
16 (6)	$-(CH_2)_3-$		464
16 (7)	Ciclohexilo	H	506
16 (8)	Fenilo	H	500
16 (9)	Hidroxietilo	H	468
16 (10)	F	H	442
16 (11)	n-Butilo	H	480
16 (12)	n-Pentilo	H	494
16 (13)	4-Fluorofenilo	H	518

Ejemplo 17

Compuesto 17

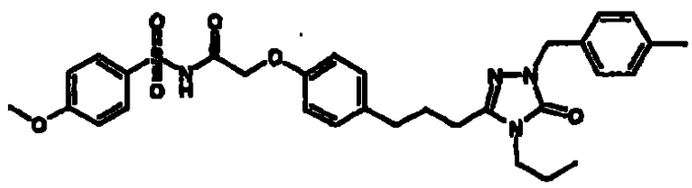


A una solución del **compuesto descrito en el Ejemplo 16, **por favor, aclárese** (45 mg, 0,10 mmol), trifluorometanosulfonamida (15 mg, 0,10 mmol) y 4-dimetilaminopiridina (12 mg, 0,10 mmol) en cloruro de metileno (1 ml) a temperatura ambiente se le añadieron *N,N*-diisopropiletilamina (26 mg, 0,20 mmol) y clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (31 mg,

0,16 mmol). Después de agitar durante 24 horas, la mezcla de reacción se concentró al vacío, dando un residuo que se repartió entre acetato de etilo y ácido clorhídrico 1 N. La capa orgánica se lavó con agua y salmuera, se secó (Na_2SO_4) y se concentró hasta un aceite que se purificó por cromatografía ultrarrápida (elución en gradiente, 1:4 de acetato de etilo:hexanos y después acetato de etilo al 100%), dando el producto deseado en forma de un sólido blanco. $C_{25}H_{29}F_3N_4O_5S$ (PM = 554,59); espectroscopía de masas (MH^+) = 555.

Ejemplo 18

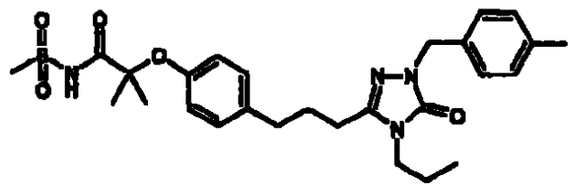
Compuesto 18



El compuesto del título se preparó utilizando el producto del Ejemplo 16 y 4-metoxibencenosulfonamida, de acuerdo con el procedimiento descrito en el Ejemplo 17. $C_{31}H_{36}N_4O_6S$ (PM = 592,72); espectroscopía de masas (MH^+) = 593.

Ejemplo 19

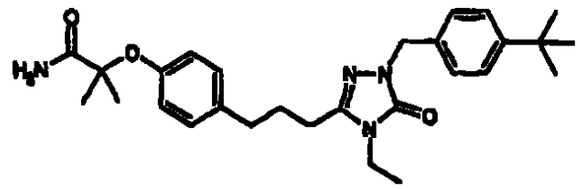
Compuesto 19



El compuesto del título se preparó utilizando el compuesto descrito en el Ejemplo 5, Compuesto 5 (8), y metanosulfonamida, de acuerdo con el procedimiento descrito en el Ejemplo 17. $C_{27}H_{36}N_4O_5S$ (PM = 528,68); espectroscopía de masas (MH^+) = 529.

Ejemplo 20

Compuesto 20

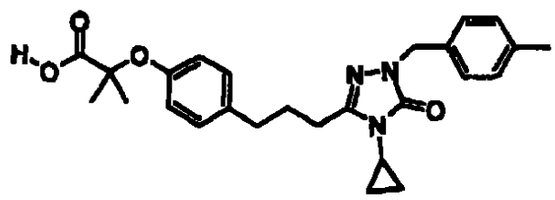


A una solución enfriada (0°C) del compuesto descrito en el Ejemplo 4, Compuesto 4 (19) (164 mg, 0,34 mmol) en cloruro de metileno (3 ml) se le añadió cloruro de oxalilo (178 µl, 2,0 mmol) seguido de *N,N*-dimetilformamida (1 gota). Después de agitar en un baño de refrigeración durante 0,25 horas, la mezcla de reacción se agitó a temperatura ambiente durante una hora y después se concentró a sequedad. El residuo se disolvió en tetrahidrofurano (15 ml) y la solución resultante se añadió gota a gota a hidróxido amónico concentrado frío (0°C) (30 ml) con agitación vigorosa. La mezcla se agitó a

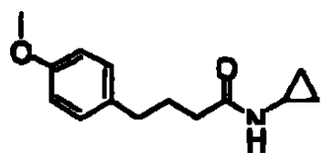
0°C durante una hora y después se agitó a temperatura ambiente durante 20 horas. La concentración dio un residuo que se repartió entre acetato de etilo y bicarbonato sódico acuoso saturado. La capa de acetato de etilo se lavó con agua y salmuera, se secó (Na_2SO_4) y se concentró, dando el producto deseado en forma de una espuma. $C_{26}H_{38}N_4O_3$ (PM = 478,64); espectroscopía de masas (MH^+) = 479.

Ejemplo 21

Compuesto 21



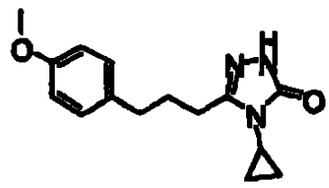
Etapa A: Preparación de:



A una solución de ácido 4-(4-metoxifenil)-butírico (2,13 g, 11 mmol), ciclopropilamina (1,14 ml, 16 mmol), HOAt (1,49 g, 11 mmol) y DMAP (134 mg, 1 mmol) en 70 ml de DMF seca, se le añadieron en una porción 3,07 g de EDC (16 mmol). La mezcla resultante se dejó en reposo en una atmósfera de N_2 durante 8 horas. Después, la mezcla se diluyó con 50 ml de Et_2O. La capa orgánica se lavó con HCl

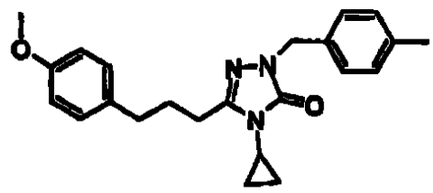
1 N (3 x 20 ml) y salmuera (3 x 20 ml), se secó sobre Na_2SO_4 y se filtró. El disolvente orgánico después se retiró al vacío. El residuo se purificó por cromatografía en columna, dando el compuesto del título. MS ($M+1^+$) m/z 234.

Etapa B: Preparación de:



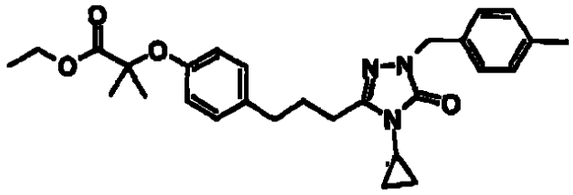
A una solución del producto de la Etapa A (1,72 g, 7,37 mmol) en 9 ml de CH_2Cl_2 seco se le añadieron en una porción 2,18 g de tetrafluoroborato de trimetiloxonio (14,7 mmol). La mezcla se dejó en reposo a temperatura ambiente durante 4 horas. El disolvente orgánico después se retiró al vacío. El residuo se disolvió de nuevo en 50 ml de Et_2O y se lavó con K_2CO_3 acuoso saturado frío (3 x 10 ml) y salmuera (3 x 10 ml). La capa de éter después se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se disolvió en 30 ml de tolueno seco. A la solución se le añadieron 0,79 g de carbazato de etilo. La mezcla se calentó a reflujo durante 38 horas. Después, el disolvente orgánico se retiró al vacío. El residuo se purificó por cromatografía, dando el compuesto del título. MS ($M+1^+$) m/z 274.

Etapa C: Preparación de



Una mezcla del producto de la Etapa B (1,53 g, 5,6 mmol), bromuro de 4-metilbencilo (2,1 g, 11,2 mmol) y K_2CO_3 (7,7 g, 56 mmol) en 25 ml de DMF seca se calentó a 60°C durante 12 horas. La mezcla después se diluyó con 75 ml de Et_2O y se filtró. La capa orgánica se lavó con HCl 1 N (3 x 15 ml) y salmuera (3 x 15 ml), se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía, dando el compuesto del título. MS ($M+1^+$) m/z 377.

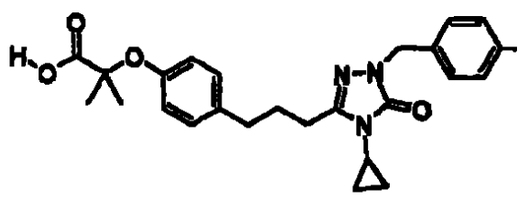
Etapa D: Preparación de



A una solución del producto de la Etapa C (1,01 g, 2,7 mmol) en 50 ml de CH_2Cl_2 seco a -78°C se le añadieron gota a gota 0,8 ml de BBr_3 (8,1 mmol). La solución resultante se calentó a 0°C en 10 minutos y se mantuvo a la misma temperatura durante 2 horas. La mezcla después se diluyó con 200 ml de Et_2O. La capa orgánica se lavó con H_2O

(3 x 20 ml) y salmuera (3 x 20 ml), se secó sobre Na_2SO_4 y se filtró. El disolvente orgánico se retiró al vacío. El residuo se disolvió en 25 ml de EtOH absoluto. A la solución se le añadieron 3,1 ml de butirato de 2-bromo-etilo (21,2 mmol), 1,26 g de K_2CO_3 (9,1 mmol) y 365 mg de $MgSO_4$ (3,03 mmol). La mezcla resultante se calentó a 70°C durante 12 horas. El sólido se filtró y el disolvente orgánico se retiró al vacío. El residuo después se disolvió en 75 ml de CH_2Cl_2. La capa orgánica se lavó con HCl 1 N (3 x 10 ml) y salmuera (3 x 10 ml), se secó sobre Na_2SO_4, se filtró y después se concentró. El residuo se purificó por cromatografía, dando el compuesto del título. MS ($M+1^+$) m/z 478.

Etapa E: Preparación de

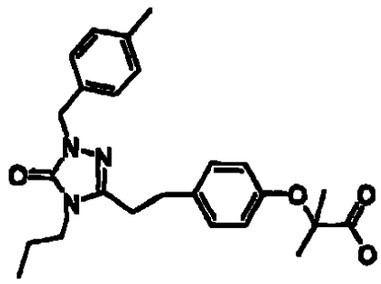


A una solución del producto de la Etapa D (490 mg, 1,03 mmol) en 20 ml de EtOH se le añadió 1,0 ml de NaOH 5 N. La solución resultante se calentó a reflujo durante 30 minutos. EL disolvente orgánico se retiró al vacío. El residuo se disolvió en 30 ml de CH_2Cl_2 y se lavó con HCl 1 N (2 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica después se secó sobre Na_2SO_4, se filtró y se concentró. El

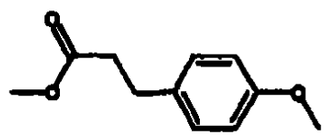
residuo se purificó por cromatografía, dando el compuesto del título. MS ($M+1^+$) m/z 450.

Ejemplo 22

Compuesto 22

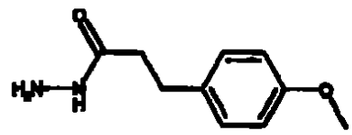


Etapa A: Preparación de



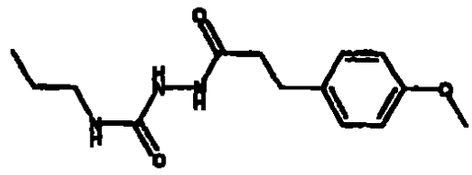
Una solución en metanol (500 ml) de ácido 3-(4-metoxifenil)propiónico (Aldrich, 10,15 g, 0,056 mol) se trató con H_2SO_4 (concentrado, 3 ml) y se agitó a temperatura ambiente durante una noche. EL disolvente se evaporó y el residuo se diluyó con CH_2Cl_2 (150 ml). La solución resultante se extrajo con bicarbonato sódico saturado acuoso (1 x 150 ml) seguido de salmuera (1 x 150 ml) y después se secó sobre Na_2SO_4. Tras la evaporación del disolvente se obtuvo el éster metílico deseado en forma de un aceite incoloro. $C_{11}H_{14}O_3$ (PM = 194,23); espectroscopía de masas (MH^+) = 195,1.

Etapa B: Preparación de



Una solución en metanol (60 ml) del éster metílico de la Etapa A (10,6 g, 0,055 mol) se trató con hidrato de hidrazina (30 g, 0,60 mol) y se agitó durante una noche. El disolvente se evaporó y el residuo se disolvió en acetato de etilo (300 ml). La solución resultante se extrajo con H_2O (300 ml). El extracto acuoso se extrajo de nuevo con acetato de etilo (300 ml), después los extractos combinados se secaron sobre Na_2SO_4 y se concentraron, dando un sólido blanco. EL producto se suspendió en hexano (100 ml) y después se filtró, dando la acilhidrazida deseada en forma de un sólido. $C_{10}H_{14}N_2O_2$ (PM = 194,23); espectroscopía de masas (MH^+) = 195,1.

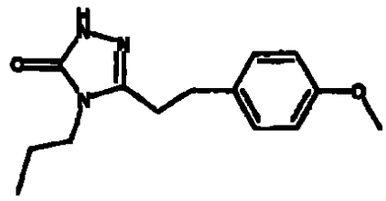
Etapa C: Preparación de



Una solución en THF (125 ml) de acilhidrazida de la Etapa B (92 g, 0,047 mol) se trató con una solución en THF (50 ml) de isocianato de n-propilo (Aldrich, 5,3 ml, 0,057 mol) añadida gota a gota durante 15 minutos. La mezcla se agitó durante una noche mientras se formaba un precipitado

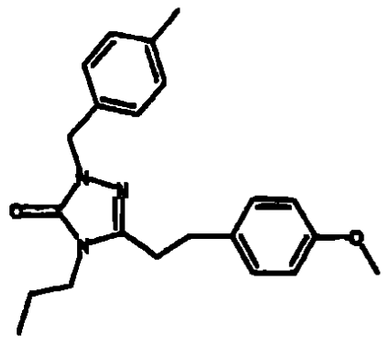
espeso. La suspensión resultante se trató con metanol (100 ml) y se agitó aproximadamente durante 2 horas. El disolvente después se concentró, dando la acil semicarbazida deseada en forma de un sólido blanco que se usó sin purificación adicional.

Etapa D: Preparación de



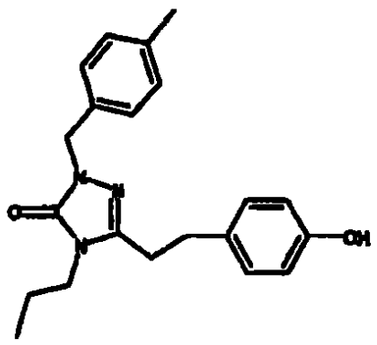
La acil semicarbazida de la Etapa C (13,4 g, 0,048 mol) se disolvió en metanol (100 ml), se trató con KOH (27 g, 0,48 mol) y después se calentó a 60°C durante 16 horas y a 85°C durante 6 horas más. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en H_2O y después se extrajo con acetato de etilo (3 x 500 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y después se concentraron, dando la N4-propil-triazolinona deseada en forma de un sólido ligeramente amarillo. $C_{14}H_{19}N_3O_2$ (PM = 261,33); espectroscopía de masas (MH^+) = 262,1.

Etapa E: Preparación de



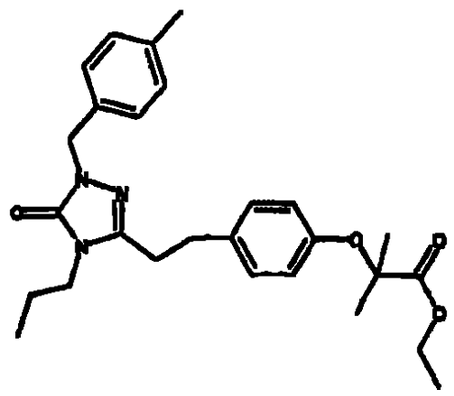
La N4-propil-triazolinona de la Etapa D (1,05 g, 4,0 mmol) se disolvió en DMF (25 ml) y se trató con α-bromo-p-xileno (1,17 g, 6,3 mmol) y K_2CO_3 en polvo (3,17 g, 0,023 mol). La mezcla resultante se calentó a 50°C en un tubo de secado durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en HCl acuoso (1 N, 75 ml) y se extrajo en acetato de etilo (75 ml). El extracto orgánico se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio la N2-p-metilbencil-triazolinona deseada en forma de un aceite ligeramente amarillo. $C_{22}H_{27}N_3O_2$ (PM = 365,48); espectroscopía de masas (MH^+) = 366,1.

Etapa F: Preparación de



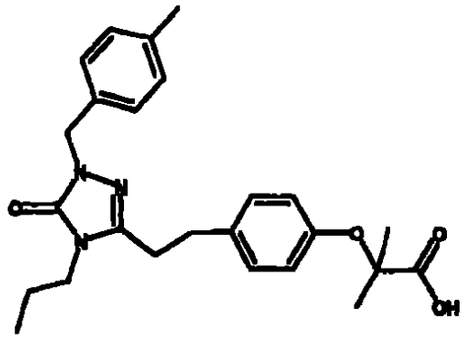
La N2-p-metilbencil-triazolinona de la Etapa E (0,95 g, 2,6 mmol) se disolvió en CH_2Cl_2 y se enfrió a 0°C en una atmósfera de N_2. A esta solución se le añadió gota a gota una solución en CH_2Cl_2 (10 ml) de BBr_3 (1,0 ml, 10,6 mmol). Después de agitar durante 2 horas a 0°C, la mezcla de reacción se inactivó por la adición gota a gota de metanol/CH_2Cl_2. La mezcla resultante se vertió en H_2O y se extrajo con más CH_2Cl_2 (50 ml). El extracto orgánico se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, dando el fenol deseado en forma de un aceite ligeramente amarillo. $C_{21}H_{25}N_3O_2$ (PM = 351,45); espectroscopía de masas (MH^+) = 352,2.

Etapa G: Preparación de



El fenol de la Etapa F (0,81 g, 2,3 mmol) se disolvió en etanol (absoluto, 15 ml) y se trató con 2-bromoisobutirato de etilo (1,2 ml, 8,2 mmol), K_2CO_3 en polvo (1,4 g, 10,1 mmol) y $MgSO_4$ (1,0 g, 8,3 mmol). La mezcla resultante se calentó a 60°C en un tubo de secado durante una noche. Después de enfriar a temperatura ambiente, la mezcla de reacción se filtró a través de una capa de Celite y el filtrado se concentró. El residuo resultante se disolvió en CH_2Cl_2 (100 ml) y se lavó con HCl acuoso (1 N, 100 ml) seguido de salmuera. El extracto orgánico se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio el éster etílico deseado en forma de un aceite. $C_{27}H_{35}N_3O_4$ (PM = 465,60); espectroscopía de masas (MH^+) = 466,2.

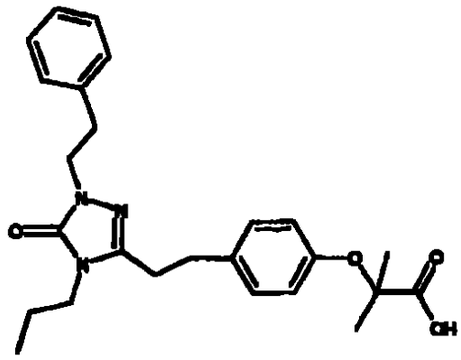
Etapa H: Preparación de



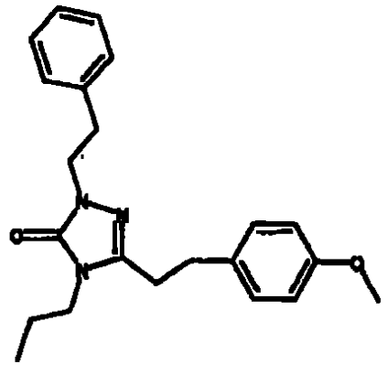
El éster etílico de la Etapa G (277,3 mg, 0,60 mmol) se disolvió en dioxano/H_2O (10 ml/3 ml) y se trató con LiOH (44 mg, 1,8 mmol). La mezcla resultante se agitó durante una noche y después se concentró. El residuo resultante se diluyó con CH_2Cl_2 (25 ml) y se extrajo con NaOH acuoso (1 N, 2 x 25 ml). Los extractos acuosos combinados se acidificaron por la adición cuidadosa de HCl acuoso (5 N) y después se extrajeron en CH_2Cl_2 (2 x 25 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron, dando el ácido carboxílico deseado en forma de un aceite incoloro. $C_{25}H_{31}N_3O_4$ (PM = 437,54); espectroscopía de masas (MH^+) = 438,2 (MH^-) = 436,3.

Ejemplo 23

Compuesto 23



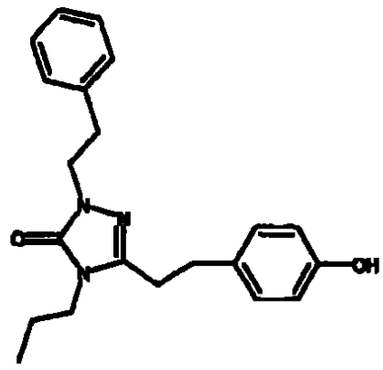
Etapa A: Preparación de



La N4-propil-triazolinona del Ejemplo 22, Etapa D (1,13 g, 4,3 mmol) se disolvió en THF (25 ml) y se trató con bromuro de fenetilo (710 µl, 5,2 mmol) y K_2CO_3 en polvo (1,25 g, 9,0 mmol). La mezcla resultante se calentó a 50-60°C en un tubo de secado durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en HCl acuoso (1 N, 75 ml) y se extrajo en acetato de etilo (100 ml). El extracto orgánico se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida

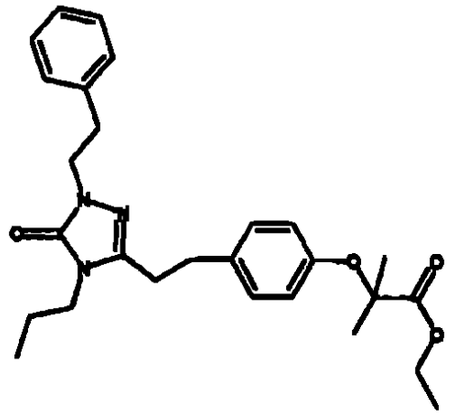
(gradiente de 2:1 a 1:1 de hexanos:acetato de etilo) dio la N2-fenetil-triazolinona deseada en forma de un aceite. $C_{22}H_{27}N_3O_2$ (PM = 365,48); espectroscopía de masas (MH^+) = 366,1.

Etapa B. Preparación de



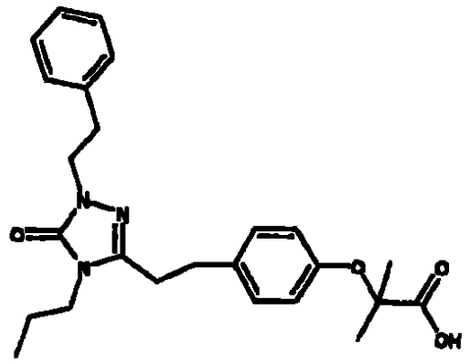
La N2-fenetil-triazolinona de la Etapa A (0,83 g, 2,3 mmol) se disolvió en CH_2Cl_2 y se enfrió a 0°C en una atmósfera de N_2. A esta solución se le añadió gota a gota una solución en CH_2Cl_2 (10 ml) de BBr_3 (1,0 ml, 10,6 mmol). Después de agitar durante 2 horas a 0°C, la mezcla de reacción se inactivó por la adición gota a gota de metanol/CH_2Cl_2. La mezcla resultante se vertió en H_2O y se extrajo con más CH_2Cl_2 (50 ml). El extracto orgánico se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, dando el fenol deseado en forma de un aceite ligeramente amarillo. $C_{21}H_{25}N_3O_2$ (PM = 351,45); espectroscopía de masas (MH^+) = 352,2.

Etapa C: Preparación de



El fenol de la Etapa B (0,78 g, 2,2 mmol) se disolvió en etanol (absoluto, 15 ml) y se trató con 2-bromoisobutirato de etilo (1,2 ml, 8,2 mmol), K_2CO_3 en polvo (,4 g, 10,1 mmol) y $MgSO_4$ (1,0 g, 8,3 mmol). La mezcla resultante se calentó a 60°C en un tubo de secado durante una noche. Después de enfriar a temperatura ambiente, la mezcla de reacción se filtró a través de una capa de celite y el filtrado se concentró. El residuo resultante se disolvió en CH_2Cl_2 (100 ml) y se lavó con HCl acuoso (1 N, 100 ml) seguido de salmuera. El extracto orgánico se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio el éster etílico deseado en forma de un aceite. $C_{27}H_{35}N_3O_4$ (PM = 465,60); espectroscopía de masas (MH^+) = 466,3.

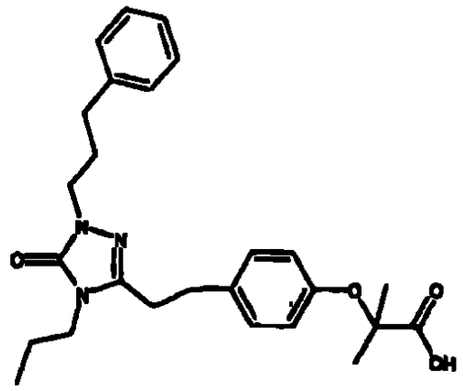
Etapa D: Preparación de



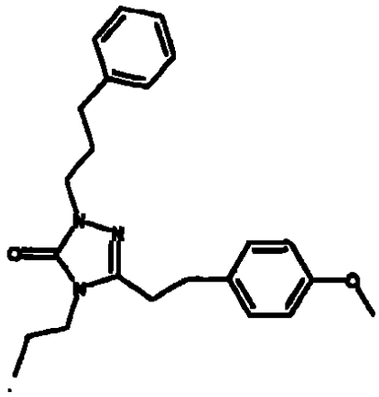
El éster etílico de la Etapa C (0,78 g, 1,7 mmol) se disolvió en dioxano/H_2O (20 ml, 3/1) y se trató con LiOH (122 mg, 5,1 mmol). La mezcla resultante se agitó durante una noche y después se concentró. El residuo resultante se diluyó con acetato de etilo (50 ml) y se extrajo con HCl acuoso (1 N, 50 ml). El extracto orgánico se extrajo de nuevo con NaOH acuoso (1 N, 1 x 50 ml). El lavado acuoso resultante se acidificó por la adición de HCl acuoso (5 N) y después se extrajo con acetato de etilo (2 x 50 ml). Los extractos orgánicos se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron, dando el ácido carboxílico deseado en forma de un aceite incoloro. $C_{25}H_{31}N_3O_4$ (PM = 437,54); espectroscopía de masas (MH^+) = 438,2; (MH^-) = 436,3.

Ejemplo 24

Compuesto 24



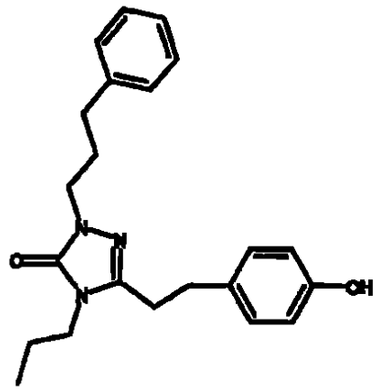
Etapa A: Preparación de



La N4-propil-triazolinona del Ejemplo 22, Etapa D (1,07 g, 4,1 mmol) se disolvió en DMF (25 ml) y se trató con bromuro de 3-fenilpropilo (750 µl, 4,9 mmol) y K_2CO_3 en polvo (1,2 g, 8,7 mmol). La mezcla resultante se calentó a 50-60°C en un tubo de secado durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en HCl acuoso (1 N, 75 ml) y se extrajo en acetato de etilo (100 ml). El extracto orgánico se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, dando el producto

bruto. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio la N2-(3-fenilpropil)triazolinona deseada en forma de un aceite ligeramente amarillo. $C_{23}H_{29}N_3O_2$ (PM = 379,51); espectroscopía de masas (MH^+) = 380,1.

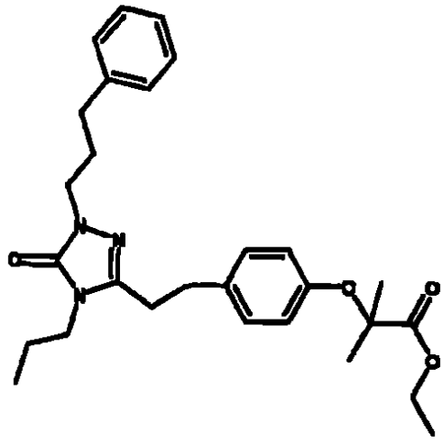
Etapa B: Preparación de



La N2-(3-fenilpropil)triazolinona de la Etapa A (0,92 g, 2,4 mmol) se disolvió en CH_2Cl_2 y se enfrió a 0°C en una atmósfera de N_2. A esta solución se le añadió gota a gota una solución en CH_2Cl_2 (10 ml) de BBr_3 (0,60 ml, 5,6 mmol). Después de agitar durante aproximadamente 1,5 horas a 0°C, la mezcla de reacción se inactivó por la adición gota a gota de metanol/CH_2Cl_2. La mezcla resultante se vertió en H_2O y se extrajo con más CH_2Cl_2 (2 x 50 ml). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron, dando el fenol bruto en forma de un aceite incoloro (usado sin purificación adicional). $C_{22}H_{27}N_3O_2$ (PM = 365,48); espectroscopía de

masas (MH^+) = 366,2.

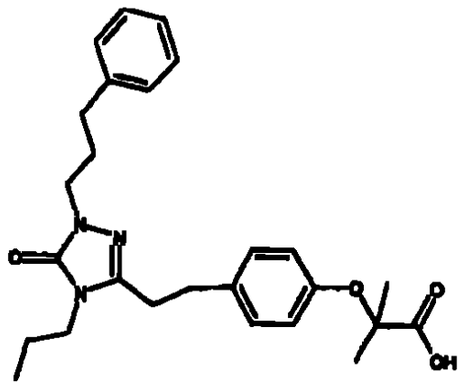
Etapa C: Preparación de



El fenol de la Etapa B (0,91 g, 2,5 mmol) se disolvió en etanol (absoluto, 15 ml) y se trató con 2-bromoisobutirato de etilo (1,2 ml, 8,2 mmol), K_2CO_3 en polvo (1,4 g, 10,1 mmol) y $MgSO_4$ (0,62 g, 5,2 mmol). La mezcla resultante se calentó a 60°C en un tubo de secado durante una noche. Después de enfriar a temperatura ambiente, la mezcla de reacción se filtró a través de una capa de celite y el filtrado se concentró. El residuo resultante se diluyó con HCl acuoso (0,5 N, 75 ml) y se extrajo con CH_2Cl_2 (2 x 75 ml). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4 y después se concentraron, dando el producto bruto. La purificación por cromatografía ultrarrápida (gradiente de 5:1 a 1:1 de hexanos:acetato de etilo) dio el éster etílico deseado en forma de un aceite incoloro.

$C_{28}H_{37}N_3O_4$ (PM = 479,62); espectroscopía de masas (MH^+) = 480,2.

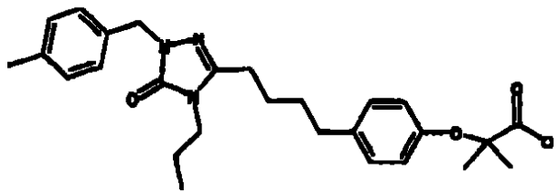
Etapa D: Preparación de



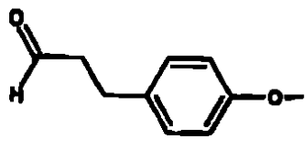
El éster etílico de la Etapa C (0,82 g, 1,7 mmol) se disolvió en dioxano/H_2O (16 ml, 3/1) y se trató con LiOH (140 mg, 5,8 mmol). La mezcla resultante se agitó a temperatura ambiente durante 2 horas y después a 45°C durante 2 horas más. La mezcla se concentró y el residuo resultante se diluyó con acetato de etilo (50 ml) y se extrajo con HCl acuoso. El extracto orgánico se extrajo de nuevo con NaOH acuoso (1 N, 1 x 50 ml). El lavado acuoso resultante se acidificó por la adición de HCl acuoso (5 N) y después se extrajo con acetato de etilo (1 x 50 ml). El extracto orgánico se secó sobre Na_2SO_4 y se concentró, dando el ácido carboxílico deseado en forma de un aceite incoloro. $C_{26}H_{33}N_3O_4$ (PM = 451,25); espectroscopía de masas (MH^+) = 452,3; (MH^-) = 450,3.

Ejemplo 25

Compuesto 25

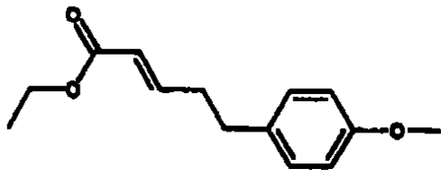


Etapa A: Preparación de



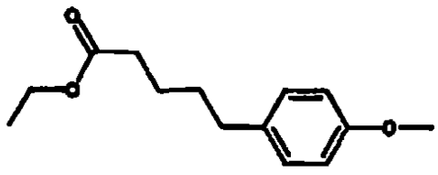
Una solución en cloruro de metileno (300 ml) de 3-(4-metoxifenil)-1-propanol (Aldrich, 15,0 g, 0,090 mol) se enfrió a 0°C y se agitó. A la solución se le añadió lentamente clorocromato de piridinio (Aldrich, 23,4 g, 0,108 mol) y después se enfrió a temperatura ambiente, se puso en un tubo de secado y se agitó durante un fin de semana (aprox. 72 horas). La mezcla de reacción se filtró a través de una capa de Florisil (Aldrich) y el filtrado se concentró, dando el producto bruto en forma de un aceite oscuro. La purificación por cromatografía ultrarrápida (6:1 de hexanos:acetato de etilo) dio el producto deseado, 3-(4-metoxifenil)propionaldehído, en forma de un aceite amarillo pálido.

Etapa B: Preparación de



Una solución acuosa (18 ml) del aldehído de la Etapa A (8,5 g, 0,052 mol) se trató con fosfonoacetato de trietilo (Aldrich, 14,0 g, 0,062 mol) y carbonato potásico (14,4 g, 0,104 mol). La solución bifásica se agitó a temperatura ambiente durante una noche. A la mezcla se le añadió más agua (60 ml) y se extrajo con hexanos (3 x). Las capas orgánicas combinadas se lavaron con salmuera y después se secaron sobre sulfato sódico. La evaporación del disolvente dio el producto bruto en forma de un aceite. La purificación por cromatografía en columna (10:1 de hexanos:acetato de etilo) dio el éster etílico insaturado deseado.

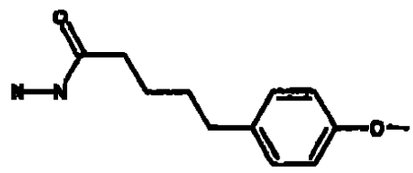
Etapa C: Preparación de



Una solución en acetato de etilo (100 ml) del éster etílico insaturado de la Etapa B (6,2 g, 0,026 mol) se agitó en un matraz de 3 bocas. La atmósfera del matraz se reemplazó con nitrógeno alternando vacío y nitrógeno en el matraz. Se añadió paladio sobre carbono (5%), la atmósfera

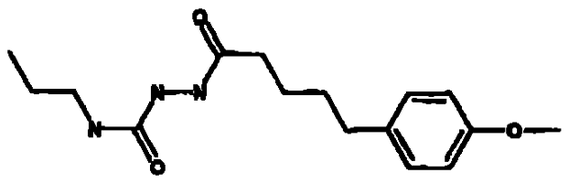
se purgó de nuevo y después se introdujo en un globo de hidrógeno mientras se agitaba durante una noche. La atmósfera de hidrógeno se reemplazó con nitrógeno como se ha indicado anteriormente, la mezcla resultante se filtró a través de una capa de Celite y la torta de filtro se lavó con acetato de etilo. El filtrado se concentró, dando el producto saturado deseado en forma de un aceite transparente.

Etapa D: Preparación de



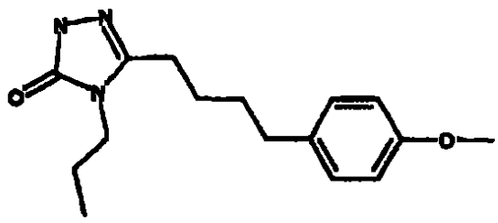
Una solución en etanol del éster de la Etapa C (6,0 g, 0,025 mol) e hidrato de hidrazina (EM Sciences, 12,7 g, 0,254 mol) se agitó y se calentó a 60°C durante 4 horas y después se enfrió a temperatura ambiente y se agitó durante un fin de semana (aproximadamente 72 horas). La solución resultante se concentró, se añadió a agua y se extrajo con acetato de etilo (2 x). Las capas orgánicas se combinaron, se lavaron con salmuera y después se secaron sobre sulfato sódico. La evaporación del disolvente dio un producto sólido que se lavó con hexanos y se filtró, dando la acilhidrazida deseada en forma de un sólido blanco. $C_{12}H_{18}O_2N_2$ (PM = 222,29); espectroscopía de masas (MH^+) = 223,2.

Etapa E: Preparación de



Una solución en tetrahidrofurano (25 ml) de la acilhidrazida de la Etapa D (2,6 g, 0,012 mol) se trató con isocianato de propilo (Aldrich, 1,2 g, 0,014 mol) y se agitó a temperatura ambiente durante una noche, tiempo durante el que se formó un precipitado. La suspensión resultante se trató con metanol y se agitó durante 30 minutos más. El disolvente después se evaporó, dando la acil semicarbazida deseada en forma de un sólido blanco que se usó sin purificación adicional.

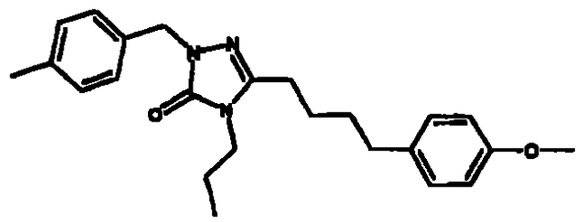
Etapa F: Preparación de



Una solución en metanol (50 ml) de la acil semicarbazida de la Etapa E (3,4 g, 0,011 mol) se agitó y se trató con hidróxido potásico sólido (6,2 g, 0,110 mol). La mezcla se calentó a 60°C durante 48 horas. La mezcla resultante se enfrió, se añadió a agua (150 ml) y se extrajo con acetato de etilo (3 x). Las capas orgánicas se

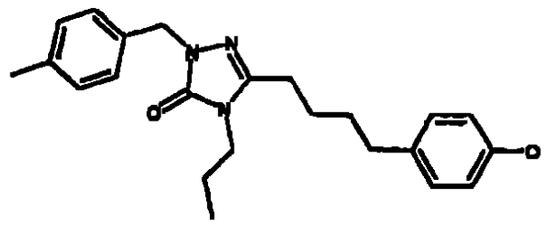
combinaron, se lavaron con salmuera y se secaron sobre sulfato sódico. La evaporación del disolvente dio un sólido que se lavó con hexano, dando la N4-propil-triazolinona deseada en forma de un sólido blanco. $C_{16}H_{23}N_3O_2$ (PM = 289); espectroscopía de masas (MH^+) = 290,2.

Etapa G: Preparación de



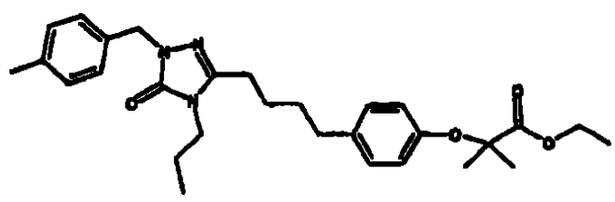
La N4-propil-triazolinona de la Etapa F (1,2 g, 0,0042 mol) se disolvió en DMF (25 ml) y se trató con α-bromo-p-xileno (Aldrich, 1,2 g, 0,0063 mol) y carbonato potásico en polvo (Aldrich, 2,3 g, 0,0168 mol). La mezcla resultante se calentó a 45°C durante 2 horas y después se dejó enfriar a temperatura ambiente y se agitó durante una noche. La mezcla de reacción se añadió a HCl acuoso (1 N, 75 ml) y se extrajo con acetato de etilo (3 x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico y se concentraron, dando el producto bruto en forma de un aceite. La purificación por cromatografía ultrarrápida (gradiente: hexanos a 1:1 de hexanos:acetato de etilo) dio la N2-p-metil-bencil-triazolinona deseada.

Etapa H: Preparación de



La N2-p-metilbencil-triazolinona de la Etapa G (1,2 g, 0,0031 mol) se disolvió en cloruro de metileno (25 ml) y se enfrió a 0°C en un tubo de secado. Se añadió gota a gota una solución de tribromuro de boro (0,6 ml, 0,006 mol) en cloruro de metileno (5 ml). La mezcla de reacción se agitó a 0°C durante 1 hora. Se añadieron dos equivalentes más de tribromuro de boro (0,6 ml, 0,006 mol) y se continuó agitando durante 0,5 horas más. La reacción se inactivó por la adición gota a gota de metanol (4 ml) en cloruro de metileno (4 ml). La reacción se añadió a 60 ml más de cloruro de metileno y se lavó con agua. La capa orgánica después se secó sobre sulfato sódico y se concentró, dando el fenol deseado en forma de un sólido amarillo. $C_{23}H_{29}N_3O_2$ (PM = 379,5); espectroscopía de masas (MH^+) = 380,3.

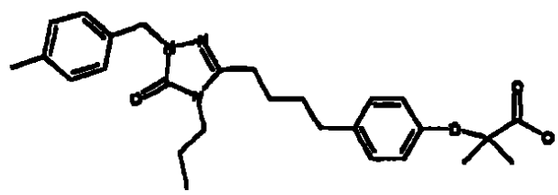
Etapa I: Preparación de



El fenol de la Etapa H (1,0 g, 0,0026 mol) se

disolvió en etanol (absoluto, 25 ml) y se trató con 2-bromoisobutirato de etilo (Aldrich, 1,5 g, 1,1 ml, 0,0078 mol), carbonato potásico en polvo (Aldrich, 1,4 g, 0,010 mol) y sulfato de magnesio (0,3 g, 0,0026 mol). La mezcla resultante se agitó y se calentó a 60°C, en un tubo de secado, durante 16 horas. La mezcla de reacción se filtró a través de una capa de Celite y el filtrado se concentró. El residuo resultante se disolvió en acetato de etilo y se lavó con HCl (1 N) y salmuera. La capa orgánica después se secó sobre sulfato sódico y se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio el éster etílico deseado. $C_{29}H_{30}N_3O_4$ (PM = 493,6); espectroscopía de masas (MH^+) = 494,3.

Etapa J: Preparación de

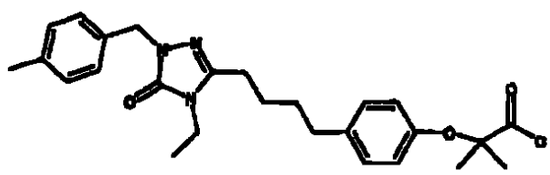


El éster etílico de la Etapa I (0,6 g, 0,0012 mol) se disolvió en metanol (6 ml) y se añadió una solución acuosa de hidróxido de litio (0,06 g, 0,0024 mol) en agua (6 ml). La mezcla resultante se calentó a 60°C durante 2 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se añadió a acetato de etilo (70 ml) y se lavó con agua, dando como resultado una emulsión que se

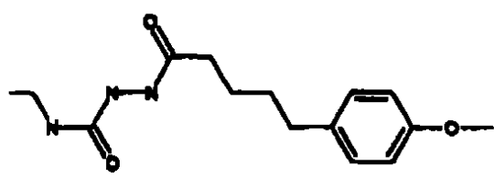
disolvió por la adición de HCl (1 N). Ésta se extrajo con acetato de etilo (2 x). Estas dos capas se combinaron y se extrajeron con NaOH (1 N), la capa acuosa se acidificó con HCl (5 N) y se extrajo con acetato de etilo (2 x). Estas dos capas orgánicas se combinaron, se secaron sobre sulfato sódico y se concentraron, dando el ácido carboxílico deseado en forma de un aceite. $C_{27}H_{35}N_4O_3$ (PM = 465,6); espectroscopía de masas (MH^+) = 466,3; (MH^-) = 464,3.

Ejemplo 26

Compuesto 26



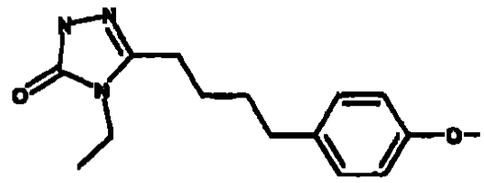
Etapa A: Preparación de



La acilhidrazida del Ejemplo 25, Etapa D (2,6 g, 0,012 mol) se disolvió en tetrahidrofurano (25 ml) y se trató con isocianato de etilo (Aldrich, 1,2 g, 0,014 mol). La mezcla resultante se agitó a temperatura ambiente durante una noche. La suspensión resultante se trató con metanol y se agitó durante 30 minutos más. El disolvente

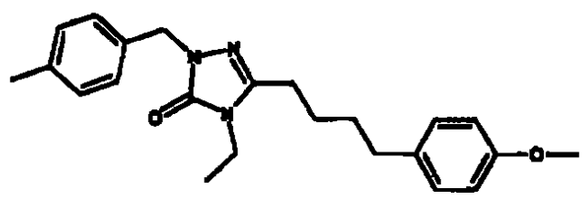
después se evaporó, dando la acil semicarbazida deseada en forma de un sólido blanco que se usó sin purificación adicional.

Etapa B: Preparación de



Una solución en metanol (50 ml) de la acil semicarbazida de la Etapa A (3,3 g, 0,011 mol) se agitó y se trató con hidróxido potásico sólido (6,2 g, 0,11 mol). La mezcla se calentó a 60°C durante una noche. La mezcla resultante se enfrió, se añadió a agua (125 ml) y se extrajo con acetato de etilo (3 x). Las capas orgánicas se combinaron, se lavaron con salmuera y se secaron sobre sulfato sódico. La evaporación del disolvente dio la N4-etil-triazolinona deseada en forma de un sólido. $C_{15}H_{21}N_3O_2$ (PM = 275,35); espectroscopía de masas (MH^+) = 276,1.

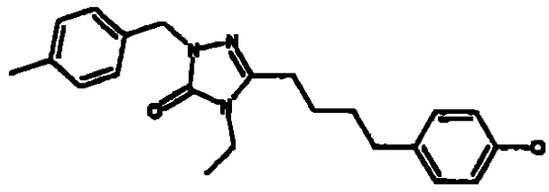
Etapa C: Preparación de



La N4-etil-triazolinona de la Etapa B (1,2 g, 0,0044

mol) se añadió lentamente a una suspensión de hidruro sódico (dispersión al 60% en aceite mineral, 0,3 g, 0,009 mol) en una atmósfera de nitrógeno. La suspensión resultante se agitó durante 45 minutos y después se trató con α-bromo-p-xileno (Aldrich, 1,2 g, 0,006 mol). La mezcla resultante se agitó a temperatura ambiente durante una noche. La mezcla de reacción se añadió lentamente a HCl acuoso (1 N, 100 ml) y se extrajo con acetato de etilo (3 x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato sódico y se concentraron, dando el producto bruto en forma de un aceite. La purificación por cromatografía ultrarrápida (gradiente de 1:1 de hexanos:acetato de etilo a 4:1 de acetato de etilo:hexanos) dio la N2-p-metilbencil-triazolinona deseada.

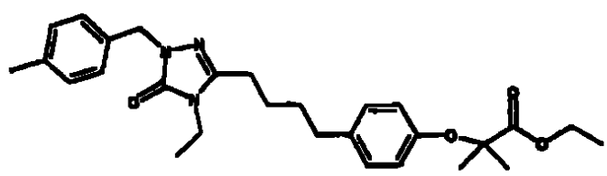
Etapa D: Preparación de



La N2-p-metilbencil-triazolinona de la Etapa C (1,1 g, 0,0026 mol) se disolvió en cloruro de metileno (25 ml) y se enfrió a 0°C en un tubo de secado. Se añadió gota a gota una solución de tribromuro de boro (0,4 ml, 0,004 mol) en cloruro de metileno durante 5 minutos. la mezcla

de reacción se agitó a 0°C durante 10 minutos y después se añadió más solución de tribromuro de boro (0,4 ml, 0,004 mol) en cloruro de metileno y se continuó agitando durante 1 hora. La reacción se interrumpió con la adición gota a gota de metanol (2 ml). La reacción se añadió a 100 ml más de agua y se extrajo con cloruro de metileno (3 x). Las capas orgánicas se combinaron, se lavaron con salmuera y se secaron sobre sulfato sódico. La evaporación del disolvente dio el fenol deseado en forma de un sólido blanco. $C_{22}H_{27}N_3O_2$ (PM = 365,48); espectroscopía de masas (MH^+) = 366,2.

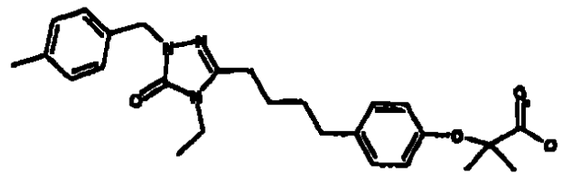
Etapa E: Preparación de



El fenol de la Etapa D (0,8 g, 0,0022 mol) se disolvió en etanol (absoluto, 20 ml) y se trató con 2-bromoisobutirato de etilo (Aldrich, 1,3 g, 0,0066 mol), carbonato potásico en polvo (Aldrich, 1,2 g, 0,0088 mol) y sulfato de magnesio (0,2 g, 0,002 mol). La mezcla resultante se agitó y se calentó a 65°C, en un tubo de secado, durante 48 horas. La mezcla de reacción se filtró a través de una capa de Celite y el filtrado se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (gradiente: de 3:2 de hexanos:acetato de

etilo a 1:1 de hexanos:acetato de etilo) dio el éster etílico deseado. $C_{28}H_{37}N_3O_4$ (PM = 479,62); espectroscopía de masas (MH^+) = 480,3.

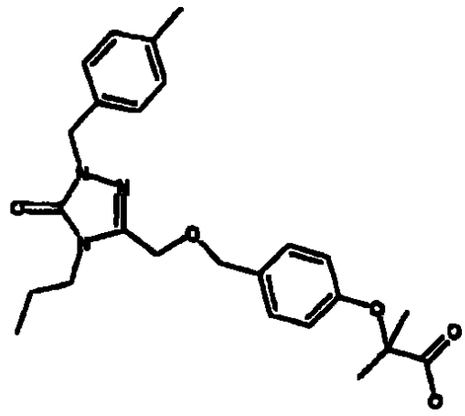
Etapa F: Preparación de



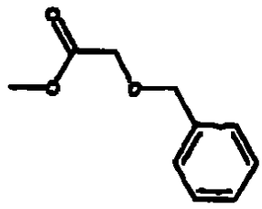
El éster etílico de la Etapa E (0,75 g, 0,0016 mol) se disolvió en metanol (7 ml) y se añadió una solución acuosa de hidróxido de litio (0,08 g, 0,0032 mol) en agua (7 ml). La mezcla resultante se calentó a 60°C durante 1 hora. La mezcla de reacción se añadió a agua (60 ml) y se lavó con éter. La capa acuosa se acidificó con HCl acuoso (concentrado) hasta un pH de 4 y se extrajo con acetato de etilo (2 x). Estas dos capas se combinaron, se lavaron con salmuera y se secaron sobre sulfato sódico. El disolvente se evaporó, dando el ácido carboxílico deseado en forma de un aceite. $C_{26}H_{33}N_3O_4$ (PM = 451,57); espectroscopía de masas (MH^+) = 452,2; (MH^-) = 450,3.

Ejemplo 27

Compuesto 27

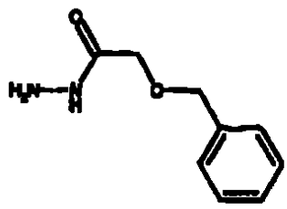


Etapa A: Preparación de



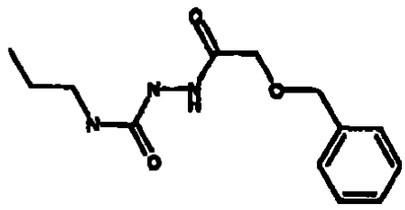
Una solución en metanol (75 ml) de ácido benciloxiacético (Aldrich, 15,0 g, 0,090 mol) se trató con H_2SO_4 (concentrado, 1 ml) y se agitó a temperatura ambiente durante una noche. El disolvente se evaporó y el residuo se diluyó con CH_2Cl_2 (150 ml). La solución resultante se extrajo con bicarbonato sódico acuoso saturado (1 x 150 ml) seguido de salmuera (1 x 150 ml) y después se secó sobre Na_2SO_4. Tras la evaporación del disolvente se obtuvo el éster metílico deseado en forma de un aceite incoloro. $C_{10}H_{12}O_3$ (PM = 180,21); espectroscopía de masas (MH^+) = 195,1.

Etapa B: Preparación de



Una solución en metanol (100 ml) del éster metílico de la Etapa A (6,45 g, 0,036 mol) se trató con hidrato de hidrazina (20 ml, 0,41 mol) y se agitó a temperatura ambiente durante varios días. El disolvente se evaporó y el residuo se disolvió en acetato de etilo (200 ml). El extracto orgánico se secó sobre Na_2SO_4 y se concentró, dando la acilhidrazida deseada en forma de un aceite.

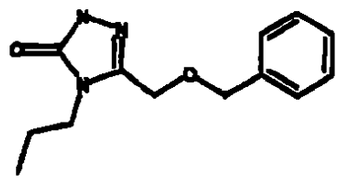
Etapa C: Preparación de



Se añadió gota a gota durante 15 minutos una solución en THF (50 ml) de la acilhidrazida de la Etapa B (3,56 g, 0,020 mol) enfriada a 0°C y tratada con una solución en THF (25 ml) de isocianato de n-propilo (Aldrich, 2,3 ml, 0,024 mol). La mezcla se calentó a temperatura ambiente y se agitó durante una noche mientras que se formaba un precipitado espeso. La suspensión resultante se trató con metanol (25 ml) y se agitó durante aproximadamente 1 hora. El disolvente después se concentró, dando la acil

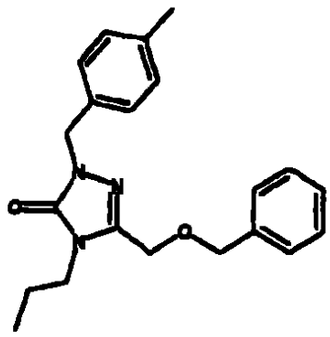
semicarbazida deseada en forma de un sólido blanco que se usó sin purificación adicional. $C_{13}H_{19}N_3O_3$ (PM = 265,31); espectroscopía de masas (MH^+) = 266,1.

Etapa D: Preparación de



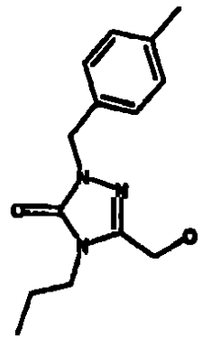
La acil semicarbazida de la Etapa C (5,02 g, 18,9 mmol) se disolvió en metanol (75 ml), se trató con KOH (10,2 g, 18,3 mmol) y después se calentó a reflujo durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en H_2O (300 ml) y después se extrajo con acetato de etilo (3 x 300 ml). Los extractos orgánicos combinados se lavaron con salmuera (1 x 300 ml), se secaron sobre Na_2SO_4 y después se concentraron, dando la N4-propil-triazolinona deseada en forma de un sólido ligeramente amarillo. $C_{13}H_{17}N_3O_2$ (PM = 247,30); espectroscopía de masas (MH^+) = 248,1.

Etapa E: Preparación de



La N4-propil-triazolinona de la Etapa D (4,32 g, 17,5 mmol) se disolvió en DMF (100 ml) y se trató con α-bromo-p-xileno (4,0 g, 21,6 mmol) y K_2CO_3 en polvo (5,2 g, 38 mmol). La mezcla resultante se calentó a 50°C en un tubo de secado durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en HCl acuoso (1 N, 200 ml) y se extrajo en acetato de etilo (200 ml). El extracto orgánico se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida dio la N2-p-metilbencil-triazolinona deseada en forma de un aceite ligeramente amarillo. $C_{21}H_{25}N_3O_2$ (PM = 351,45); espectroscopía de masas (MH^+) = 352,2.

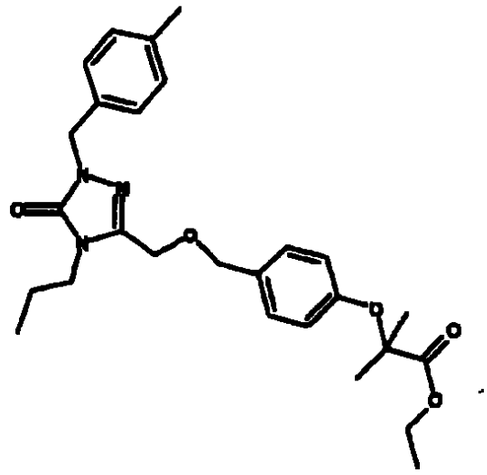
Etapa F: Preparación de



A una suspensión que contenía Pd al 5%/C (320 mg) en etanol (50 ml) se le añadió el éster bencílico de la Etapa E (2,9 g, 8,25 mmol) en forma de una solución en THF (50 ml). La mezcla resultante se purgó con nitrógeno y después con hidrógeno. Se mantuvo una atmósfera de hidrógeno durante la mezcla de reacción por medio de un globo. Después de 48 horas, se observó que la reacción (TLC y MS) se completó sólo al 50%. El catalizador se retiró por filtración a través de una capa de celite. El filtrado resultante se concentró hasta un aceite y se disolvió de nuevo en CH_3OH (50 ml). Se añadió una suspensión que contenía Pd al 5%/C (210 mg) en CH_3OH (10 ml) y la mezcla se purgó con nitrógeno. Se estableció una atmósfera de hidrógeno como se ha descrito anteriormente y se mantuvo durante 5 días. De nuevo se retiró el catalizador por filtración a través de una capa de celite. La concentración del filtrado dio el producto bruto que se purificó por cromatografía ultrarrápida (gradiente: de 5:1 a 1:2 de hexanos:acetato de etilo), proporcionando el

alcohol deseado en forma de un sólido blanco. $C_{14}H_{19}N_3O_2$ (PM = 261,33); espectroscopía de masas (MH^+) = 262,0.

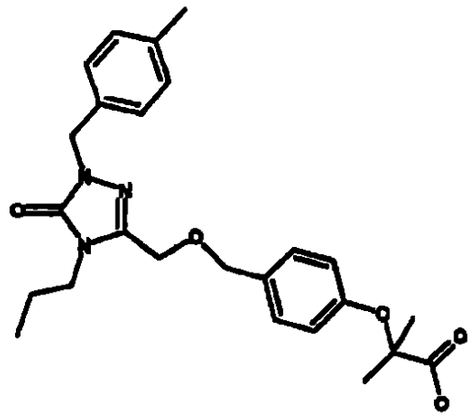
Etapa G: Preparación de



A una suspensión de NaH (al 60% en aceite, 130 mg, 3,25 mmol) en DMF (10 ml) a 0°C se le añadió una solución en DMF (5 ml) del alcohol de la Etapa F (383,7 mg, 1,47 mmol). La mezcla resultante se agitó durante 5 minutos y después se trató con una solución en DMF (5 ml) de 2-[4-(bromometil)fenoxi]-2-metil-propionato de etilo (registro 58336-71-3, 457,2 mg, 1,52 mmol). La mezcla de reacción se calentó a temperatura ambiente y se agitó durante una noche. La mezcla después se vertió en HCl acuoso (1 N, 100 ml) y se extrajo en CH_2Cl_2 (100 ml). El extracto orgánico se lavó una segunda vez con HCl acuoso (1 N) seguido de salmuera, se secó sobre Na_2SO_4 y se concentró. La cromatografía ultrarrápida (3:1 de hexanos:acetato de etilo) dio el producto deseado en forma de un aceite

amarillo. El análisis por RMN indicó la presencia de DMF, por lo que el aceite se diluyó en Et_2O (50 ml) y se lavó con HCl acuoso (1 N, 50 ml) seguido de salmuera (1 x 50 ml). La solución orgánica se secó sobre Na_2SO_4 y después se concentró. La purificación por cromatografía ultrarrápida (3:1 de hexanos:acetato de etilo) dio el éster etílico deseado. $C_{27}H_{35}N_3O_5$ (PM = 481,60); espectroscopía de masas (MH^+) = 482,2.

Etapa H: Preparación de

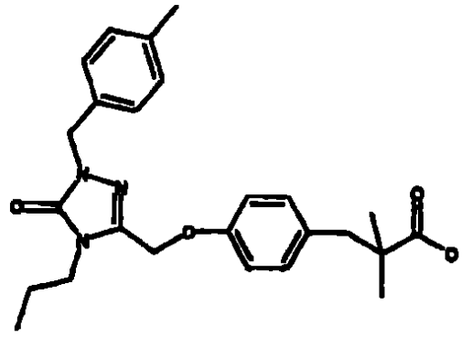


El éster etílico de la Etapa G (252,9 mg, 0,53 mmol) se disolvió en dioxano/H_2O (15 ml/5 ml) y se trató con LiOH (50 mg, 2,1 mmol). La mezcla resultante se agitó durante una noche y después se concentró. El residuo resultante se diluyó con H_2O (70 ml) y se lavó con Et_2O (1 x 75 ml). El extracto acuoso se acidificó con HCl acuoso y después se extrajo con acetato de etilo (2 x 70 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y después se concentraron, dando el ácido carboxílico deseado en forma

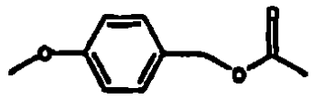
de un aceite incoloro espeso. $C_{25}H_{31}N_3O_5$ (PM = 453,54); espectroscopía de masas (MH^+) = 454,2; (MH^-) = 452,2.

Ejemplo 28

Compuesto 28

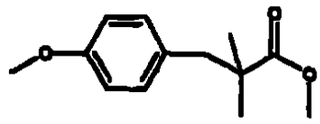


Etapa A: Preparación de



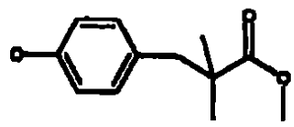
Una solución de alcohol 4-metoxibencílico (11 ml, 0,088 mol) en cloruro de metileno (865 ml) se enfrió a 0°C y después se trató con trietilamina (18 ml, 0,129 mol). A la mezcla se le añadió cloruro de acetilo (7,2 ml, 0,101 mol). La reacción se dejó en agitación durante una hora. La solución se lavó con HCl 1 N, $NaHCO_3$ saturado y salmuera y después se secó sobre Na_2SO_4. La capa orgánica se concentró, dando el compuesto deseado en forma de un aceite pardo.

Etapa B: Preparación de



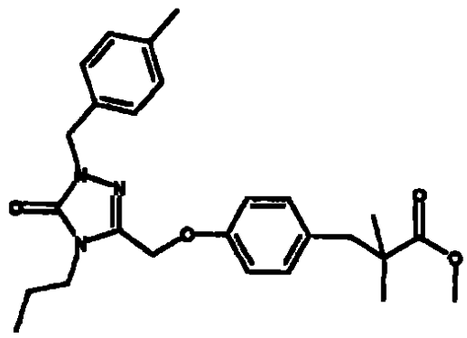
El acetato de la Etapa A (13 g, 0,072 mol) se disolvió en cloruro de metileno (600 ml) y se trató con 1-metoxi-1-trimetilsiloxi-2-metil-1-propeno (Aldrich, 29 ml, 0,193 mol) seguido de $Mg(ClO_4)_2$ (1,7 g, 0,0073 mol). La mezcla se agitó durante una noche a temperatura ambiente. La solución se lavó con agua y después con salmuera. La capa orgánica se concentró, produciendo un aceite amarillo. El material se usó sin purificación adicional.

Etapa C: Preparación de



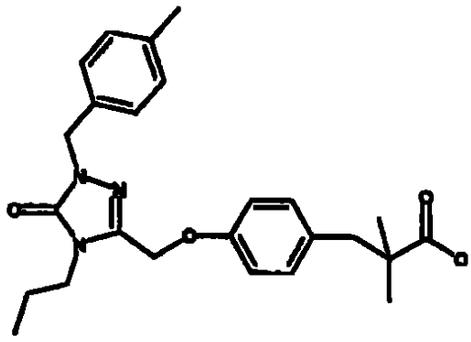
Una solución de BBr_3 (9 ml, 0,048 mol) en cloruro de metileno (180 ml) se enfrió a 0°C y se trató con una solución del éster metílico de la Etapa B (10,56 g, 0,095 mol) en cloruro de metileno (180 ml). La reacción se dejó en agitación durante 30 minutos. Se añadieron cloruro de metileno y metanol (1:1, 70 ml) para interrumpir la reacción. El disolvente se concentró. La purificación del residuo por cromatografía ultrarrápida (3:1 de hexanos:acetato de etilo) produjo el fenol en forma de un aceite incoloro.

Etapa D: Preparación de



Una solución en THF del fenol de la Etapa C (173,3 mg, 0,83 mmol) y el alcohol del Ejemplo 27, Etapa F (204,5 mg, 0,78 mmol) se trató con trifenilfosfina (218,5 mg, 0,83 mmol) y azodicarboxilato de dietilo (145 µl, 0,92 mmol). La mezcla resultante se agitó durante una noche a temperatura ambiente en una atmósfera de N_2. La mezcla se concentró y el residuo se disolvió en CH_2Cl_2 (50 ml). La solución orgánica se lavó con H_2O (1 x 50 ml) y salmuera (1 x 50 ml), se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (4:1 de hexanos:acetato de etilo) dio el éster metílico deseado en forma de un aceite. $C_{26}H_{33}N_3O_4$ (PM = 451,57); espectroscopía de masas (MH^+) = 452,2.

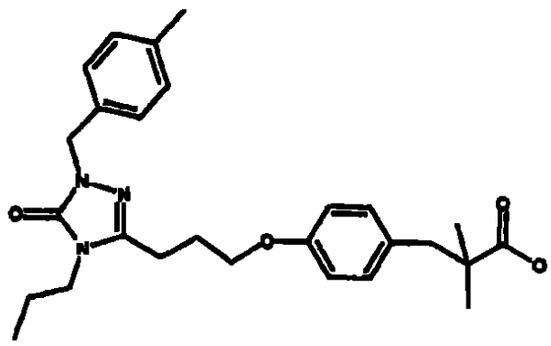
Etapa E: Preparación de



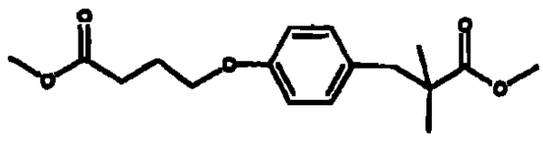
El éster metílico de la Etapa D (190 mg, 0,42 mmol) se disolvió en dioxano/H_2O (6 ml/3 ml) y se trató con LiOH (50 mg, 2,1 mmol). La mezcla resultante se agitó durante una noche y después se concentró. El residuo resultante se diluyó con H_2O (50 ml) y se lavó con Et_2O (1 x 50 ml). El extracto acuoso se acidificó con HCl acuoso y después se extrajo con acetato de etilo (1 x 50 ml). El extracto orgánico se lavó con salmuera (1 x 50 ml), se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (gradiente de 1:1 a 1:2 de hexanos:acetato de etilo) dio el ácido carboxílico deseado en forma de un aceite incoloro. $C_{25}H_{31}N_3O_4$ (PM = 437,54); espectroscopía de masas (MH^+) = 438,1; (MH^-) = 436,1.

Ejemplo 29

Compuesto 29

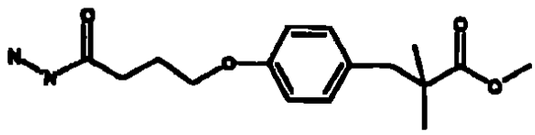


Etapa A: Preparación de



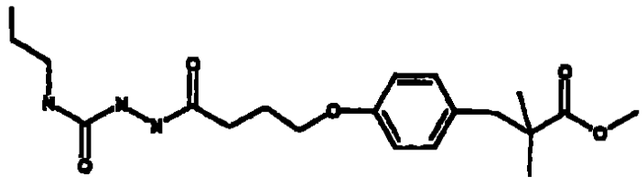
Una solución en DMF (65 ml) del fenol del Ejemplo 28, Etapa C (2,1 g, 0,010 mol) y 4-bromobutirato de metilo (2,2 g, 0,012 mol) se trató con K_2CO_3 en polvo (4,0 g, 0,030 mol) y $MgSO_4$ (4,0 g, 0,033 mol). La mezcla resultante se calentó a 60-70°C en un tubo de secado. Después de calentar durante una noche, la mezcla se enfrió a temperatura ambiente y se filtró a través de una capa de celite. El filtrado se diluyó con HCl acuoso (1 N, 150 ml) y se extrajo con Et_2O. La solución orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. La purificación por cromatografía ultrarrápida (10:1 de hexanos:acetato de etilo) produjo el éster metílico deseado en forma de un aceite ligeramente amarillo. $C_{17}H_{24}O_5$ (PM = 308,38); espectroscopía de masas (MH^+) = 309,1.

Etapa B: Preparación de



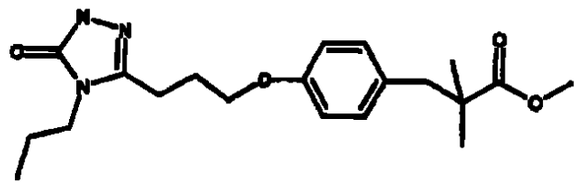
Una solución en metanol (76 ml) del éster metílico de la Etapa A (2 g, 0,0065 mol) se trató con hidrato de hidrazina (0,95 ml, 0,019 mol) y se agitó durante una noche. Se añadió más hidrato de hidrazina (0,95 ml, 0,019 mol) para completar la reacción. El disolvente se concentró y el residuo resultante se diluyó con acetato de etilo. La capa orgánica se lavó con agua seguido de salmuera y después se evaporó, produciendo la acilhidrazida deseada en forma de un aceite amarillo. $C_{16}H_{24}N_2O_4$ (PM = 308,38); espectroscopía de masas (MH^+) = 309,2.

Etapa C: Preparación de



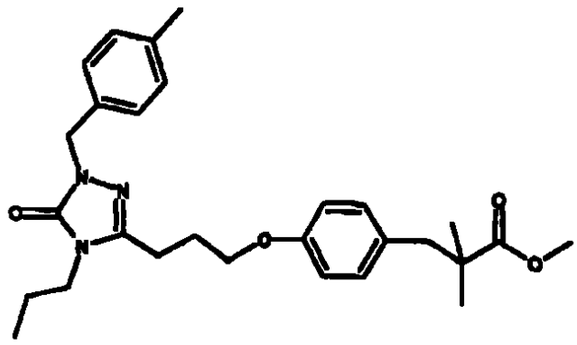
Una solución en THF (20 ml) de la acilhidrazida de la etapa B (2 g, 0,006 mol) se trató con una solución en THF (20 ml) de isocianato de n-propilo (Aldrich, 0,791 ml, 0,084 mol), añadida gota a gota. La mezcla se agitó durante una noche. El disolvente se concentró, dando un rendimiento cuantitativo de la acil semicarbazida deseada que se usó más adelante sin purificación adicional.

Etapa D: Preparación de



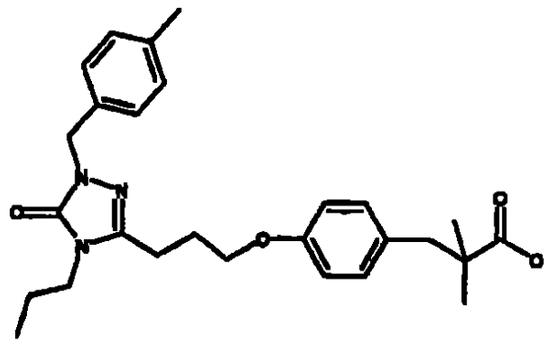
La acil semicarbazida de la Etapa C (2,68 g, 0,0068 mol) se disolvió en metanol y se trató con KOH (3,82 g, 0,068 mol). La reacción se calentó a reflujo durante una noche. Después de enfriar, a la mezcla de reacción se le añadió agua y la solución después se acidificó usando HCl 1 N hasta pH = 3. La capa ácida después se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó y se concentró. El material resultante se diluyó con metanol y se trató con una cantidad catalítica de H_2SO_4 concentrado. La solución se agitó durante una noche. El disolvente se evaporó, después el residuo se diluyó con cloruro de metileno y se lavó con agua. La capa orgánica se concentró, dando el éster metílico. $C_{20}H_{29}N_3O_4$ (PM = 375,47); espectroscopía de masas (MH^+) = 376,2.

Etapa E: Preparación de



La N4-propil-triazolinona de la Etapa D (1,5 g, 0,004 mol) se disolvió en THF (7 ml) y se trató con α-bromo-p-xileno (1,11 g, 0,006 mol) y K_2CO_3 en polvo. La mezcla resultante se agitó durante una noche a 67°C. La fuente de calor se retiró y a la mezcla de reacción se le añadió acetato de etilo. La capa orgánica se extrajo con agua seguido de salmuera, se secó y se concentró. La purificación del aceite amarillo por cromatografía ultrarrápida (4:1 de hexanos:acetato de etilo) produjo la N4-p-metil bencil triazolinona. $C_{28}H_{37}N_3O_4$ (PM = 479,62); espectroscopía de masas (MH^+) = 480,3.

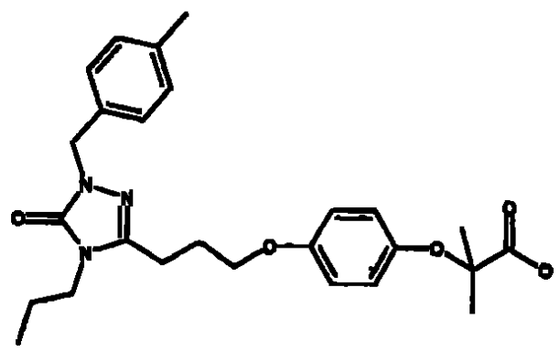
Etapa F:



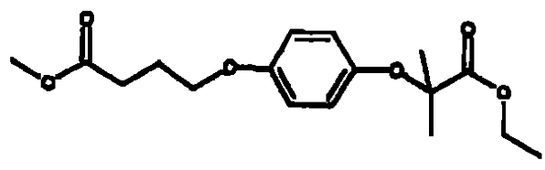
El éster metílico de la Etapa E (0,160 g, 0,00033 mol) se disolvió en etanol (5 ml) y se trató con NaOH 2 N (3 ml). La reacción se calentó a reflujo durante una hora. La reacción se enfrió y a la solución se le añadió agua (20 ml). La solución después se acidificó usando HCl 1 N hasta pH = 3 y después se extrajo con acetato de etilo. La capa orgánica se concentró, produciendo el ácido carboxílico deseado en forma de un aceite incoloro. $C_{27}H_{35}N_3O_4$ (PM = 465,60); espectroscopía de masas (MH^+) = 466,3.

Ejemplo 30

Compuesto 30



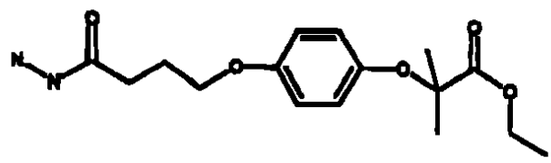
Etapa A: Preparación de



Se combinaron en un matraz 4-bromo-butirato de metilo (3 g, 0,0166 mol) y éster etílico del ácido 2-(4-

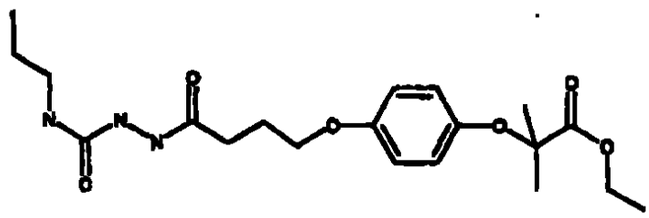
hidroxifenil)-2-metilpropanoico (American Home Products Patente de Estados Unidos número 3795691, 313 g, 0,014 mol) y se calentaron a 70°C. La reacción se agitó durante una noche. Tras la refrigeración, la mezcla de reacción se filtró a través de celite. El filtrado se diluyó con agua y se extrajo con éter etílico. La capa orgánica se lavó con salmuera y después se concentró. La purificación por cromatografía ultrarrápida (4:1 de hexanos:acetato de etilo) proporcionó el diéster deseado en forma de un aceite amarillo. $C_{17}H_{24}O_6$ (PM = 324,38); espectroscopía de masas (MH^+) = 325,2.

Etapa B: Preparación de



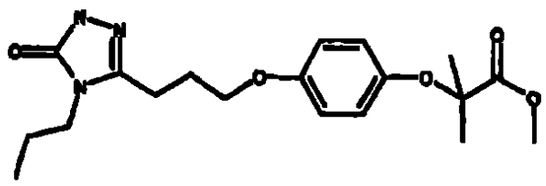
Una solución en metanol (60 ml) del diéster de la Etapa A (1,64 g, 0,005 mol) se trató con hidrato de hidrazina (1,23 ml, 0,025 mol) y se agitó durante una noche. Se añadió más hidrato de hidrazina (2,46 ml, 0,050 mol) y la reacción se agitó durante una noche. El disolvente se evaporó. El residuo resultante se diluyó con acetato de etilo y se lavó con agua seguido de salmuera. La concentración de la capa orgánica dio la acilhidrazida.

Etapa C: Preparación de



Una solución en THF (10 ml) de la acilhidrazida de la Etapa B (0,860 g, 0,00265 mol) se trató con una solución en THF (10 ml) de isocianato de n-propilo (Aldrich, 0,323 ml, 0,00345 mol) añadida gota a gota. La mezcla se agitó durante una noche. El disolvente se concentró, dando un rendimiento cuantitativo de la acil semicarbazida deseada que se usó más adelante sin purificación adicional.

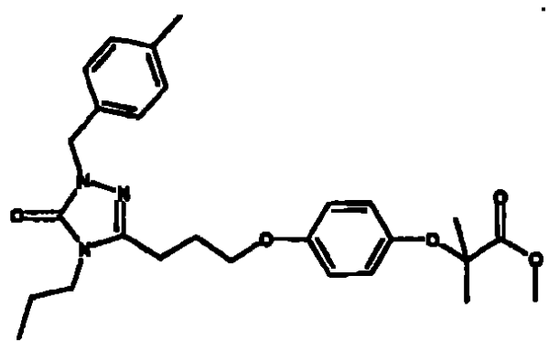
Etapa D: Preparación de



La acil semicarbazida de la Etapa C (1 g, 0,0026 mol) se disolvió en metanol y se trató con KOH (1,48 g, 0,026 mol). La reacción se calentó a reflujo durante una noche. Tras la refrigeración, a la mezcla de reacción se le añadió agua y la solución después se acidificó usando HCl 1 N hasta pH = 3. La capa ácida después se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El material resultante se diluyó con metanol y se trató con una cantidad

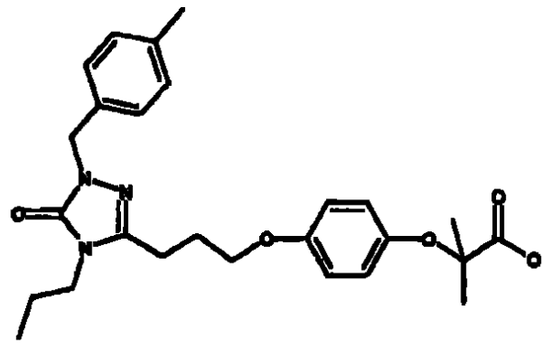
catalítica de H_2SO_4 concentrado. La solución se agitó durante una noche. El disolvente se evaporó, después el residuo se diluyó con cloruro de metileno y se lavó con agua. La capa orgánica se concentró, dando la N-4-propil-triazolinona deseada. $C_{19}H_{27}N_3O_5$ (PM = 377,44); espectroscopía de masas (MH^+) = 378,2.

Etapa E: Preparación de



La N4-propil-triazolinona de la Etapa D (0,92 g, 0,0024 mol) se disolvió en DMF (7 ml) y se trató con α-bromo-p-xileno (0,476 ml, 0,036 mol) y K_2CO_3 en polvo (1,68 g, 0,012 mol). La mezcla resultante se agitó durante dos horas a 67°C. La fuente de calor se retiró y a la mezcla de reacción se le añadió acetato de etilo. La capa orgánica se extrajo con agua seguido de salmuera, se secó sobre Na_2SO_4 y después se concentró. La purificación del aceite amarillo por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) produjo la N2-p-metil-bencil-triazolinona en forma de un aceite amarillo. $C_{27}H_{35}N_3O_5$ (PM = 481,60); espectroscopía de masas (MH^+) = 482,3.

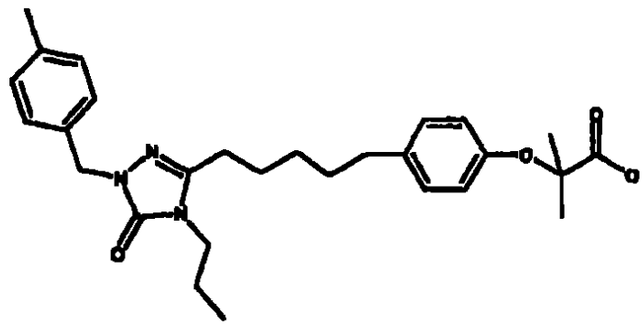
Etapa F: Preparación de



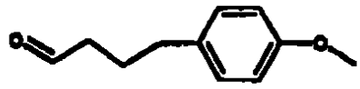
El éster metílico de la Etapa E (0,250 g, 0,0005 mol) se disolvió en etanol (8 ml) y se trató con NaOH 2 N (4 ml). La reacción se calentó a reflujo durante treinta minutos. La reacción se enfrió y a la solución se le añadió agua (10 ml). La solución después se acidificó usando HCl 1 N hasta pH = 3 y después se extrajo con acetato de etilo. La capa orgánica se concentró, produciendo el ácido carboxílico deseado. $C_{26}H_{33}N_3O_5$ (PM = 467,57); espectroscopía de masas (MH^+) = 468,2.

Ejemplo 31

Compuesto 31

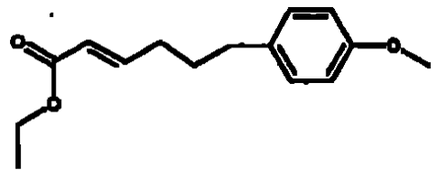


Etapa A: Preparación de



Se añadió lentamente clorocromato de piridinio (14,2 g, 0,066 mol) a una solución de 4-(4-metoxifenil)-1-butanol (10 g, 0,055 mol) en cloruro de metileno a 0°C. La reacción se calentó a temperatura ambiente y se agitó durante una noche. La mezcla de reacción se filtró a través de una capa de Florisil y el disolvente se evaporó. La purificación por cromatografía ultrarrápida (4:1 de hexanos:acetato de etilo) produjo el aldehído deseado en forma de un aceite incoloro.

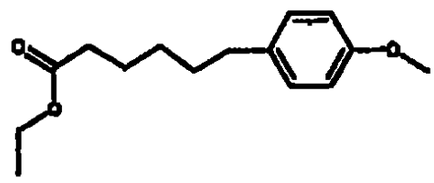
Etapa B: Preparación de



El aldehído de la Etapa A (6,28 g, 0,035 mol) se combinó con fosfonoacetato de trietilo (Aldrich, 8,39 ml, 0,042 mol) y carbonato potásico (9,66 g, 0,07 mol) en agua (120 ml) y se agitó durante una noche. Se añadió dioxano (120 ml) y la reacción se agitó durante varios días. La solución se extrajo con hexanos. La capa orgánica se evaporó. El material resultante se purificó por cromatografía ultrarrápida (4:1 de hexanos:acetato de

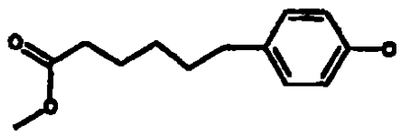
etilo), dando la olefina.

Etapa C: Preparación de



La olefina de la Etapa B (2,5 g, 0,010 mol) se disolvió en acetato de etilo (40 ml) y se purgó con nitrógeno. Tras la adición de Pd al 5%/C (0,40 g), la solución se purgó con nitrógeno y después se liberó gas H_2 a través del sistema. La reacción se agitó durante una noche. La solución se filtró a través de una capa de celite. El disolvente se concentró, dando el éster metílico deseado que se usó sin purificación adicional.

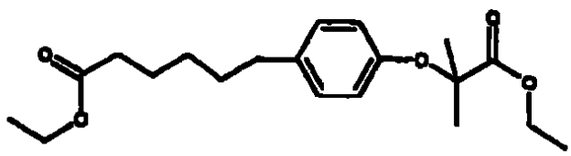
Etapa D: Preparación de



El éster metílico, preparado como se ha descrito en la Etapa C, (3,92 g, 0,016 mol) se disolvió en cloruro de metileno (50 ml) y se enfrió a 0°C. A esta solución se le añadió gota a gota una solución de BBr_3 (4,5 ml, 0,48 mol) en cloruro de metileno (20 ml). Después de agitar durante aproximadamente 45 minutos a temperatura ambiente, la mezcla de reacción se enfrió a 0°C y se inactivó mediante la adición gota a gota de metanol/cloruro de metileno.

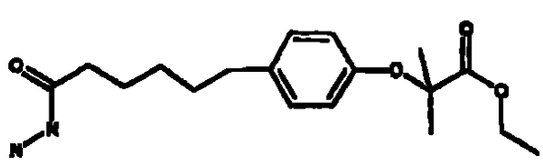
Durante la inactivación, ocurrió la transesterificación del éster etílico al éster metílico. El disolvente se concentró, dando un aceite oscuro. La purificación por cromatografía ultrarrápida (4:1 de hexanos:acetato de etilo) dio el fenol deseado.

Etapa E: Preparación de



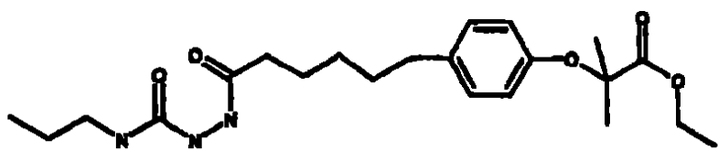
El fenol de la Etapa D (2,5 g, 0,011 mol) se disolvió en etanol (absoluto, 40 ml) y se trató con 2-bromoisobutirato de etilo (11,56 ml, 0,079 mol), K_2CO_3 en polvo (4,55 g, 0,033 mol) y $MgSO_4$. La reacción se agitó durante una noche a 75°C. Tras la refrigeración, la mezcla de reacción se filtró y el filtrado se concentró. El residuo resultante se diluyó con acetato de etilo y se extrajo con agua seguido de salmuera. La capa orgánica se concentró a sequedad. La purificación por cromatografía ultrarrápida (9:1 de hexanos:acetato de etilo) dio el diéster deseado.

Etapa F: Preparación de



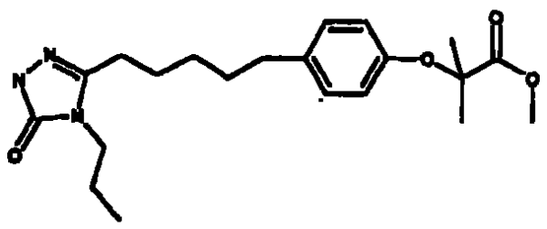
Una solución en metanol (76 ml) del diéster de la Etapa E (2,65 g, 0,0076 mol) se trató con hidrato de hidrazina (1,84 ml, 0,038 mol) y se agitó durante una noche. Después de aproximadamente seis horas, se añadió más hidrato de hidrazina (1,84 ml, 0,038 mol) y la reacción se agitó durante una noche. De nuevo, se añadió más hidrato de hidrazina (1,84 ml, 0,038 mol). Después de varias horas, la reacción se interrumpió y el disolvente se evaporó. La mezcla resultante se purificó por cromatografía ultrarrápida (gradiente de acetato de etilo al 100% a 6:1 de acetato de etilo:metanol), dando la acilhidrazida deseada.

Etapa G: Preparación de



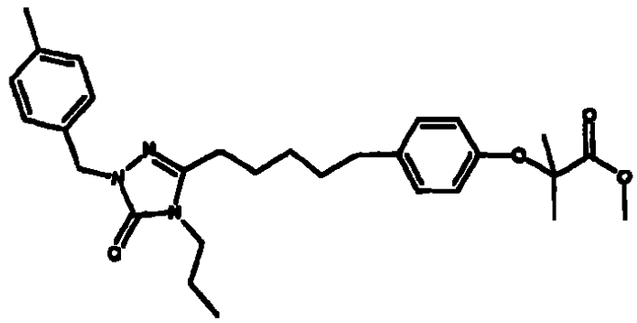
Una solución en THF (7 ml) de la acilhidrazida de la Etapa F (0,5 g, 0,0015 mol) se trató con una solución en THF (7 ml) de isocianato de n-propilo (Aldrich, 0,181 ml, 0,019 mol) añadida gota a gota. La mezcla se agitó durante una noche. El disolvente se concentró, dando un rendimiento cuantitativo de la acil semicarbazida deseada que se usó más adelante sin purificación adicional.

Etapa H: Preparación de



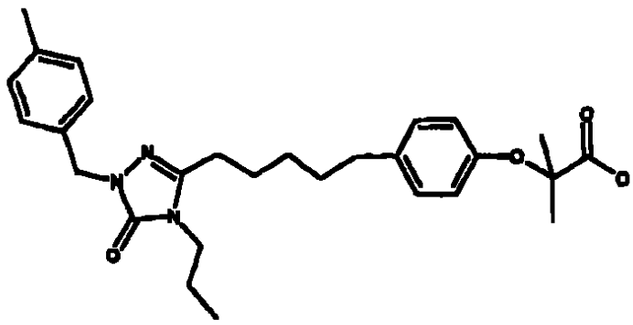
La acil semicarbazida de la Etapa G (1 g, 0,0024 mol) se disolvió en metanol y se trató con KOH (1,34 g, 0,024 mol). La reacción se calentó a reflujo durante una noche. Tras la refrigeración, a la mezcla de reacción se le añadió agua y la solución después se acidificó usando HCl 1 N hasta pH = 3. La capa ácida después se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó y se concentró. El material resultante se diluyó con metanol y se trató con una cantidad catalítica de H_2SO_4 concentrado. La solución se agitó durante una noche. El disolvente se evaporó, después el residuo se diluyó con cloruro de metileno y se lavó con agua. La capa orgánica se concentró, dando la N4-propil-triazolinona deseada. $C_{21}H_{31}N_3O_6$ (PM = 389,50); espectroscopía de masas (MH^+) = 390,3.

Etapa I: Preparación de



La N4-propil-triazolinona de la Etapa H (0,5 g, 0,0013 mol) se disolvió en DMF (7 ml) y se trató con α-bromo-p-xileno (0,885 g, 0,0064 mol) y K_2CO_3 en polvo (0,885 g, 0,0064 mol). La mezcla resultante se agitó durante noventa minutos a 67°C. La fuente de calor se retiró y a la mezcla de reacción se le añadió acetato de etilo. La capa orgánica se extrajo con agua seguido de salmuera, se secó y después se concentró. La purificación del aceite amarillo por cromatografía ultrarrápida (2:1 de hexanos:acetato de etilo) produjo la N2-p-metil-bencil-triazolinona deseada. $C_{29}H_{39}N_3O_4$ (PM = 493,65); espectroscopía de masas (MH^+) = 494,3.

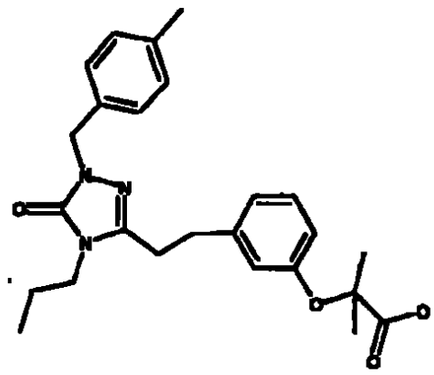
Etapa J: Preparación de



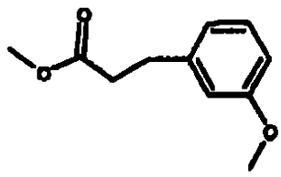
El éster metílico de la Etapa I (0,129 g, 0,00026 mol) se disolvió en etanol (4 ml) y se trató con NaOH 2 N (2 ml). La reacción se calentó a reflujo durante cuarenta y cinco minutos. La reacción se enfrió y a la solución se le se añadió agua (10 ml). La solución después se acidificó usando HCl 1 N hasta pH = 3 y después se extrajo con acetato de etilo. La capa orgánica se concentró, produciendo el ácido carboxílico deseado en forma de un aceite incoloro. $C_{28}H_{37}N_3O_2$ (PM = 479,62); espectroscopía de masas (MH^+) = 480,3.

Ejemplo 32

Compuesto 32



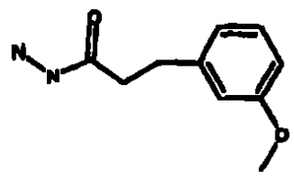
Etapa A: Preparación de



Una solución en metanol (75 ml) de ácido 3-(3-metoxifenil)-propiónico (Aldrich, 10,0 g, 0,055 mol) se

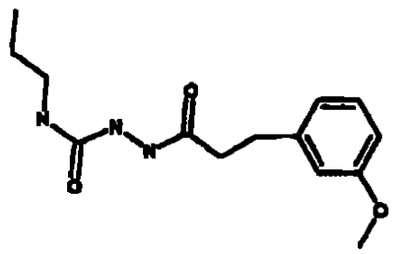
trató con H_2SO_4 (concentrado, 2 ml) y se agitó a temperatura ambiente durante 2 días. El disolvente se evaporó y el residuo se diluyó con CH_2Cl_2 (150 ml). La solución resultante se extrajo con bicarbonato sódico acuoso saturado (1 x 150 ml) seguido de salmuera (1 x 150 ml) y después se secó sobre Na_2SO_4. Tras la evaporación del disolvente, se obtuvo el éster metílico deseado en forma de un aceite amarillento. $C_{13}H_{14}O_3$ (PM = 194,23); espectroscopía de masas (MH^+) = 195,0.

Etapa B: Preparación de



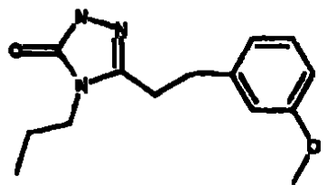
Una solución en metanol (100 ml) del éster metílico de la Etapa A (10,3 g, 0,053 mol) se trató con hidrato de hidrazina (30 ml, 0,60 mol) y se agitó durante una noche. El disolvente se evaporó y el residuo se disolvió en acetato de etilo (200 ml). La solución resultante se lavó con H_2O (200 ml), se secó sobre Na_2SO_4 y se concentró, dando la acilhidrazida deseada en forma de un sólido blanco. $C_{10}H_{14}N_2O_2$ (PM = 194,23); espectroscopía de masas (MH^+) = 195,1.

Etapa C: Preparación de



Una solución en THF (125 ml) de la acilhidrazida de la Etapa B (7,3 g, 0,038 mol) se trató con una solución en THF (25 ml) de isocianato de n-propilo (Aldrich, 4,5 ml, 0,048 mol) añadida gota a gota durante 15 minutos. La mezcla se agitó durante una noche, tiempo durante el que se formó un precipitado espeso. La suspensión resultante se trató con metanol (100 ml) y se agitó durante aproximadamente 2 horas. El disolvente después se concentró, dando la acil semicarbazida deseada en forma de un sólido blanco que se usó sin purificación adicional. $C_{14}H_{21}N_3O_3$ (PM = 279,34); espectroscopía de masas (MH^+) = 280,2.

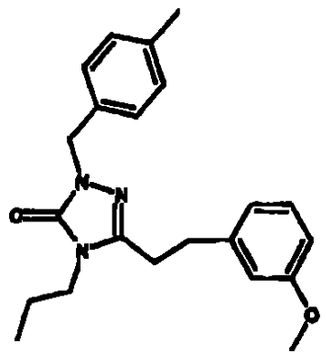
Etapa D: Preparación de



La acil semicarbazida de la Etapa C (10,0 g, 0,036 mol) se disolvió en metanol (200 ml), se trató con KOH (20 g, 0,36 mol) y después se calentó a reflujo durante una

noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en H_2O (500 ml) y se extrajo con acetato de etilo (2 x 500 ml). Los extractos orgánicos combinados se lavaron con salmuera (1 x 500 ml), se secaron sobre Na_2SO_4 y después se concentraron, dando la N4-propil-triazolinona deseada en forma de un aceite amarillo. $C_{24}H_{19}N_3O_2$ (PM = 261,33); espectroscopía de masas (MH^+) = 262,1.

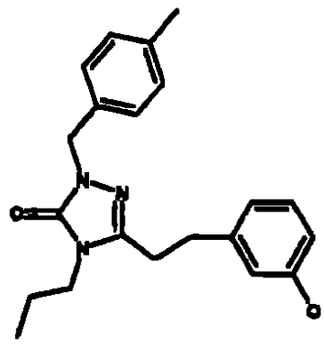
Etapa E: Preparación de:



La N4-propil-triazolinona de la Etapa D (1,25 g, 4,8 mmol) se disolvió en DMF (25 ml) y se trató con α-bromo-p-xileno (1,36 g, 7,3 mol) y K_2CO_3 en polvo (4,2 g, 0,030 mol). La mezcla resultante se calentó a 50°C en un tubo de secado durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en HCl acuoso (1 N, 200 ml) y se extrajo en acetato de etilo (200 ml). El extracto orgánico se lavó con salmuera (1 x 200 ml), se secó sobre Na_2SO_4 y después se concentró, dando el producto bruto. La purificación por cromatografía ultrarrápida (gradiente de

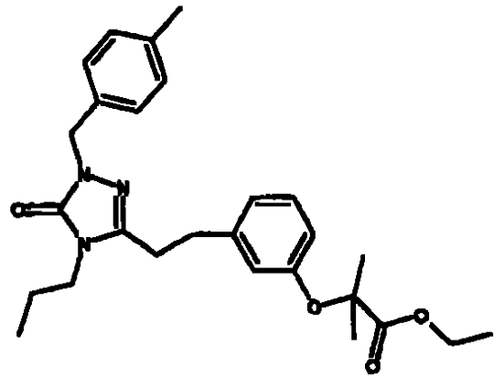
2:1 a 1:1 de hexanos:acetato de etilo) dio la N2-p-metilbencil-triazolinona deseada en forma de un aceite incoloro. $C_{22}H_{27}N_3O_2$ (PM = 365,48); espectroscopía de masas (MH^+) = 366,1.

Etapa F: Preparación de



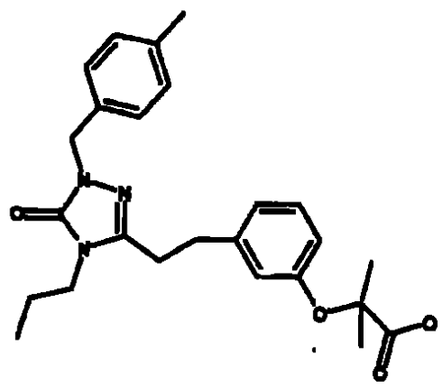
La N2-p-metilbencil-triazolinona de la Etapa E (1,06 g, 0,0029 mol) se disolvió en cloruro de metileno (15 ml) y se enfrió a 0°C. A esta solución se le añadió gota a gota una solución de BBr_3 (0,548 ml, 0,0058 mol) en cloruro de metileno (5 ml). Después de agitar durante dos horas, la mezcla de reacción se enfrió a 0°C y se inactivó mediante la adición gota a gota de metanol/cloruro de metileno. El disolvente se concentró y el material resultante se disolvió en cloruro de metileno. La capa orgánica se extrajo con agua seguido de salmuera. Tras la evaporación del disolvente, se obtuvo el fenol deseado. $C_{21}H_{25}N_3O_2$ (PM = 351,45); espectroscopía de masas (MH^+) = 352,19.

Etapa G: Preparación de



El fenol de la Etapa F (1 g, 0,0028 mol) se disolvió en etanol (absoluto, 15 ml) y se trató con 2-bromoisobutirato de etilo (2,88 ml, 0,0196 mol), K_2CO_3 en polvo (1,157 g, 0,0084 mol) y $MgSO_4$. La reacción se agitó durante una noche a 71°C. Tras la refrigeración, la mezcla de reacción se filtró y el filtrado se concentró. El residuo resultante se diluyó con cloruro de metileno y se extrajo con agua seguido de salmuera. Se produjo una emulsión. La capa orgánica se separó mediante la adición de salmuera y después se concentró a sequedad. La purificación por cromatografía ultrarrápida (gradiente: de 3:1 de hexanos:acetato de etilo a 2:1 de hexanos:acetato de etilo) dio el éster deseado. $C_{27}H_{35}N_3O_4$ (PM = 465,60); espectroscopía de masas (MH^+) = 466,3.

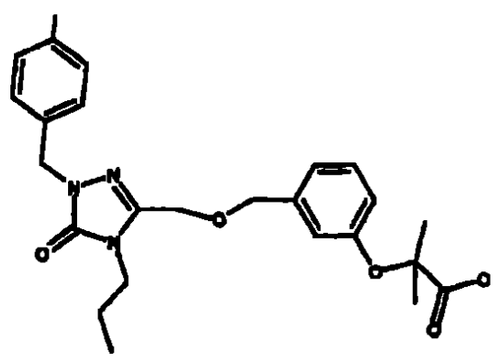
Etapa H: Preparación de



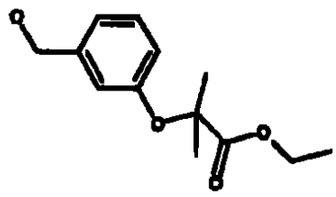
El éster de la Etapa G (0,600 g, 0,0013 mol) se disolvió en metanol (6 ml) y se trató con una solución acuosa de LiOH (0,062 g, 0,0026 mol). La reacción se agitó durante una noche a temperatura ambiente. A la mezcla de reacción se le añadió agua (20 ml) y la solución se extrajo con acetato de etilo. La capa acuosa después se acidificó usando HCl 1 N hasta pH = 3 y después se extrajo con acetato de etilo. La capa orgánica se concentró, produciendo el ácido carboxílico deseado. $C_{25}H_{31}N_3O_4$ (PM = 437,54); espectroscopía de masas (MH^+) = 438,2.

Ejemplo 33

Compuesto 33

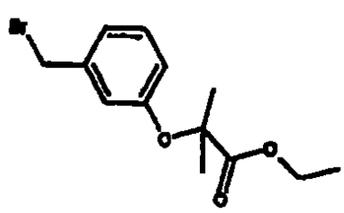


Etapa A: Preparación de



Una solución en etanol de alcohol 3-hidroxibencílico (Aldrich, 5 g, 0,040 mol) se combinó con carbonato potásico (en polvo, 18 g, 0,130 mol), 2-bromoisobutirato de etilo (17 ml, 0,116 mol) y sulfato de magnesio (15 g). La reacción se agitó durante una noche a 50°C. La mezcla de reacción se filtró y el filtrado se concentró. El residuo resultante se disolvió en cloruro de metileno y se extrajo con agua seguido de salmuera. La purificación por cromatografía ultrarrápida (gradiente de 5:1 de hexanos:acetato de etilo a 2:1 de hexanos:acetato de etilo) dio el alcohol deseado en forma de un aceite amarillo.

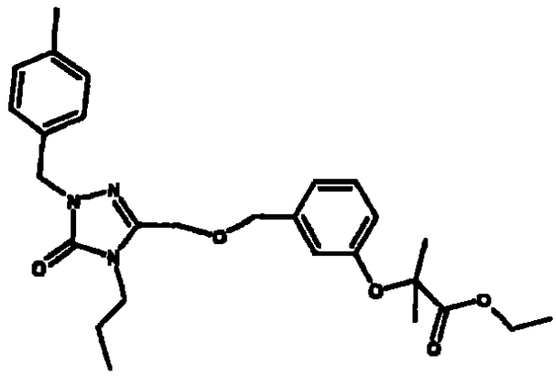
Etapa B: Preparación de



El alcohol de la Etapa A (8,68 g, 0,036 mol) se disolvió en cloruro de metileno (150 ml) y se enfrió a 0°C. A la solución se le añadió tetrabromuro de carbono

(14,5 g, 0,044 mol) seguido de la adición lenta de trifenilfosfina (11,5 g, 0,044 mol). El disolvente se evaporó y el material resultante se diluyó con éter etílico provocando que precipitara dela solución un subproducto de óxido de trifenilfosfina. El subproducto se filtró y el filtrado se concentró. El material resultante se disolvió en hexano provocando que precipitara más subproducto. Se realizó una segunda filtración y el filtrado se concentró. Se purificó una porción de 5 g del material bruto por cromatografía ultrarrápida (gradiente de 95:5 de hexanos:acetato de etilo a 9:1 de hexanos:acetato de etilo), produciendo el éster. $C_{13}H_{17}BrO_3$ (PM = 301,18); espectroscopía de masas (MH^+) = 302,0.

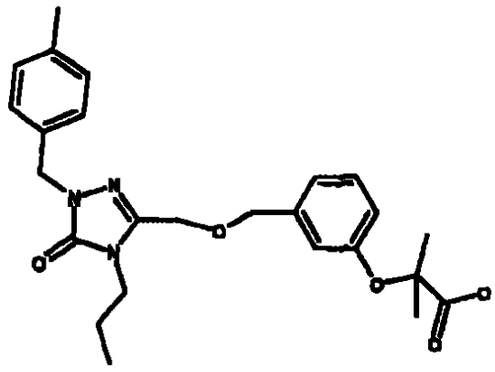
Etapa C: Preparación de



A un matraz de fondo redondo de tres bocas se le añadió una solución de hidruro sódico (dispersión al 60% en aceite, 0,134 g, 0,0033 mol) en THF (12 ml) y se enfrió a 0°C. Se añadió una solución del alcohol (0,4 g, 0,0015

mol) del Ejemplo 27, Etapa F en THF (12 ml) y la mezcla se agitó durante 5 minutos. Después se añadió el bromuro de la Etapa B en forma de una solución en THF (12 ml) y la mezcla resultante se agitó durante una noche. La mezcla de reacción se vertió en HCl 1 N y se extrajo con cloruro de metileno. La capa orgánica se lavó con agua y después con salmuera. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) produjo el producto deseado. $C_{27}H_{35}N_3O_5$ (PM = 481,60); espectroscopía de masas (MH^+) = 482,1.

Etapa D: Preparación de

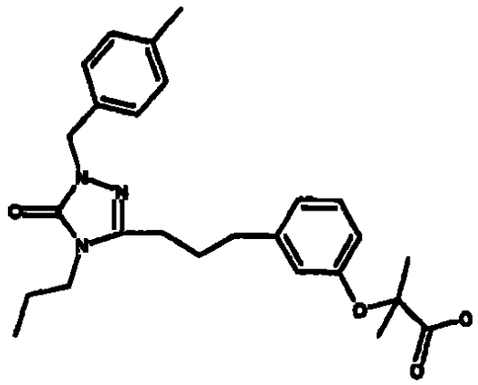


El éster etílico de la Etapa C (0,270 g, 0,00056 mol) se disolvió en etanol (12 ml) y se trató con NaOH 2 N (6 ml). La reacción se calentó a reflujo durante una hora. La reacción se enfrió y a la solución se le añadió agua (25 ml). La solución después se acidificó usando HCl 1 N hasta pH = 3 y después se extrajo con acetato de etilo. La capa orgánica se concentró, produciendo el ácido carboxílico

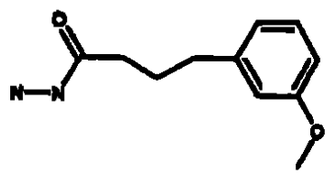
deseado en forma de un aceite espeso. $C_{25}H_{31}N_3O_5$ (PM = 453,54); espectroscopía de masas (MH^+) = 454,2.

Ejemplo 34

Compuesto 34



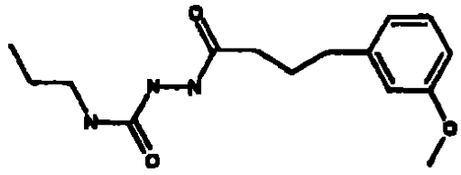
Etapa A: Preparación de



Una solución en metanol (15 ml) de 3-(3-metoxi-fenil)butirato de etilo (Registro 57816-01-0, 1,91 g, 0,0086 mol) se trató con hidrato de hidrazina (4,2 ml, 0,086 mol) y se agitó durante una noche. El disolvente se evaporó y el residuo se disolvió en acetato de etilo (50 ml). La solución resultante se lavó con H_2O (50 ml) y salmuera (50 ml), después se secó sobre Na_2SO_4 y se concentró, dando la acilhidrazida deseada en forma de un sólido blanco. $C_{11}H_{16}N_2O_2$ (PM = 208,26); espectroscopía de

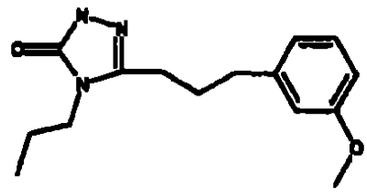
masas (MH^+) = 209,0.

Etapa B: Preparación de



Una solución en THF (20 ml) de la acilhidrazida de la Etapa A (1,03 g, 0,0050 mol) se trató con una solución en THF de isocianato de n-propilo (Aldrich, 0,60 ml, 0,0064 mol) añadida gota a gota durante 15 minutos. La mezcla se agitó y después se trató con H_2O (50 ml) y se agitó durante aproximadamente 2 horas. La mezcla se concentró hasta una solución acuosa que se extrajo con CH_2Cl_2 (2 x 75 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y después se concentraron, dando la acil semicarbazida deseada en forma de un sólido blanco, que se usó sin purificación adicional. $C_{15}H_{23}N_3O_3$ (PM = 293,37); espectroscopía de masas (MH^+) = 292,2.

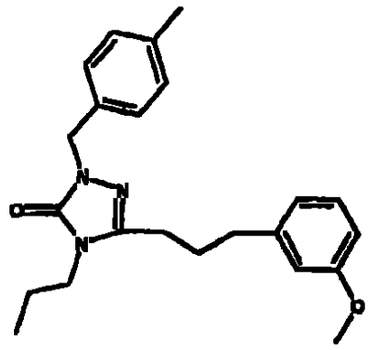
Etapa C: Preparación de



La acil semicarbazida de la Etapa B se disolvió en metanol (60 ml), se trató con KOH (3,0 g, 0,053 mol) y

después se calentó a reflujo durante 48 horas. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en H_2O (200 ml) y después se extrajo con acetato de etilo (2 x 200 ml). Los extractos orgánicos combinados se lavaron con salmuera (250 ml), se secaron sobre Na_2SO_4 y después se concentraron, dando la N4-propil-triazolinona deseada en forma de un sólido. $C_{15}H_{21}N_3O_2$ (PM = 275,35); espectroscopía de masas (MH^+) = 276,1.

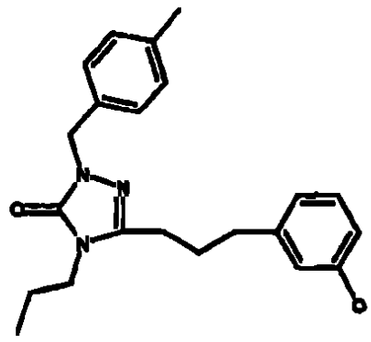
Etapa D: Preparación de



La N4-propil-triazolinona de la Etapa C (1,20 g, 4,4 mmol) se disolvió en THF (20 ml) y se trató con bromuro de p-metilbencilo (1,60 g, 8,6 mmol), K_2CO_3 en polvo (3,2 g, 0,023 mol) y $MgSO_4$ (1,2 g, 0,010 mol). La mezcla resultante se calentó a 80°C en un tubo de secado durante una noche. La mezcla de reacción se enfrió a temperatura ambiente, se vertió en HCl acuoso (1 N, 100 ml) y se extrajo en Et_2O (2 x 100 ml). Los extractos orgánicos combinados se lavaron con salmuera (1 x 200 ml), se secaron sobre Na_2SO_4 y se concentraron, dando el producto bruto. La purificación por

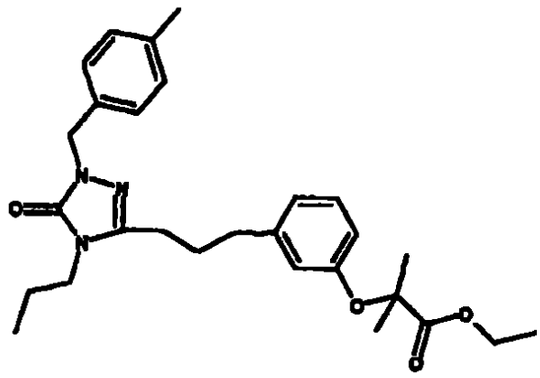
cromatografía ultrarrápida (2:1 de hexanos:acetato de etilo) dio la N2-p-metilbencil-triazolinona deseada en forma de un aceite incoloro. $C_{23}H_{29}N_3O_2$ (PM = 379,51); espectroscopía de masas (MH^+) = 380,2.

Etapa E: Preparación de



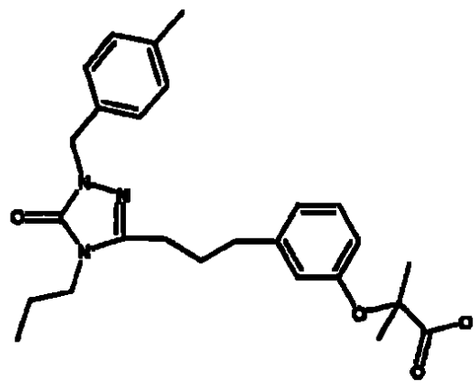
La N2-p-metilbencil-triazolinona de la Etapa D (0,7879 g, 0,002 mol) se disolvió en cloruro de metileno (15 ml) y se enfrió a 0°C. A esta solución se le añadió gota a gota una solución de BBr_3 (0,392 ml, 0,004 mol) en cloruro de metileno (5 ml). Después de agitar durante aproximadamente 90 minutos, la mezcla de reacción se enfrió a 0°C y se inactivó mediante la adición gota a gota de metanol/cloruro de metileno. El disolvente se concentró y el material resultante se disolvió en cloruro de metileno. La capa orgánica se extrajo con agua seguido de salmuera. Tras la evaporación del disolvente, se obtuvo el fenol deseado. $C_{22}H_{27}N_3O_2$ (PM = 365,48); espectroscopía de masas (MH^+) = 366,3.

Etapa F: Preparación de



El fenol de la Etapa E (0,70 g, 0,0019 mol) se disolvió en DMF (40 ml) y se trató con 2-bromoisobutirato de etilo (1,97 ml, 0,013 mol), K_2CO_3 (0,797 g, 0,0057 mol) y $MgSO_4$. La reacción se agitó durante una noche a 75°C. Tras la refrigeración, la mezcla de reacción se filtró y el filtrado se concentró. El residuo resultante se diluyó con acetato de etilo y se extrajo con agua seguido de salmuera. La capa orgánica se concentró a sequedad. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio el éster deseado. $C_{28}H_{37}N_3O_4$ (PM = 479,62); espectroscopía de masas (MH^+) = 480,3.

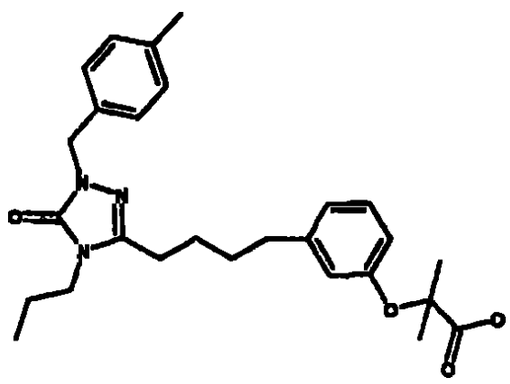
Etapa G: Preparación de



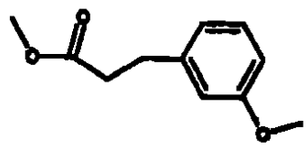
El éster de la Etapa F (0,250 g, 0,00052 mol) se disolvió en etanol (8 ml) y se trató con NaOH 2 N (4 ml). La reacción se calentó a reflujo durante treinta minutos. La reacción se enfrió y a la solución se le añadió agua (20 ml). La solución después se acidificó usando HCl 1 N hasta pH = 3 y después se extrajo con acetato de etilo. La capa orgánica se concentró, produciendo el ácido carboxílico deseado. $C_{26}H_{33}N_3O_4$ (PM = 451,57); espectroscopía de masas (MH^+) = 452,3.

Ejemplo 35

Compuesto 35

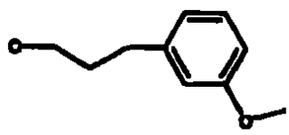


Etapa A: Preparación de



Una solución en metanol (75 ml) de ácido 3-(3-metoxifenil)-propiónico (Aldrich, 10 g, 0,055 mol) se trató con una cantidad catalítica de H_2SO_4 concentrado y se agitó a temperatura ambiente durante una noche. El disolvente se concentró y el residuo se diluyó con cloruro de metileno (150 ml). La solución resultante se extrajo con bicarbonato sódico acuoso saturado (1 x 150 ml) seguido de salmuera (1 x 150 ml) y después se secó sobre Na_2SO_4. Tras la evaporación del disolvente, se obtuvo el éster metílico deseado en forma de un aceite incoloro. $C_{11}H_{14}O_3$ (PM = 194,23); espectroscopía de masas (MH^+) = 195,1.

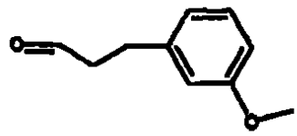
Etapa B: Preparación de



El éster de la Etapa A (5 g, 0,0257 mol) se disolvió en tolueno (100 ml) y se enfrió a 0°C. Se añadió lentamente a la solución un exceso de DIBAL (1 M, 50 ml, 0,050 mol). La reacción se agitó durante 1 hora. Se añadió una solución acuosa de sal de Rochelle (saturada) y la

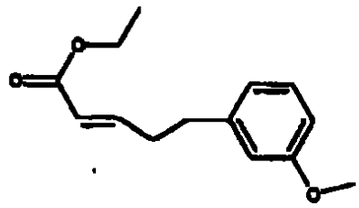
mezcla se agitó durante un fin de semana. La solución bifásica resultante se diluyó con agua y se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró. La purificación por cromatografía ultrarrápida (gradiente de 4:1 a 3:1 de hexanos:acetato de etilo) dio el alcohol deseado.

Etapa C: Preparación de



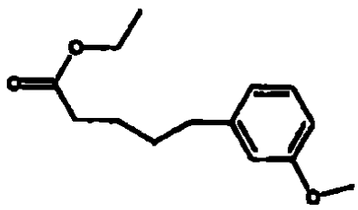
El alcohol, preparado como se ha descrito en la Etapa B (5,5 g, 0,033 mol), se disolvió en cloruro de metileno (165 ml) y se enfrió a 0°C. A la solución se le añadió lentamente clorocromato de piridinio (8,57 g, 0,040 mol). La reacción se calentó a temperatura ambiente y se agitó durante una noche. La mezcla de reacción se filtró a través de una capa de celite y después se concentró. La purificación por cromatografía ultrarrápida (4:1 de hexanos:acetato de etilo) produjo el aldehído deseado.

Etapa D: Preparación de



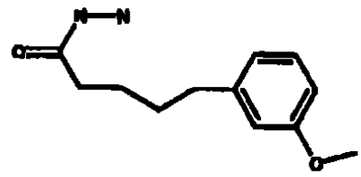
El aldehído (3,73 g, 0,023 mol) de la Etapa C se combinó con fosfonoacetato de trietilo (Aldrich, 6,12 g, 0,027 mol) y carbonato potásico (6,26 g, 0,045 mol) en agua y se agitó durante una noche. Se añadió dioxano y la reacción se agitó de nuevo durante una noche. La solución de reacción se diluyó con hexanos y se extrajo. La capa orgánica se concentró. La purificación por cromatografía ultrarrápida (15:1 de hexanos:acetato de etilo) dio la olefina deseada.

Etapa E: Preparación de



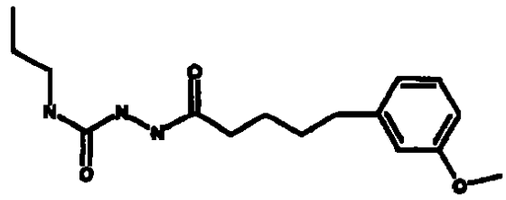
La olefina de la Etapa D (2,5 g, 0,010 mol) se disolvió en acetato de etilo y se purgó con nitrógeno. Tras la adición de Pd al 5%/C (0,250 g), la solución se purgó con nitrógeno y después se sometió a una presión de gas H_2. La reacción se agitó durante una noche. La solución se filtró a través de una capa de celite. EL disolvente se concentró, dando el éster saturado que se usó sin purificación adicional.

Etapa F: Preparación de



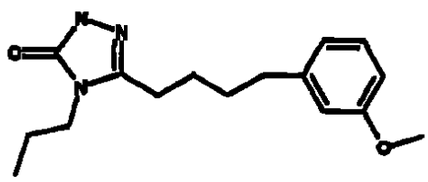
Una solución en metanol (60 ml) del éster de la Etapa E (2,5 g, 0,0105 mol) se trató con hidrato de hidrazina (5,14 ml, 0,105 mol) y se agitó durante tres días. El disolvente se evaporó. La mezcla resultante se disolvió en acetato de etilo y la solución se extrajo con agua y después con salmuera. La capa orgánica se concentró, dando la acilhidrazida deseada. $C_{12}H_{18}N_2O_2$ (PM = 222,29); espectroscopía de masas (MH^+) = 223.

Etapa G: Preparación de



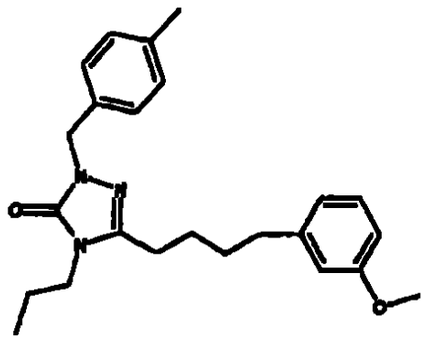
Una solución en THF (20 ml) de la acilhidrazida de la Etapa F (2,1 g, 0,0095 mol) se trató con una solución en THF (20 ml) de isocianato de n-propilo (Aldrich, 1,15 ml, 0,012 mol) añadida gota a gota. La mezcla se agitó durante una noche. El disolvente se concentró, dando la acil semicarbazida que se usó más adelante sin purificación adicional. $C_{16}H_{25}N_3O_3$.

Etapa H: Preparación de



La acil semicarbazida de la Etapa G (2,95 g, 0,0096 mol) se disolvió en metanol y se trató con KOH (5,39 g, 0,096 mol). La reacción se calentó a reflujo durante una noche. Tras la refrigeración, a la mezcla de reacción se le añadió agua y la solución después se acidificó usando HCl 1 N hasta pH = 3. La capa ácida después se extrajo con acetato de etilo. La capa orgánica se lavó con salmuera, se secó y se concentró. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio la N4-propil-triazolinona deseada. $C_{16}H_{23}N_3O_2$ (PM = 289,38); espectroscopía de masas (MH^+) = 290,2.

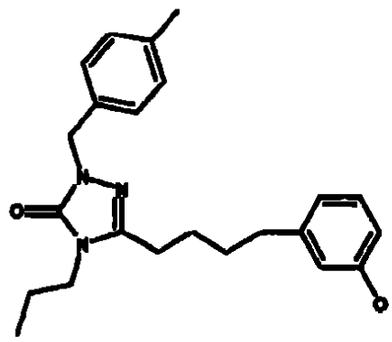
Etapa I: Preparación de



La N4-propil-triazolinona de la Etapa H (2,13 g, 0,0073 mol) se disolvió en DMF (75 ml) y se trató con α-

cloro-p-xileno (1,54 g, 0,0110 mol) y K_2CO_3 en polvo (5,09 g, 0,037 mol). La mezcla resultante se agitó durante una noche a 67°C. La fuente de calor se retiró y a la mezcla de reacción se le añadió acetato de etilo. La capa orgánica se extrajo con agua seguido de salmuera, se secó sobre Na_2SO_4 y después se concentró. La purificación del residuo por cromatografía ultrarrápida (2:1 de hexanos:acetato de etilo) produjo la N-2-p-metil-bencil-triazolinona deseada. $C_{24}H_{31}N_3O_2$ (PM = 393,53); espectroscopía de masas (MH^+) = 394,3.

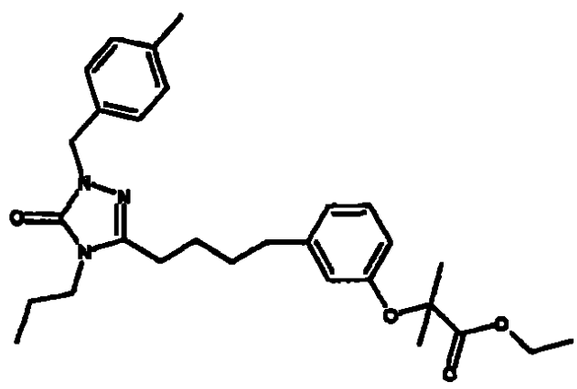
Etapa J: Preparación de



La N2-p-metil-bencil-triazolinona de la Etapa I (1,96 g, 0,005 mol) se disolvió en cloruro de metileno (30 ml) y se enfrió a 0°C. A esta solución se le añadió gota a gota una solución de BBr_3 (0,942 ml, 0,010 mol) en cloruro de metileno (10 ml). Después de agitar durante aproximadamente una hora, se añadieron dos equivalentes de BBr_3. La mezcla de reacción se enfrió a 0°C y se inactivó

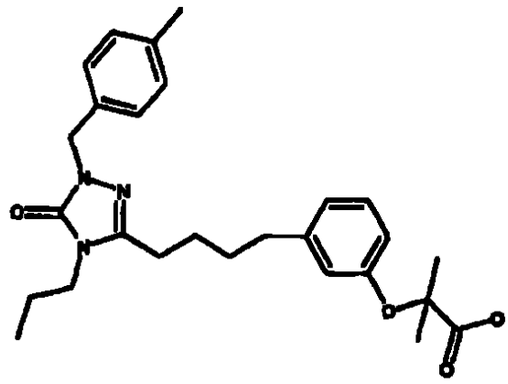
mediante la adición gota a gota de metanol/cloruro de metileno. El disolvente se concentró, dando el fenol deseado, que se usó sin purificación adicional. $C_{23}H_{29}N_3O_2$ (PM = 379,51); espectroscopía de masas (MH^+) = 380,3.

Etapa K: Preparación de



El fenol de la Etapa J (1,75 g, 0,0046 mol) se disolvió en etanol (absoluto, 20 ml) y se trató con 2-bromoisobutirato de etilo (4,74 ml, 0,032 mol), K_2CO_3 en polvo (1,90 g, 0,014 mol) y $MgSO_4$. La reacción se agitó durante una noche a 77°C. Tras la refrigeración, la mezcla de reacción se filtró y el filtrado se concentró. El residuo resultante se diluyó con acetato de etilo y se extrajo con agua seguido de salmuera. La capa orgánica se concentró a sequedad. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio el éster en forma de un aceite incoloro. $C_{29}H_{39}N_3O_4$ (PM = 493,65); espectroscopía de masas (MH^+) = 494,3.

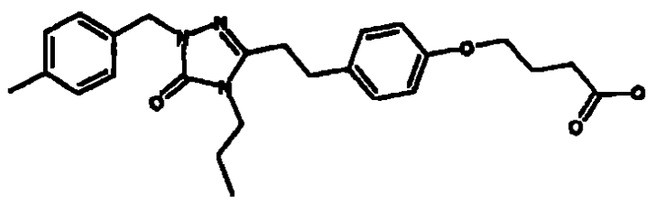
Etapa L: Preparación de



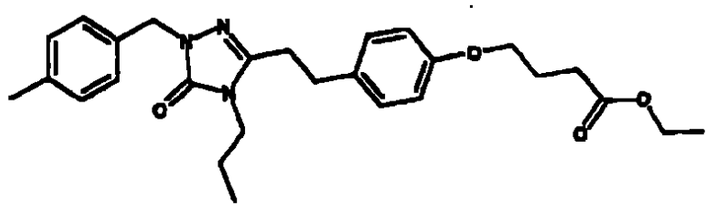
El éster etílico de la Etapa K (1 g, 0,002 mol) se disolvió en etanol (24 ml) y se trató con NaOH 2 N (12 ml). La reacción se calentó a reflujo durante una hora. La reacción se enfrió y a la solución se le añadió agua (25 ml). La solución después se acidificó usando HCl 1 N hasta pH = 3 y después se extrajo con acetato de etilo. La capa orgánica se concentró, produciendo el ácido carboxílico deseado en forma de un aceite incoloro. $C_{27}H_{35}N_3O_4$ (PM = 465,6); espectroscopía de masas (MH^+) = 466,7.

Ejemplo 36

Compuesto 36

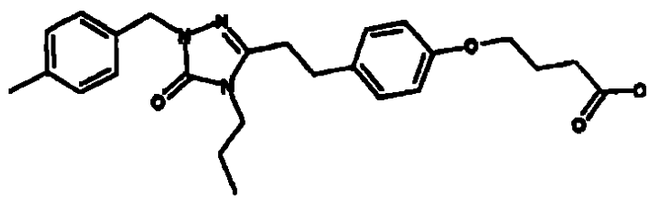


Etapa A: Preparación de



El fenol (2,1 g, 0,0060 mol), preparado como en el Ejemplo 22, Etapa F, se disolvió en DMF (25 ml) y se trató con 4-bromobutirato de etilo (Aldrich, 1,4 g, 0,0072 mol), carbonato potásico en polvo (Aldrich, 3,3 g, 0,0240 mol) y una pequeña cantidad de sulfato de magnesio. La mezcla resultante se agitó y se calentó a 65°C durante 18 horas. La mezcla de reacción resultante se añadió lentamente a HCl (1 N, 100 ml) y se extrajo con éter (3 x). Las capas de éter se combinaron, se lavaron con agua y se secaron sobre sulfato sódico. La evaporación del disolvente dio el producto bruto. La purificación por cromatografía ultrarrápida (1:1 de hexanos:acetato de etilo) dio el éster etílico deseado en forma de un aceite transparente.

Etapa B: Preparación de

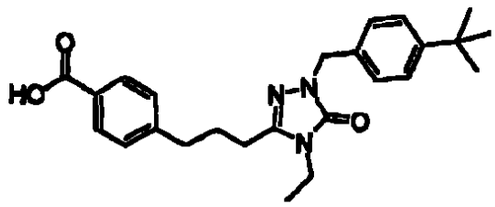


El éster etílico de la Etapa A (0,1 g, 0,0002 mol) se disolvió en metanol (2 ml) y se trató con una solución acuosa de hidróxido de litio (0,01 g, 0,0004 mol) en agua

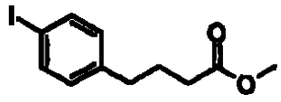
(2 ml). La mezcla resultante se calentó a 50°C durante 2 horas y después se agitó a temperatura ambiente durante una noche. La mezcla de reacción se añadió a agua y se acidificó con HCl acuoso (concentrado) hasta un pH de 3 y se extrajo con acetato de etilo (2 x). Estas dos capas se combinaron, se lavaron con salmuera y se secaron sobre sulfato sódico. El disolvente se evaporó, dando el ácido carboxílico deseado en forma de un aceite. $C_{25}H_{31}N_3O_4$ (PM = 437,54); espectroscopía de masas (MH^+) = 438,1.

Ejemplo 37

Compuesto 37



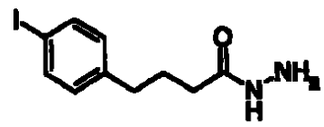
Etapa A: Preparación de 4-(4-yodofenil)-butirato de metilo



A una solución de ácido 4-(p-yodofenil)-butírico (45,0 g, 0,155 mol) en metanol (1,3 l), se le añadió gota a gota ácido sulfúrico (concentrado, 8,4 ml) y se agitó a temperatura ambiente en una atmósfera de nitrógeno durante 3 horas. La mezcla de reacción se concentró en un evaporador rotatorio, el residuo después se repartió entre

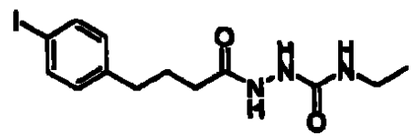
acetato de etilo (700 ml) y una solución acuosa de bicarbonato sódico saturado (500 ml). La fase orgánica se separó, se lavó con salmuera (2 x 200 ml), después se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio el compuesto del título en forma de un aceite que se usó en la Etapa B sin purificación adicional.

Etapa B: Preparación de



Una mezcla de 4-(4-yodofenil)-butirato de metilo (47,0 g, 0,155 mol) de la Etapa A e hidrato de hidrazina (38,8 g, 0,775 mol) en metanol (200 ml) a temperatura ambiente se agitó durante una noche. El disolvente se evaporó y el residuo se repartió entre acetato de etilo (500 ml) y agua (100 ml). La capa orgánica se lavó con agua (3 x 100 ml) y salmuera (2 x 100 ml), se secó sobre Na_2SO_4, se filtró y se concentró a sequedad, dando el compuesto del título en forma de un cristal blanco que se usó en la Etapa C sin purificación adicional.

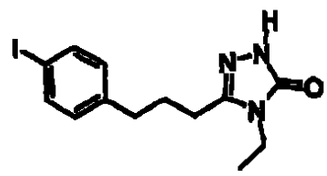
Etapa C: Preparación de



A una solución del producto de la Etapa B (47 g,

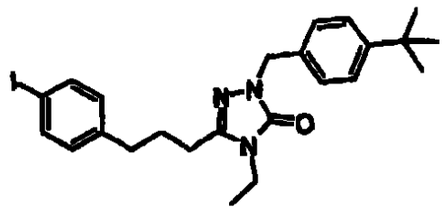
0,155 mol) en THF (500 ml) se le añadió gota a gota una solución de isocianato de etilo (Aldrich, 14,7 ml, 0,186 mol) en THF (200 ml) y la mezcla se agitó a temperatura ambiente durante una hora. La evaporación del disolvente dio el compuesto del título en forma de un polvo blanquecino que se usó en la Etapa D sin purificación adicional.

Etapa D: Preparación de



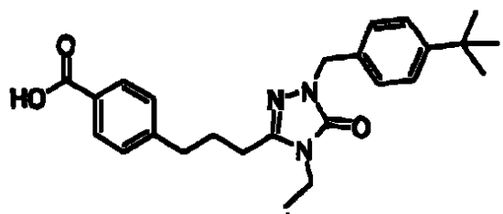
A una solución del producto de la Etapa C (58 g, 0,155 mol) en metanol (775 ml) se le añadió en una sola porción hidróxido potásico (43,5 g, 0,775 mol). La mezcla de reacción se calentó a 85°C durante 48 horas. La mitad del volumen después se evaporó en un evaporador rotatorio, el residuo después se repartió entre acetato de etilo (1,0 l) y agua (500 ml) y las dos capas se separaron. la capa acuosa se extrajo con acetato de etilo (2 x 200 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se filtraron. La evaporación del disolvente dio el compuesto del título en forma de un sólido blanco.

Etapa E: Preparación de



A una solución del producto de la Etapa D (2,05 g, 0,00574 mol) en metiletilcetona (60 ml) se le añadió bromuro de 4-(*terc*-butil)bencilo (1,93 ml, 0,00861 mol) seguido de carbonato potásico en polvo (4,75 g, 0,0344 mol). La mezcla resultante se agitó con calentamiento a reflujo en un tubo de secado durante 24 horas. La mezcla de reacción se enfrió a temperatura ambiente y después se repartió entre acetato de etilo (100 ml) y una solución saturada acuosa de NH_4Cl (100 ml). La capa acuosa se extrajo con acetato de etilo (100 ml) y la fase orgánica combinada se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio un producto bruto que se purificó sobre una columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano, dando el compuesto del título en forma de un aceite incoloro.

Etapa F: Preparación de

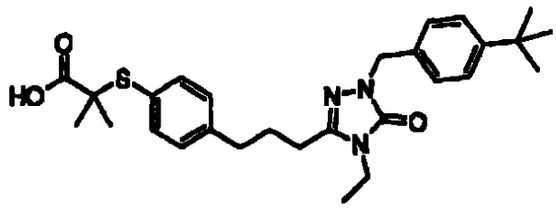


A una solución del producto de la Etapa E (2,4 g,

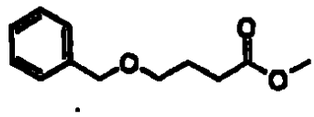
0,0048 mol) en benceno (5 ml) a temperatura ambiente, se le añadieron una solución de KOH (5,35 g, 0,0953 mol) en agua (8,9 ml), cloroformo (12,2 ml) y $Pd(Ph_3P)_2Cl_2$ (0,34 g, 0,00048 mol) y la mezcla se agitó durante 24 horas. Después, la mezcla se diluyó con éter dietílico (20 ml) y el pH se ajustó a pH = 1-2 mediante la adición de HCl 1 N. Las capas se separaron y la capa acuosa se extrajo con éter dietílico (3 x 100 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se filtraron y se evaporaron, dando un producto bruto que se purificó sobre una columna de gel de sílice eluyendo primero con acetato de etilo al 70% en hexano y después con acetato de etilo. El compuesto del título se obtuvo en forma de un sólido blanco. Masa (MH+ = 422,5).

Ejemplo 38

Compuesto 38



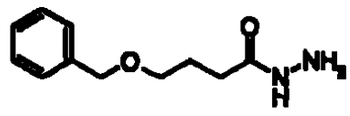
Etapa A: Preparación de 4-benciloxibutirato de metilo



A una solución de ácido 4-benciloxibutírico (54,8 g, 0,282 mol) en metanol (1,4 l) se le añadió gota a gota

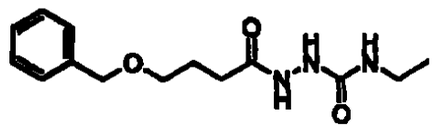
ácido sulfúrico (concentrado, 1,4 ml) y se agitó a temperatura ambiente en una atmósfera de nitrógeno durante una noche. La mezcla de reacción se concentró en un evaporador rotatorio, el residuo después se repartió entre acetato de etilo (700 ml) y una solución acuosa saturada de bicarbonato sódico (200 ml). La fase orgánica se separó, se lavó con salmuera (2 x 100 ml), después se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio el compuesto del título en forma de un aceite que se usó en la Etapa B sin purificación adicional.

Etapa B: Preparación de



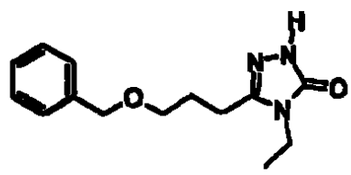
Una mezcla de 4-benciloxibutirato de metilo (58,7 g, 0,282 mol) de la Etapa A e hidrato de hidrazina (56,4 g, 1,13 mol) en metanol (300 ml) se agitó a temperatura ambiente durante una noche. El disolvente se evaporó y el residuo se repartió entre acetato de etilo (1 l) y agua (100 ml). La capa orgánica se lavó con agua (3 x 100 ml) y salmuera (2 x 100 ml), se secó sobre Na_2SO_4, se filtró y se concentró a sequedad, dando el compuesto del título en forma de un cristal blanco que se usó en la Etapa C sin purificación adicional.

Etapa C: Preparación de



A una solución del producto de la Etapa B (58,7 g, 0,282 mol) en THF (600 ml) se le añadió gota a gota una solución de isocianato de etilo (Aldrich, 26,8 ml, 0,338 mol) en THF (300 ml) y la mezcla se agitó a temperatura ambiente durante una hora. La evaporación del disolvente dio el compuesto del título en forma de un polvo blanquecino que se usó en al Etapa D sin purificación adicional.

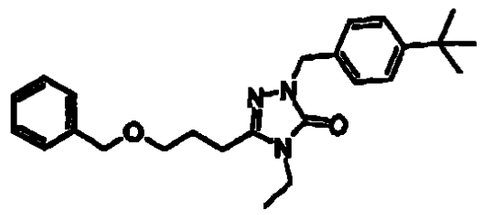
Etapa D: Preparación de



Una suspensión del producto de la Etapa C (78,6 g, 0,282 mol) en una solución de KOH (19,0 g, 0,339 mol) en agua (380 ml) (1,2 equiv. de una solución acuosa al 5% de KOH) se calentó a 100°C durante 1 hora (la suspensión desaparece tan pronto como se incrementa la temperatura). En este momento, la TLC mostró que no había restos de material de partida y la reacción se enfrió a temperatura ambiente. Después, el pH se ajustó a pH = 6-7 mediante la adición de HCl 1 N y se extrajo con AcOEt (3 x 500 ml). Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se

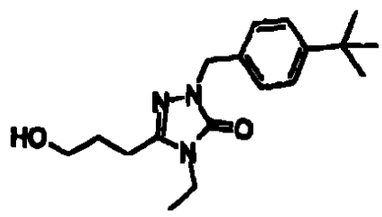
filtraron y se evaporaron, dando el compuesto del título en forma de un sólido blanco.

Etapa E: Preparación de



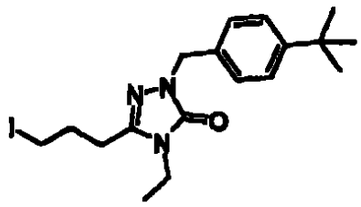
A una solución del producto de la Etapa D (9,7 g, 0,00374 mol) en metiletilcetona (400 ml) se le añadió bromuro de 4-(*terc*-butil)bencilo (17,2 ml, 0,00935 mol) seguido de carbonato potásico en polvo (25,8 g, 0,187 mol). La mezcla resultante se agitó a 80-85°C en un tubo de secado durante 24 horas. La mezcla de reacción se enfrió a temperatura ambiente y después se repartió entre acetato de etilo (300 ml) y una solución acuosa saturada de NH_4Cl (300 ml). La capa acuosa se extrajo con acetato de etilo (20 ml) y la fase orgánica combinada se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio un producto bruto que se purificó sobre una columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano, dando el compuesto del título en forma de un aceite incoloro.

Etapa F: Preparación de



A una solución del producto de la Etapa E (4,2 g, 0,0101 mol) en etanol (100 ml) a temperatura ambiente, se le añadió paladio al 10% sobre carbono activado (1,03 g). La mezcla se agitó en una atmósfera de hidrógeno (globo) durante 3 horas y después se filtró a través de un lecho corto de celite. La evaporación del disolvente dio el compuesto del título en forma de un sólido blanco que se usó en la Etapa G sin purificación adicional.

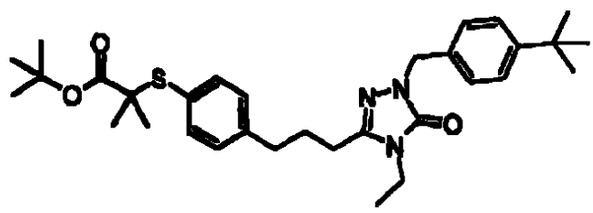
Etapa G: Preparación de



A una solución de trifenilfosfina (1,23 g, 4,68 mmol) e imidazol (0,32 g, 4,68 mmol) en una mezcla de 3:1 de Et_2O-CH_3CN (20 ml) a 0°C en una atmósfera de nitrógeno, se le añadió yodo (1,19 g, 4,68 mmol) en pequeñas porciones con agitación vigorosa. La mezcla resultante se calentó a temperatura ambiente y se agitó durante 30 minutos. Después, la mezcla se enfrió a 0°C y se añadió una solución del producto de la Etapa F (1,35 g, 4,25 mmol) en

una mezcla de 1:1 de Et_2O-CH_3CN (5 ml). La reacción se agitó a 0°C durante 15 minutos y a temperatura ambiente durante 30 minutos y después se vertió en HCl 0,5 N (50 ml). La capa acuosa se extrajo dos veces con una mezcla de 1:1 de Et_2O-hexanos (100 ml) y la fase orgánica combinada se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio un producto bruto que se purificó sobre una columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano, dando el compuesto del título en forma de un aceite amarillo.

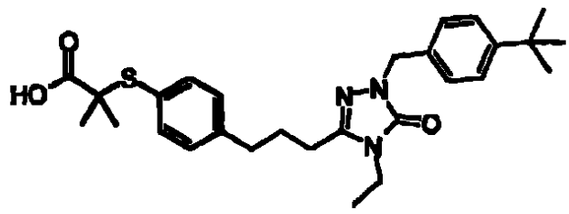
Etapa H: Preparación de



A una suspensión agitada de polvo de cinc (0,21 g, 3,22 mmol) en THF anhidro (0,5 ml) en una atmósfera de nitrógeno a 60°C se le añadió 1,2-dibromoetano (13,9 µl, 0,16 mmol). Después de 15 minutos de agitación vigorosa, la suspensión se dejó enfriar a temperatura ambiente y se añadió clorotrimetilsilano (17,1 µl, 0,135 mmol). La mezcla se agitó durante 30 minutos y después se calentó de nuevo a 60°C. Después, se añadió gota a gota una solución del producto de la Etapa G (0,23 g, 0,54 mmol) en THF anhidro (1 ml) y la mezcla se agitó durante 30 minutos. Se

añadió una mezcla de 2-(4-bromofenilsulfanil)-2-metilpropionato de *terc*-butilo (0,36 g, 1,08 mmol), $Pd(dba)_2$ (0,0155 g, 0,027 mmol) y tri-o-tolilfosfina (0,0164 g, 0,054 mmol) en THF anhidro (1 ml) y la solución resultante se mantuvo a 60°C durante 2 horas. La reacción después se enfrió a temperatura ambiente y se vertió en una solución acuosa de NH_4Cl saturado (20 ml). La capa acuosa se extrajo con acetato de etilo (50 ml) y la capa orgánica se lavó con una solución acuosa de NH_4Cl saturado (2 x 10 ml). La fase acuosa combinada se extrajo con acetato de etilo (50 ml) y la fase orgánica combinada se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio un producto bruto que se purificó sobre una columna de gel de sílice eluyendo con acetato de etilo al 40% en hexano, dando el compuesto del título en forma de un aceite incoloro. MS: m/z (M^+ + 1): 552,4.

Etapa I: Preparación de



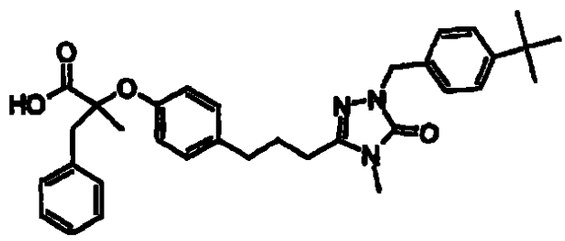
El producto de la Etapa I (180 mg) se trató con una mezcla de ácido trifluoroacético y diclorometano (10 ml, 50% v/v) con agitación durante 3 horas. El disolvente se retiró en un evaporador rotatorio y el residuo se secó a

alto vacío, dando el compuesto del título.

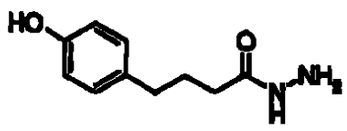
Ejemplo 39

Compuesto 39

Ácido 2-(4-{3-[4-*terc*-butilbencil)-4-metil-5-oxo-4,5,-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metil-3-fenilpropiónico



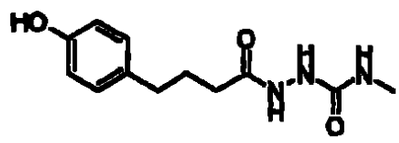
Etapa A: Preparación de hidrazida del ácido 4-(4-hidroxifenil)butírico



Una mezcla de 4-(4-hidroxifenil)butirato de metilo (4,93 g, 0,025 mol) e hidrato de hidrazina (25,4 g, 0,254 mol) en metanol (64 ml) se calentó a reflujo durante una hora. Después se enfrió a temperatura ambiente y se agitó durante una noche. El disolvente se evaporó y el residuo se repartió entre acetato de etilo (100 ml) y agua (100 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró a sequedad, dando el compuesto del título en forma de un cristal blanco (3,30 g, 67%). 400 MHz ^1H RMN

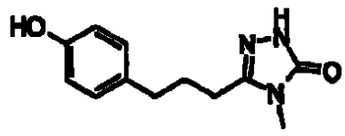
(DMSO-d^6) δ 9,10 (s, 1H), 8,89 (s, 1H), 6,93 (d, J = 8,8 Hz, 2H), 6,63 (d, J = 8,8 Hz, 2H), 3,32 (s, 2H), 2,40 (t, J = 7,6 Hz, 2H), 1,97 (t, J = 7,2 Hz, 2H), 1,71-1,67 (m, 2H); Masa ($M-H^-$) = 193,27.

Etapa B: Preparación de



A una solución del producto de la Etapa A (3,49 g, 0,0180 mol) en THF (900 ml) se le añadió gota a gota isocianato de metilo (Aldrich, 1,17 ml, 0,0198 mol) y la mezcla se agitó a temperatura ambiente durante una hora. La evaporación del disolvente dio el compuesto del título en forma de un polvo blanquecino (3,2 g, 71%). Masa ($M-H^-$) = 250,30.

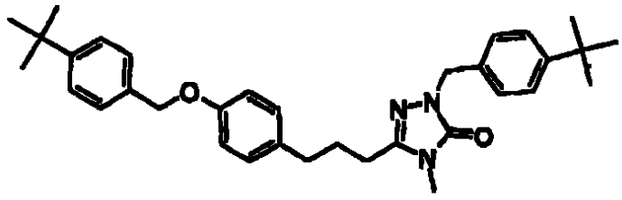
Etapa C: Preparación de 5-[3-(4-hidroxifenil)propil]-4-metil-2,4-dihidro-[1,2,4]triazol-3-ona



A una solución del producto de la Etapa B (3,21 g, 0,0128 mol) en metanol (64 ml) se le añadió en una porción hidróxido potásico (10,8 g, 0,181 mol). La mezcla de reacción se calentó a 70°C durante 36 horas. El residuo se concentró a presión reducida y se disolvió en agua (80

ml). La solución acuosa se acidificó a pH = 2 mediante HCl concentrado, dando como resultando la precipitación de producto. La mezcla heterogénea se agitó durante 18 horas y el producto se recogió por filtración, produciendo el compuesto del título en forma de un sólido blanquecino (4,5 g, en exceso de rendimiento teórico). 400 MHz ^{1}H RMN (DMSO-d^6) δ 11,37 (s, 1H); 6,97 (d, J = 8,0 Hz, 2H), 6,65 (d, J = 8,4 Hz, 2H), 3,01 (s, 3H), 2,50 (t, J = 7,6 Hz, 2H), 2,42 (t, J = 7,6 Hz, 2H), 1,80-1,77 (m, 2H); Masa (M+H$^+$) = 234,21, (M-H$^-$) = 232,29.

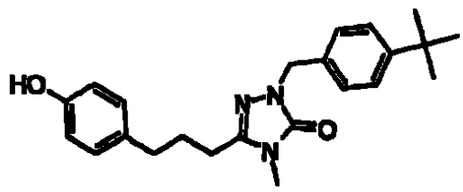
Etapa D: Preparación de 2-(4-*terc*-butilbencil)-5-{3-[4-(4-*terc*-butilbenciloxi)-fenil]propil}-4-metil-2,4-dihidro[1,2,4]triazol-3-ona



A una solución del producto de la Etapa C (1,00 g, 4,3 mmol) en DMF (21,2 ml) se le añadió bromuro de 4-t-butilbencilo (3,86 g, 17 mmol) seguido de carbonato potásico en polvo (2,92 g, 22 mmol). La mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante una noche. La mezcla de reacción se repartió entre acetato de etilo (20 ml) y agua (20 ml). La fase orgánica se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente dio

un producto bruto que se purificó sobre una columna de gel de sílice eluyendo con acetato de etilo al 20% en hexano, dando el compuesto del título en forma de un aceite incoloro. (1,12 g, 59%). 400 MHz ^{1}H RMN ($CDCl_3$) δ 7,42-7,26 (m, 8H), 7,06 (d, J = 8,8 Hz, 2H), 6,90 (d, J = 8,8 Hz, 2H), 5,00 (s, 2H), 4,89 (s, 2H), 3,15 (s, 3H), 2,63 (t, J = 7,2 Hz, 2H), 2,46 (t, J = 7,6 Hz, 2H), 1,95 (quintuplete, J = 7,6 Hz, 2H), 1,29 (m, 18H); Masa ($M+H^+$) = 526,43.

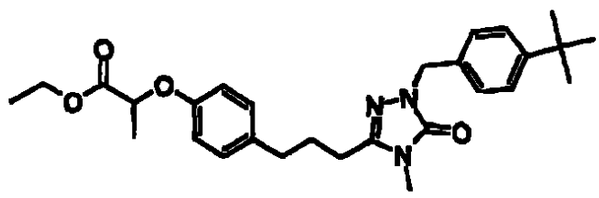
Etapa E: Preparación de 2-(4-*terc*-butilbencil)-5-[3-(4-hidroxifenil)propil]-4-metil-2,4-dihidro-[1,2,4]triazol-3-ona



A una solución del producto de la Etapa D (1,12 g, 2,1 mmol) en EtOH (21 ml) se le añadió Pd al 5%/C (22 mg) y una atmósfera de globo de hidrógeno. La reacción se agitó durante 18 horas. Después de filtrar el catalizador sobre celite, el filtrado se concentró, produciendo el compuesto del título en forma de un sólido blanco (0,746 mg, 92%). 400 MHz ^{1}H RMN ($CDCl_3$) δ 7,33 (d, J = 8,4 Hz, 2H), 7,28 (d, J = 8,4 Hz, 2H), δ 6,99 (d, J = 8,4 Hz, 2H), 6,74 (d, J = 8,4 Hz, 2H), 4,89 (s, 2H), 3,15 (s, 3H), 2,61

(t, J = 7,6 Hz, 2H), 2,46 (t, J = 7,2 Hz, 2H), 1,97-1,92 (m, 2H), 1,28 (s, 9H); Masa ($M+H^+$) = 380,26.

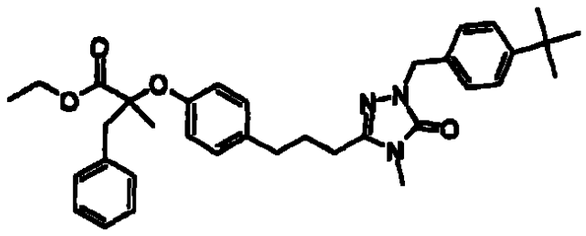
Etapa F: Preparación de éster etílico del ácido 2-(4-{3-[1-(4-*terc*-butilbencil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)propiónico



A una solución del producto de la Etapa E (0,746 g, 1,97 mmol) en DMF (7,9 ml) se le añadió bromopropionato de etilo (0,713 g, 3,94 mmol) seguido de carbonato potásico en polvo (1,36 g, 9,85 mmol). La reacción se agitó a temperatura ambiente durante una noche, después se diluyó con acetato de etilo (20 ml) y se lavó con agua (10 ml). La capa acuosa se extrajo de nuevo con acetato de etilo (20 ml) y después los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron. El producto se purificó por cromatografía en columna (90 g de SiO_2, de acetato de etilo al 50% en hexano a acetato de etilo al 100%) proporcionando el éster etílico en forma de un aceite (0,754 g, 80%). 400 MHz ^1H RMN ($CDCl_3$) δ 7,33 (d, J = 8,4 Hz, 2H), 7,28 (d, J = 8,4 Hz, 2H), 7,04 (d, J = 8,4 Hz, 2H), 6,79 (d, J = 8,4 Hz, 2H), 4,89 (s, 2H), 4,70 (c, J = 6,8 Hz, 2H), 4,21 (c, J = 7,2 Hz, 2H), 3,15 (s, 3H), 2,62 (t, J = 7,6 Hz, 2H), 2,45 (t, J = 7,2 Hz, 2H), 1,94

(quintuplete, J = 7,2 Hz, 2H), 1,60 (d, J = 6,8 Hz, 3H), 1,28-1,23 (m, 12H); Masa ($M+H^+$) = 480,2.

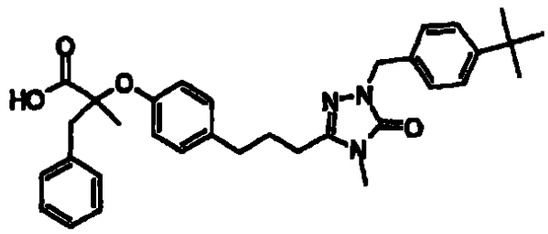
Etapa G: Preparación de éster etílico del ácido 2-(4-{3-[1-(4-*terc*-butilbencil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metil-3-fenil-propiónico



Una solución agitada magnéticamente del producto de la Etapa F (0,752 g, 1,6 mmol) en THF (12 ml) se enfrió a -78°C en una atmósfera de nitrógeno. Se añadió gota a gota LHMDS (solución 1 M en THF, 1,96 ml) mediante una jeringa, seguido de la adición de una mezcla de bromuro de bencilo (0,992 g, 5,8 mmol) y yoduro de tetrabutilamonio (57 mg, 0,15 mmol). La reacción procedió durante 1 hora a -78°C, después durante 4 horas a -20°C y finalmente durante 1 hora a temperatura ambiente. La reacción se inactivó con cloruro amónico acuoso saturado y se añadió acetato de etilo. Las capas se separaron y la fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El producto se purificó por cromatografía en columna (50 g de SiO_2, de acetato de etilo al 50% en hexano a acetato de etilo al 100%) proporcionando el éster etílico en forma de

un aceite (0,224 g, 25%). 400 MHz ^{1}H RMN ($CDCl_3$) δ 7,34-7,25 (m, 9H), 6,99 (d, J = 8,8 Hz, 2H), 6,75 (d, J = 8,8 Hz, 2H), 4,88 (s, H), 4,12 (c, J = 7,2 Hz, 2H), 3,31 (d, J = 9,6 Hz, 2H), 3,16 (d, J = 9,6 Hz, 2H), 3,14 (s, 3H), 2,60 (t, J = 7,6 Hz, 2H), 2,44 (t, J = 7,2 Hz, 2H), 1,95-1,91 (m, 2H), 1,34 (s, 3H), 1,27-1,20 (m, 12H); Masa ($M+H^+$) = 570,3, ($M+NH_4^+$) = 587,3.

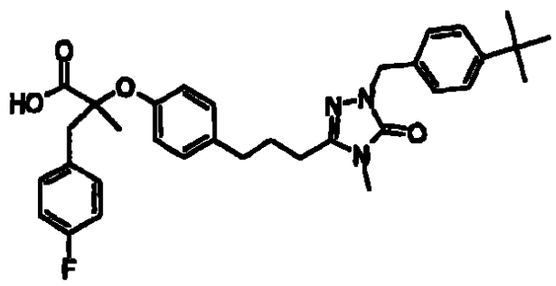
Etapa H: Preparación de ácido 2-(4-{3-(4-*terc*-butilbencil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metil-3-fenil-propiónico



Una solución agitada magnéticamente del producto de la Etapa G (0,073 g, 0,13 mmol) en EtOH (1,3 ml) se trató con NaOH (solución acuosa 5 M, 0,128 ml) y se calentó a reflujo durante 18 horas. La mezcla de reacción se acidificó a pH = 1 usando HCl 1 M y se enfrió a temperatura ambiente. Se añadió acetato de etilo (10 ml), las capas se separaron y la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, proporcionando el producto en forma de un sólido pegajoso (0,054 g, 77%). Masa ($M+H^+$) = 542,2, ($M-H^-$) = 540,2.

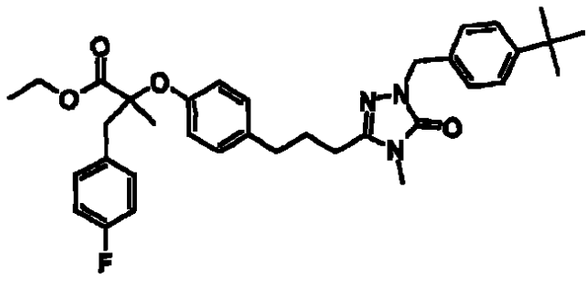
Ejemplo 40

Compuesto 40



Éster etílico del ácido 2-(4-{3-[1-(4-*terc*-butilbencil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-3-(4-fluorofenil)-2-metilpropiónico

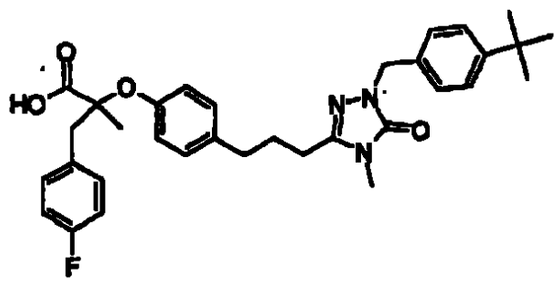
Etapa A: Preparación de éster etílico del ácido 2-(4-{3-[1-(4-*terc*-butilbencil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-3-(4-fluorofenil)-2-metilpropiónico



Una solución agitada magnéticamente del éster etílico del ácido 2-(4-{3-[1-(4-*terc*-butilbencil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-3-(4-fluorofenil)-2-metilpropiónico (Ejemplo 1, etapa F) (0,119 g, 0,25 mmol) en THF (1,7 ml) se enfrió a -78°C en una

atmósfera de nitrógeno. Se añadió gota a gota LHMDS (solución 1 M en THF, 0,31 ml) mediante una jeringa, seguido de la adición mediante una jeringa de una mezcla de bromuro de 4-fluorobencilo (0,173 g, 0,91 mmol) y yoduro de tetrabutilamonio (10 mg, 0,03 mmol). La reacción procedió durante 1 hora a -78°C, después durante 4 horas a -20°C y finalmente durante 1 hora a temperatura ambiente. La reacción se inactivó con cloruro amónico saturado y se añadió acetato de etilo. Las capas se separaron y la fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró. El producto se purificó por cromatografía en columna (30 g de SiO_2, acetato de etilo al 50% en hexano) proporcionando el éster etílico en forma de un aceite (0,051 g, 35%). 400 MHz ^1H RMN ($CDCl_3$) δ 7,34-7,22 (m, 8H), 7,00 (d, J = 8,4 Hz, 2H), 6,74 (d, J = 8,4 Hz, 2H), 4,88 (s, 2H), 4,20 (c, J = 7,2 Hz, 2H), 3,28 (d, J = 14,0 Hz, 2H), 3,14 (s, 3H), 3,12 (d, J = 14,0 Hz, 2H), 2,61 (t, J = 7,6 Hz, 2H), 2,44 (t, J = 7,2 Hz, 2H), 1,95-1,91 (m, 2H), 1,28-1,22 (m, 18H).

Etapa B: Preparación de ácido 2-(4-{3-[1-(4-*terc*-butilbencil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-3-(4-fluorofenil)-2-metilpropiónico



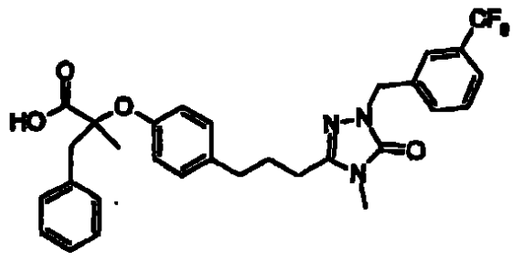
Una solución agitada magnéticamente del producto de la Etapa A (54 mg, 0,09 mmol) en EtOH (0,9 ml) se trató con NaOH (solución acuosa 5 M, 0,091 ml) y se calentó a reflujo durante 18 horas. La mezcla de reacción se acidificó a pH = 1 usando HCl 1 M y se enfrió a temperatura ambiente. Se añadió acetato de etilo (10 ml), las capas se separaron y la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, proporcionando el producto en forma de un sólido pegajoso (0,029 g, 57%). 400 MHz ^{1}H RMN (DMSO-d^6) δ 7,15 (d, J = 8,0 Hz, 2H), 7,26 (d, J = 8,4 Hz, 2H), 7,14 (d, J = 8,0 Hz, 2H), 7,09 (d, J = 8,4 Hz, 2H), 7,05 (d, J = 8,4 Hz, 2H), 6,72 (d, J = 8,4 Hz, 2H), 4,76 (s, 2H), 3,08 (s, 2H), 2,53-2,45 (m, 4H), 1,82-1,78 (m, 2H), 1,25 (s, 3H), 1,22 (s, 9H); Masa ($M+H^+$) = 560,3, ($M-H^-$) = 558,3.

Ejemplo 41

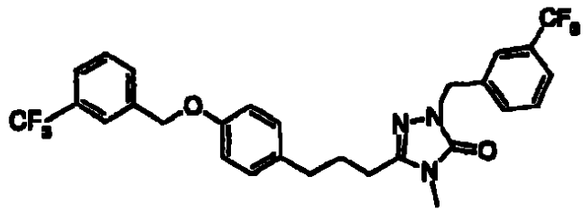
Compuesto 41

Ácido 2-metil-2-(4-{3-[4-metil-5-oxo-1-(3-trifluorometil-bencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]-propil}-

fenoxi)-3-fenil-propiónico



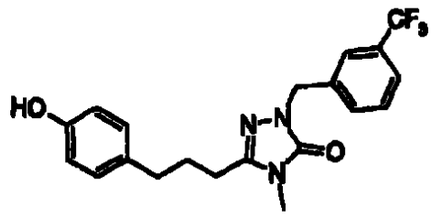
Etapa A: Preparación de 4-metil-2-(3-trifluorometil-bencil)-5-{3-[4-(3-trifluorometil-benciloxi)-fenil]-propil}-2,4-dihidro-[1,2,4]triazol-3-ona



A una solución de 5-[3-(4-hidroxifenil)propil]-4-metil-2,4-dihidro-[|,2,4]triazol-3-ona (Ejemplo 1, Etapa C) (0,350 g, 1,50 mmol) en DMF (5 ml) se le añadió bromuro de 3-trifluorobencilo (1,03 g, 4,29 mol) seguido de carbonato potásico en polvo (0,74 g, 5,35 mmol). La mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante una noche. La mezcla de reacción se repartió entre acetato de etilo (20 ml) y agua (20 ml). La fase orgánica se secó sobre $MgSO_4$ y se filtró. La evaporación del disolvente dio un producto bruto que se purificó sobre una columna de gel de sílice (125 ml de SiO_2) eluyendo con EtOAc al 50%/hexanos, dando el compuesto

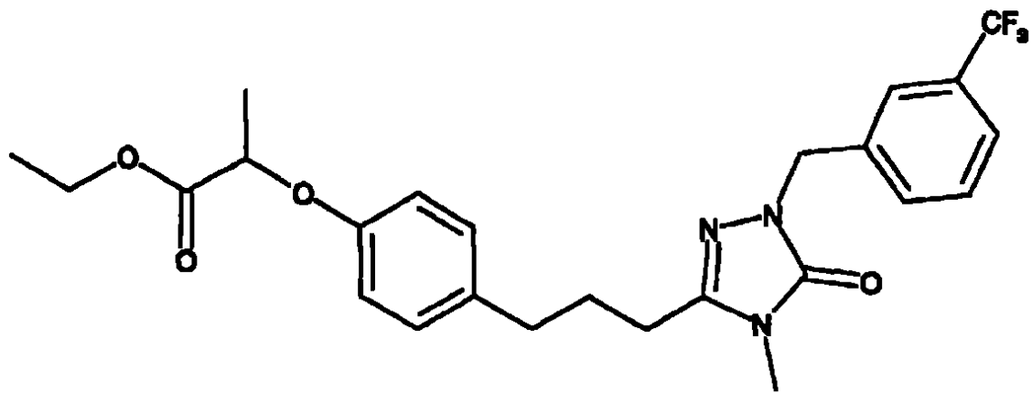
del título en forma de un aceite incoloro (0,675 g, 82%). 400 MHz ^{1}H RMN ($CDCl_3$) δ 7,70 (s, 1H), 7,63-7,42 (m, 7H), 7,08 (d, J = 8,4 Hz, 2H), 6,89 (d, J = 8,4 Hz, 2H), 5,09 (s, 2H), 4,98 (s, 2H), 3,18 (s, 3H), 2,64 (t, J = 7,2 Hz, 2H), 2,48 (t, J = 7,6 Hz, 2H), 1,97 (quintuplete, J = 7,6 Hz, 2H); Masa ($M+H^+$) = 550,3.

Etapa B: Preparación de 5-[3-(4-hidroxi-fenil)-propil]-4-metil-2-(3-trifluorometil-bencil)-2,4-dihidro-[1,2,4]triazol-3-ona



A una solución del producto de la Etapa A (0,67 g, 1,22 mmol) en EtOH (50 ml) se le añadió Pd al 5%/C (85 mg) y un globo de hidrógeno. La reacción se agitó durante 18 horas. Después de filtrar el catalizador sobre celite, el filtrado se concentró, produciendo el compuesto del título (aceite, 0,29 g, 60%). Masa ($M+H^+$) = 392,2.

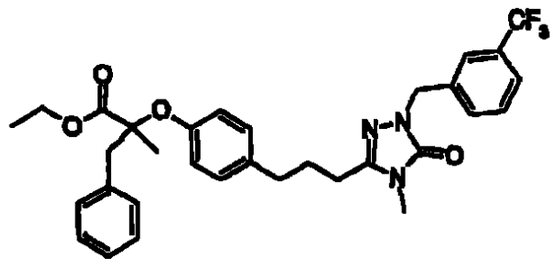
Etapa C: Preparación de éster etílico del ácido 2-metil-3-(4-{3-[4-metil-5-oxo-1-(3-trifluorometil-bencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]-propil}-fenoxi)-propiónico



A una solución del producto de la Etapa B (0,29 g, 0,74 mmol) en DMF (3 ml) se le añadió bromopropionato de etilo (0,27 g, 1,47 mmol, 0,19 ml) seguido de carbonato potásico en polvo (0,51 g, 3,7 mmol). La reacción se agitó a temperatura ambiente durante una noche, después se diluyó con acetato de etilo (20 ml) y se lavó con agua (10 ml). La capa acuosa se extrajo con acetato de etilo (20 ml), después los extractos orgánicos combinados se secaron sobre $MgSO_4$ y se concentraron. El producto se purificó por cromatografía en columna (100 ml de SiO_2, de acetato de etilo al 50% en hexano a acetato de etilo al 100%), proporcionando el éster etílico en forma de un aceite (0,754 g, 80%). 400 MHz ^1H RMN ($CDCl_3$) δ 7,57 (s, 1H), 7,51-7,49 (m, 2H), 7,42 (d, J = 8,0 Hz, 1H), 7,02 (d, J = 8,6 Hz, 2H), 6,78 (d, J = 8,4 Hz, 2H), 4,95 (s, 2H), 4,68 (c, J = 7,2 Hz, 2H), 4,19 (c, J = 7,2 Hz, 2H), 3,15 (s, 3H), 2,60 (t, J = 7,6 Hz, 2H), 2,44 (t, J = 7,2 Hz, 2H), 1,93 (quintuplete, J = 7,6 Hz, 2H), 1,58 (d, J = 6,8 Hz,

3H), 1,22 (t, J = 7,2 Hz, 3H); Masa ($M+H^+$) = 492,1.

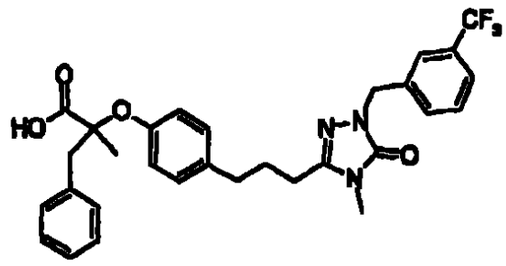
Etapa D: Preparación de éster etílico del ácido 2-metil-2-(4-{3-[4-metil-5-oxo-1-(3-trifluorometil-bencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]-propil}-fenoxi)-3-fenil-propiónico



Una solución agitada magnéticamente del producto de la Etapa C (0,22 g, 0,45 mmol) en THF (2,8 ml) se enfrió a -78°C en una atmósfera de nitrógeno. Se añadió gota a gota LHMDS (solución 1 M en THF, 0,56 ml) mediante una jeringa, seguido de la adición mediante una jeringa de una mezcla de bromuro de bencilo (0,27 g, 1,6 mmol) y yoduro de tetrabutilamonio (16 mg, 0,045 mmol). La reacción procedió durante 1 hora a -78°C, después durante 4 hora a -20°C y finalmente durante 1 hora a temperatura ambiente. La reacción se inactivó con cloruro amónico acuoso saturado y se añadió acetato de etilo. Las capas se separaron y la fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró. El producto se purificó por cromatografía en columna (100 ml de SiO_2, de EtOAc al 15%/hexanos a EtOAc al 70%/hexanos) proporcionando el

éster etílico en forma de un aceite (23 mg, 9%). 400 MHz ^{1}H RMN ($CDCl_3$) δ 7,34-7,22 (m, 9H), 7,00 (d, J = 8,4 Hz, 2H), 6,74 (d, J = 8,4 Hz, 2H), 4,97 (s, 2H9, 4,20 (c, J = 7,2 Hz, 2H), 3,28 (d, J = 14,0 Hz, 2H), 3,14 (s, 3H), 3,12 (d, J = 14,0 Hz, 2H), 2,61 (t, J = 7,6 Hz, 2H), 2,44 (t, J = 7,6 Hz, 2H), 1,95-1,91 (m, 2H), 1,38 (s, 3H), 1,28 (s, 3H), 1,21 (t, J = 7,2 Hz, 3H); Masa ($M+H^+$) = 582,4; ($M+NH_4^+$) = 599,4.

Etapa E: Preparación de ácido 2-metil-2-(4-{3-[4-metil-5-oxo-1-(3-trifluorometil-bencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]-propil}-fenoxi)-3-fenil-propiónico



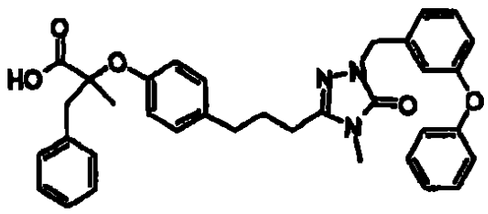
Una solución agitada magnéticamente del producto de la Etapa D (20 mg, 0,034 mmol) en EtOH (2 ml) se trató con NOH (solución acuosa 5 M, 40 µl) y se calentó a reflujo durante 18 horas. La mezcla de reacción se acidificó a pH = 1 usando HCl 1 M y se enfrió a temperatura ambiente. Se añadió acetato de etilo (10 ml), las capas se separaron y la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron, proporcionando el producto en forma de un

sólido pegajoso (10,3 mg, 54%). Masa ($M+H^+$) = 554,3, ($M-H^-$) = 552,3.

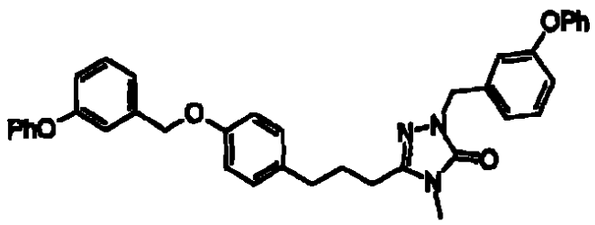
Ejemplo 42

Compuesto 42

Ácido 2-metil-2-(4-{3-[4-metil-5-oxo-1-(3-fenoxibencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-3-fenilpropiónico



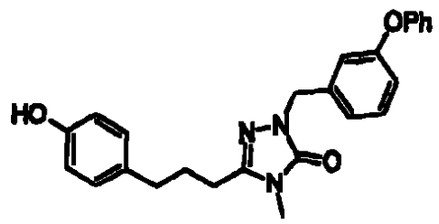
Etapa A: Preparación de 4-metil-2-(3-fenoxi-bencil)-5-{3-[4-(3-fenoxi-benciloxi)-fenil]-propil}-2,4-dihidro-[1,2,4]triazol-3-ona



A una solución de 5-[3-(4-hidroxifenil)propil]-4-metil-2,4-dihidro-[1,2,4]triazol-3-ona (Ejemplo 1, etapa C) (0,350 g, 1,50 mmol) en DMF (5 ml) se le añadió cloruro de 3-fenoxibencilo (0,94 g, 4,29 mmol) seguido de carbonato potásico en polvo (0,74 g, 5,35 mmol). La mezcla se agitó a temperatura ambiente en una atmósfera de nitrógeno durante una noche. La mezcla de reacción se

repartió entre acetato de etilo (20 ml) y agua (20 ml). La fase orgánica se secó sobre $MgSO_4$ y se filtró. La evaporación del disolvente dio un producto bruto que se purificó sobre una columna de gel de sílice (125 ml de SiO_2) eluyendo con EtOAc al 50%/hexanos, dando el compuesto del título en forma de un aceite incoloro (0,078 g, 87%). 400 MHz ^1H RMN ($CDCl_3$) δ 7,32 (c, J = 7,6 Hz, 4H), 7,30-7,25 (m, 3H), 7,20-6,90 (m, 10H), 6,97 (d, J = 8,8 Hz, 2H), 6,87 (d, J = 8,8 Hz, 2H), 5,01 (s, 2H), 4,91 (s, 2H), 3,16 (s, 3H), 2,63 (t, J = 7,2 Hz, 2H), 2,46 (t, J = 7,6 Hz, 2H), 1,94 (quintuplete, J = 7,6 Hz, 2H); Masa ($M+H^+$) = 598,4.

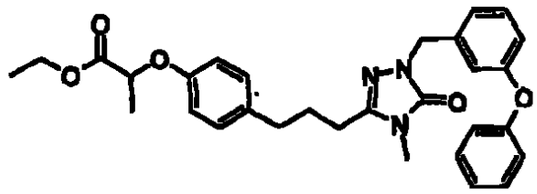
Etapa B: Preparación de 5-[3-(4-hidroxi-fenil)-propil]-4-metil-2-(3-fenoxi-bencil)-2,4-dihidro-[1j,2,4]triazol-3-ona



A una solución del producto de la Etapa A (0,78 g, 1,30 mmol) en EtOH (10 ml) y EtOAc (2 ml) se le añadió Pd al 5%/C (85 mg) y un globo de hidrógeno. La reacción se agitó durante 72 horas. Después de filtrar el catalizador sobre celite, el filtrado se concentró, produciendo el compuesto del título en forma de un aceite (0,138 g, 25%).

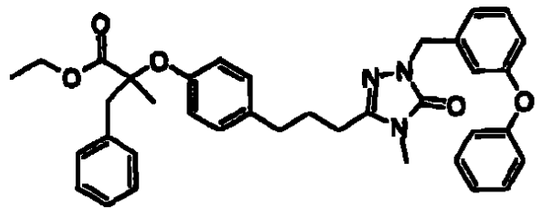
Masa ($M+H^+$) = 416,1.

Etapa C: Preparación de éster etílico del ácido 2-(4-{3-[4-metil-5-oxo-1-(3-fenoxibencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)propiónico



A una solución del producto de la Etapa B (0,138 g, 0,33 mmol) en DMF (1,3 ml) se le añadió bromopropionato de etilo (0,120 g, 0,66 mmol) seguido de carbonato potásico en polvo (0,23 g, 0,0017 mol). La reacción se agitó a temperatura ambiente durante una noche, después se diluyó con acetato de etilo (20 ml) y se lavó con agua (10 ml). La capa acuosa se extrajo con acetato de etilo (20 ml), después los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron. El producto se purificó por cromatografía en columna (20 g de SiO_2, acetato de etilo al 50% en hexano) proporcionando el éster etílico en forma de un aceite (0,144 g, 84%). 400 MHz ^1H RMN ($CDCl_3$) δ 7,22-7,15 (m, 4H), 7,00-6,69 (m, 9H), 4,81 (s, 2H), 4,61 (c, J = 6,8 Hz, 2H), 4,12 (c, J = 7,2 Hz, 2H), 3,07 (s, 3H), 2,52 (t, J = 7,2 Hz, 2H), 2,36 (t, J = 7,2 Hz, 2H), 1,86-1,82 (m, 2H), 1,51 (d, J = 6,8 Hz, 3H), 1,16 (d, J = 7,2 Hz, 3H); Masa ($M+H^+$) = 516,3, ($M+NH_4^+$) = 533,3.

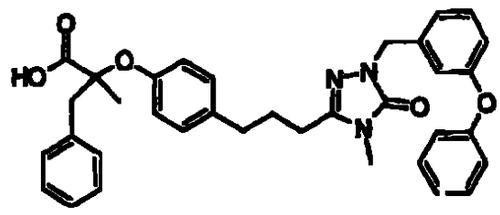
Etapa D: Preparación de éster etílico del ácido 2-metil-2-(4-{3-[4-metil-5-oxo-1-(3-fenoxibencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-3-fenilpropiónico



Una solución agitada magnéticamente del producto de la Etapa C (0,144 g, 0,00028 mol) en THF (2 ml) se enfrió a -78°C en una atmósfera de nitrógeno. Se añadió gota a gota LHMD (solución 1 M en THF, 0,348 ml) mediante una jeringa, seguido de la adición mediante una jeringa de una mezcla de bromuro de bencilo (0,176 g, 0,00103 mol) y yoduro de tetrabutilamonio (0,010 g, 0,00003 mol). La reacción prodeció durante 1 hora a -78°C, después durante 4 horas a -20°C y finalmente durante 1 hora a temperatura ambiente. La reacción se inactivó con cloruro amónico acuoso saturado y se añadió acetato de etilo. Las capas se separaron y la fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró. El producto se purificó por cromatografía en columna (50 g de SiO_2, acetato de etilo al 50% en hexano) proporcionando el éster etílico en forma de un aceite (0,146 g, 87%). 400 MHz ^1H RMN ($CDCl_3$) δ 7,31-7,24 (m, 8H), 7,09-6,74 (m, 10H), 4,90 (s, 2H), 4,20 (c, J = 7,2 Hz, 2H), 3,30-3,15 (m, 5H), 2,60

(t, J = 7,2 Hz, 2H), 2,44 (t, J = 7,2 Hz, 2H), 1,94-1,91 (m, 2H), 1,38 (s, 3H), 1,27-1,20 (m, 3H); Masa ($M+H^+$) = 606,2, ($M+NH_4^+$) = 623,2.

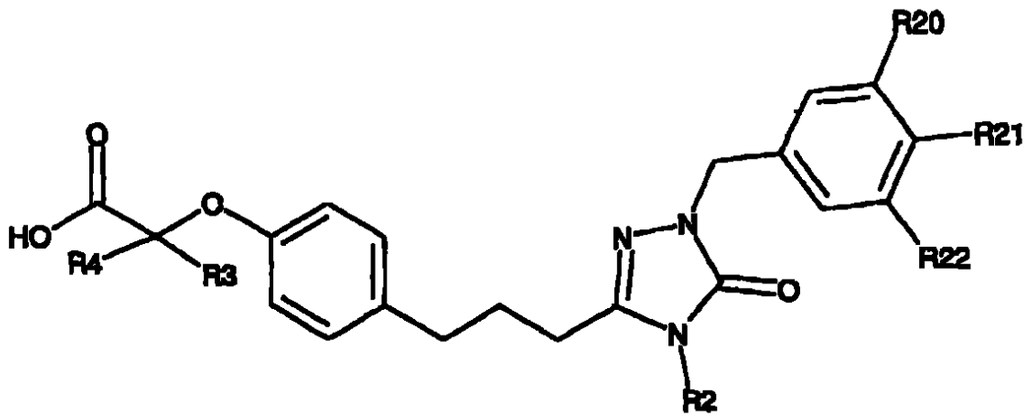
Etapa E: Preparación de ácido 2-metil-2-(4-{3-[4-metil-5-oxo-1-(3-fenoxibencil)-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-3-fenilpropiónico



Una solución agitada magnéticamente del producto de la Etapa D (0,120 g, 0,00020 mol) en EtOH (2,0 ml) se trató con NaOH (solución acuosa 5 M, 0,198 ml) y se calentó a reflujo durante 48 horas. La mezcla de reacción se acidificó a pH = 1 usando HCl 1 M y se enfrió a temperatura ambiente. Se añadió acetato de etilo (10 ml), las capas se separaron y la fase acuosa se extrajo con EtOAc (3 x 10 ml). Las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, proporcionando el producto en forma de un sólido pegajoso (0,097 g, 85%). 400 MHz ^1H RMN (DMSO-d^6) δ 7,38-7,24 (m, 8H), 7,14-6,73 (m, 10H), 4,81 (s, 2H), 3,25-3,07 (m, 5H), 2,52 (,m 4H), 1,82-1,76 (m, 2H), 1,26 (s, 3H); Masa ($M+H^+$) = 578,3, ($M-H^-$) = 576,3.

Otros compuestos de la presente invención, cuya

fórmula estructural se muestra a continuación, se sintetizaron por procedimientos similares a los descritos en los ejemplos anteriores.



Estos compuesto adicionales se ejemplifican adicionalmente en la siguiente tabla.

Tabla I

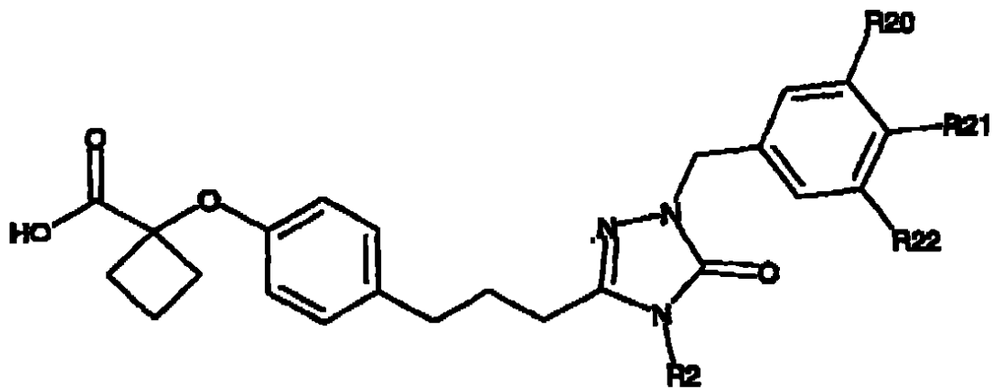
Ejemplo Número	R4	R3	R2	R20	R21	R22
43	CH_3	CH_3	propilo	OH	H	H
44	CH_3	CH_3	butilo	H	H	OCH_3
45	CH_3	CH_3	CH_3	H	H	OCH_3
46	CH_3	CH_3	propilo	H	NO_2	H
47	CH_3	CH_3	etilo	H	H	OCH_3
48	etilo	CH_3	propilo	H	CH_3	H
49	bencilo	CH_3	propilo	H	CH_3	H
50	H	H	propilo	CH_3	CH_3	H
51	CH_3	H	propilo	CH_3	CH_3	H
52	etilo	H	propilo	CH_3	CH_3	H
53	isopropilo	H	propilo	CH_3	CH_3	H

54	F	F	propilo	CH_3	CH_3	H
55	ciclohexilo	H	propilo	CH_3	CH_3	H
56	fenilo	H	propilo	CH_3	CH_3	H
57	2-hidroxietilo	H	propilo	CH_3	CH_3	H
58	F	H	propilo	CH_3	CH_3	H
59	butilo	H	propilo	CH_3	CH_3	H
60	pentilo	H	propilo	CH_3	CH_3	H
61	H	H	propilo	H	t-butilo	H
62	CH_3	H	propilo	H	t-butilo	H
63	etilo	H	propilo	H	t-butilo	H
64	isopropilo	H	propilo	H	t-butilo	H
65	F	F	propilo	H	t-butilo	H
66	ciclohexilo	H	propilo	H	t-butilo	H
67	fenilo	H	propilo	H	t-butilo	H
68	2-hidroxietilo	H	propilo	H	t-butilo	H
69	butilo	H	propilo	H	t-butilo	H
70	pentilo	H	propilo	H	t-butilo	H
71	CH_3	CH_3	2-metoxi-etilo	CH_3	CH_3	H
72	H	H	etilo	H	CH_3	H
73	CH_3	H	etilo	H	CH_3	H

74	etilo	H	etilo	H	CH_3	H
75	isopropilo	H	etilo	H	CH_3	H
76	ciclohexilo	H	etilo	H	CH_3	H
77	fenilo	H	etilo	H	CH_3	H
78	CH_3	CH_3	t-butilo	CH_3	CH_3	H
79	CH_3	CH_3	i-propilo	CH_3	CH_3	H
80	CH_3	CH_3	H	H	H	Cl
81	CH_3	CH_3	H	CF_3	H	CF_3
82	CH_3	CH_3	H	H	Cl	Cl
83	CH_3	CH_3	H	H	F	F
84	CH_3	H	propilo	H	t-butilo	H
85	CH_3	CH_3	H	H	t-amilo	H
86	CH_3	CH_3	H	H	CF_3	H
87	CH_3	CH_3	H	H	OCF_3	H
88	CH_3	CH_3	H	H	CF_3	F
89	CH_3	CH_3	2-fenoxi-etilo	CH_3	CH_3	H
90	CH_3	CH_3	ciclo-propil-metilo	CH_3	CH_3	H
91	CH_3	CH_3	propilo	H	amino	H
92	CH_3	CH_3	2,4-dimetoxi-bencilo	H	CH_3	H
93	CH_3	CH_3	2,4-dimetoxi-bencilo	CH_3	H	CH_3
94	CH_3	CH_3	2,4-dimetoxi-bencilo	H	t-butilo	H
95	CH_3	CH_3	2,4-	H	H	fenoxi

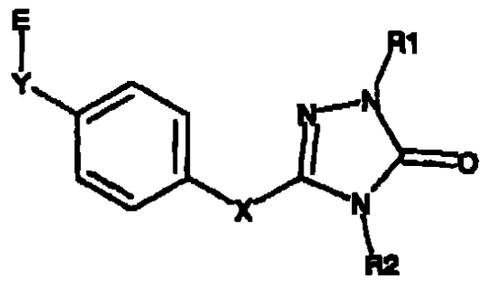
			dimetoxi-bencilo			
96	CH_3	CH_3	2,4-dimetoxi-bencilo	H	H	CH_3
97	CH_3	CH_3	2,4-dimetoxi-bencilo	H	H	CF_3
98	CH_3	CH_3	2,4-dimetoxi-bencilo	CH_3	CH_3	H
99	CH_3	CH_3	2,4,6-trimetoxi-bencilo	H	CH_3	H

Otros compuestos de la presente invención, cuya fórmula estructural se muestra a continuación, se sintetizaron por procedimientos similares a los descritos en los ejemplos anteriores.



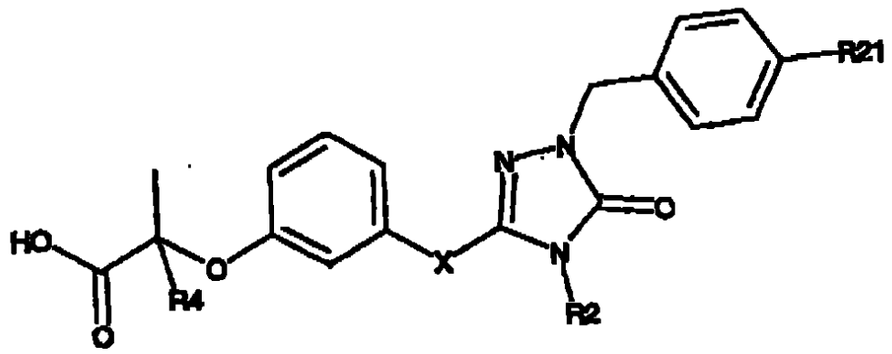
Ejemplo	R2	R20	R21	R22
100	propilo	CH_3	CH_3	H

101	propilo	H	t-butilo	H
102	etilo	H	CH_3	H
103	metilo	H	CH_3	H



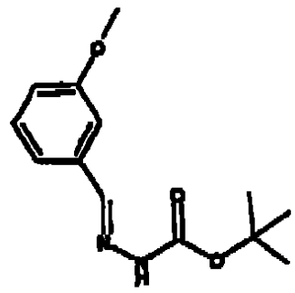
Ejemplo	E	Y	X	R1	R2
104	ácido 2(2-metil)-propanoico	O	butileno	4-metil-bencilo	etilo
105	ácido 2(2-metil)-propanoico	O	butileno	4-metil-bencilo	propilo
106	ácido etanoico	O	propileno	fenilo	propilo
107	ácido 2(2-metil)-propanoico	O	propileno	fenilo	propilo
108	ácido 2(2-metil)-propanoico	O	propileno	β-naftil metilo	ácido 2(2-metil)-propanoico
109	2(2-tetrazol)-etilo	O	propileno	4-t-butil-bencilo	propilo
110	ácido 2(2-	O	etileno	3-metoxi-	hexilo

	metil)-propanoico			bencilo	
111	COOH	-	propileno	4-t-butil-bencilo	etilo
112	2(2-metil-3-tetrazol)-etilo	O	propileno	3,4-dimetoxi-bencilo	CH_3



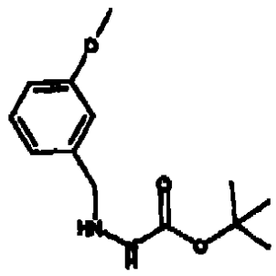
Ejemplo	R4	X	R2	R21
113	CH_3	propileno	CH_3	t-butilo
114	bencilo	propileno	CH_3	t-butilo
115	CH_3	butileno	propilo	metilo

Ejemplo 116



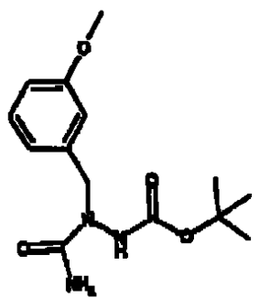
Ácido (3-metoxifenil)metilenohidrazinacarboxílico, 1,1-dimetiletil éster

A una solución de carbazato de *t*-butilo (5,59 g, 42,3 mmol) en acetato de etilo (15 ml) se le añadió con agitación *m*-anisaldehído (5,17 ml, 5,76 g, 42,3 mmol). Se añadieron lentamente hexanos (70 ml) y se produjo cristalización. La suspensión resultante se agitó a temperatura ambiente durante 45 minutos, después se filtró y se aclaró con hexanos fríos (20 ml) y se secó al vacío a 40°C, produciendo el compuesto del título en forma de un sólido (9,68 g, 91,4%): p.f. 135,6-137,4°C; ^{1}H RMN (DMSO-d_6) δ 10,93 (s, 1H), 7,29 (t, 1H, *J* = 8 Hz), 7,14 (d, 2H, *J* = 7 Hz), 6,92 (c, 1H, *J* = 7 Hz), 3,75 (s, 3H9, 1,45 (s, 9H); ^{13}C RMN (DMSO-d_6) δ 160,2, 153,1, 143,7, 136,8, 130,5, 120,0, 116,2, 111,3, 80,1, 55,7, 28,7; IR (KBr mull): 3360, 3010, 2982, 2838, 1510, 1487 cm^{-1}; una porción se recristalizó en acetato de etilo y se sometió a análisis elemental. Análisis calculado para $C_{13}H_{18}N_2O_3$: C, 62,38; H, 7,25; N, 11,19. Encontrado: C, 62,34; H, 7,46; N, 11,19.



Ácido (3-metoxibencil)hidrazinacarboxílico, 1,1-dimetiletil éster

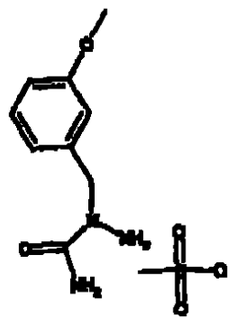
Se suspendieron ácido (3-metoxifenil)metilenohidrazinacarboxílico, 1,1-dimetiletil éster (7,03 g, 28,1 mmol) y Pd/C (5%, seco, 5,07 g) en THF (80 ml) y se hidrogenó a temperatura ambiente y a 344,73 kPa durante 8 horas. Después, la suspensión se filtró a través de celite y se concentró al vacío a 50°C, produciendo el compuesto del título en forma de un aceite transparente (6,68 g, 94,0%): ^{1}H RMN (DMSO-d_6) ácido 2(2-metil)-propanoico 8,22 (s, 1H), 7,19 (t, 1H, J = 8 Hz), 6,85 (d, 1H, J = 7 Hz), 6,77 (d, 1H, J = 7 Hz), 3,84 (s, 2H), 3,72 (s, 3H), 1,37 (s, 9H); ^{13}C (DMSO-d_6) ácido 2(2-metil)-propanoico 159,9, 157,1, 141,1, 129,7, 121,1, 114,1, 113,1, 78,9, 55,5, 54,9, 28,9; IR ($CHCl_3$): 3008, 2982, 2935, 1712 cm^{-1}; Masa exacta: Calculada m/z para $C_{13}H_{20}N_2O_3Na$: 275,1372, Encontrada: 275,1381.



Ácido 3-(aminocarbonil)-2-(3-metoxifenilmetil)hidrazinacarboxílico, 1,1-dimetiletil éster

Se disolvió ácido (3-metoxibencil)hidrazinacarboxílico, 1,1-dimetiletil éster (6,30 g, 25,0 mmol) en alcohol isopropílico (IPA, 65 ml). Se añadió isocianato de trimetilsililo (4,73 g, 34,9 mmol) en una porción mediante una jeringa y la solución se dejó agitar a temperatura ambiente durante 7 h. La suspensión se enfrió a 0-5°C, se filtró y los sólidos se aclararon con IPA frío. Los sólidos se secaron al vacío a 40°C durante una noche, produciendo el compuesto del título en forma de un sólido blanco (4,71 g, 63,9%). El filtrado se concentró y se purificó por cromatografía en columna (SiO_2, EtOAc), produciendo más compuesto (0,91 g, 12,3%). Estas dos porciones se combinaron, produciendo 5,82 g (76,2%) del compuesto del título: p.f. 136,3-138,5°C; ^{1}H RMN /DMSO-d_6, 60°C) δ 8,70 (s, 1H), 7,20 (t, 1H, J = 8 Hz), 6,80 (m, 3H), 5,90 (s, 2H), 4,50 (s, 2H), 3,74 (s, 3H), 1,36 (s, 9H); ^{13}C RMN (DMSO-d_6, 20°C) δ 159,9, 159,6, 155,0, 140,2,

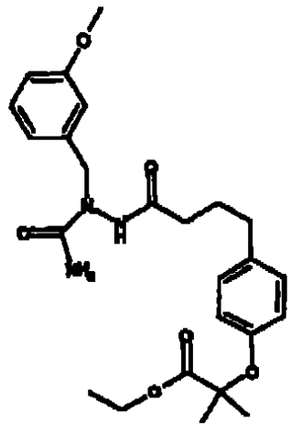
129,8, 120,9, 114,0, 113,2, 80,2, 55,6, 51,1, 28,7; IR ($CHCl_3$): 3003, 2984, 2938, 1745, 1680 cm^{-1}; Análisis calculado para $C_{14}H_{21}N_3O_4$: C, 56,94; H, 7,17; N, 14,23. Encontrado: C, 56,54; H, 7,17; N, 13,98.



Metanosulfonato de 1-(3-metoxifenilmetil)hidrazinacarboxamida

Se disolvió ácido 3-(aminocarbonil)-2-(3-metoxifenilmetil)hidrazinacarboxílico, 1,1-dimetiletil éster (5,30 g, 17,9 mmol) en diclorometano (60 ml). Se añadió en una porción ácido metanosulfónico (1,93 g, 19,9 mmol) y la solución se dejó en agitación a temperatura ambiente durante una noche. La suspensión resultante se enfrió a 0-5°C, se filtró y los sólidos se aclararon con diclorometano frío. Los sólidos se secaron al vacío a 40°C durante una noche, produciendo el compuesto del título en forma de un sólido blanco (5,05 g, 96,6%). P.f. 130,3-132,1°C; ^1H RMN (DMSO-d_6) δ 9,7 (s ancho, 3H), 7,30 (t, 1H, J = 8 Hz), 7,05 (s ancho, 2H), 6,88 (s, 3H), 4,69 (s, 2H), 3,74 (s, 3H), 3,34 (s, 3H); ^{13}C (DMSO-d_6) δ 160,1, 158,2,

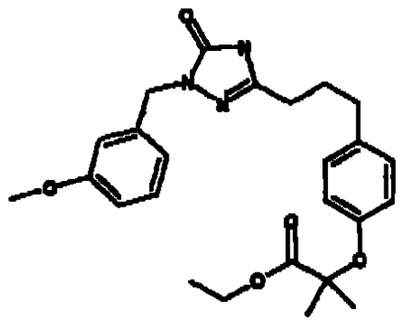
137,3, 130,5, 120,7, 114,3, 114,0, 55,7, 52,7, 40,4; IR (KBr mull): 3186, 2939, 1719, 1707, 1168 cm^{-1}; Análisis calculado para $C_9H_{13}N_3O_2$: C, 41,23; H, 5,88; N, 14,42. Encontrado: C, 40,86; H, 5,92; N, 14,61.



1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3-metoxifenilmetil)semicarbazida

Se disolvió ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)-fenilbutírico (4,86 g, 16,5 mmol) en acetato de etilo (40 ml). A esta solución se le añadió gota a gota cloruro de oxalilo (2,43 g, 19,14 mmol) en presencia de una cantidad catalítica de N,N-dimetilformamida (100 mg, 1,37 mmol). La formación completada de cloruro de ácido se verificó por HPLC. Esta solución después se añadió gota a gota a una suspensión de metanosulfonato de 1-(3-metoxifenilmetil)hidrazinacarboxamida (4,80 g, 16,5 mmol) y piridina (1,30 g, 16,5 mmol) en acetato de etilo (55 ml) a 0-5°C. Después de agitar a 0-5°C durante 6 horas, se

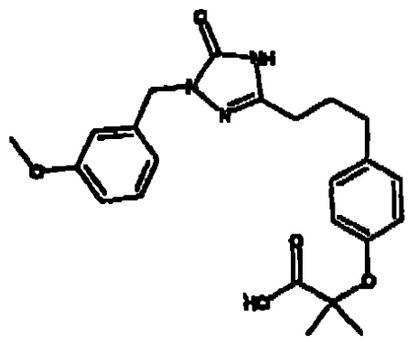
añadió una carga adicional de piridina (1,30 g, 16,5 mmol) y la solución se agitó a 0-5°C durante 1 hora, momento en el que la reacción se completó- La solución se calentó a temperatura ambiente y se lavó dos veces con HCl 1 N (80 ml) y dos veces con $NaHCO_3$ acuoso al 5% (80 ml). La capa orgánica se secó ($MgSO_4$), se filtró y se concentró para dar un sólido céreo. Los sólidos se recristalizaron en una mezcla de tolueno (17 ml) y n-heptano (7 ml) a 60°C, se enfrió a 0-5°C y se filtró. Los sólidos se secaron al vacío a 40°C durante una noche, produciendo el compuesto del título en forma de un sólido blanco (5,05 g, 65%): ^1H RMN (DMSO-d_6, 60°C) δ 9,60 (s, 1H), 7,19 (t, 1H, J = 8 Hz), 7,00 (d, 2H), 6,80 (m, 3H), 6,71 (d, 2H, J = 8 Hz), 5,92 (s, 2H), 4,52 (s, 2H), 4,15 (c, J = 7 Hz), 3,71 (s, 3H), 2,45 (t, 2H, J = 7 Hz), 2,07 (t, 2H, J = 7 Hz), 1,73 (quint., 2H, J = 7 Hz), 1,48 (s, 6H), 1,17 (t, 3H, J = 7 Hz); ^{13}C RMN (DMSO-d_6) δ 174,0, 171,9, 159,9, 159,3, 153,7, 140,5, 135,9, 129,9; 129,7, 120,9, 119,4, 114,1, 113,1, 79,2, 61,6, 55,5, 50,9, 34,3, 27,2, 25,7, 14,6; IR (KBr mull): 3450, 3320, 3275, 3202, 2997, 2940, 1730, 1646, 1511 cm^{-1}; Análisis calculado para $C_{25}H_{33}N_3O_6$: C, 63,68; H, 7,05; N, 8,91. Encontrado: C, 63,49; H, 7,02; N, 8,99.



Éster etílico del ácido 2-(4-{3-[1-(3-metoxibencil)-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]-propil}-fenoxi)-2-metilpropionico

Se disolvió 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3-metoxifenilmetil)semicarbazida (4,08 g, 8,65 mmol) en acetato de etilo (7,5 ml). Se añadió en una porción ácido 1S(+)-10-canforsulfónico (2,21 g, 9,51 mmol) y la solución se calentó a reflujo durante una noche. La solución se enfrió a temperatura ambiente y se lavó con $NaHCO_3$ acuoso saturado (40 ml x 2) seguido de HCl 1 N (40 ml x 2). Los extractos orgánicos se concentraron para dar un aceite naranja. Este aceite se redisolvió en acetato de etilo (40 ml). Se añadió resina Amberlyst-15 (4,41 g) y la mezcla se calentó a 50°C y se agitó durante 4 horas para retirar las impurezas desureadas. Después la mezcla se enfrió a temperatura ambiente, se filtró, se concentró y se purificó por cromatografía en columna (SiO_2, 9:1 de acetato de etilo:hexanos), produciendo el compuesto del título en

forma de un aceite naranja (1,93 g, 49,2%). ^{1}H RMN (DMSO-d_6) δ 11,47 (s, 1H), 7,22 (t, 1H, *J* = 8 Hz), 7,04 (d, 2H, *J* = 8 Hz), 6,82 (d, 1H, *J* = 2 Hz), 6,76 (m, 2H9, 6,68 (d, 2H, *J* = 2 Hz), 4,73 (s, 2H9, 4,13 (c, 2H, *J* = 7 Hz), 3,69 (s, 3H9, 2,48 (t, 2H, *J* = 8 Hz), 2,36 (t, 2H, *J* = 8 Hz), 1,80 (quint., 2H, *J* = 7 Hz), 1,47 (s, 6H), 1,14 (t, 3H, *J* = 7 Hz); ^{13}C RMN (DMSO-d_6) δ 174,0, 160,0, 155,0, 153,8, 146,7, 139,8, 135,5, 130,2, 129,8, 120,1, 119,5, 113,8, 113,2, 79,2, 61,6, 55,6, 47,8, 34,0, 28,4, 26,2, 25,7, 14,6; IR ($CHCl_3$) 2940, 1692, 1508, 1467 cm^{-1}; Análisis calculado para $C_{25}H_{31}N_3O_5$: C, 66,21; H, 6,89; N, 9,26. Encontrado: C, 66,29; H, 6,75; N, 9,19.

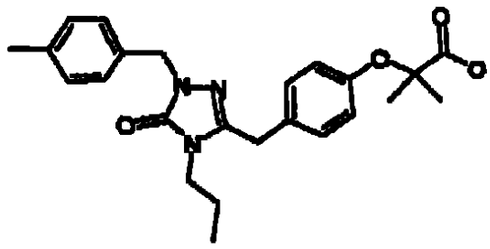


Ácido 2-(4-{3-[1-(3-metoxibencil)-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]-propil}-fenoxi)-2-metilpropionico

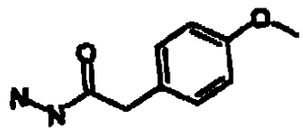
Se disolvió éster etílico del ácido 2-(4-{3-[1-(3-metoxibencil)-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]-propil}-fenoxi-2-metilpropionico (1,55 g, 3,42 mmol) en una mezcla de etanol (7,5 ml) y agua desionizada (7,5 ml). Se añadió hidróxido sódico sólido (0,36 g, 8,73 mmol) en

una porción y la solución se calentó a 70°C y se agitó durante una hora. La solución se enfrió a temperatura ambiente y el pH se ajustó a 7 con HCl 6 N. La solución se concentró para dar un aceite amarillo turbio. Este aceite se repartió entre HCl 1 N (10 ml) y acetato de etilo (15 ml). La capa acuosa después se extrajo de nuevo con acetato de etilo (15 ml) y las capas orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío a 50°C durante una noche para producir el compuesto del título en forma de un aceite transparente (1,41 g, 97,0%). ^1H RMN (DMSO-d_6) δ 13,0 (s ancho, 1H), 11,47 (s, 1H), 7,23 (t, 1H, *J* = 8 Hz), 7,03 (d, 2H, J = 8 Hz), 6,82 (d, 1H, *J* = 2 Hz), 6,75 (m, 5H), 4,73 (s, 2H), 3,70 (s, 3H), 3,35 (s ancho, 1H), 2,48 (t, 2H, *J* = 8 Hz), 2,36 (t, 2H, *J* = 8 Hz), 1,80 (quint., 2H, *J* = 7 Hz), 1,46 (s, 6H); ^{13}C RMN (DMSO-D_6, 20°C) δ 175,8, 160,0, 155,0, 154,1, 146,8, 139,8, 135,0, 130,3, 129,7, 120,1, 119,1, 113,8, 113,2, 78,9, 55,6, 47,8, 40,6, 40,5, 34,0, 28,4, 27,5, 26,2, 25,7; IR ($CHCl_3$) 1707, 1603, 1509, 1159 cm^{-1}; Análisis calculado para $C_{23}H_{27}N_3O_5$: C, 64,93; H, 6,40; N, 9,88. Encontrado: C, 65,02; H, 6,65; N, 9,57.

Ejemplo 117



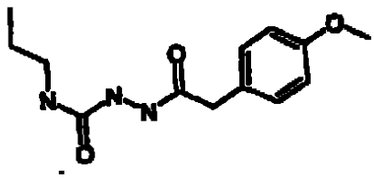
Etapa A:



Una solución en metanol de 4-metoxifenilacetato de metilo (Aldrich, 10,0 g, 0,056 mol) e hidrato de hidrazina (EM Sciences, 27,8 g, 0,556 mol) se agitó a temperatura ambiente durante una noche. La solución resultante se concentró, se añadió a agua y se extrajo con acetato de etilo (2 X). Las capas orgánicas se combinaron y se lavaron con salmuera acuosa y después se secaron sobre sulfato sódico. La evaporación del disolvente da un producto sólido que se lava con hexanos/éter y se filtra para dar la acil hidrazida deseada en forma de un sólido blanco.

$C_9H_{12}O_2N_2$ (PM = 180,21); espectrometría de masas (MH^+) = 181,0

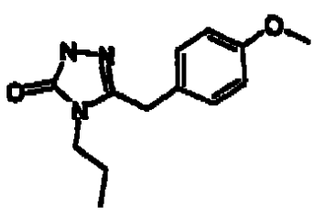
Etapa B:



Una solución en tetrahidrofurano (150 ml) de la acil hidrazida de la Etapa A (7,0 g, 0,044 mol) se trató con isocianato de propilo (Aldrich, 1,2 g, 0,014 mol) y se agitó a temperatura ambiente durante una noche, tiempo durante el cual se formó un precipitado. La suspensión resultante se trató con metanol (20 ml) y se agitó durante 30 minutos más. Después se añadió hexano y la mezcla se filtró para dar la acil semicarbazida deseada en forma de un sólido blanco que se usó sin purificación adicional.

$C_{13}H_{19}N_3O_3$ (PM = 265,31).

Etapa C:

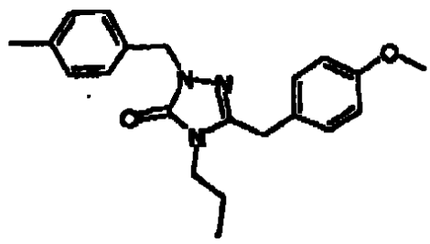


Una solución en metanol (150 ml) de la acil semicarbazida de la **Etapa B** (10,0 g, 0,038 mol) se agitó y se trató con hidróxido potásico sólido (21,1 g, 0,377 mol). La mezcla se calentó a 60°C durante 24 horas y después se enfrió a temperatura ambiente y se agitó durante 48 horas. El disolvente se redujo a

aproximadamente 75 ml, se añadió a agua, se acidificó a pH 6 con HCl concentrado y se extrajo con acetato de etilo (3 X). Las capas orgánicas se combinaron, se lavaron con salmuera acuosa y se secaron sobre sulfato sódico. La evaporación del disolvente dio un sólido que se lavó con hexano/éter, dando la N4-propil triazolinona deseada en forma de un sólido blanco.

$C_{13}H_{17}N_3O_2$ (PM = 247,30); espectroscopía de masas (MH+) = 248,1

Etapa D:

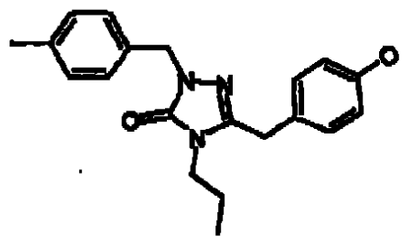


La N4-propil triazolinona de la **Etapa C** (7,0 g, 0,028 mol) se disuelve en DMF (75 ml) y se trata con cloro-*p*-xileno (Aldrich, 6,0 g, 0,043 mol) y carbonato potásico en polvo (Aldrich, 15,6 g, 0,113 mol). La mezcla resultante se calentó a 60°C durante una noche. La mezcla de reacción fría se añadió a HCl acuoso (1 N, 200 ml) y se extrajo con acetato de etilo (3 X). Las capas orgánicas combinadas se lavaron con salmuera acuosa, se secaron sobre sulfato sódico y se concentraron para dar el producto bruto en forma de un aceite. La purificación por cromatografía ultrarrápida (gradiente: hexano al 100% a 2:1 de

hexanos:acetato de etilo) da la N2-*p*-metilbencil triazolilona deseada.

$C_{21}H_{25}N_3O_2$ (PM = 351,45); espectrometría de masas (MH+) = 352,2

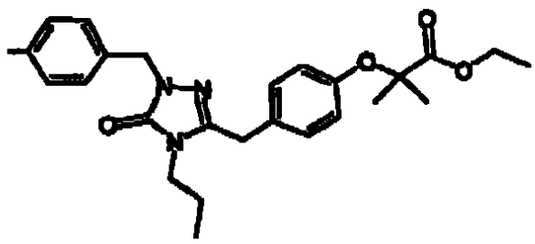
Etapa E:



La N2-*p*-metilbencil triazolinona de la **Etapa D** (1,5 g, 0,004 mol) se disolvió en cloruro de metileno (25 ml) y se enfrió en un tubo de secado. Se añadió gota a gota una solución de tribromuro de boro (3,1 g, 1,2 ml, 0,013 mol). La mezcla de reacción después se dejó calentar a temperatura ambiente y se agitó durante 2 horas. La reacción se interrumpió por la adición gota a gota de metanol (5 ml), se añadió a agua y se extrajo con cloruro de metileno (2 X). Las capas orgánicas se combinaron, se secaron sobre sulfato sódico y se concentraron para dar el fenol deseado en forma de un aceite que se usó sin purificación.

$C_{20}H_{23}N_3O_2$ (PM = 337,4); espectrometría de masas (MH^+) = 338,3.

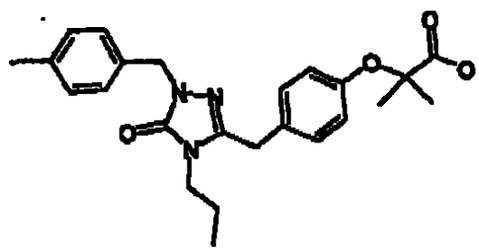
Etapa F:



Se disolvió el fenol de la **Etapa E** (1,3 g, 0,004 mol) en etanol (50 ml) y se trató con 2-bromoisobutirato de etilo (Aldrich, 2,3 g, 1,7 ml, 0,012 mol), carbonato potásico en polvo (Aldrich, 2,2 g, 0,016 mol) y sulfato de magnesio (0,6 g, 0,005 mol). La mezcla resultante se agitó y se calentó a 55°C, en un tubo de secado, durante una noche. La mezcla de reacción fría se añadió a HCl (5 N, 70 ml) y se extrajo con acetato de etilo (2 X). Las capas orgánicas combinadas se secaron sobre sulfato sódico y se concentraron para dar el producto bruto. La purificación por cromatografía ultrarrápida (gradiente: hexanos al 100% a 3:2 de acetato de etilo:hexano) da el éster etílico deseado.

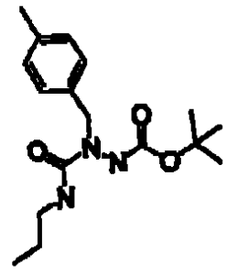
$C_{26}H_{33}N_3O_4$ (PM =) 451,6); espectrometría de masas (MH^+) = 452,3.

Etapa G:



El éster etílico de la **Etapa F** (0,8 g, 0,002 mol) se disolvió en metanol (12 ml) y se añadió hidróxido sódico (2 N, 3,0 ml, 0,006 mol). La mezcla resultante se agitó a temperatura ambiente durante una noche. La mezcla de reacción se añadió a HCl (5 N, 15 ml) y se extrajo con acetato de etilo (2 X). Las capas orgánicas se combinaron, se secaron sobre sulfato sódico y se concentraron para dar el producto bruto. La purificación por cromatografía ultrarrápida (gradiente: hexanos al 100% a 1:1 de acetato de etilo/hexano y después metanol al 10% en acetato de etilo) da el ácido carboxílico deseado en forma de una espuma blanca.

$C_{24}H_{29}N_3O_4$ (PM = 423,5); espectrometría de masas (MH^+) = 424,3; (MH^-) = 422,1.

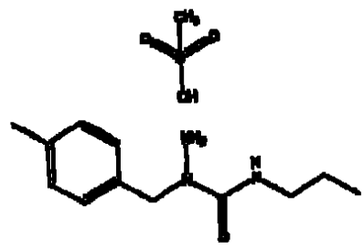


EJEMPLO 118

Ácido 2-(n-propilaminocarbonil)-2-(4-metilfenilmetil)hidrazina carboxílico, 1,1-.dimetiletil éster

Se disolvió ácido 4-metilfenilmetil hidrazina carboxílico, 1,1-dimetiletil éter (5,02 g, 21,2 mmol) en

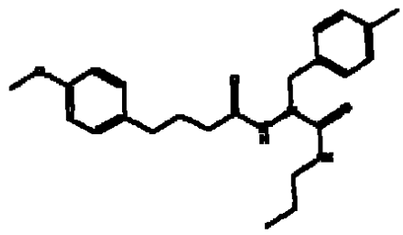
isopropanol (50 ml). Se añadió en una porción mediante una jeringa isocianato de propilo (2,71 g, 31,9 mmol) y la solución se dejó en agitación a temperatura ambiente durante 1 h. La solución se concentró para dar un aceite amarillo transparente y se purificó por cromatografía en columna (SiO_2, 2:3 de acetato de etilo:hexanos), produciendo el compuesto del título en forma de un sólido blanco (5,58 g, 82%); p.f. 87,8-89,4°C; ^{1}H RMN (DMSO-d_6, 60°C) δ 8,45 (s, 1H), 7,10 (d-d, 4H, J = 8,2 Hz), 6,21 (s, 1H), 4,43 (s, 1H), 3,01 (c, 2H, J = 6,4 Hz), 2,27 (s, 3H), 1,41 (sext., 2H, J = 7,3 Hz), 1,35 (s, 9H), 0,82 (t, 3H, J = 7,4 Hz); ^{13}C RMN (DMSO-d_6, 20°C) δ 158,6, 155,1, 136,6, 135,5, 129,3, 129,0, 80,2, 51,0, 42,2, 28,6, 23,7, 21,4, 11,8. Análisis calculado para $C_{17}H_{27}N_3O_3$: C, 63,53; H, 8,47; N, 13,07.



Metanosulfonato de N-propil-1-(4-metilfenilmetil)hidrazinacarboxamida

A una solución de ácido 2-(propilaminocarbonil)-2-(4-metilfenilmetil)hidrazinacarboxílico, 1,1-dimetiletil éster (3,0204 g, 9,397 mol) en diclorometano (25 ml) y la mezcla se agitó durante 21 h. La mezcla después se

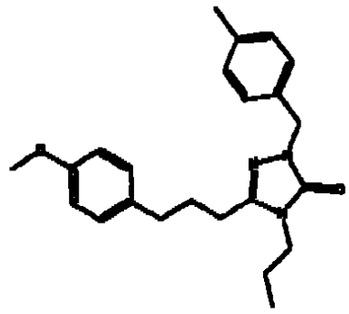
concentró al vacío para dar un aceite y se recristalizó (acetato de etilo), produciendo el compuesto del título en forma de un sólido blanco (2,0639, 6,502 mol, 69%): p.f. 108,5-111,4°C; ^{1}H RMN (DMSO-d_6) δ 7,56 (s, 1H), 7,18 (s, 4H), 4,67 (s, 2H), 3,06 (t, 2H, *J* = 7,0 Hz), 2,35 (s, 3H), 2,81 (s, 3H), 1,44 (m, 2H), 0,82 (t, 3H, *J* = 7,5 Hz); ^{13}C RMN (DMSO-d_6) δ 157,7, 138,0, 132,5, 129,9, 128,8, 52,7, 42,7, 40,6, 23,3, 21,4, 11,9; IR ($CHCl_3$) 3416, 3009, 2967, 2936, 2877, 1691, 1543 cm^{-1}. Análisis Calculado para $C_{12}H_{19}N_3O \cdot CH_4O_3S$: C, 49,19; H, 7,30; N, 13,24. Encontrado: C, 48,87; H, 7,32; N, 13,28.



1-[(4-Metoxifenil)butiril]-2-(4-metilfenilmetil)-4-propil)semicarbazida

A una solución de ácido 4-(4-metoxifenil)butírico (2,0207 g, 10,42 mmol) y *N,N*-dimetilformamida (2 gotas) en acetato de etilo (25 ml) se le añadió gota a gota durante 5 minutos cloruro de oxalilo (1,13 ml, 13,02 mmol). La mezcla resultante se agitó durante 30 minutos y después se concentró al vacío para retirar el exceso de cloruro de oxalilo. El aceite resultante se redisolvió en acetato de

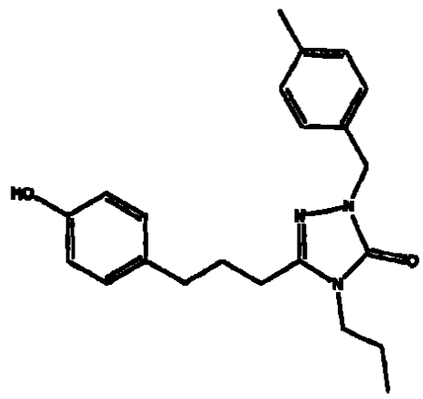
etilo (15 ml) y después se añadió en una porción a una solución de metanosulfonato de *N*-propil-2-(4-metilfenilmetil)hidrazinacarboxílico (3,1578 g, 9,95 mmol) y piridina (2 ml, 24 mmol) en acetato de etilo (10 ml) a 0-5°C. La reacción se agitó durante 1 hora a temperatura ambiente, después se lavó con HCl 1 N (2 x 50 ml), $NaHCO_3$ acuoso saturado (2 x 50 ml) y NaCl acuoso saturado (25 ml). La capa orgánica se secó ($MgSO_4$), se filtró, se concentró y se purificó por cromatografía en gel de sílice (3:1 de acetato de etilo:hexanos), produciendo el compuesto del título en forma de un sólido blanco (3,76 g, 9,47 mmol, 95%): p.f. 86,5-88,2°C; ^1H RMN (DMSO-d_6, 60°C) δ (9,45 (s, 1H), 7,10 (m, 4H), 6,92 (AB, 4H, *J* = 8,0 Hz), 6,25 (s, 1H), 4,50 (s, 1H), 3,71 (2, 3H), 2,99 (m, 2H), 2,45 (t, 2H, *J* = 8,0 Hz), 2,26 (s, 3H), 1,40 (m, 2H), 0,81 (t, 3H, *J* = 8,0 Hz); ^{13}C RMN (DMSO-d_6) δ 172,0, 158,2, 158,1, 136,7, 135,8, 134,1, 129,9, 129,4, 128,9, 114,3, 55,6, 50,8, 42,3, 34,3, 33,4, 27,3, 23,7, 21,4, 11,9; IR ($CHCl_3$) 3456, 2996, 2963, 2936, 2876, 1708, 1669 cm^{-1}. Análisis calculado para $C_{23}H_{31}N_3O_3$: C, 69,49; H, 7,86; N, 10,57. Encontrado: C, 69,36; H, 7,71; N, 10,54.



5-[3-(4-Metoxifenil)-propil]-2-(4-metilbencil)-4-propil-2,4-dihidro[1,2,4]triazol-3-ona

A una solución de 1-[(4-metoxifenil)butiril]-2-(4-metilfenilmetil)-4-propil)semicarbazida (1,24 g, 3,12 mmol) en acetato de etilo (25 ml) se le añadió ácido canforsulfónico (0,80 g, 3,43 mmol) y la mezcla resultante se agitó a reflujo durante 2 horas. La capa orgánica se lavó con $NaHCO_3$ acuoso saturado (2 x 125 ml) y HCl 1 N (2 x 25 ml) seguido de NaCl acuoso saturado (25 ml). Después, la capa orgánica se secó ($MgSO_4$), se filtró y se concentró, produciendo el compuesto del título en forma de un aceite (1,14 g, 3,00 mmol, 96%): ^1H RMN (DMSO-d_6) δ 7,10 (s, 4H), 7,06 (d, 2H, J = 8,5 Hz), 6,81 (c, 2H, J = 5,0 Hz), 4,27 (s, 2H), 3,69 (s, 3H), 3,46 (t, 2H, J = 7,5 Hz), 2,54 (t, 2H, 7,5 Hz), 2,47 (t, 2H, J = 7,5 Hz), 2,23 (s, 3H), 1,82 (m, 2H), 1,52 (m, 2H), 0,79 (t, 3H, J = 7,5 Hz); ^{13}C RMN (DMSO-d_6) δ 158,2, 154,1, 146,8, 137,2, 135,1, 133,9, 129,9, 129,7, 128,1, 114,4, 55,6, 48,3, 42,8, 34,0, 28,1, 24,8, 22,5, 21,3, 11,5; IR ($CHCl_3$) 1691, 1513, 1465, 1247,

1225 cm^{-1}. Análisis calculado para $C_{23}H_{29}N_3O_2$: C, 72,79; H, 7,70; N, 11,07. Encontrado: C, 72,82; H, 7,87; N, 11,11.

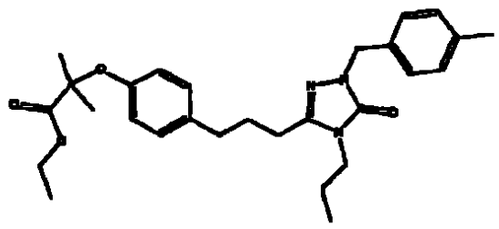


Ejemplo 119

5-[3-(4-Hidroxifenil)propil]-2-(4-metilbencil)-4-propil-2,4-dihidro-[1,2,4]-triazol-3-ona. Se fundieron conjuntamente 5-[3-(4-metoxifenil)propil]-2-(4-metilbencil)-4-propil-2,4-dihidro[1,2,4]triazol-3-ona (0,770 g, 2,03 mmol) y clorhidrato de piridina en exceso durante 2 horas con agitación a 180°C. Después de enfriar a temperatura ambiente, los contenidos se diluyeron en acetato de etilo (50 ml) y agua (50 ml). La fase acuosa se extrajo con acetato de etilo (2 x 25 ml). Las fracciones orgánicas combinadas se lavaron con HCl 5 N (50 ml), NaCl acuoso saturado (25 ml), se secaron ($MgSO_4$), se filtraron y se concentraron, proporcionando el compuesto del título en forma de un aceite amarillo (0,670 g, 1,83 mmol, 90%): ^{1}H-RMN (DMSO-d_6) δ 9,13 (s, 1H), 7,10 (c, 4H, J= 3,0 Hz), 6,79

(AB, 4H, *J*= 8,5 Hz), 4,77 (s, 2H), 2,5 (t, 2H, *J*= 7,5 Hz), 2,46 (t, 2H, *J*= 7,5 Hz), 2,24 (s, 3H), 1,79 (m, 2H), 1,51 (m, 2H), 0,79 (t, 3H, *J*= 7,5 Hz); ^{13}C-RMN (DMSO-d_6) δ 156,1, 154,1, 146,8, 137,2, 135,1, 132,1, 129,9, 129,7, 128,1, 115,7, 48,3, 42,8, 34,1, 28,2, 24,7, 22,5, 21,3, 11,5; IR ($CHCl_3$) 3007, 2937, 1690, 1515, 1463 cm^{-1}. Masa exacta calculada para $C_{22}H_{28}N_3O_2$: 366,2182. Encontrada: 366,2191.

Ejemplo 120



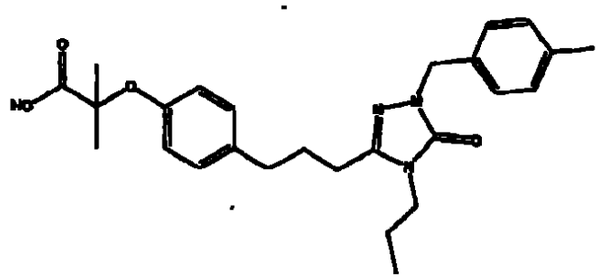
Éster etílico del ácido 2-metil-2-(4-{3-[1-(4-metilbencil)-5-oxo-4-propil-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)propiónico. Se añadió 5-[3-(4-hidroxifenil)propil]-2-(4-metilbencil)-4-propil-2,4-dihidro-[1,2,4]triazol-3-ona (1,2 g, 3,28 mmol) en etanol (10 ml) a una mezcla de etóxido de sodio (1,22 ml, 3,28 mmol) y acetato de etilo (322 µl, 3,28 mmol), y la mezcla resultante se agitó a reflujo durante 1 hora. Después, se añadió isobutirato de etil-2-butilo (1,08 ml, 7,38 mmol) y la reacción continuó a reflujo durante 1 hora. Después, se añadió gota a gota etóxido de sodio (1,22 ml, 3,28 mmol) durante 5 minutos, y la reacción continuó a reflujo durante 4,5 horas. Se añadieron etóxido de sodio (520 µl,

1,4 mmol) e isobutirato de etil-2-butilo (205 µl, 1,4 mmol) adicionales y la reacción continuó a reflujo durante 4 horas. Se añadieron etóxido de sodio (336 µl, 0,903 mmol) e isobutirato de etil-2-butilo (132 µl, 0,903 mmol) adicionales y la reacción continuó a reflujo durante 3 horas. Finalmente, se añadieron etóxido de sodio (200 µl, 0,54 mmol) e isobutirato de etil-2-butilo (100 µl, 0,133 mmol) adicionales y la reacción continuó a reflujo durante 1,5 horas. La mezcla se permitió enfriar hasta temperatura ambiente y se inactivó después en una solución de HCl concentrado (1,5 g, 41 mmol) en agua (50 ml). La solución resultante se concentró después a vacío, se recogió en acetato de etilo (100 ml) y se desechó la fase acuosa. La fase orgánica se lavó con $NaHCO_3$ acuoso saturado (2 x 50 ml) seguido de NaCl acuoso saturado (2 x 25 ml). La fase orgánica se secó ($MgSO_4$), se filtró, se concentró y se purificó por cromatografía en gel de sílice (acetato de etilo:hexanos 1:1), proporcionando el compuesto del título en forma de un aceite amarillo (990 mg, 2,06 mmol, 63%).

^{1}H-RMN (DMSO-d_6) δ 7,10 (s, 4H), 6,87 (AB, 4H, *J*= 8,0 Hz), 4,77 (s, 2H), 4,14 (c, 2H, *J*= 7,0 Hz), 3,46 (t, 2H, *J*= 6,5 Hz), 2,54 (t, 2H, *J*= 7,5 Hz), 2,47 (t, 2H, *J*= 7,5 Hz), 2,24 (s, 3H), 1,82 (m, 2H), 1,51 (m, 2H), 1,47 (s, 6H), 1,14 (t, 3H, *J*= 7,5 Hz), 0,79 (t, 3H, *J*= 7,0 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 154,1, 153,8, 146,7, 137,2, 135,6,

135,1, 129,75, 129,66, 128,1, 119,6, 79,2, 61,6, 48,3, 42,8, 34,0, 27,8, 25,7, 24,8, 22,5, 21,3, 14,5, 11,5; IR ($CHCl_3$) 3005, 2939, 2878, 1729, 1692, 1509 cm^{-1}. Anal. calculado para $C_{28}H_{37}N_3O_4$: C 70,12, H 7,78, N 8,76. Encontrado: C 69,92, H 7,84, N 8,77.

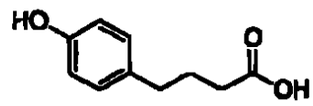
Ejemplo 121



Se añadió NaOH 1 N (2 ml, 2 mmol) con agitación a temperatura ambiente durante 18 horas a una solución de éster etílico del ácido 2-metil-2-(4-{3-[1-(4-metilbencil)-5-oxo-4-propil-4,5-dihidro-1*H*-[1,2,4]triazol-3-il)propil}-fenoxi)propiónico (0,45 g, 0,938 mmol) en metanol (7 ml). La mezcla de reacción se concentró hasta una película delgada y se repartió entre acetato de etilo (25 ml) y HCl 1 N (25 ml). La fase orgánica se lavó con NaCl acuoso saturado (25 ml), se secó ($MgSO_4$), se filtró y se concentró, proporcionando el compuesto del título en forma de un sólido amarillo (0,400 g, 0,886 mmol, 94%): pf: 94,0-96,5°C; ^{1}H-RMN (DMSO-d_6) δ 12,92 (s a, 1H), 7,10 (s, 4H), 6,88 (AB, 4H, *J*= 8,5 Hz), 4,77 (s, 2H), 3,46 (t, 2H, *J*= 7,5 Hz), 2,54 (t, 2H, *J*= 7,5 Hz), 2,48 (m, 2H),

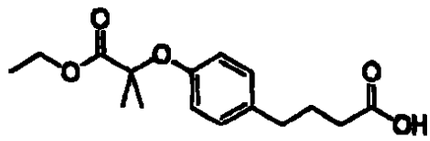
2,24 (s, 3H), 1,82 (m, 2H), 1,52 (t, 2H, *J*= 7,5 Hz), 1,46 (s, 6H), 0,79 (t, 3H, *J*= 8,0 Hz); ^{13}C-RMN (DMSO-d_6) δ 175,8, 154,1, 146,8, 137,2, 135,2, 135,1, 129,7, 128,1, 119,3, 79,0, 60,4, 48,3, 42,8, 34,0, 27,9, 25,7, 24,8, 22,5, 21,3, 14,8, 11,5; IR ($CHCl_3$) 3007, 2939, 2878, 1692, 1573, 1508 cm^{-1}; anal. calculado para $C_{26}H_{33}N_3O_4$: C 69,16, H 7,37, N 9,31. Encontrado: C 68,90, H 7,55, N 9,14.

Ejemplo 122



Ácido 4-(4-hidroxifenil)butírico. Se equipó un matraz de fondo redondo de 4 bocas de 22 l con un condensador, una entrada de nitrógeno, una sonda termométrica y un dispositivo de agitación suspendido. El matraz se cargó con ácido 4-(4-metoxifenil)butírico (2250 g, 11,58 moles), seguido de clorhidrato de piridina (5360 g, 46,34 moles, 4 eq.). La mezcla resultante de los dos sólidos se calentó en atmósfera de nitrógeno a 185-195°C con agitación empezando a 50°C. Los contenidos del matraz se mantuvieron a 185-195°C, y se controló el progreso de la reacción por TLC (hexanos/acetato de etilo 50/50, v/v + ácido acético al 1%, v/v con tinción con *p*-anisaldehído para visualización). Después de dos horas, el análisis por TLC indicó el consumo completo del material de partida. La fuente de calor se retiró y la mezcla se permitió enfriar

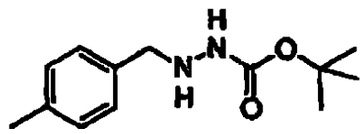
hasta 90°C, después de lo cual se añadieron secuencialmente HCl 5 N (2900 ml, 14,47 moles, 1,25 eq.) y H_2O (2700 ml). Se continuó la agitación hasta que la temperatura del matraz alcanzó 35°C. La mezcla se transfirió a un matraz de 22 l con salida inferior, y se diluyó con *terc*-butilmetiléter (MTBE, 6000 ml). Las fases se separaron y la porción acuosa se reextrajo con MTBE (3 x 4000 ml). Las porciones orgánicas se combinaron y se volvieron a lavar con HCl 5 N (750 ml). Después de secar (Na_2SO_4) y filtrar, la solución se concentró a vacío, proporcionando el compuesto del título en forma de un sólido blanco (2020 g, 96,7%). ^{1}H-RMN (500 MHz, DMSO-d_6) δ 1,70 (m, 2H), 2,15 (t, 2H), 2,45 (t, 2H), 3,33 (s, 1H), 6,65 (d, 2H), 6,95 (d, 2H). ^{13}C-RMN (DMSO-d_6) δ 26,5, 32,5, 33,5, 114,6, 129,0, 131,2, 155,3, 174,2.



Ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butírico. Se equipó un matraz de fondo redondo de 3 bocas de 12 l con un dispositivo de agitación accionado por aire suspendido, un condensador, una entrada de nitrógeno, un termómetro/termopar y una manta calefactora. El matraz se cargó con acetato de etilo (450 ml) y etóxido de sodio al 21% (en peso) en solución de etanol (3318 ml, 8,87 moles,

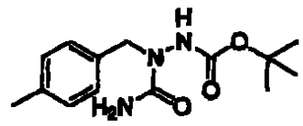
2 eq.). La mezcla resultante se calentó a reflujo en atmósfera de nitrógeno y se mantuvo a reflujo durante 30 minutos. La mezcla se permitió enfriar después ligeramente por debajo del reflujo, y se añadió ácido 4-(4-hidroxifenil)butírico (800 g, 4,43 moles). Los contenidos del matraz se recalentaron a reflujo durante 30 minutos, en cuyo punto se añadió 2-bromoisobutirato de etilo (EBIB, 1954 ml, 13,32 moles, 3,0 eq.). Después de 1 hora a reflujo, el matraz se equipó con un embudo de adición de 2 l, que se cargó con etóxido de sodio en solución de etanol (1660 ml, 4,43 moles, 1 eq.). la solución de etóxido de sodio se añadió gota a gota a la reacción a reflujo durante 1 hora. Después de 30 minutos adicionales a reflujo, el análisis por HPLC mostró que la reacción se había completado. La fuente de calor se retiró y los contenidos del matraz se enfriaron a 5-10°C y después se transfirieron a un matraz de 22 l con salida inferior. Agitando, la mezcla se inactivó con ácido fosfórico diluido (6000 ml), se transfirió a un matraz Buchi de 20 l y se concentró a vacío para eliminar el etanol. La mezcla acuosa resultante de cristales y EBIB en exceso se refrigeró durante una noche. Los cristales se filtraron después y se lavaron con agua (2000 ml). Los sólidos se eliminaron del embudo y se dispusieron en un matraz Buchi de 20 l equipado con un dispositivo de agitación

suspendido. Después de la adición de agua (2000 ml), los sólidos se agitaron a temperatura ambiente durante 30 minutos, después se filtraron y se lavaron con heptano (2 x 2500 ml). Los sólidos se dispusieron después en una estufa a vacío y se secaron a 45°C, proporcionando el compuesto del título en forma de un sólido blanquecino (1247 g, 95,5%). ^{1}H-RMN (500 MHz, $CDCl_3$) δ 1,25 (t, 3H), 1,57 (s, 6H), 1,92 (m, 2H), 2,35 (t, 2H), 2,60 (t, 2H), 4,23 (c, 2H), 6,76 (d, 2H), 7,03 (d, 2H). ^{13}C-RMN ($CDCl_3$) δ 14,1, 25,4, 26,3, 33,3, 34,2, 61,4, 119,4, 129,1, 134,9, 153,7, 174,4, 179,7.



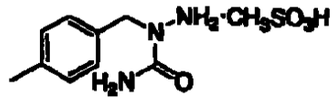
Éster 1,1-dimetiletílico del ácido (4-metilbencil)hidrazinocarboxílico. Se cargó carbazato de *terc*-butilo (1,25 kg, 9,46 mol) seguido de isopropanol (2 l) en atmósfera de nitrógeno en un autoclave de acero inoxidable de 37,85 l que contenía isopropanol (10 l). Los contenidos se agitaron y calentaron a 35°C durante 30 minutos, después se añadió 4-metilbenzaldehído (1,142 kg, 9,51 mol) seguido de isopropanol (0,3 l). Los contenidos se calentaron a 45°C, y se añadió una suspensión de Pd/C al 5% (0,3 kg) en agua (0,3 l) e isopropanol (4 l), seguida de lavados con isopropanol (2 x 1 l). Los

contenidos se hidrogenaron a 276 kPa y 45°C durante 4 horas, después se añadió una segunda carga de Pd/C al 5% (0,3 kg) en agua (0,3 l) e isopropanol (4 l), seguida de lavados con isopropanol (2 x 1 l). La hidrogenación se continuó a 276 kPa y 45°C durante 14 horas, cuando la reacción se determinó que se había completado por HPLC. Los contenidos se enfriaron después a 15°C y se filtraron, y la torta de filtro se lavó con isopropanol (15 l). El filtrado se concentró a vacío, proporcionando el compuesto del título (1,97 kg, 88,2%) en forma de una solución al 33,8% en peso en isopropanol.



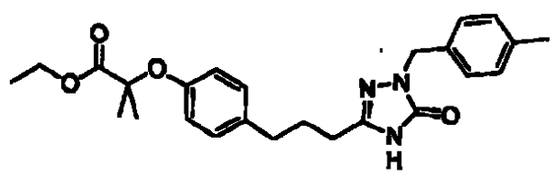
Éster 1,1-dimetiletílico del ácido 2-(aminocarbonil)-2-(4-metilfenilmetil)-hidrazinocarboxílico. Se equipó un matraz de 4 bocas de 22 litros con un dispositivo de agitación suspendido, un baño refrigerante, una sonda termométrica y un embudo de adición de 2 l. El matraz se cargó con una solución de éster 1,1-dimetiletílico del ácido (4-metilbencil)hidrazinocarboxílico en isopropanol (4988 g de una solución al 31,73% p/p, 1583 g, 6,70 moles). Se añadió isopropanol adicional (3130 ml) para diluir la solución hasta un volumen total de 8933 ml. Se cargó isocianato de trimetilsililo (1179 ml, 8,71 mol, 1,3 eq.) al embudo de

adición de 2 l y se añadió gota a gota a la solución de reacción agitando durante 45 minutos, manteniendo la temperatura entre 15-25°C utilizando un baño de agua fría. Se controló el progreso de la reacción por TLC (hexano/acetato de etilo 50/50, v/v, I_2; Rf (sm)= 0,6, Rf (prod)= 0,1). Después de agitar durante una noche a temperatura ambiente, la TLC indicó que la reacción se había completado esencialmente. La mezcla de reacción se trató con heptano (7800 ml), se enfrió a 5-10°C y se agitó durante 0,5 horas. La mezcla se filtró y la torta se lavó con heptano (2 x 1000 ml). El material se secó en una estufa a vacío a 30-35°C, proporcionando el compuesto del título en forma de un sólido blanco (1423 g, 96%). ^{1}H-RMN (DMSO-d_6, 300 MHz): δ 1,35 (s, 9H), 2,26 (s, 1H), 4,45 (s a, 2H), 6,06 (s, 2H), 7,10 (s, 4H), 8,88 (s a, 1H); anal. calculado para $C_{14}H_{21}N_3O_3$: C 60,20, H 7,58, N 15,04. Encontrado: C 59,65, H 7,34, N 14,87.



Metanosulfonato de 1-(4-metilfenilmetil)hidrazinocarboxamida. Se equipó un matraz de 4 bocas de 22 l con un dispositivo de agitación suspendido, un baño de calentamiento/refrigeración, una sonda termométrica, un condensador y un embudo de adición de 500 ml. El matraz se cargó con éster 1,1-dimetiletílico

del ácido 2-(aminocarbonil)-2-(4-metilfenilmetil)hidrazino-carboxílico (1100 g, 3,94 moles) y diclorometano (12 l). La mezcla se calentó a 30-35°C para disolver completamente todos los sólidos, después se enfrió a 25-30°C y se añadió ácido metanosulfónico (MsOH) (398 g, 4,14 moles) durante 30 minutos. El baño de agua se reemplazó por una manta calefactora, la solución de reacción se calentó a reflujo durante 12-20 horas, y se controló por análisis TLC (acetato de etilo al 100%; I_2, Rf (sm)= 0,3, Rf (prod)= 0,1). Cuando se completó, la mezcla de reacción se diluyó con heptano (4000 ml), se enfrió a 10-20°C y se agitó durante 30 minutos. Después de la filtración, la torta se lavó con heptano (2 x 1000 ml) y se secó a vacío a 35-45°C, proporcionando el compuesto del título en forma de un sólido blanco (1070 g, 98,6%). ^{1}H-RMN (DMSO-d_6, 300 MHz): δ 1,35 (s, 9H), 2,26 (s, 1H), 4,45 (s a, 2H), 6,06 (s, 2H), 7,10 (s, 4H), 8,88 (s a, 1H). Anal. calculado para $C_{10}H_{17}N_3O_4S$: C 43,62, H 6,22, N 15,26, S 11,64. Encontrado: C 43,33, H 6,21, N 14,97.

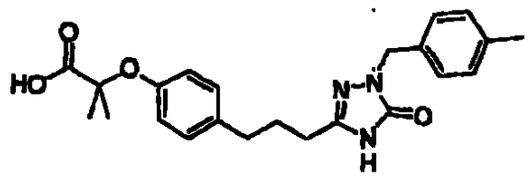


Éster etílico del ácido 2-(4-{3-[1-(4-metilfenilmetil)-4-metil-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Se equipó un matraz

de 4 bocas de 22 l con un termómetro/termopar, un embudo de adición, un dispositivo de agitación suspendido, una entrada de nitrógeno y un baño de refrigeración. El matraz se cargó con ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)-fenil]butírico (1250 g, 4,247 moles), acetato de etilo (11,250 ml) y DMF (16,4 ml) y la mezcla resultante se agitó para disolver los sólidos. Se añadió gota a gota cloruro de oxalilo (426 ml, 4,88 moles, 1,15 eq.) a la mezcla de reacción durante 45 minutos, utilizando un baño de agua para mantener la temperatura por debajo de 30°C. La mezcla de reacción se concentró después a vacío para eliminar tanto el disolvente como el cloruro de oxalilo en exceso, proporcionando cloruro del ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butírico bruto. Se equipó un matraz de 4 bocas de 22 l separado con un termómetro/termopar, un embudo de adición, una entrada de nitrógeno, un dispositivo de agitación suspendido y un baño de refrigeración. El matraz se carbón con metanosulfonato de 1-(4-metilfenilmetil)hidrazinocarboxamida (1169 g, 4,247 moles, 1 eq.), acetato de etilo (8750 ml) y piridina (790 ml, 9,77 moles, 2,3 eq.). Los contenidos del matraz se enfriaron a 0-5°C. El cloruro de ácido bruto se disolvió en acetato de etilo (1000 ml) y se añadió gota a gota a la mezcla que contenía metanosulfonato de 1-(4-

metilfenilmetil)hidrazino-carboxamida durante 20 minutos, manteniendo la temperatura del matraz por debajo de 25°C. La mezcla resultante se agitó a temperatura ambiente durante 1 hora, después se añadió ácido (±)-canfosulfónico (1973 g, 8,494 moles, 2 eq.). Los contenidos del matraz se calentaron después a reflujo durante 16 horas. La reacción se enfrió a 20°C y se transfirió a un matraz que contenía HCl 1 N (7500 ml). Después de agitar, las fases se separaron y la fase orgánica se lavó con una solución saturada de Na_2CO_3 (7500 ml) y agua (1000 ml), después se secó sobre $MgSO_4$. La solución de acetato de etilo se transfirió a un matraz de 4 bocas equipado con un condensador, una entrada de nitrógeno, un termómetro/termopar y una manta calefactora. El matraz se cargó con resina Amberlyst-15 (1975 g) y la mezcla se calentó a reflujo durante 1 hora. Después de enfriar a 20°C, el material se filtró para eliminar la resina y la resina se lavó con acetato de etilo (2 x 2000 ml). El filtrado se concentró a vacío, proporcionando un sólido de color tostado. Se añadió MTBE (5000 ml) al material bruto y la mezcla se calentó a 45-50°C hasta que se disolvieron todos los sólidos. Agitando lentamente el matraz, la solución se permitió enfriar, tras de lo cual apareció cristalización. La suspensión se enfrió a 0-5°C durante 1 hora, se filtró, se lavó con MTBE frío (1500 ml) y se secó

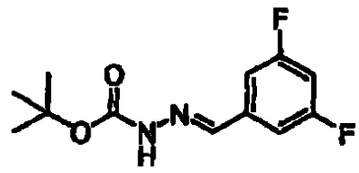
a vacío a 45°C, proporcionando el compuesto del título en forma de un sólido blanco (1027 g, 55,2%). ^{1}H-RMN (500 MHz, DMSO-d_6) δ 1,14 (t, 3H), 1,47 (s, 6H), 1,76 (m, 2H), 2,26 (t, 2H), 2,49 (t, 2H), 3,55 (s, 3H), 4,15 (c, 2H), 6,69 (d, 2H), 7,05 (d, 2H). ^{13}C-RMN ($CDCl_3$) δ 14,0, 21,0, 25,3, 26,1, 28,1, 34,1, 48,3, 61,2, 79,0, 119,3, 127,8, 128,1, 129,0, 129,3, 133,2, 134,8, 137,5, 147,2, 148,3, 153,6, 155,8, 174,3.



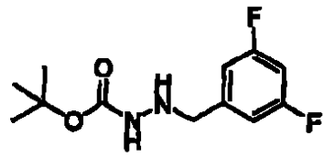
Ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metilpropanoico. Se equipó un matraz de 4 bocas con un dispositivo de agitación suspendido y una sonda termométrica. El matraz se cargó con éster etílico del ácido 2-(4-{3-[1-(4-metilfenilmetil)-4-metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónio (800 g, 1,828 moles) y tolueno (4000 ml) seguido de NaOH 1 N (4023 ml, 2,194 mol, 1,2 eq.). La mezcla resultante se agitó a temperatura ambiente durante 5 horas. La mezcla se transfirió a un matraz de 22 l con salida inferior y se separaron las fases. La fase acuosa de la separación de fases anterior se cargó al matraz y se acidificó a pH 2 con HCl concentrado (337 ml). Se añadió acetato de etilo

(8000 ml) y la mezcla se transfirió a un matraz de 22 l con salida inferior. Las fases se separaron y la solución orgánica se transfirió a un matraz de fondo redondo de 3 bocas de 22 l equipado con una cabeza de destilación y un dispositivo de agitación suspendido. La mezcla se concentró por destilación del acetato de etilo hasta aproximadamente 4000 ml, y se añadió acetato de etilo fresco (3600 ml) al recipiente de reacción. La destilación se continuó hasta que se recuperaron 3600 ml de destilado. Se detuvo el calentamiento y la mezcla se permitió enfriar lentamente hasta 60-65°C, en cuyo punto se añadieron cristales de siembra (0,8 g) del producto deseado. Los contenidos del matraz se permitieron enfriar lentamente hasta que se inició la cristalización (55-57°C), después la mezcla se enfrió a 0-5°C y se agitó durante 1 hora. El producto se filtró, se lavó con acetato de etilo frío y se secó a vacío a 55°C, proporcionando el compuesto del título en forma de un sólido blanco (713,6 g, 95,3%). ^{1}H-RMN (DMSO-d_6, 500 MHz): δ 1,46 (s, 6H), 1,79 (m, 2H), 2,25 (s, 3H), 2,35 (t, 2H), 2,47 (t, 2H), 4,70 (s, 2H), 6,71 (d, 2H), 7,03 (d, 2H), 7,10 (m, 4H). ^{13}C-RMN (DMSO-d_6) δ 20,6, 25,0, 25,5, 27,7, 47,0, 78,3, 118,6, 127,4, 127,7, 128,9, 128,9, 134,4, 134,5, 136,4, 145,9, 153,4, 154,3, 175,0.

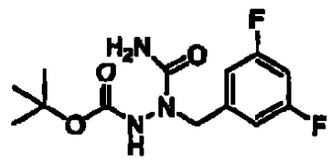
Ejemplo 123



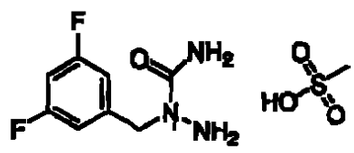
Éster 1,2-dimetiletílico del ácido (3,5-difluorofenil)metilenhidrazino-carboxílico. Se añadió con agitación 3,5-difluorobenzaldehído (5,50 g, 38,7 mmol) seguido de hexanos (50 ml) a una solución de carbazato de *terc*-butilo (4,99 g, 37,76 mmol) en acetato de etilo (10 ml). Apareció cristalización, y la suspensión resultante se agitó a ta durante 15 minutos, después se enfrió a 0°C y se mantuvo a esa temperatura durante 45 minutos. Los sólidos se filtraron, se lavaron con hexanos fríos y se secaron a vacío a 60°C, proporcionando el compuesto del título en forma de un sólido (9,04 g, 93,3%): pf: 196,4-196,8°C (desc.); ^{1}H-RMN (DMSO-d_6) δ 11,16 (s a, 1H), 7,96 (s, 1H), 7,28 (m, 2H), 7,21 (t, 1H, *J*= 2,2 Hz), 1,45 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 163,3 (dd, *J*= 246,1, 13,5 Hz), 152,9, 141,2, 139,2 (t, *J*= 9,6 Hz), 109,9 (dd, *J*= 20,2, 5,8 Hz), 105,1 (t, *J*= 25,9 Hz), 80,5, 28,7; IR (mull de KBr) 3263, 2987, 1709, 1584, 1536 cm^{-1}. Se recristalizó una porción (acetato de etilo) para análisis. Anal. calculado. para $C_{12}H_{14}F_2N_2O_2$: C 56,25, H 5,51, F 14,83, N 10,93. Encontrado: C 56,11, H 5,49, N 10,86.



Éster 1,1-dimetiletílico del ácido 2-(3,5-difluorofenilmetil)hidrazino-carboxílico. Se añadió tetrahidrofurano (70 ml) a un sustrato imina (7,00 g, 27,3 mmol) y Pt/C al 5% (5,05 g), y la suspensión resultante se hidrogenó a ta y 345 kPa. Después de 4 horas, se añadió una carga adicional de Pt/C al 5% (5,00 g) y continuó la hidrogenación durante 12 horas. Los contenidos se filtraron y se concentraron hasta un aceite, después se reconstituyeron en THF (70 ml) junto con Pt/C al 5% (5,00 g) y la hidrogenación continuó durante 60 horas a ta y 345 kPa. Los contenidos se filtraron después y se concentraron. La cromatografía con gel de SiO_2 (acetato de etilo al 20% en hexanos) proporcionó el compuesto del título en forma de un aceite (4,96 g, 19,2 mmol, 70%). ^{1}H-RMN (DMSO-d_6) δ 8,28 (s a, 1H), 7,03 (m, 3H), 5,03 (s a, 1H), 3,88 (s, 2H), 1,35 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 162,9 (dd, *J*= 243,6, 12,4 Hz), 144,9 (t, *J*= 9,6 Hz), 111,5 (d, *J*= 23,0 Hz), 102,5 (t, *J*= 25,9 Hz), 79,0, 53,9, 28,8; IR ($CHCl_3$) 3444, 2982, 2933, 1712, 1628, 1597 cm^{-1}; EMAR calculado para $C_{12}H_{16}F_2N_2O_2$ $(M + H)^+$: 259,1258. Encontrado: 259,1252.

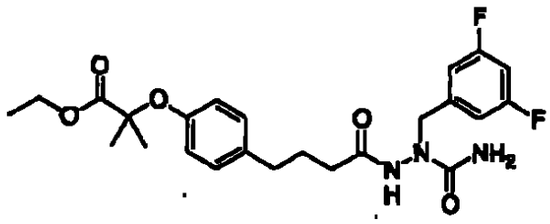


Éster 1,1-dimetiletílico del ácido 2-(aminocarbonil)-2-(3,5-difluorofenilmetil)hidrazinocarboxílico. Se añadió isocianato de trimetilsililo (1,808 g, 15,7 mmol) en una porción al sustrato difluorobencilhidrazina (2,5469 g, 9,93 mmol) en isopropanol (20 ml) a ta. La reacción se agitó a ta durante 36 horas, después se concentró hasta un sólido. La recristalización (acetato de etilo:hexanos 1:1) seguida de dilución con hexanos (100 ml) para facilitar la agitación proporcionó el compuesto del título en forma de un sólido (2,84 g, 9,43 mmol, 95%): pf: 128,7-129,9°C; ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,86 (s a, 1H), 6,97 (m, 3H), 6,00 (s, 2H), 4,52 (s, 2H), 1,36 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 162,7 (dd, *J*= 245, 13 Hz), 159,5, 155,1, 143,7 (t, *J*= 9 Hz), 111,4 (d, *J*= 23 Hz), 102,8 (t, *J*= 26 Hz), 80,4, 51,4, 28,6; IR (mull de KBr) 3540, 3227, 3004, 2988, 1744, 1682 cm^{-1}. Anal. calculado para $C_{13}H_{17}F_2N_3O_3$: C 51,82, H 5,69, N 13,95. Encontrado: C 51,59, H 5,61, N 13,81.



Metanosulfonato de 1-(3,5-difluorofenilmetil)hidrazinocarboxamida. Se añadió ácido

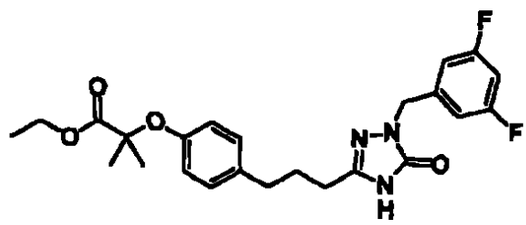
metanosulfónico (0,725 g, 6,3 mmol, 1,05 eq.) en una porción al sustrato Boc-semicarbazida (1,81 g, 6,00 mmol) en tetrahidrofurano (25 ml) a ta. La reacción se agitó a ta durante 24 horas, después se calentó a reflujo durante 22 horas. La mezcla de reacción se enfrió a ta, se filtró y la torta de filtro se lavó con diclorometano. Los sólidos se secaron a vacío durante una noche a 60°C, proporcionando el compuesto del título en forma de un sólido (1,32 g, 4,44 mmol, 74%); pf: 138,4-139,5°C (desc.); ^{1}H-RMN (DMSO-d_6, 60°C) δ 7,94 (s a, 4H), 7,10 (m, 1H), 6,98 (m, 2H), 4,70, 4,06 (s, s, 2H total, par de diastereoisómeros), 2,48, 2,41 (s, s, 3H total, par de diastereoisómeros); ^{13}C-RMN (DMSO-d_6) δ 163,6 (dd, *J*= 246, 13 Hz), 158,0, 140,9, 111,6 (dd, *J*= 20, 6 Hz), 104,0 (t, *J*= 26 Hz), 52,1; IR (mull de KBr) 3411, 3281, 3211, 1706, 1685, 1457, 1209 cm^{-1}. EMAR calculada para $C_8H_9F_2N_3O$ (M + H)$^+$: 202,0792. Encontrado: 202,0797.



1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3,5-difluorofenilmetil)-semicarbazida. Se añadieron gota a gota DMF (1 gota de pipeta), seguida de cloruro de oxalilo (0,728 g, 5,73 mmol) durante 5 minutos a ácido 4-

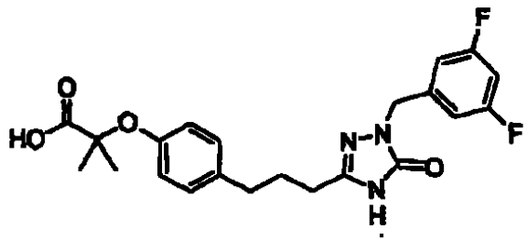
[4-(1-etoxicarbonil-1-metiletoxi)fenil]butírico (1,0072 g, 3,42 mmol) en acetato de etilo (10 ml) a ta. La solución resultante se agitó durante 30 minutos a ta, después se concentró hasta un aceite. El aceite se reconstituyó dos veces con tolueno (20 ml) y se concentró hasta un aceite, después se disolvió en acetato de etilo (3 ml). Se suspendió metanosulfonato de 1-(3,5-difluorofenilmetil)hidrazino-carboxamida (1,025 g, 3,45 mmol) en acetato de etilo (10 ml) a 0°C, y se añadió piridina (0,65 ml, 636 mg, 8,04 mmol). La solución de cloruro de ácido en acetato de etilo se añadió después gota a gota durante 15 minutos, y la mezcla resultante se agitó durante 30 minutos a 0°C. La mezcla se diluyó después con acetato de etilo y se lavó con HCl 1 N (2 x) seguido de NaCl acuoso saturado. Se secó después ($MgSO_4$), se filtró y se concentró hasta un aceite, que se cromatografió en gel de sílice (acetato de etilo), proporcionando el compuesto del título en forma de un sólido (1,1436 g, 70%): pf: 108,1-109,4°C; ^{1}H-RMN (DMSO-d_6, 60°C) δ 9,73 (s, 1H), 7,00 (m, 5H), 6,70 (d, 2H, *J*= 6,5 Hz), 6,03 (s, 2H), 4,54 (s a, 2H), 4,15 (c, 2H, *J*= 7 Hz), 2,45 (m, 2H), 2,09 (m, 2H), 1,74 (m, 2H), 1,48 (s, 6H), 1,17 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 172,0, 162,5 (dd, *J*= 244, 13 Hz), 159,2, 153,8, 144,1, 135,8, 129,7, 119,4, 111,3 (d, *J*= 25 Hz), 102,8 (t, *J*= 26 Hz),

79,2, 51,1, 47,3, 34,3, 33,1, 27,0, 25,7, 14,6; IR (KBr) 3456, 3324, 1726, 1643, 1509, 1445 cm^{-1}; anal. calculado para $C_{24}H_{29}N_3O_5F_2$: C 60,37, H 6,12, N 8,80, F 7,96. Encontrado: C 60,48, H 6,28, N 8,67, F 7,75.



Éster etílico del ácido 2-(4-{3-[1-(3,5-difluorobencil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Se añadió acetato de etilo (12 ml) al sustrato 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3,4-diclorofenilmetil)-4-(n-propil)semicarbazida (1,06 g, 2,26 mmol) y ácido canfosulfónico (0,5283 g, 2,27 mmol), y la solución resultante se calentó a reflujo durante 22 horas. La solución se diluyó con acetato de etilo, después se lavó con $NaHCO_3$ acuoso saturado, seguido de NaCl acuoso saturado. Se secó después ($MgSO_4$), se filtró y se concentró hasta un aceite, que se cromatografió después en gel de sílice (acetato de etilo:hexanos 1:1), proporcionando el compuesto del título en forma de un aceite (0,3836 g, 37%): ^{1}H-RMN (DMSO-d_6) δ 11,54 (s, 1H), 7,13 (t, 1H, *J*= 9,3 Hz), 7,04 (d, 2H, *J*= 8,5 Hz), 6,91 (d, 2H, *J*= 6,5 Hz), 6,68 (d, 2H, *J*= 8,5 Hz), 4,81 (s, 2H), 4,13 (c, 2H, *J*= 7,0

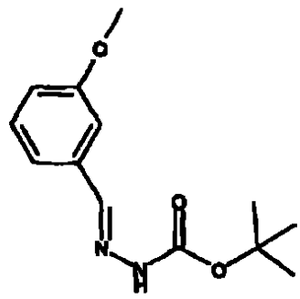
Hz), 2,49 (t, 2H, J= 7,5 Hz), 2,38 (t, 2H, J= 7,5 Hz), 1,81 (m, 2H), 1,47 (s, 6H), 1,14 (t, 3H, J= 7,0 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 162,6 (dd, J= 245, 13 Hz), 155,0, 153,8, 147,3, 142,9 (d, J= 9 Hz), 135,5, 129,8, 119,5, 111,1 (t, J= 26,6 Hz), 103,5 (t, J= 26 Hz), 79,2, 61,6, 47,1, 34,0, 28,3, 26,2, 25,7; IR ($CHCl_3$) 3004, 1727, 1695, 1601, 1509, 1464 cm^{-1}; anal. calculado para $C_{24}H_{27}F_2N_3O_4$: C 62,74, H 5,92, N 9,14. Encontrado: C 62,65, H 5,99, N 8,98.



Ácido 2-(4-{3-[1-(3,5-difluorobencil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metoxipropiónico.

Se añadió NaOH 1 N (2 ml, 2,0 mmol) al sustrato éster etílico de triazolona (0,2971 g, 0,647 mmol) en metanol (3 ml) a ta, y la mezcla resultante se agitó a ta durante 16 horas. La mezcla se acidificó después por adición de HCl 1 N y se concentró hasta un aceite, que se repartió entre acetato de etilo (35 ml) y agua (25 ml). Las fases se separaron y la fase orgánica se lavó con NaCl acuoso saturado y después se secó ($MgSO_4$), se filtró y se concentró, proporcionando el compuesto del título en forma de un aceite (0,2643 g, 95%); ^{1}H-RMN (DMSO-d_6, 60°C) δ

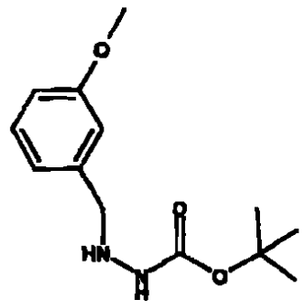
12,96 (s a, 1H), 11,54 (s, 1H), 7,13 (t, 1H, *J*= 9,5 Hz), 7,04 (d, 2H, *J*= 8 Hz), 6,91 (d, 2H, *J*= 7 Hz), 6,72 (d, 2H, *J*= 8 Hz), 4,81 (s, 2H), 2,49 (t, 2H, *J*= 7 Hz), 2,38 (t, 2H, *J*= 7 Hz), 1,82 (m, 2H), 1,46 (s, 6H); ^{13}C-RMN (DMSO-d_6) δ 175,8, 163,0 (dd, *J*= 245, 13 Hz), 155,0, 154,1, 147,3, 142,9, 135,0, 129,7, 119,2, 111,1 (m), 103,5 (t, *J*= 26 Hz), 78,9, 47,1, 34,0, 28,3, 26,2, 25,7; IR ($CHCl_3$) 3096, 3005, 2865, 1708, 1601, 1509, 1465, 1158, 1121 cm^{-1}; anal. calculado para $C_{22}H_{23}F_2N_3O_4$: C 61,25, H 5,37, N 9,74. Encontrado: C 61,21, H 5,46, N 9,48.



Ejemplo 124

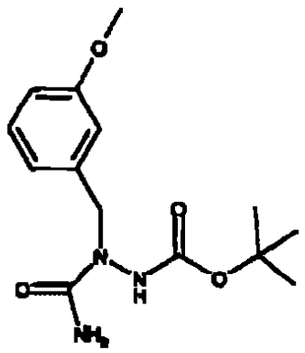
Éster 1,1-dimetiletílico del ácido (3-metoxifenil)metilenhidrazino-carboxílico. Se añadió *m*-anisaldehído (5,17 ml, 5,76 g, 42,3 mmol) con agitación a una solución de carbazato de *terc*-butilo (5,59 g, 42,3 mmol) en acetato de etilo (15 ml). Se añadieron lentamente hexanos (70 ml) y apareció cristalización. La suspensión resultante se agitó a 0°C durante 45 minutos y después se enfrió a 0°C. La suspensión se agitó a 0°C durante 60 minutos, después se filtró y se lavó con hexanos fríos (20

ml), y se secó a vacío a 40°C, proporcionando el compuesto del título en forma de un sólido (9,68 g, 91,4%): pf: 135,6-137,4°C; ^{1}H-RMN (DMSO-d_6) δ 10,93 (s, 1H), 7,29 (t, 1H, *J*= 8 Hz), 7,14 (d, 2H, *J*= 7 Hz), 6,92 (c, 1H, *J*= 7 Hz), 3,75 (s, 3H), 1,45 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 160,2, 153,1, 143,7, 136,8, 130,5, 120,0, 116,2, 111,3, 80,1, 55,7, 28,7; IR (mull de KBr) 3360, 3010, 2982, 2838, 1510, 1487 cm^{-1}. Se recristalizó una porción con acetato de etilo y se sometió a análisis elemental. Anal. calculado para $C_{13}H_{18}N_2O_3$: C 62,38, H 7,25, N 11,19. Encontrado: C 62,34, H 7,46, N 11,19.



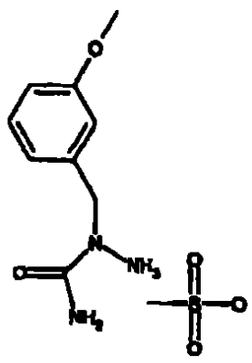
Éster 1,1-dimetiletílico del ácido (3-metoxibencil)hidrazinocarboxílico. Se suspendieron éster 1,1-dimetiletílico del ácido (3-metoxifenil)metilenhidrazino-carboxílico (7,03 g, 28,1 mmol) y Pt/C (5%, 5,07 g) en THF (80 ml), y se hidrogenó a ta y 345 kPa durante 8 horas. La suspensión se filtró después a través de celita y se concentró a vacío a 50°C, proporcionando el compuesto del título en forma de un

aceite (6,68 g, 94,0%): ^{1}H-RMN (DMSO-d_6) δ 8,22 (s, 1H), 7,19 (t, 1H, *J*= 8 Hz), 6,85 (d, 1H, *J*= 7 Hz), 6,77 (d, 1H, *J*= 7 Hz), 3,84 (s, 2H), 3,72 (s, 3H), 1,37 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 159,9, 157,1, 141,1, 129,7, 121,1, 114,1, 113,1, 78,9, 55,5, 54,9, 28,9; IR ($CHCl_3$) 3008, 2982, 2935, 1712 cm^{-1}; masa exacta: calculada para $C_{13}H_{20}N_2O_3Na$: 275,1372, encontrada: 275,1381.



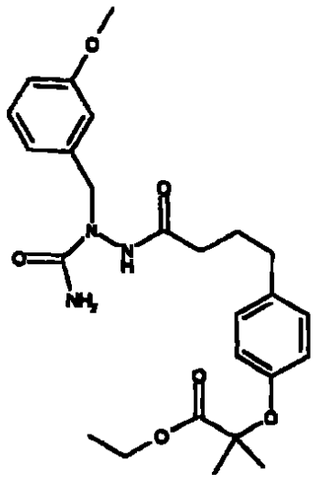
Éster 1,1-dimetiletílico del ácido 3-(aminocarbonil)-2-(3-metoxifenilmetil)-hidrazinocarboxílico. Se disolvió éster 1,1-dimetiletílico del ácido (3-metoxibencil)hidrazinocarboxílico (6,30 g, 25,0 mmol) en alcohol isopropílico (65 ml). Se añadió isocianato de trimetilsililo (4,73 g, 34,9 mmol) en una porción mediante jeringuilla, y la solución se permitió agitar a ta durante 7 horas. La suspensión se enfrió a 0°C, se filtró y los sólidos se lavaron con isopropanol frío. Los sólidos se secaron a vacío a 40°C, proporcionando el compuesto del título en forma de un sólido blanco (4,71 g, 63,9%). El filtrado se concentró y purificó mediante cromatografía en

columna (SiO_2, EtOAc), proporcionando compuesto adicional (0,91 g, 12,3%). Estas dos porciones se combinaron, proporcionando 5,82 g (76,2%) del compuesto del título: pf.: 136,3-138,5°C; ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,70 (s, 1H), 7,20 (t, 1H, *J*= 8 Hz), 6,80 (m, 3H), 5,90 (s, 2H), 4,50 (s, 2H), 3,74 (s, 3H), 1,36 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 159,9, 159,6, 155,0, 140,2, 129,8, 120,9, 114,0, 113,2, 80,2, 55,6, 51,1, 28,7; IR ($CHCl_3$) 3003, 2984, 2938, 1745, 1680 cm^{-1}; anal. calculado para $C_{14}H_{21}N_3O_4$: C 56,94, H 7,17, N 14,23. Encontrado: C 56,54, H 7,17, N 13,98.



Metanosulfonato de 1-(3-metoxifenilmetil)hidrazinocarboxamida. Se disolvió éster 1,1-dimetiletílico del ácido 3-(aminocarbonil)-2-(3-metoxifenilmetil)hidrazinocarboxílico (5,30 g, 17,9 mmol) en diclorometano (60 ml). Se añadió ácido metanosulfónico (1,93 g, 19,9 mmol) en una porción, y la solución se permitió agitar a ta durante una noche. La suspensión resultante se enfrió a 0°C, se filtró y los sólidos se lavaron con diclorometano frío. Los sólidos se secaron a

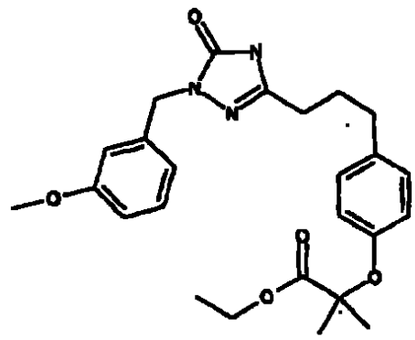
vacío a 40°C, proporcionando el compuesto del título en forma de un sólido blanco (5,05 g, 96,6%): pf: 130,3-132,1°C; ^{1}H-RMN (DMSO-d_6) δ 9,7 (s ancho, 3H), 7,30 (t, 1H, *J*= 8 Hz), 7,05 (s ancho, 2H), 6,88 (s, 3H), 4,69 (s, 2H), 3,74 (s, 3H), 3,34 (s, 3H); ^{13}C-RMN (DMSO-d_6) δ 160,1, 158,2, 137,3, 130,5, 120,7, 114,3, 114,0, 55,7, 52,7, 40,4; IR (mull de KBr) 3186, 2939, 1719, 1707, 1168 cm^{-1}; anal. calculado para $C_9H_{13}N_3O_2$: C 41,23, H 5,88, N 14,42. Encontrado: C 40,86, H 5,93, N 14,61.



1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3-metoxifenilmetil)-semicarbazida. Se disolvió ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butírico (4,86 g, 16,5 mmol) en acetato de etilo (40 ml). Se añadió gota a gota cloruro de oxalilo (2,43 g, 19,14 mmol) a esta solución en presencia de una cantidad catalítica de *N,N*-dimetilformamida (100 mg, 1,37 mmol). La terminación de la

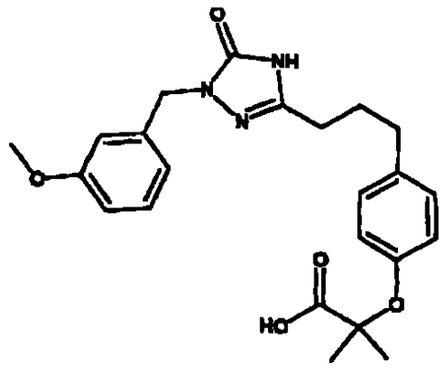
formación de cloruro de ácido se verificó por HPLC. Esta solución se añadió después gota a gota a una suspensión de metanosulfonato de 1-(3-metoxifenilmetil)hidrazinocarboxamida (4,80 g, 16,5 mmol) y piridina (1,30 g, 16,5 mmol) en acetato de etilo (55 ml) a 0°C. Después de agitar a 0°C durante 6 horas, se añadió una carga adicional de piridina (1,30 g, 16,5 mmol) y la solución se agitó a 0°C durante 1 hora. La solución se calentó a ta y se lavó con HCl 1 N (2 x 80 ml) y $NaHCO_3$ acuoso al 5% (2 x 80 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró hasta un sólido ceroso. Los sólidos se recristalizaron con una mezcla de tolueno (17 ml) y heptano (7 ml) a 60°C, se enfriaron a 0°C y se filtraron. Los sólidos se secaron a vacío a 40°C, proporcionando el compuesto del título en forma de un sólido blanco (5,05 g, 65%): pf: 91,9-93,4°C; ^{1}H-RMN (DMSO-d_6, 60°C) δ 9,60 (s, 1H), 7,19 (t, 1H, *J*= 8 Hz), 7,00 (d, 2H), 6,80 (m, 3H), 6,71 (d, 2H, *J*= 8 Hz), 5,92 (s, 2H), 4,52 (s, 2H), 4,15 (c, *J*= 7 Hz), 3,71 (s, 3H), 2,45 (t, 2H, *J*= 7 Hz), 2,07 (t, 2H, *J*= 7 Hz), 1,73 (quint., 2H, *J*= 7 Hz), 1,48 (s, 6H), 1,17 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 171,9, 159,9, 159,3, 153,7, 140,5, 135,9, 129,9, 129,7, 120,9, 119,4, 114,1, 113,1, 79,2, 61,6, 55,5, 50,9, 34,3, 33,4, 27,2, 25,7, 14,6; IR (mull de KBr) 3450, 3320, 3275, 3202, 2997, 2940, 1730, 1646, 1511 cm^{-1};

anal. calculado para $C_{25}H_{33}N_3O_6$: C 63,68, H 7,05, N 8,91. Encontrado: C 63,49, H 7,02, N 8,99.



Éster etílico del ácido 2-(4-{3-[1-(3-metoxibencil)-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Se disolvió 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3-metoxifenilmetil)semicarbazida (4,08 g, 8,65 mmol) en acetato de etilo (7,5 ml). Se añadió ácido canfosulfónico (2,21 g, 9,51 mmol) en una porción y la solución se calentó a reflujo durante una noche. La solución se enfrió a ta y se lavó con $NaHCO_3$ acuoso saturado (2 x 40 ml), seguido de HCl 1 N (2 x 40 ml). La fracción orgánica se concentró hasta un aceite, que se redisolvió en acetato de etilo (40 ml). Se añadió resina Amberlyst-15 (4,41 g) y la mezcla se calentó a 50°C y se agitó durante 4 horas. La mezcla se enfrió después a ta, se filtró, se concentró y se purificó por cromatografía en columna (SiO_2, acetato de etilo:hexanos 9:1), proporcionando el compuesto del título en forma de un aceite (1,93 g, 49,2%). ^{1}H-RMN (DMSO-d_6) δ

11,47 (s, 1H), 7,22 (t, 1H, *J*= 8 Hz), 7,04 (d, 2H, *J*= 8 Hz), 6,82 (d, 1H, *J*= 2 Hz), 6,76 (m, 2H), 6,68 (d, 2H, *J*= 2 Hz), 4,73 (s, 2H), 4,13 (c, 2H, *J*= 7 Hz), 3,69 (s, 3H), 2,48 (t, 2H, *J*= 8 Hz), 2,36 (t, 2H, *J*= 8 Hz), 1,80 (quint., 2H, *J*= 7 Hz), 1,47 (s, 6H), 1,14 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 160,0, 155,0, 153,8, 146,7, 139,8, 135,5, 130,2, 129,8, 120,1, 119,5, 113,8, 113,2, 79,2, 61,6, 55,6, 47,8, 34,0, 28,4, 26,2, 25,7, 14,6; IR ($CHCl_3$) 2940, 1692, 1508, 1467 cm^{-1}; anal. calculado para $C_{25}H_{31}N_3O_5$: C 66,21, H 6,89, N 9,26. Encontrado: C 66,29, H 6,75, N 9,19.

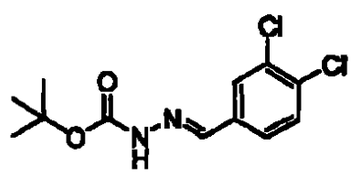


Ácido 2-(4-{3-[1-(3-metoxibencil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}-2-fenoxi)-2-metilpropiónico.

Se disolvió éster etílico del ácido 2-(4-{3-[1-(3-metoxibencil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico (1,55 g, 3,42 mmol) en una mezcla de etanol (7,5 ml) y agua (7,5 ml). Se añadió hidróxido de sodio sólido (0,36 g, 8,73 mmol) en una

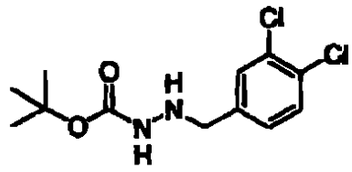
porción y la solución se calentó a 70°C y se agitó durante 1 hora. La solución se enfrió a ta y el pH se ajustó a 7 con HCl 6 N. La solución se concentró hasta un aceite, que se repartió entre HCl 1 N (10 ml) y acetato de etilo (15 ml). La fase acuosa se volvió a extraer después con acetato de etilo (15 ml) y las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron a vacío a 50°C, proporcionando el compuesto del título en forma de un aceite (1,41 g, 97,0%). ^{1}H-RMN (DMSO-d_6) δ 13,0 (s ancho, 1H), 11,47 (s, 1H), 7,23 (t, 1H, *J*= 8 Hz), 7,03 (d, 2H, *J*= 8 Hz), 6,82 (d, 1H, *J*= 2 Hz), 6,75 (m, 5H), 4,73 (s, 2H), 3,70 (s, 3H), 3,35 (s ancho, 1H), 2,48 (t, 2H, *J*= 8 Hz), 2,36 (t, 2H, *J*= 8 Hz), 1,80 (quint., 2H, *J*= 7 Hz), 1,46 (s, 6H); ^{13}C-RMN (DMSO-d_6, 20°C) δ 175,8, 160,0, 155,0, 154,1, 146,8, 139,8, 135,0, 130,3, 129,7, 120,1, 119,1, 113,8, 113,2, 78,9, 55,6, 47,8, 40,6, 40,5, 34,0, 28,4, 27,5, 26,2, 25,7; IR ($CHCl_3$) 1707, 1603, 1509, 1159 cm^{-1}; anal. calculado para $C_{23}H_{27}N_3O_5$: C 64,93, H 6,40, N 9,88. Encontrado: C 65,02, H 6,65, N 9,57.

Ejemplo 125



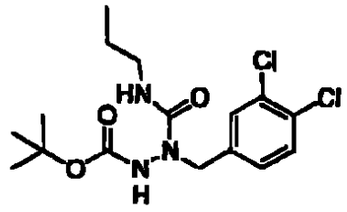
Éster 1,1-dimetiletílico del ácido (3,4-diclorofenil)metilenhidrazino-carboxílico. Se añadió con

agitación vigorosa una solución de 3,4-diclorobenzaldehído (6,77 g, 38,6 mmol) en acetato de etilo (10 ml) a una solución de carbazato de *terc*-butilo (4,99 g, 37,76 mmol) en acetato de etilo (10 ml), seguida de hexanos (40 ml). Apareció cristalización, y la suspensión resultante se agitó a ta durante 15 minutos, después se enfrió a 0°C y se mantuvo a esa temperatura durante 45 minutos. Los sólidos se filtraron, se lavaron con hexanos fríos y se secaron a vacío a 60°C, proporcionando el compuesto del título en forma de un sólido (10,10 g, 92,4%): pf: 173,8-174,4°C (desc.); ^{1}H-RMN (DMSO-d_6) δ 11,16 (s a, 1H), 7,79 (s, 1H), 7,62 (d, 1H, *J*= 1,8 Hz), 7,57 (d, 1H, *J*= 8,5 Hz), 7,55 (m, 1H), 1,44 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 152,9, 141,1, 136,1, 132,3, 132,1, 131,6, 128,6, 127,0, 80,4, 28,7; IR (mull de KBr) 3358, 3010, 2983, 1736, 1508, 1475 cm^{-1}. Se recristalizó una porción (acetato de etilo) para análisis. Anal. calculado para $C_{12}H_{14}Cl_2N_2O_2$: C 49,84, H 4,88, Cl 24,52, N 9,69. Encontrado: C 49,59, H 4,71, Cl 24,43, N 9,57.



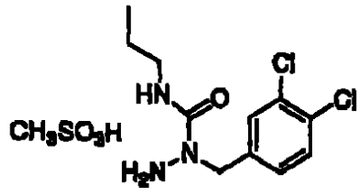
Éster 1,1-dimetiletílico del ácido 2-(3,4-diclorofenilmetil)hidrazino-carboxílico. Se añadió tetrahidrofurano (30 ml) al sustrato imina (2,90 g, 10,03

mmol) y Pt/S/C al 5% (4,31 g de catalizador húmedo al 55%, 1,94 g) y la suspensión resultante se hidrogenó a 345 kPa de hidrógeno a ta durante 16 horas. La suspensión se filtró y el filtrado se concentró hasta un aceite, que se cromatografió en gel de sílice (gradiente de hexanos a acetato de etilo al 15% en hexanos), proporcionando el compuesto del título en forma de un aceite (2,56 g, 8,79 mmol, 88%): ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,05 (s a, 1H), 7,56 (s, 1H), 7,52 (dd, 1H, *J*= 7,5, 1,5 Hz), 7,27 (d, 1H, *J*= 7,5 Hz), 3,87 (s, 2H), 1,36 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 157,0, 141,0, 131,4, 130,8, 129,8, 129,3, 79,1, 53,6, 28,8; IR ($CHCl_3$) 3443, 2983, 1713, 1472, 1455, 1369, 1369 cm^{-1}; anal. calculado para $C_{12}H_{16}Cl_2N_2O_2$: C 49,50, H 5,54, N 9,62. Encontrado: C 49,82, H 5,39, N 9,50.



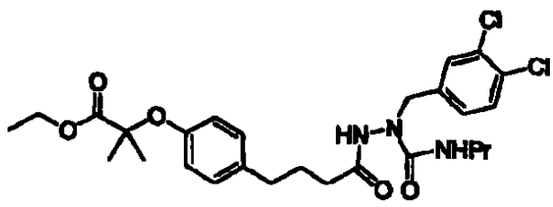
Éster 1,1-dimetiletílico del ácido 2-(propilaminocarbonil)-2-(3,4-diclorofenilmetil)hidrazinocarboxílico. Se añadió isocianato de propilo (0,89 ml, 0,808 g, 9,50 mmol) al sustrato hidrazida (2,30 g, 7,90 mmol) en isopropanol (25 ml) a ta. Después de agitar durante 30 minutos, la solución se concentró hasta un aceite y se cromatografió

en gel de sílice (acetato de etilo al 40% en hexanos), proporcionando el compuesto del título en forma de un aceite (2,63 g, 88%): ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,72 (s a, 1H), 7,52 (dd, 1H, *J*= 8,0, 2,0 Hz), 7,48 (s, 1H), 7,24 (d, 1H, *J*= 8,0 Hz), 6,39 (s a, 1H), 4,50 (s a, 2H), 3,13 (m, 2H), 1,41 (m, 2H), 1,35 (s, 9H), 0,82 (m, 3H); ^{13}C-RMN (DMSO-d_6) δ 158,4, 155,1, 140,1, 131,3, 130,9, 130,1, 129,3, 80,4, 51,2, 28,6, 23,7, 11,8; IR ($CHCl_3$) 3454, 3007, 2971, 2936, 2876, 1743, 1671, 1524 cm^{-1}; anal. calculado para $C_{16}H_{23}Cl_2N_3O_3$: C 51,07, H 6,16, N 11,17. Encontrado: C 51,01, H 6,09, N 11,15.



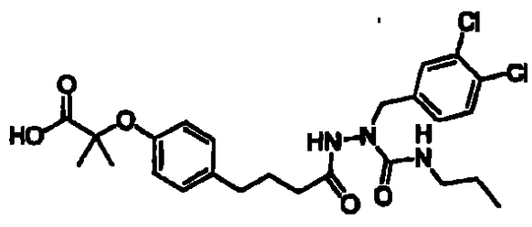
Metanosulfonato de *N*-propil-1-(3,4-diclorofenilmetil)hidrazino-carboxamida. Se añadió ácido metanosulfónico (0,39 ml, 0,578 g, 6,01 mmol) en una porción al sustrato BOC-semicarbazida (2,15 g, 5,71 mmol) en diclorometano (20 ml). La solución se enfrió y se concentró hasta una espuma, que se trituró con *terc*-butilmetiléter, proporcionando el compuesto del título en forma de un sólido (2,03 g, 5,53 mmol, 95%). Se recristalizó una porción (acetato de etilo/etanol) para análisis: pf: 134,6-135,5°C; ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,35

(2 a, 4H), 7,60 (d, 1H, *J*= 8,5 Hz), 7,51 (d, 1H, *J*= 2,0 Hz), 7,27 (dd, 1H, *J*= 8,5, 2,0 Hz), 4,66 (s, 2H), 3,06 (t, 2H, *J*= 7,0 Hz), 2,42 (s, 3H), 1,45 (m, 2H), 0,83 (t, 3H, *J*= 7,5 Hz); ^{13}C-RMN (DMSO-d_6) δ 157,6, 137,4, 131,8, 131,4, 131,2, 130,8, 129,1, 52,0, 42,7, 40,4, 23,3, 11,9; IR (mull de KBr) 3385, 2958, 2933, 2874, 1687, 1525, 1189 cm^{-1}; anal. calculado para $C_{11}H_{15}Cl_2N_3O \cdot CH_4O_3S$: C 38,72, H 5,14, N 11,29. Encontrado: C 38,76, H 5,14, N 11,26.



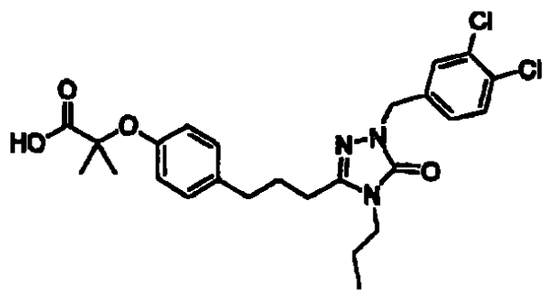
1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3,4-diclorofenilmetil)-4-(propil)semicarbazida. Se añadió gota a gota DMF (1 gota de pipeta) a ta al ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butírico (1,005 g, 3,41 mmol) en acetato de etilo (10 ml), seguido de cloruro de oxalilo (0,4 ml, 0,582 g, 4,58 mmol) durante 3 minutos. La solución resultante se agitó durante 30 mintos a ta, después se concentró hasta un aceite. El aceite se reconstituyó dos veces con tolueno (20 ml) y se concentró hasta un aceite, después se disolvió en acetato de etilo (3 ml). Se suspendió metanosulfonato de *N*-propil-1-(3,4-diclorofenilmetil)hidrazina (1,1458 g, 3,08 mmol) en acetato de etilo (10 ml) a 0°C y se añadió piridina (0,65

ml, 636 mg, 8,04 mmol). La solución de cloruro de ácido en acetato de etilo se añadió después gota a gota durante 2 minutos, y la mezcla resultante se agitó durante 15 minutos a 0°C. La mezcla se diluyó después con acetato de etilo y se lavó con HCl 1 N (2 x), seguido de NaCl acuoso saturado. Se secó después ($MgSO_4$), se filtró y se concentró hasta un aceite, que se cromatografió en gel de sílice (acetato de etilo:hexanos 3:2), proporcionando el compuesto del título en forma de un aceite (1,4397 g, 85%); ^{1}H-RMN (DMSO-d_6, 60°C) δ 9,61 (s, 1H), 7,50 (d, 1H, *J*= 8 Hz), 7,47 (d, 1H, *J*= 2 Hz), 7,23 (dd, 1H, *J*= 8, 2 Hz), 7,01 (d, 2H, *J*= 8,5 Hz), 6,71 (d, 2H, *J*= 8,5 Hz), 6,41 (m, a, 1H), 4,53 (s a, 2H), 4,15 (c, 2H, *J*= 7 Hz), 3,00 (m, 2H), 2,43 (m, 2H), 2,09 (t, 2H, *J*= 7 Hz), 1,74 (m, 2H), 1,48 (s, 6H), 1,40 (m, 2H), 0,81 (t, 3H, *J*= 7,5 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 172,1, 158,1, 153,8, 140,4, 135,8, 131,4, 130,9, 130,6, 130,1, 129,7, 129,1, 119,5, 79,2, 61,6, 50,9, 42,3, 34,4, 33,5, 27,1, 25,7, 23,7, 14,6, 11,9; IR ($CHCl_3$) 3457, 3008, 2876, 1727, 1673, 1509 cm^{-1}; anal. calculado para $C_{27}H_{35}Cl_2N_3O_5$: C 58,70, H 6,39, N 7,61. Encontrado: C 58,60, H 6,49, N 7,67.



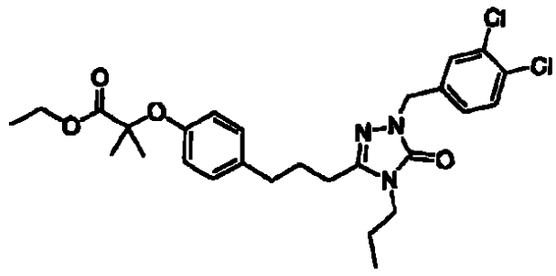
1-[4-[4-(1-Carboxi-1-metiletoxi)fenil]butiril]-2-(3,4-diclorofenilmetil)-4-(propil)semicarbazida. Se añadió NaOH 1 N (2,0 ml, 2,0 mmol) al sustrato 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3,4-diclorofenoximetil)-4-(propil)semicarbazida (0,609 g, 1,10 mmol) en metanol (5 ml) a ta, y la solución resultante se agitó durante 16 horas. La solución se concentró después hasta un aceite, y se repartió entre acetato de etilo y HCl 1 N. La fase orgánica se repartió entre acetato de etilo y HCl 1 N. La fase orgánica se lavó después con NaCl acuso saturado, se secó ($MgSO_4$), se filtró y se concentró, proporcionando el compuesto del título en forma de un sólido amorfo (0,5563 g, 1,06 mmol, 96%): ^{1}H-RMN (DMSO-d_6, 60°C) δ 9,61 (s, 1H), 7,50 (d, 1H, *J*= 8 Hz), 7,47 (d, 1H, *J*= 1,5 Hz), 7,23 (dd, 1H, *J*= 8, 1,5 Hz), 7,47 (d, 1H, *J*= 1,5 Hz), 7,23 (dd, 1H, *J*= 8, 1,5 Hz), 7,01 (d, 2H, *J*= 8,5 Hz), 6,75 (d, 2H, *J*= 8,5 Hz), 6,40 (m a, 1H), 4,53 (s a, 2H), 2,99 (c, 2H, *J*= 6,5 Hz), 2,46 (t, 2H, *J*= 7,5 Hz), 2,09 (t, 2H, *J*= 7,5 Hz), 1,74 (m, 2H), 1,47 (s, 6H), 1,40 (c, 2H, *J*= 7,5 Hz), 0,81 (t, 3H, *J*= 7,5 Hz); ^{13}C-RMN (DMSO-d_6) δ 175,8, 172,1, 158,1, 154,1, 140,4, 135,3, 131,5, 130,9, 130,6, 130,1, 129,6, 129,1, 119,1, 78,9, 50,9, 42,3, 40,7, 34,4, 33,5, 27,1, 25,7, 23,7, 11,9; IR ($CHCl_3$) 3379, 3291, 2960, 2915, 1719, 1671, 1618, 1542, 1508 cm^{-1}; anal. calculado para $C_{25}H_{31}Cl_2N_3O_5$: C 57,26, H 5,96, N 8,01.

Encontrado: C 57,15, H 5,89, N 7,94.



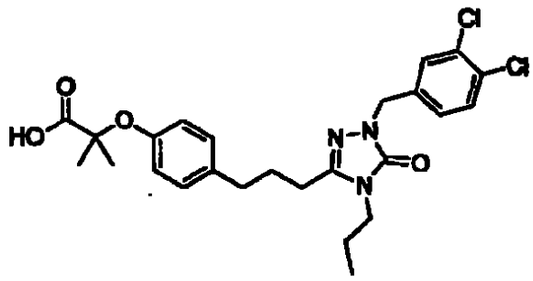
Ácido 2-(4-{3-[1-(3,4-diclorobencil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Se añadió tolueno (10 ml) al sustrato 1-[4-[4-(1-carboxi-1-metiletoxi)fenil]butiril]-2-(3,4-diclorofenilmetil)-4-(propil)-semicarbazida (0,3658 g, 0,697 mmol) y ácido canfosulfónico (0,1658 g, 0,714 mol), y la solución resultante se calentó a 90°C durante 1 hora. La solución se concentró hasta un aceite, y se cromatografió en gel de sílice (acetato de etilo:hexanos 7:3), proporcionando el compuesto del título en forma de un aceite (0,2397 g, 0,473 mmol, 68%): ^{1}H-RMN (DMSO-d_6) δ 12,95 (s a, 1H), 7,58 (d, 2H, *J*= 8 Hz), 7,46 (d, 1H, *J*= 1,5 Hz), 7,19 (dd, 1H, *J*= 8, 1,5 Hz), 7,03 (d, 2H, *J*= 8,5 Hz), 6,72 (d, 2H, *J*= 8,5 Hz), 4,85 (d, 2H), 3,47 (t, 2H, *J*= 7 Hz), 2,54 (t, 2H, *J*= 7,5 Hz), 1,83 (m, 2H), 1,52 (c, 2H, *J*= 7 Hz), 1,45 (s, 6H), 0,79 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 175,8, 154,1, 147,3, 139,2, 135,2, 131,7, 131,5, 130,8, 130,1, 129,7, 128,4, 119,3, 79,0, 47,3, 42,9, 34,0, 27,8, 25,7, 24,8, 22,5, 11,5; IR ($CHCl_3$) 3028, 3005, 2939, 2878, 1696,

1574, 1509, 1472 cm^{-1}; anal. calculado para $C_{25}H_{29}Cl_2N_3O_4$: C 59,29, H 5,77, N 8,30. Encontrada: C 59,33, H 5,63, N 8,10.



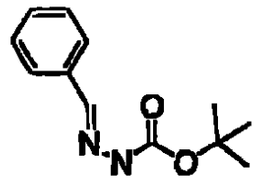
Éster etílico del ácido 2-(4-{3-[1-(3,4-diclorobencil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Se añadió acetato de etilo (10 ml) al sustrato 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3,4-diclorofenilmetil)-4-(propil)semicarbazida (0,4976 g, 0,901 mmol) y ácido canfosulfónico (0,2078 g, 0,895 mmol), y la solución resultante se agitó a reflujo durante 12 horas. La solución se diluyó con acetato de etilo, después se lavó con $NaHCO_3$ acuoso saturado, seguido de NaCl acuoso saturado. Se secó después ($MgSO_4$), se filtró y se concentró, proporcionando el compuesto del título en forma de un aceite (0,4532 g, 0,848 mmol, 94%); ^{1}H-RMN (DMSO-d_6) δ 7,59 (d, 1H, *J*= 8,5 Hz), 7,47 (d, 1H, *J*= 2, Hz), 7,19 (dd, 1H, *J*= 8,5, 2 Hz), 7,03 (d, 2H, *J*= 8,5 Hz), 6,69 (d, 2H, *J*= 8,5 Hz), 4,85 (s, 2H), 4,13 (c, 2H, *J*= 7 Hz), 3,48 (t, 2H, *J*= 8 Hz), 2,55 (t, 2H, *J*= 7 Hz), 1,83 (m, 2H),

1,52 (c, 2H, *J*= 7 Hz), 1,47 (s, 6H), 1,14 (t, 3H, *J*= 7 Hz), 0,79 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 154,1, 153,8, 147,3, 139,2, 135,6, 131,7, 131,5, 130,8, 130,1, 129,8, 128,4, 119,6, 79,3, 61,6, 47,3, 42,9, 34,0, 27,7, 25,7, 24,7, 22,4, 14,6, 11,5; IR ($CHCl_3$) 3003, 2939, 1728, 1696, 1509 cm^{-1}; EMAR calculada para $C_{27}H_{34}Cl_2N_3O_4$ $(M + H)^+$: 524,1926. Encontrado: 534,1935.

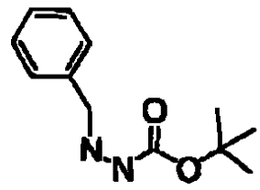


Ácido 2-(4-{3-[1-(3,4-diclorobencil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Se añadió hidróxido de sodio (2,0 ml de una solución 2,0 M, 2,0 mmol) al sustrato éster etílico de triazolona (0,3879 g, 0,726 mmol) en metanol (5 ml) a ta, y la mezcla resultante se agitó a ta durante 16 horas. La mezcla se concentró después hasta un aceite y se repartió entre acetato de etilo y HCl 1 N. La fase orgánica se lavó con NaCl acuoso saturado, se secó ($MgSO_4$), se filtró y se concentró, proporcionando el compuesto del título (0,336 g, 0,646 mmol, 89%) en forma de un aceite.

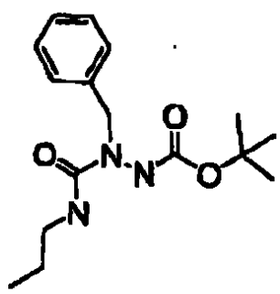
Ejemplo 126



Éster 1,1-dimetiletílico del ácido fenilmetilenhidrazinocarboxílico. Se añadió con agitación benzaldehído (4,51 g, 42,5 mmol) a una solución de carbazato de *terc*-butilo (5,62 g, 42,5 mmol) en acetato de etilo (15 ml). Apareció cristalización, y la suspensión resultante se agitó a ta durante 45 minutos. Se añadieron hexanos (70 ml) y la suspensión se enfrió a 0°C. La suspensión se agitó a 0°C durante 60 minutos, después se filtró y se lavó con hexanos fríos (20 ml) y se secó a vacío a 40°C, proporcionando el compuesto del título en forma de un sólido (8,34 g, 89,0%): pf: 184,1-184,9°C; ^{1}H-RMN (DMSO-d_6) δ 10,91 (s, 1H), 7,99 (s, 1H), 7,58 (d, 2H, *J*= 3 Hz), 7,39 (m, 3H), 1,45 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 153,0, 143,8, 135,3, 130,0, 129,4, 127,2, 80,1, 28,8; IR (mull de KBR) 2983, 1735, 1511, 1157 cm^{-1}. Se recristalizó una porción (acetato de etilo) para análisis. Anal. calculado para $C_{12}H_{16}N_2O_2$: C 65,43, H 7,32, N 12,72. Encontrado: C 65,16, H 7,43, N 12,62.

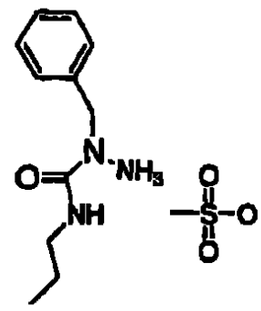


Éster 1,1-dimetiletílico del ácido fenilmetilhidrazinocarboxílico. Se suspendió éster 1,1-dimetiletílico del ácido fenilmetilenhidrazinocarboxílico (7,00 g, 31,8 mmol) y Pt/C al 5% (5,32 g) en THF (70 ml), y se agitó e hidrogenó (345 kPa) a ta durante 3 horas. La suspensión se filtró después a través de celita para eliminar el catalizador, y se concentró a vacío a 50°C, proporcionando el compuesto del título en forma de un aceite transparente (6,36 g, 90,0%); ^{1}H-RMN (DMSO-d_6) δ 8,23 (s, 1H), 7,29 (m, 4H), 7,20 (m, 1H), 4,62 (s a, 1H), 3,85 (s, 2H), 1,37 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 157,1, 139,4, 129,1, 128,7, 127,4, 79,0, 55,1, 28,9; IR ($CHCl_3$) 2982, 1712, 1454, 1273, 1159 cm^{-1}; masa exacta calculada para $C_{12}H_{21}N_2O_2$: 245,1266. Encontrada: 245,1273.

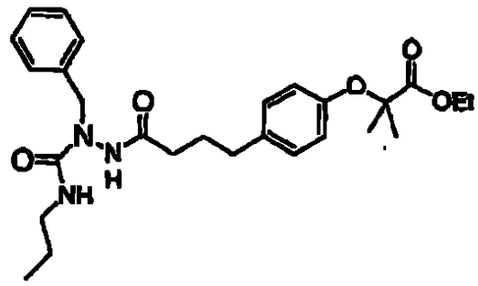


Éster 1,1-dimetiletílico del ácido 2-(propilaminocarbonil)-2-(fenilmetil)-hidrazinocarboxílico.

Se añadió isocianato de propilo (1,51 g, 17,6 mmol) a una solución de éster 1,1-dimetiletílico del ácido fenilmetilhidrazinocarboxílico (2,54 g, 11,4 mmol) en isopropanol (25 ml), y la solución se agitó a ta durante 1 hora. La solución se concentró hasta un sólido blanco. Este sólido se disolvió en acetato de etilo (25 ml) y se lavó con agua (25 ml) y NaCl acuoso al 10% (25 ml), se secó ($MgSO_4$), se filtró y se concentró hasta un sólido blanquecino. Se recristalizó después (acetato de etilo:hexanos 2:3) y se secó a vacío, proporcionando el compuesto del título en forma de un sólido blanco (2,53 g, 72,1%): pf: 122,8-124,5°C; ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,58 (s, 1H), 7,28 (m, 2H), 7,23 (m, 3H), 6,26 (s, 1H), 4,53 (s, 2H), 3,02 (c, 2H, *J*= 7 Hz), 1,41 (quint., 2H, *J*= 7 Hz), 1,35 (s, 9H), 0,83 (t, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 158,6, 155,0, 138,7, 128,9, 128,8, 127,6, 80,2, 51,5, 42,3, 28,6, 23,7, 11,8; IR ($CHCl_3$) 3007, 1745, 1665, 1523 cm^{-1}. Anal. calculado para $C_{16}H_{25}N_3O_3$: C 62,52, H 8,20, N 13,67. Encontrado: C 62,28, H 8,14, N 13,51.



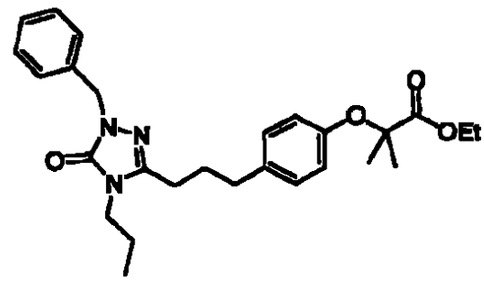
Metanosulfonato de N-propil-1-fenilmetilhidrazinocarboxamida. Se disolvió éster 1,1-dimetiletílico del ácido 2-(propilaminocarbonil)-2-(fenilmetil)-hidrazinocarboxílico (2,33 g, 7,58 mmol) en diclorometano (25 ml). Se añadió ácido metanosulfónico en una porción y la solución se permitió agitar a ta durante una noche. La solución se calentó a reflujo durante 8 horas, después se concentró, proporcionando el compuesto del título en forma de un sólido blanco bruto (2,47 g, 107%): pf: 78,1-82,9°C; ^{1}H-RMN (DMSO-d_6) δ 9,7 (s a, 3H), 7,61 (s a, 1H), 7,38 (t, 1H, *J*= 8 Hz), 7,32 (m, 4H), 4,74 (s, 2H), 3,07 (t, 2H, *J*= 8 Hz), 2,38 (s, 3H), 1,43 (quint., 2H, *J*= 8 Hz), 0,81 (t, 3H, *J*= 8 Hz); ^{13}C-RMN (DMSO-d_6) δ 157,5, 135,6, 129,3, 128,7, 128,6, 52,8, 42,7, 40,3, 23,3, 11,9; IR ($CHCl_3$) 3009, 1691, 1543, 1196 cm^{-1}; masa exacta calculada para $C_{11}H_{17}N_3O$: 208,1450. Encontrada: 208,1462.



1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-fenilmetil-4-(propil)-semicarbazida. Se disolvió ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butírico (1,50 g,

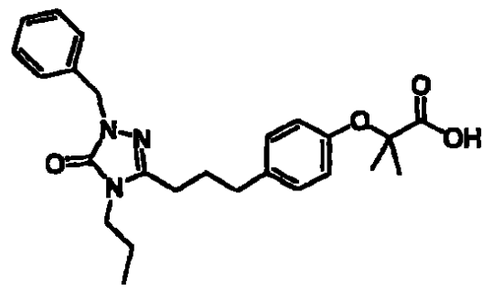
5,04 mmol) en acetato de etilo (10 ml). Se añadió gota a gota cloruro de oxalilo (524 µl, 6,01 mmol) a esta solución en presencia de una cantidad catalítica de *N,N*-dimetilformamida (30,1 µl, 0,41 mmol). La terminación de la formación de cloruro de ácido se verificó por HPLC. Esta solución se concentró después para eliminar el cloruro de oxalilo residual y se redisolvió el aceite resultante en acetato de etilo (10 ml). Esta solución se añadió después gota a gota a una suspensión de metanosulfonato de *N*-propil-1-fenilmetilhidrazina (1,52 g, 5,01 mmol) y piridina (970 µl, 12,6 mmol) en acetato de etilo (15 ml) a 0°C. Después de agitar a 0°C durante 1 hora, se calentó la solución a ta y se lavó con HCl 1 N (2 x 20 ml) y $NaHCO_3$ acuoso al 5% (2 x 20 ml), seguido de NaCl acuoso saturado (20 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró hasta un aceite amarillo. El aceite se purificó por cromatografía en columna (SiO_2, acetato de etilo:hexanos 1:1), proporcionando el compuesto del título en forma de un aceite transparente (1,42 g, 59%): ^{1}H-RMN (DMSO-d_6, 60°C) δ 9,51 (s, 1H), 7,20 (m, 5H), 7,01 (d, 2H, *J*= 8 Hz), 6,71 (t, 1H, *J*= 7 Hz), 4,55 (s, 2H), 4,17 (c, *J*= 7 Hz), 3,00 (c, 2H, *J*= 7 Hz), 2,45 (t, 2H, *J*= 2 Hz), 2,07 (t, 2H, *J*= 2 Hz), 1,73 (quint., 2H, *J*= 7 Hz), 1,48 (s, 6H), 1,40 (c, 2H, *J*= 7 Hz), 1,17 (t, 3H, *J*= 7 Hz), 0,81 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0,

172,0, 158,2, 153,8, 139,0, 135,8, 129,7, 128,84, 128,79, 127,6, 119,4, 79,2, 61,6, 51,3, 42,3, 34,3, 33,4, 27,1, 25,7, 23,7, 14,6, 11,9; IR ($CHCl_3$) 3009, 1726, 1672, 1143 cm^{-1}; anal. calculado para $C_{27}H_{37}N_3O_5$: C 67,05, H 7,71, N 8,69. Encontrado: C 66,65, H 7,63, N 8,57.



Éster etílico del ácido 2-{4-[3-(1-fenilmetil-5-oxo-4-propil-4,5-dihidro-1*H*-[1,2,4]triazol-3-il)propil]fenoxi}-2-metilpropiónico. Se disolvió 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-fenilmetil-4-(propil)semicarbazida (1,26 g, 2,61 mmol) en acetato de etilo (15 ml). Se añadió ácido canfosulfónico en una porción (670 mg, 2,88 mmol) y la solución se calentó a reflujo durante 1 hora. La solución se enfrió a rt y se lavó con $NaHCO_3$ acuoso saturado (2 x 10 ml), seguido de HCl 1 N (2 x 10 ml). La fase orgánica se secó ($MgSO_4$) y se concentró hasta un aceite transparente incoloro. El material se purificó mediante filtración en almohadilla de gel de sílice (gradiente de diclorometano a acetato de etilo), proporcionando el compuesto del título en forma de un aceite incoloro transparente (0,86 g, 71%). ^{1}H-RMN

(DMSO-d_6) δ 7,30 (t, 3H, *J*= 7 Hz), 7,24 (d, 1H, *J*= 7 Hz), 7,20 (d, 2H, *J*= 7 Hz), 7,04 (d, 2H, *J*= 8 Hz), 6,69 (d, 2H, *J*= 8 Hz), 4,13 (c, 2H, *J*= 7 Hz), 3,47 (t, 2H, *J*= 7 Hz), 2,55 (t, 2H, *J*= 7 Hz), 2,48 (t, 2H, *J*= 7 Hz), 1,83 (quint., 2H, *J*= 7 Hz), 1,52 (m, 2H), 1,47 (s, 6H), 1,14 (t, 3H, *J*= 7 Hz), 0,79 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 154,1, 153,8, 146,9, 138,1, 135,6, 129,8, 129,1, 128,0, 119,6, 79,3, 61,6, 48,5, 42,8, 34,0, 27,8, 25,7, 24,8, 22,5, 14,5, 11,5; IR ($CHCl_3$) 2878, 1692, 1509, 1143 cm^{-1}; anal. calculado para $C_{27}H_{35}N_3O_4$: C 69,65, H 7,58, N 9,03. Encontrado: C 69,28, H 7,96, N 8,84.

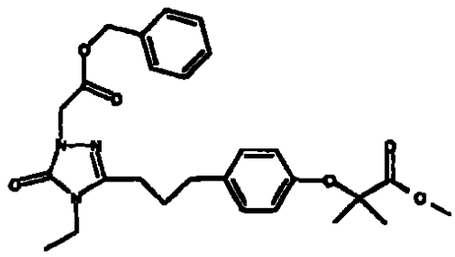


Ácido 2-(4-{3-[1-(fenilmetil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}-fenoxi)-2-metilpropiónico. Se disolvió éster etílico del ácido 2-(4-{3-[1-(fenilmetil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metil-propiónico (557 mg. 1,20 mmol) en etanol (5 ml), y se añadió NaOH acuoso 1 N (3,6 ml, 3,6 mmol) en una porción, y la solución se agitó a temperatura ambiente durante 16 horas. La solución se concentró después hasta un aceite turbio incoloro. Este aceite se diluyó con agua

(5 ml) y se lavó con *terc*-butilmetiléter (5 ml). El pH de la fase acuosa se ajustó a <1 con HCl concentrado, y la fracción acuosa se extrajo con acetato de etilo (10 ml, después 5 ml). Esta solución se lavó con HCl acuoso 1 N (5 ml) y NaCl acuoso saturado (5 ml), se secó ($MgSO_4$) y se concentró a vacío, proporcionando el compuesto del título en forma de un aceite transparente incoloro (442 mg, 84,5%). ^{1}H-RMN (DMSO-d_6) δ 12,9 (s a, 1H), 7,30 (t, 2H, *J*= 7 Hz), 7,25 (d, 1H, *J*= 7 Hz), 7,20 (d, 2H, *J*= 7 Hz), 7,04 (d, 2H, *J*= 8 Hz), 6,72 (d, 2H, *J*= 8 Hz), 4,83 (s, 2H), 3,47 (t, 2H, *J*= 7 Hz), 2,54 (t, 2H, *J*= 8 Hz), 2,49 (t, 2H, *J*= 8 Hz), 1,83 (quint., 2H, *J*= 7 Hz), 1,53 (m, 2H), 1,46 (s, 6H), 0,80 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 175,8, 154,1, 146,0, 138,1, 135,2, 129,7, 129,2, 128,0, 119,3, 79,0, 48,5, 42,8, 34,0, 27,9, 25,7, 24,8, 22,5, 11,5; IR ($CHCl_3$) 2938, 1509, 1468, 1233, 1155 cm^{-1}; anal. calculado para $C_{25}H_{31}N_3O_4$: C 68,63, H 7,14, N 9,60. Encontrado: C 68,24, H 6,95, N 9,40.

Ejemplo 127:

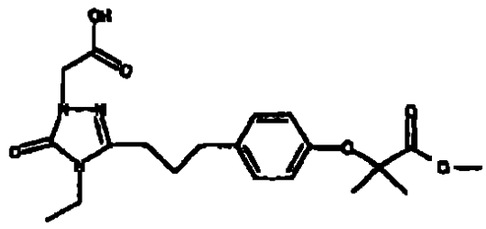
Etapa A:



Se combinó *N*-4-etiltriazolinona (1 g, 0,003 mol) con bromoacetato de bencilo (0,089 ml, 0,0056 mol) y K_2CO_3 en polvo (1,99 g, 0,014 mol) en DMF (28 ml), y se agitó a 67°C durante una noche. Se añadió éter a la mezcla de reacción y la solución se extrajo con agua. La purificación por cromatografía ultrarrápida (hexanos:acetato de etilo 2:1), proporcionó la amida deseada.

$C_{27}H_{33}N_3O_6$ (PM= 495,65); espectrometría de masas (MH^+)= 496,2.

Etapa B:

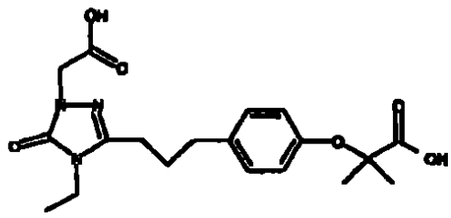


Se disolvió la amida de la **etapa A** (1,28 g, 0,0026 mol) en acetato de etilo (20 ml) y se purgó con nitrógeno. Se añadió catalizador de paladio (0,128 g, 10%) a la solución. La mezcla de reacción se purgó de nuevo. Se

liberó gas hidrógeno a través del sistema y se agitó la reacción durante una noche. La mezcla de reacción se filtró y se concentró el filtrado. El residuo resultante se pasó a la siguiente etapa sin purificación adicional.

$C_{20}H_{27}N_3O_6$ (PM = 405,45); espectrometría de masas (MH^+)= 406,3.

Etapa C:

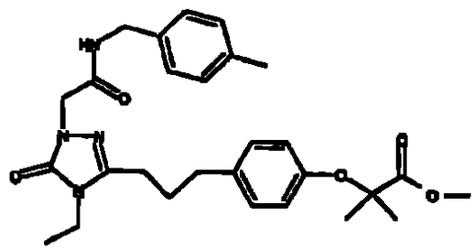


El éster de la **etapa B** (0,200 g, 0,0049 mol) se disolvió en etanol (6 ml) y se trató con NaOH 2 N (3 ml). La solución se calentó a reflujo durante 1 hora. Se añadió agua a la mezcla y la fase se extrajo con éter. Se acidificó la fase acuosa con HCl 1 N y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, proporcionando el producto deseado en forma de una espuma blanca.

$C_{19}H_{25}N_3O_6$ (PM = 391, 43); espectrometría de masas (MH^+) = 392,3

Ejemplo 128

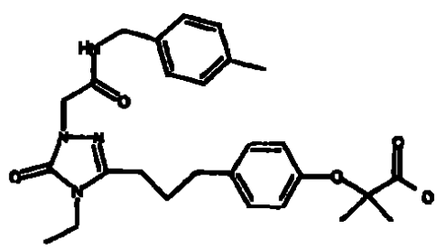
Etapa A:



Se trató una solución en THF del ácido descrito en el **ejemplo 127, etapa B** (0,190 g, 0,00047 mol) con EDC (0,134 g, 0,0007 mol) y HOAt (0,064 g, 0,047 mol). Se añadió un equivalente de 4-metilbencilamina (0,060 ml, 0,00047 mol), y la reacción se agitó durante una noche. El disolvente se concentró, y el residuo se redisolvió en cloruro de metileno y se extrajo con agua. La purificación por cromatografía ultrarrápida (acetato de etilo al 100%) proporcionó la amida deseada.

$C_{28}H_{36}N_4O_5$ (PM = 508,63); espectrometría de masas (MH^+) = 509,4.

Etapa B:

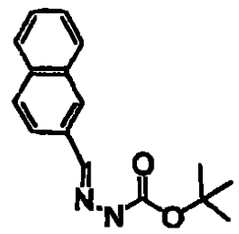


Se disolvió la amida de la **etapa A** (0,150 g, 0,00029

mol) en dioxano (3 ml) y agua (3 ml), después se trató con LiOH (0,007 g, 0,00029 mol). La reacción se agitó durante 2 horas. Se añadió agua a la mezcla y se extrajo la fase con éter. La fase acuosa se acidificó con HCl 1 N y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y después se concentró, proporcionando el producto deseado en forma de una espuma blanca.

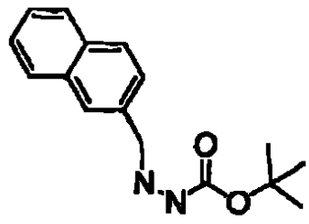
$C_{27}H_{34}N_4O_5$ (PM= 494,60); espectrometría de masas (MH^+) = 495,4.

Ejemplo 129



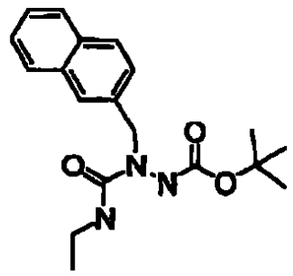
Éster 1,1-dimetiletílico del ácido (naftalen-2-il)metilenhidrazinocarboxílico. Se añadió con agitación 2-naftaldehído (8,98 g, 57,5 mmol) a una solución de carbazato de *terc*-butilo (7,59 g, 57,4 mmol) en acetato de etilo (22 ml). Se agitó esta solución amarilla transparente a ta durante 15 minutos. Se añadieron gota a gota hexanos (105 ml) y precipitaron sólidos de la solución. La suspensión se enfrió a 0°C, se filtraron después los sólidos y se lavaron con hexanos fríos (20

ml). Se obtuvo una segunda recogida de sólidos del filtrado, se filtraron y se combinaron con la primera recogida. Los sólidos combinados se recristalizaron (AcOEt) y se filtraron. Se recogió una segunda recogida concentrando el filtrado a la mitad de su volumen original y filtrando los sólidos resultantes a 0°C. Se combinaron las dos recogidas de sólidos y se secaron a vacío a 40°C, proporcionando el compuesto del título en forma de un sólido (13,17 g, 85,0%): pf: 182,1-190°C (desc.); ^{1}H-RMN (DMSO-d_6) δ 11,04 (s, 1H), 8,17 (s, 1H), 7,99 (s, 1H), 7,93-7,86 (m, 4H), 7,52-7,49 (m, 2H), 1,47 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 153,1, 143,9, 134,1, 133,6, 133,1, 129,1, 128,9, 128,5, 128,4, 127,5, 127,3, 123,1, 80,1, 28,8; IR ($CHCl_3$) 3061, 3010, 2982, 1733, 1505, 1369 cm^{-1}; anal. calculado para $C_{16}H_{18}N_2O_2$: C 71,09, H 6,71, N 10,36. Encontrado: C 70,95, H 6,89, N 10,31.



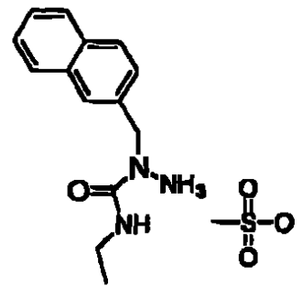
Éster 1,1-dimetiletílico del ácido (naftalen-2-il)metilhidrazinocarboxílico. Se suspendieron éster 1,1-dimetiletílico del ácido (naftalen-2-il)metilenhidrazinocarboxílico (7,08 g, 26,2 mmol) y Pt/C al 5% (7,11 g) en THF (70 ml), y se hidrogenaron a 345 kPa

a ta durante 4 horas. Se añadió una segunda carga de Pt/C al 5% (1,78 g) y la hidrogenación continuó durante 16 horas. La suspensión se filtró después a través de celita para eliminar el catalizador, y se concentró a vacío a 50°C, proporcionando el compuesto del título en forma de un aceite transparente (7,01 g, 98,3%): ^{1}H-RMN (DMSO-d_6) δ 8,27 (s, 1H), 7,83 (m, 4H), 7,48 (m, 3H), 6,97 (m, 1H), 4,88 (s, 1H), 4,04 (s, 2H), 1,37 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 137,1, 133,6, 132,9, 128,2, 128,1, 127,7, 127,3, 126,6, 126,4, 126,2, 79,0, 55,1, 28,9, 23,5; IR ($CHCl_3$) 3445, 1711, 1454, 1393, 1331 cm^{-1}; masa exacta calculada para $C_{16}H_{20}N_2O_2$: 295,1422. Encontrada: 295,1414.



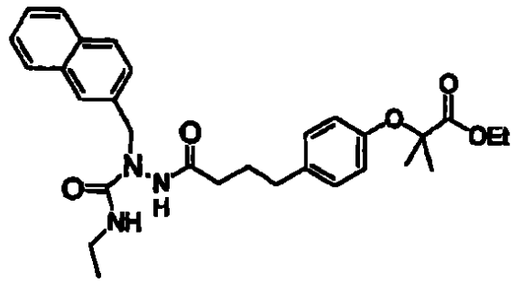
Éster 1,1-dimetiletílico del ácido 2-(etilaminocarbonil)-2-(naftalen-2-il)metilhidrazinocarboxílico. Se disolvió éster 1,1-dimetiletílico del ácido (naftalen-2-il)metilhidrazinocarboxílico (2,84 g, 10,4 mmol) en isopropanol (30 ml). Se añadió isocianato de etilo (1,23 ml, 15,6 mmol) en una porción, y la solución se agitó a ta durante 1 hora, después se concentró hasta un aceite amarillo. La cromatografía en columna (SiO_2, EtOAc:hexano

2:3) proporcionó el compuesto del título en forma de un aceite transparente incoloro (2,66 g, 55%); ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,60 (s, 1H), 7,8 (m, 3H), 7,72 (s, 1H), 7,4 (m, 3H), 6,37 (s, 1H), 4,71 (s, 2H), 3,11 (quint., 2H, *J*= 6 Hz), 1,32 (s, 9H), 1,04 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_4) δ 158,6, 155,0, 136,2, 133,5, 133,0, 129,3, 128,2, 128,1, 127,5, 126,7, 126,3, 60,4, 35,4, 28,6, 16,3, 14,7; IR ($CHCl_3$) 3453, 2983, 1664, 1370, 1156 cm^{-1}; masa exacta calculada para $C_{19}H_{25}N_3O_3$: 366,1794. Encontrada: 366,1797.



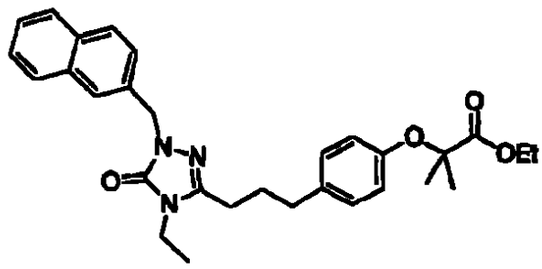
Metanosulfonato de *N*-etil-2-(naftalen-2-il)metilhidrazinocarboxamida. Se disolvió éster 1,1-dimetiletílico del ácido 2-(etilaminocarbonil)-2-(naftalen-2-il)metilhidrazinocarboxílico (2,52 g, 7,34 mmol) en diclorometano (25 ml). Se añadió ácido metanosulfónico (524 µl, 8,07 mmol) en una porción y la solución se agitó a ta durante una noche. La solución se calentó después a reflujo durante 8 horas y después se concentró, proporcionando el compuesto del título en forma de un sólido blanco amorfo (2,49 g, 96%): pf: 46,2-48,1°C; ^{1}H-RMN (DMSO-d_6) δ 9,7 (s a, 3H), 7,9 (m, 3H), 7,82 (s,

1H), 7,61 (s a, 1H), 7,52 (m, 2H), 7,44 (s, 1H, *J*= 7 Hz), 3,18 (quint., 2H, *J*= 8 Hz), 2,38 (s, 3H), 1,07 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 157,5, 133,4, 133,3, 133,1, 129,0, 128,5, 128,3, 127,7, 127,1, 126,9, 126,7, 53,2, 40,4, 35,9, 15,8; IR ($CHCl_3$) 3415, 2939, 1543, 1191, 1043 cm^{-1}; masa exacta calculada para $C_{14}H_{17}N_3O$: 244,1450. Encontrada: 244,1460.



1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(naftalen-2-il)metil-4-(propil)semicarbazida. Se disolvió ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)-fenil]butírico (1,35 g, 4,59 mmol) en acetato de etilo (10 ml). Se añadió gota a gota cloruro de oxalilo (425 µl, 4,86 mmol) a esta solución en presencia de una cantidad catalítica de *N,N*-dimetilformamida (25 µl, 0,34 mmol). La terminación de la formación de cloruro de ácido se verificó por HPLC. Esta solución se concentró después para eliminar el cloruro de oxalilo residual, y el aceite resultante se disolvió en acetato de etilo (10 ml). Se añadió después gota a gota esta solución a una suspensión de metanosulfonato de *N*-etil-2-(naftalen-2-il)metilhidrazinocarboxamida (1,50 g,

4,42 mmol) y piridina (895 µl, 11,1 mmol) en acetato de etilo (15 ml) a 0°C. Después de agitar a 0°C durante 4 horas, la solución se calentó a ta y se lavó con HCl 1 N (2 x 25 ml) y $NaHCO_3$ acuoso al 5% (2 x 25 ml), seguido de NaCl acuoso saturado (25 ml). La fase orgánica se secó ($MgSO_4$), se filtró y se concentró hasta un aceite amarillo, que se purificó por cromatografía en columna (SiO_2, acetato de etilo:hexanos 7:3), proporcionando el compuesto del título en forma de un aceite (1,59 g, 69%); ^{1}H-RMN (DMSO-d_6, 60°C) δ 9,51 (s, 1H), 7,85 (m, 3H), 7,70 (s, 1H), 7,42 (m, 3H), 6,94 (d, 2H, *J*= 7 Hz), 6,67 (d, 2H, *J*= 7 Hz), 6,38 (s, 1H), 4,72 (s, 2H), 4,16 (c, *J*= 7 Hz), 3,08 (t, 2H, *J*= 7 Hz), 2,41 (t, 2H, *J*= 8 Hz), 2,07 (t, 2H, *J*= 8 Hz), 1,72 (quint., 2H, *J*= 7 Hz), 1,47 (s, 6H), 1,17 (t, 3H, *J*= 7 Hz), 1,01 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 172,1, 158,2, 153,7, 136,4, 135,8, 133,5, 133,0, 129,7, 128,4, 128,2, 128,1, 127,4, 126,7, 126,3, 119,4, 79,2, 61,6, 51,3, 35,4, 34,3, 33,5, 27,2, 25,7, 16,3, 14,6; IR ($CHCl_3$) 3454, 2938, 1727, 1670, 1509, 1233, 1142 cm^{-1}; anal. calculado para $C_{30}H_{37}N_3O_5$: C 69,34, H 7,18, N 8,09. Encontrado: C 69,19, H 7,49, N 7,93.



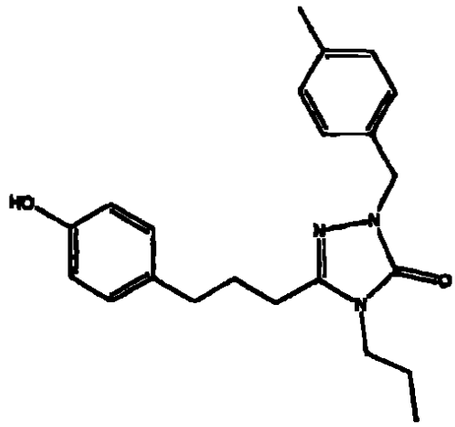
Éster etílico del ácido 2-{4-[3-(4-etil-1-(naftalen-2-il)metil-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il)propil]fenoxi}-2-metilpropiónico. Se disolvió 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(naftalen-2-il)metil-4-(propil)-semicarbazida (1,30 g, 2,51 mmol) en acetato de etilo (15 ml). Se añadió ácido canfosulfónico (0,645 g, 2,78 mmol) en una porción y la solución se calentó a reflujo durante 4 horas. La solución se enfrió a ta y se lavó con $NaHCO_3$ acuoso saturado (2 x 20 ml) seguido de HCl 1 N (2 x 20 ml). La fracción orgánica se secó ($MgSO_4$) y se concentró, proporcionando el compuesto del título en forma de un aceite transparente incoloro (1,23 g, 98%). ^{1}H-RMN (DMSO-d_6) δ 7,85 (t, 3H, *J*= 8 Hz), 7,73 (s, 1H), 7,48 (quint., 2H, *J*= 4 Hz), 7,38 (d, 1H, *J*= 8 Hz), 7,02 (d, 2H, *J*= 8 Hz), 6,66 (d, 2H, *J*= 8 Hz), 4,99 (s, 2H), 4,13 (c, 2H, *J*= 7 Hz), 3,57 (c, 2H, *J*= 8 Hz), 2,53 (m, 4H), 1,82 (quint., 2H, *J*= 7 Hz), 1,46 (s, 6H), 1,13 (m, 6H); ^{13}C-RMN (DMSO-d_6) δ 174,0, 154,0, 146,7, 135,6, 135,5, 133,5, 132,9, 129,7, 128,9, 128,3, 128,2, 127,0, 126,8, 126,4, 119,5, 79,2, 61,6, 48,7, 36,4, 34,0, 27,9,

25,7, 24,8, 14,9, 14,5; IR ($CHCl_3$) 2940, 1729, 1693, 1509, 1233, 1179, 1142 cm^{-1}; anal. calculado para $C_{30}H_{35}N_3O_4$: C 71,83, H 7,03, N 8,38. Encontrado: C 71,64, H 7,12, N 8,19.

Ácido 2-{4-[3-(4-etil-1-(naftalen-2-il)metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]-triazol-3-il)propil]fenoxi}-2-metilpropiónico. Se disolvió éster etílico del ácido 2-{4-[3-(4-etil-1-(naftalen-2-il)metil-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il)propil]-fenoxi}-2-metilpropiónico (725 mg, 1,45 mmol) en etanol (10 ml), se añadió NaOH 1 N (4,3 ml, 4,3 mmol) en una porción y la solución se agitó a temperatura ambiente durante 1 hora. La solución se concentró después hasta un aceite, que se lavó con *terc*-butilmetiléter (5 ml). El pH de la fase acuosa se ajustó a < 1 con HCl concentrado, y se extrajo con acetato de etilo (2 x 10 ml). Los extractos combinados se secaron ($MgSO_4$), se filtraron y se concentraron, proporcionando el compuesto del título en forma de un aceite amarillo transparente (0,570 g, 83%); ^{1}H-RMN (DMSO-d_6) δ 12,9 (s a, 1H), 7,86 (t, 2H, *J*= 8 Hz), 7,73 (s, 1H), 7,48 (quint., 2H, *J*= 4 Hz), 7,38 (d, 1H), 7,01 (d, 2H, *J*= 7 Hz), 6,69 (d, 2H, *J*= 7 Hz), 4,99 (s, 2H), 3,57 (quint., 2H, *J*= 7 Hz), 2,52 (t, 2H, *J*= 8 Hz), 1,82 (quint., 2H, *J*= 7 Hz), 1,45 (s, 6H), 1,12 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ

175,8, 154,1, 154,0, 146,8, 135,6, 135,2, 133,5, 132,9, 129,7, 128,9, 128,3, 128,2, 127,0, 126,8, 126,7, 126,4, 119,2, 79,0, 48,7, 36,4, 34,0, 27,9, 25,7, 24,8, 14,9; IR ($CHCl_3$) 2940, 1693, 1509, 1469, 1156 cm^{-1}; masa exacta calculada para $C_{28}H_{31}N_3O_4$: 474,2393. Encontrada: 474,2393.

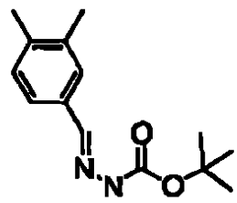
Ejemplo 130



5-[3-(4-Hidroxifenil)propil]-2-(4-metilbencil)-4-propil-2,4-dihidro-[1,2,4]-triazol-3-ona. Se fundieron conjuntamente 1-[(4-metoxifenil)butiril]-2-(4-metilfenilmetil)-4-propil)semicarbazida (0,312 g, 0,785 mmol) y clorhidrato de piridina en exceso con agitación a 180°C durante 1 hora. Después de enfriar a temperatura ambiente, los contenidos se diluyeron con acetato de etilo (25 ml) y HCl 5 N (25 ml). La fase orgánica se lavó con HCl 5 N adicional (25 ml) seguido de $NaHCO_3$ acuoso saturado (2 x 25 ml). La fase orgánica se lavó después con NaCl

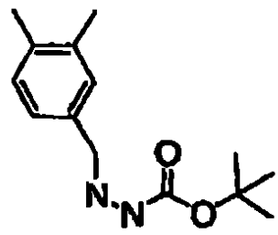
acuoso saturado (25 ml), se secó ($MgSO_4$), se filtró y se concentró, proporcionando el compuesto del título en forma de un aceite amarillo (0,201 g, 0,55 mmol, 70%). Datos espectrales según el ejemplo previo. Masa exacta calculada para $C_{22}H_{28}N_3O_3$ $(M + H)^+$: 366,2182. Encontrada: 266,2192.

Ejemplo 131

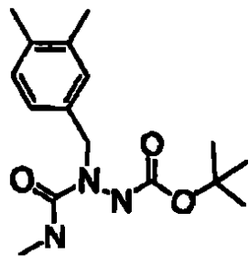


Éster 1,1-dimetiletílico del ácido (3,4-dimetilfenil)metilenhidrazino-carboxílico. Se añadió con agitación 3,4-dimetilbenzaldehído (5,20 ml, 5,26 g, 39,2 mmol) a una solución de carbazato de *terc*-butilo (5,06 g, 38,3 mmol) en acetato de etilo (15 ml). Apareció cristalización y la suspensión resultante se agitó a ta durante 45 minutos. Se añadieron hexanos (70 ml) y la suspensión se enfrió a 0°C. La suspensión se agitó a 0°C durante 60 minutos, después se filtró y se lavó con hexanos fríos (20 ml), y se secó a vacío a 40°C, proporcionando el compuesto del título en forma de un sólido (8,76 g, 92,1%): pf: 167,7-168,6°C; ^{1}H-RMN (DMSO-d_6) δ 10,82 (s, 1H), 7,92 (s, 1H), 7,36 (s, 1H), 7,28 (d, 2H, *J*= 3 Hz), 7,14 (d, 2H, *J*= 3 Hz), 2,206 (s, 3H), 2,20 (s, 3H), 1,44 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 153,0, 144,1, 138,5,

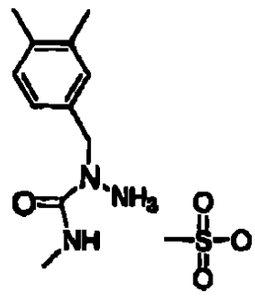
137,3, 132,9, 130,5, 128,1, 124,8, 79,9, 28,8, 19,99, 19,97; IR (mull de KBr) 3361, 3009, 2981, 2981, 1513, 1495 cm^{-1}. Se purificó adicionalmente una porción por recristalización con acetato de etilo para análisis. Anal. calculado para $C_{14}H_{20}N_2O_2$: C 67,71, H 8,12, N 11,28. Encontrado: C 67,51, H 8,07, N 11,22.



Éster 1,1-dimetiletílico del ácido (3,4-dimetilbencil)hidrazinocarboxílico. Se suspendieron éster 1,1-dimetiletílico del ácido (3,4-dimetilfenil)-metilenhidrazinocarboxílico (7,02 g, 28,3 mmol) y Pt/C al 5% (5,04 g) en THF (70 ml), y se hidrogenó a 345 kPa a ta durante 4 horas. Se filtró después la suspensión a través de celita y se concentró a vacío a 50°C, proporcionando el compuesto del título en forma de un aceite transparente (6,74 g, 95,2%): ^{1}H-RMN (DMSO-d_6, 20°C) δ 8,20 (s, 1H), 7,06 (s, 1H), 7,01 (dd, 2H, *J*= 8, 2 Hz), 4,56 (s, 1H), 3,77 (s, 2H), 2,18 (s, 6H), 1,38 (s, 9H); ^{13}C-RMN (DMSO-d_6) δ 157,1, 136,5, 136,3, 135,2, 130,4, 129,8, 126,5, 78,9, 54,9, 28,9, 20,0, 19,7; IR ($CHCl_3$) 2982, 1712, 1453, 1369 cm^{-1}; masa exacta calculada para $C_{14}H_{22}N_2O_2$: 251,1759. Encontrada: 251,1757.

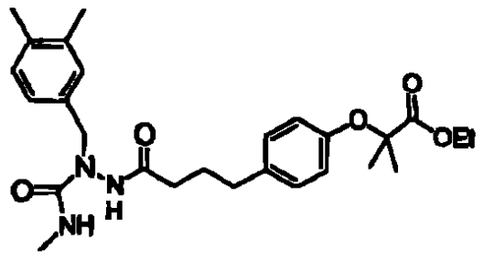


Éster 1,1-dimetiletílico del ácido 2-(metilaminocarbonil)-2-(3,4-dimetilfenilmetil)hidrazinocarboxílico. Se disolvió éster 1,1-dimetiletílico del ácido (3,4-dimetilfenilmetil)hidrazinocarboxílico (2,51 g, 10,0 mmol) en isopropanol (25 ml). Se añadió isocianato de metilo (1,0 ml, 16,7 mmol) en una porción mediante jeringuilla y se permitió agitar la solución a temperatura ambiente durante 1 hora. La solución se concentró, proporcionando el compuesto del título en forma de un sólido blanco (3,30 g de material de 87% de potencia por ^{1}H-RMN, 2,86 g, 93%): pf: 99,7-104,9°C; ^{1}H-RMN (DMSO-d_6, 60°C) δ 8,45 (s, 1H), 7,03 (d, 1H, *J*= 8 Hz), 6,99 (s, 1H), 6,93 (d, 1H), 6,26 (s, 1H), 4,45 (s, 2H), 2,60 (d, 3H, *J*= 7 Hz), 2,18 (s, 6H), 1,35 (s, 9H); ^{13}C-RMN (DMSO-d_6, 20°C) δ 159,0, 155,0, 136,3, 135,7, 135,3, 130,3, 129,9, 126,6, 80,1, 50,8, 28,7, 27,7, 20,1, 19,7; IR ($CHCl_3$) 3466, 1681, 1528, 1247, 1155 cm^{-1}. Se recristalizó una porción para análisis elemental: anal. calculado para $C_{16}H_{25}N_3O_3$: C 62,52, H 8,20, N 13,67. Encontrado: C 62,87, N 8,15, N 13,59.



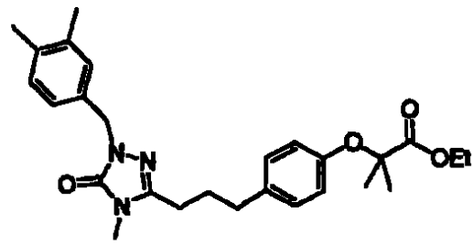
Metanosulfonato de *N*-metil-1-(3,4-dimetilfenilmetil)hidrazinocarboxamida. Se disolvió éster 1,1-dimetiletílico del ácido 2-(metilaminocarbonil)-2-(3,4-dimetilfenilmetil)hidrazinocarboxílico (2,52 g, 8,20 mmol) en diclorometano (25 ml). Se añadió ácido metanosulfónico (717 µl, 11,04 mmol) en una porción y la solución se permitió agitar a ta durante 4 horas. Se añadió una carga adicional de ácido metanosulfónico (132 µl, 2,0 mmol) y la solución se agitó a ta durante 12 horas. La suspensión resultante se enfrió a 0°C, se filtró y los sólidos se lavaron con diclorometano frío. Los sólidos se secaron a vacío a 40°C durante una noche, proporcionando un sólido blanco (1,44 g). El filtrado se concentró y se purificó por recristalización (acetato de etilo), proporcionando una cantidad adicional de sólido blanco (0,73 g). Las dos recogidas se combinaron y homogeneizaron, proporcionando el compuesto del título en forma de un sólido blanco (2,17 g, 87%): pf: 124,3-125,6°C; ^{1}H-RMN (DMSO-d_6) δ 9,4 (s ancho, 3H), 7,45 (s ancho, 1H), 7,10 (d, 1H, *J*= 8 Hz), 7,05 (s, 1H), 7,00 (d,

1H, *J*= 8 Hz), 4,61 (s, 2H), 2,67 (s, 3H), 2,36 (s, 3H), 2,19 (s, 6H); ^{13}C-RMN (DMSO-d_6) δ 158,2, 137,0, 136,7, 132,8, 130,4, 129,9, 126,2, 52,7, 40,4, 27,7, 20,2, 19,7; IR ($CHCl_3$) 3004, 2946, 1693, 1505, 1171 cm^{-1}; anal. calculado para $C_{12}H_{21}N_3O_5$: C 47,51, H 6,98, N 13,85. Encontrado: C 47,30, H 7,01, N 13,51.



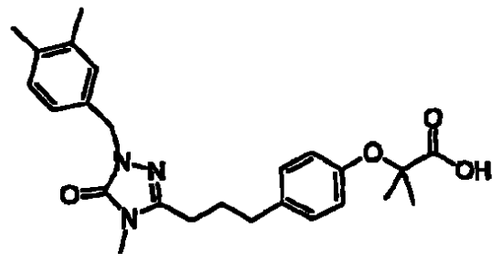
1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3,4-dimetilfenilmetil)-4-metilsemicarbazida. Se disolvió ácido 4-[4-(1-etoxicarbonil-1-metiletoxi)-fenil]butírico (1,46 g, 4,96 mmol) en acetato de etilo (10 ml). Se añadió gota a gota cloruro de oxalilo (474 µl, 5,46 mmol) a esta solución en presencia de una cantidad catalítica de *N,N*-dimetilformamida (30,6 µl, 0,39 mmol). La terminación de la formación de cloruro de ácido se verificó por HPLC. Esta solución se añadió después gota a gota a una suspensión de metanosulfonato de *N*-metil-1-(3,4-dimetilfenilmetil)hidrazinocarboxamida (1,50 g, 4,95 mmol) y piridina (1,00 ml, 12,9 mmol) en acetato de etilo (15 ml) a 0°C. Después de agitar a 0°C durante 6 horas, la solución se calentó a ta y se lavó con HCl 1 N (2 x 20

ml), $NaHCO_3$ acuoso al 5% (2 x 20 ml) y NaCl acuoso saturado. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró hasta un aceite amarillo. El aceite se purificó por cromatografía en columna (SiO_2, acetato de etilo:hexanos 9:1), proporcionando el compuesto del título en forma de un aceite transparente (1,48 g, 62%); ^{1}H-RMN (DMSO-d_6, 60°C) δ 9,42 (s, 1H), 6,97 (m, 5H), 6,71 (d, 2H, *J*= 8 Hz), 6,23 (s, 1H), 4,46 (s, 2H), 4,15 (c, *J*= 7 Hz), 2,59 (s, 3H), 2,43 (t, 2H, *J*= 8 Hz), 2,15 (s, 6H), 2,06 (t, 2H, *J*= 8 Hz), 1,70 (quint., 2H, *J*= 7 Hz), 1,48 (s, 6H), 1,17 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 172,0, 158,7, 153,8, 136,4, 136,0, 135,9, 135,4, 130,2, 129,9, 129,7, 126,5, 119,5, 79,2, 61,6, 50,6, 34,4, 33,5, 27,6, 27,2, 25,7, 20,0, 19,7, 14,6; IR ($CHCl_3$) 3009, 1669, 1509, 1142 cm^{-1}; masa exacta calculada para $C_{27}H_{38}N_3O_5$: 484,2811. Encontrado: 484,2822.



Éster etílico del ácido 2-(4-{3-[1-(3,4-dimetilfenilmetil)-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Se disolvió 1-[4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(3,4-dimetilfenilmetil)-4-metilsemi-carbazida (1,20 g, 2,47

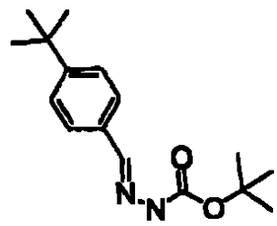
mmol) en acetato de etilo (10 ml). Se añadió ácido canfosulfónico (0,64 g, 2,72 mmol) en una porción y la solución se calentó a reflujo durante 1 hora. Se enfrió la solución a ta y se lavó con $NaHCO_3$ acuoso saturado (2 x 8 ml) seguido de HCl 1 N (2 x 8 ml). La fase orgánica se secó ($MgSO_4$) y se concentró, proporcionando el compuesto del título en forma de un aceite incoloro transparente (1,08 g, 94%). ^{1}H-RMN (DMSO-d_6) δ 7,04 (m, 3H), 7,03 (s, 1H), 6,93 (d, 1H, *J*= 2 Hz), 6,68 (d, 2H, *J*= 7 Hz), 4,72 (s, 2H), 4,13 (c, 2H, *J*= 7 Hz), 3,08 (s, 3H), 2,53 (t, 2H, *J*= 8 Hz), 2,47 (t, 2H, *J*= 8 Hz), 1,80 (quint., 2H, *J*= 7 Hz), 1,47 (s, 6H), 1,14 (t, 3H, *J*= 7 Hz); ^{13}C-RMN (DMSO-d_6) δ 174,0, 154,1, 147,1, 136,8, 135,9, 135,6, 135,3, 130,1, 129,8, 129,4, 125,7, 119,5, 79,2, 61,6, 48,4, 34,1, 27,7, 27,6, 25,7, 25,0, 20,0, 19,7, 14,6; IR ($CHCl_3$) 2941, 1729, 1509, 1238, 1143 cm^{-1}; anal. calculado para $C_{27}H_{35}N_3O_4$: C 69,65, H 7,58, N 9,03. Encontrado: C 69,25, H 7,47, N 8,88.



Ácido 2-(4-{3-[1-(3,4-dimetilfenilmetil)-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-

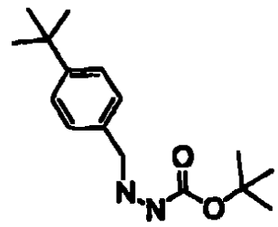
metilpropiónico. Se disolvió el éster etílico del ácido 2-(4-{3-[1-(3,4-dimetilfenilmetil)-5-oxo-4,5-dihidro-1*H*-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico (916 mg, 1,97 mmol) en etanol (10 ml), y se añadió NaOH 2 N (2,0 ml, 6,0 mmol) en una porción. La solución se agitó a temperatura ambiente durante 1 hora, después se concentró hasta un aceite incoloro turbio. Este aceite se repartió entre HCl 1 N (10 ml) y acetato de etilo (10 ml). La fase acuosa se volvió a extraer con acetato de etilo (10 ml). Precipitaron sólidos de esta solución al agitar. La suspensión se enfrió a 0°C, se filtró y se secó a vacío a 50°C durante una noche, proporcionando el compuesto del título en forma de un sólido blanco (695 mg, 80%): pf: 145,8-149,6°C; ^{1}H-RMN (DMSO-d_6) δ 12,98 (s, 1H), 7,05 (dd, 3H, *J*= 8,5, 3,0 Hz), 7,00 (s, 1H), 6,93 (d, 1H, *J*= 7,5 Hz), 6,73 (d, 2H, *J*= 8,5 Hz), 4,73 (s, 2H), 2,52 (t, 2H, *J*= 7,5 Hz), 2,47 (t, 2H, *J*= 7,5 Hz), 2,14 (s, 6H), 1,80 (quint., 2H, *J*= 7,5 Hz), 1,46 (s, 6H); ^{13}C-RMN (DMSO-d_4, 20°C) δ 175,8, 154,1, 154,0, 147,1, 136,8, 135,9, 135,3, 135,2, 130,1, 129,7, 129,4, 125,7, 119,2, 78,9, 48,4, 34,1, 27,7, 27,6, 25,7, 25,1, 20,0, 19,7; IR ($CHCl_3$) 2936, 2490, 1730, 1658, 1510, 1148 cm^{-1}; anal. calculado para $C_{25}H_{31}N_3O_4$: C 68,63, H 7,14, N 9,60. Encontrado C 68,23, H 7,01, N 9,44.

Ejemplo 132

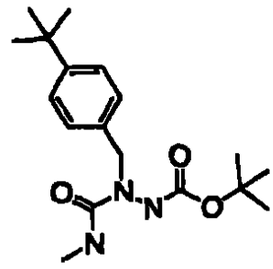


Éster 1,1-dimetiletílico del ácido (4-t-butil)metilenhidrazincarboxílico. A una solución de carbazato de t-butilo (5,02 g, 37,9 mmoles) en acetato de etilo (15 ml) se añadió con agitación 4-t-butilbenzaldehído (6,40 ml, 6,21 g, 37,9 mmoles). Se produjo la cristalización y la suspensión resultante se agitó a temperatura ambiente durante 15 minutos. Se añadieron hexanos (30 ml) y se enfrió la suspensión hasta 0°C. Se agitó la suspensión a 0°C durante 30 minutos, se filtró y se aclaró con hexanos fríos (20 ml), después se secó a vacío a 40°C para proporcionar el compuesto del título en forma de sólido (9,27 g, 88,3%: p. f. 173,7 - 175,7°C (dec); ^{1}H - RMN (DMSO - d_6) δ 10,85 (s, 1 H), 7,96 (s, 1 H), 7,63 (s, 1 H), 7,50 (d, 2 H, J = 3 Hz), 7,40 (d, 2 H, J = 3 Hz), 1,45 (s, 9 H), 1,25 (s, 9 H); ^{13}C - RMN (DMSO - d_6) δ 152,7, 143,8, 132,6, 127,0, 126,2, 80,0, 39,7, 35,2, 31,7, 28,8; IR (suspensión de KBr) 3361, 3010,

2968, 1514, 1500 cm^{-1}; Una porción se volvió a cristalizar (acetato de etilo) para análisis. Anal. Calculado para $C_{16}H_{24}N_2O_2$: C, 69,53; H, 8,75; N, 10,13. Encontrado: C, 69,20; H, 8,85; N, 10,09.



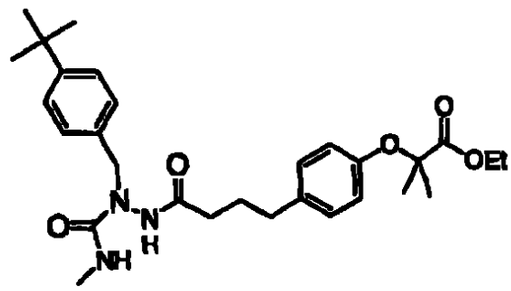
Éster 1,1-dimetiletílico del ácido (4-t-butilbencil)hidrazincarboxílico. Éster 1,1-dimetiletílico del ácido (4-t-butilfenil)metilenhidrazincarboxílico (7,05 g, 25,5 mmoles) y Pt al 5% /C (5,01 g) se suspendió en THF (70 ml) y se hidrogenó a 50 psgi a temperatura ambiente durante 3 horas. Después la suspensión se filtró a través de celite para retirar el catalizador y se concentró a vacío a 50°C para proporcionar el compuesto del título en forma de un aceite transparente (6,79 g, 95,6%): ^1H - RMN (DMSO - d_6, 60°C) δ 7,30 (m, 2 H), 7,23 (m, 2 H), 4,44 (s, 1 H), 3,82 (s, 1 H), 1,38 (s, 9 H), 1,27 (s, 9 H); ^{13}C - RMN (DMSO - d_6) δ 157,1, 149,8, 136,3, 128,9, 125,5, 78,9, 54,7, 34,8, 31,9, 28,9; IR ($CHCl_3$) 3008, 3967, 2869, 1712 cm^{-1}; Anal. Calculado para $C_{16}H_{26}N_2O_2$: C, 69,03; H, 9,41; N, 10,06. Encontrado: C, 68,83; H, 9,21; N, 9,98.



Éster 1,1-dimetiletílico del ácido 2-(metilaminocarbonil)-2-(4-t-butilfenilmetil)hidrazincarboxílico. Éster 1,1-dimetiletílico del ácido (4-t-butilbencill)hidrazincarboxílico (2,54 g, 9.12 mmoles) se disolvió en isopropanol (25 ml). Se añadió isocianato de metilo (0,83 g, 14,11 mmoles) en una porción mediante una jeringa y se dejó la solución en agitación a temperatura ambiente durante 1 hora. Se concentró la solución para proporcionar el compuesto del título en forma de un sólido céreo blanco (3,22 g de 89% de material puro mediante ^{1}H - RMN, 2,87 g, 93,7%); p. f. 124,1 - 128,6°C;); ^{1}H - RMN (DMSO - d_6 60°C) δ 8,54 (s a, 1 H), 7,30 (d, 2 H, J = 2 Hz), 7,16 (d, 2 H, J = 2 Hz), 6,28 (s, 1 H), 4,48 (s, 2 H), 2,59 (d, 3 H, J = 2 Hz), 1,31 (s, 9 H), 1,26 (s, 9 H); ^{13}C - RMN (DMSO - d_6 60°C) δ 159,1, 155,0, 149,9, 135,5, 128,9, 125,5, 80,1, 50,9, 34,8, 31,9, 28,7, 27,7; IR ($CHCl_3$) 3005, 2968, 2938, 1666 cm^{-1}; Una porción se volvió

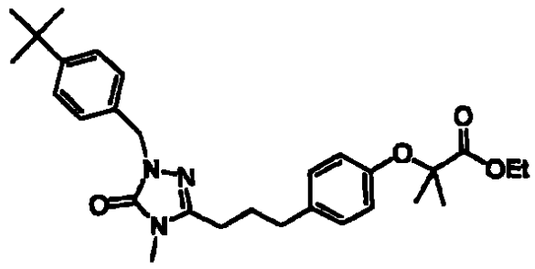
a cristalizar (tolueno) para análisis. Anal. Calculado para $C_{18}H_{29}N_3O_3$: C, 64,45; H, 8,71; N, 12,53. Encontrado: C, 63,91; H, 8,51; N, 12,44.

Metanosulfonato de N-metil-1-(4-t-butilfenilmetil)hidracincarboxamida. Éster 1,1-dimetiletílico del ácido 3-(metilaminocarbonil)-2-(4-t-butilfenilmetil)hidracincarboxílico (2,56 g, 7.90 mmoles) se disolvió en diclorometano (25 ml). Se añadió ácido metanosulfónico (641 µl, 9,88 mmoles) en una porción y se agitó la solución a temperatura ambiente durante una noche. La suspensión resultante se enfrió hasta 0°C, se filtró y se aclararon los sólidos con diclorometano frío. Se secaron los sólidos a vacío a 40°C para proporcionar el compuesto del título en forma de un sólido blanco (2,10 g, 80,1%); p. f. 96,8 - 97,4°C;); ^{1}H - RMN (DMSO - d_6) δ 9,7 (s a, 3 H), 7,5 (s a, 3 H), 7,5 (s a, 1 H), 7,39 (d, 2 H, J = 3 Hz), 7,20 (d, 2 H, J = 3 Hz), 4,65 (s, 2 H), 2,67 (s, 3 H), 2,35 (s, 3 H), 1,26 (s, 9 H); ^{13}C - RMN (DMSO - d_6) δ 158,2, 151,1, 132,7, 128,4, 126,1, 52,6, 40,4, 34,9, 31,8, 27,7; IR (suspensión de KBr) 2967, 1690, 1550, 1188, 1076 cm^{-1}; Masa exacta calculada para $C_{13}H_{22}N_3O$: 236,1763. Encontrado: 236,1758.



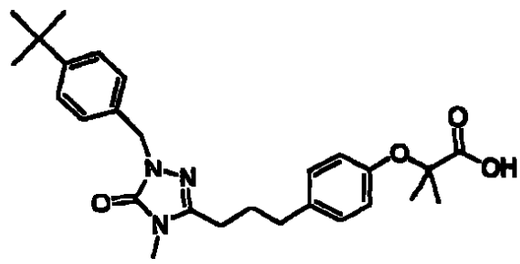
1-[4-[4-(1-Etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(4-t-butilfenilmetil)-4-metilsemicarbazida. Ácido [4-[4-(1-etoxicarbonil-1-metiletoxi)fenil]butírico (0,89 g. 3,02 mmoles) se disolvió en acetato de etilo (10 ml). Se añadió a esta solución gota a gota cloruro oxálico (316 µl, 3,62 mmoles) en presencia de una cantidad de N,N-dimetilformamida (17 µl, 0,24 mmoles). La finalización de la formación de cloruro de ácido se verificó mediante HPLC. Después se concentró la solución para retirar el exceso de cloruro oxálico y después se volvió a disolver en acetato de etilo (7 ml). Después esta solución se añadió gota a gota a una suspensión de metanosulfonato de N-metil-1-(4-t-butilfenilmetil)hidracincarboxamida (1,02 g, 3,07 mmoles) y piridina (256 µl, 6,14 mmoles) en acetato de etilo (10 ml) a 0°C. Después de agitar a 0°C durante 3 horas se añadió una carga adicional de piridina (256 µl, 6,14 mmoles) y se agitó la solución a 0°C durante 1 hora. Se calentó la solución hasta temperatura ambiente y se lavó con HCl 1N (2 x 10 ml) y después con $NaHCO_3$

acuoso al 5% (2 x 10 ml). Se secó la fase orgánica ($MgSO_4$), se filtró y se concentró hasta un aceite naranja. La cromatografía en columna (SiO_2, acetato de etilo) produjo el compuesto del título en forma de un aceite transparente (1,06 g, 68%); ^1H - RMN (DMSO - d_6, 60°C) δ 9,50 (s, 1 H), 7,29 (d, 2 H, J = 8 Hz), 7,16 (d, 2 H, J = 8 Hz), 7,01 (d, 2 H, J = 8 Hz), 6,71 (d, 2 H, J = 8 Hz), 6,27 (s a, 1 H), 4,52 (s a, 2 H), 4,15 (c, J = 7 Hz), 4,15 (c, J = 7 Hz), 2,58 (d, 3 H, J = 4 Hz), 2,44 (t, 2 H, J = 7 Hz), 2,07 (t, 2 H, J = 7 Hz), 1,72 (quint, 2 H, J = 7 Hz), 1,48 (s, 6 H), 1,25 (s, 9H), 1,17 (t, 3 H, J = 7 Hz); ^{13}C - RMN (DMSO - d_6) δ 174,0, 172,0, 158,7, 153,8, 149,9, 135,9, 129,7, 128,7, 125,6, 119,5, 79,2, 61,6, 50,8, 34,8, 34,4, 33,4, 31,8, 27,7, 27,1, 25,7, 14,6; IR ($CHCl_3$) 3009, 2966, 1671, 1509, 1211 cm^{-1}; Anal. calculado para $C_{29}H_{41}N_3O_5$: C, 68,08; H, 8,08; N, 8,21. Encontrado: C, 67,70; H, 7,86; N, 8,11.



Éster etílico del ácido 2-(4-{3-[1-(4-t-butilfenilmetil)-4-metil-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. 1-[4-[4-(1-

etoxicarbonil-1-metiletoxi)fenil]butiril]-2-(4-t-butilfenilmetil)-4-metilsemicarbazida (0,93 g, 1,82 mmoles) se disolvió en acetato de etilo (10 ml). Se añadió a la solución en una porción ácido canforsulfónico (0,46 g, 1,98 mmoles) y se calentó la solución a reflujo y se agitó durante 1 hora. Se enfrió la solución hasta temperatura ambiente y se lavó con $NaHCO_3$ acuoso saturado (2 x 8 ml), HCl 1 N (2 x 8 ml) y NaCl acuoso saturado (8 ml). Se secó la fase orgánica ($MgSO_4$), se filtró y se concentró para proporcionar el compuesto del título en forma de un aceite transparente e incoloro (0,84 g, 93,6%); ^1H - RMN (DMSO - d_6) δ 7,30 (d, 2 H, J = 8 Hz), 7,15 (d, 2 H, J = 8 Hz), 7,05 (d, 2 H, J = 8 Hz), 6,68 (d, 2 H, J = 8 Hz), 4,77 (s, 2 H), 4,13 (c, 2 H, J = 7 Hz), 3,69 (s, 3 H), 2,53 (t, 2 H, J = 8 Hz), 2,47 (t, 2 H, J = 8 Hz), 1,81 (quint, 2 H, J = 7 Hz), 1,47 (s, 6 H), 1, 22 (s, 9 H), 1,14 (t, 3 H, J = 7 Hz); ^{13}C - RMN (DMSO - d_6) δ 174,0, 154,1, 153,8, 150,4, 147,1, 135,6, 135,0, 129,8, 128,0, 125,9, 119,5, 79,2, 61,6, 48,3, 34,9, 34,1, 31,8, 27,7, 27,6, 25,7, 25,1, 14,6; IR ($CHCl_3$) 2967, 1695, 1509, 1475, 1232 cm^{-1}; Anal. calculado para $C_{29}H_{39}N_3O_4$: C, 70,56; H, 7,96; N, 8,51. Encontrado: C, 70,28; H, 7,85; N, 8,43.

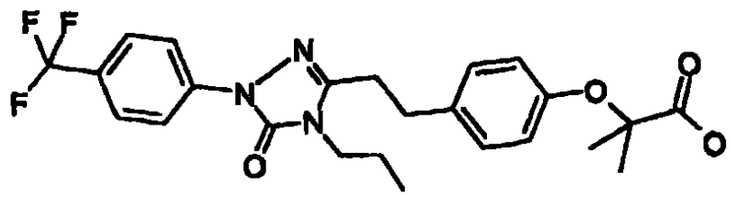


Ácido 2-(4-{3-[1-(4-t-butilbencil)-4-metil-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. Éster etílico del ácido 2-(4-{3-[1-(4-t-butilbencil)-4-metil-5-oxo-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropiónico. (0,69 g, 1,39 mmoles) se disolvió en etanol (4 ml), se añadió NaOH 1 N (4,75 ml) en una porción y se agitó la solución a temperatura ambiente durante una noche. Se concentró la solución hasta un aceite nebuloso incoloro. Este aceite se repartió entre HCl 1 N (5 ml) y acetato de etilo (5 ml). Después la fase acuosa se volvió a extraer con acetato de etilo (5 ml) y las fases se reunieron, se secaron ($MgSO_4$), se filtraron y se concentraron a vacío a 50°C para proporcionar el compuesto del título en forma de un aceite transparente (0,56 g, 86%); ^1H - RMN (DMSO - d_6) δ 12, 9 (s a, 1 H), 7,31 (d, 2 H, J = 6 Hz), 7,14 (d, 2 H, J = 8 Hz), 7,05 (d, 2 H, J = 7 Hz), 6,73 (d, 2 H, J = 2 Hz), 4,77 (s, 2 H), 3,09 (s, 3 H), 2,53 (t, 2 H, J = 8 Hz), 2,49 (t, 2 H, J = 8 Hz), 1,81 (quint, 2 H, J = 7 Hz), 1,46 (s, 6

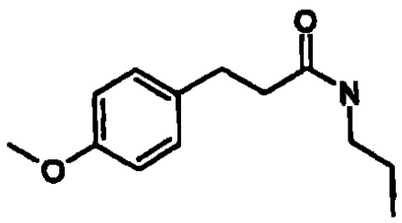
H), 1, 22 (s, 9 H); ^{13}C - RMN (DMSO - d_6) δ 175,8, 154,14, 154,10, 150,5, 147,2, 135,2, 135,0, 129,7, 128,0, 125,9, 119,2, 79,0, 48,3, 34,9, 34,1, 31,8, 27,7, 27,6, 25,7, 25,1; IR ($CHCl_3$) 2966, 1695, 1509, 1235 cm^{-1}; Anal. calculado para $C_{27}H_{35}N_3O_4$: C, 69,65; H, 7,58; N, 9,02. Encontrado: C, 69,30; H, 7,30; N, 8,96.

Ejemplo 133

Ácido 2-Metil-2-(4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)propiónico.



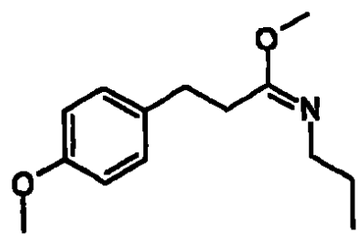
Fase A: Preparación de 3-(4-metoxifenil)-N-propilpropionamida



A una solución de ácido 3-(4-metoxifenil)propiónico (8,0

g, 44,4 mmoles), clorhidrato de propilamina (4,24 g, 44,4 mmoles), 4-dimetilaminopiridina (0,65 g, 5,33 mmoles) y trietilamina (6,9 ml, 48,96 mmoles) en cloruro de metileno (70 ml) se añadió clorhidrato de 1-[(3-dimetilamino)propil]-3-etilcarbodiimida (10,21 g, 53,28 mmoles). Se agitó la mezcla de reacción durante una noche a temperatura ambiente seguido de dilución con cloruro de metileno. Se lavó la mezcla con ácido clorhídrico 1 N, hidróxido sódico 2 N, agua, salmuera y se secó. La evaporación del disolvente produjo el producto puro (10, 36 g, 95,4%): ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 7, 76 (s a, 1 H), 7,10 (d, 2 H, J = 8,8 Hz), 6,79 (d, 2 H, J = 8,0 Hz), 3,68 (s, 3 H), 2,95 (c, 2 H, J = 5,6 Hz), 2,71 (t, 2 H, J = 7,6 Hz), 2,28 (t, 2 H, J = 7,2 Hz), 1,34 (m, 2 H), 0,77 (t, 3 H, J = 7,2 Hz); EMES *m/z* (intensidad relativa) 222,2 ($M + H^+$, 100).

Fase B: Preparación de éster metílico del ácido 3-(4-metoxifenil)-N-propilpropionimídico

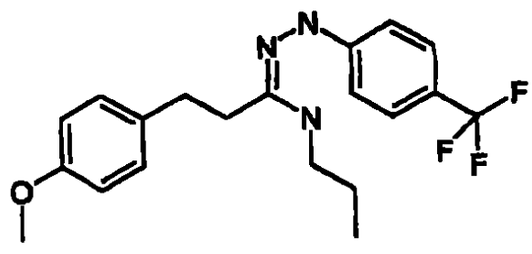


A una solución de 3-(4-metoxifenil)-N-propilpropionamida (3,0 g, 13,57 mmoles en cloruro de metileno (15 ml) se

añadió tetrafluoroborato de trimetiloxonio (2,0 g, 13,57 mmoles) y se agitó la mezcla de reacción durante una noche a temperatura ambiente. El análisis de HPLC y TLC indicó la presencia del material de partida. Se añadió más tetrafluoroborato de trimetiloxonio (0,25 g) y se dejó la mezcla de reacción en agitación durante 2,5 horas y se inactivó con solución saturada de carbonato potásico acuoso. Se extrajo la mezcla con acetato de etilo. Se lavaron los extractos reunidos orgánicos con agua, salmuera, se secaron y se evaporaron hasta sequedad para proporcionar el producto puro (3,0 g, 93,8%); ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 7,10 (d, 2 H), 6,80 (d, 2 H, J = 8,4 Hz), 3,78 (s, 3 H), 3,61 (s, 3 H), 3,08 (t, 2 H, J = 7,6 Hz), 2,70 (m, 2 H), 2,48 (m, 2 H), 1,45 (m, 2 H), 0,86 (t, 3 H, J = 7,6 Hz); EMES *m/z* (intensidad relativa) 236,1 (M + H^+, 100).

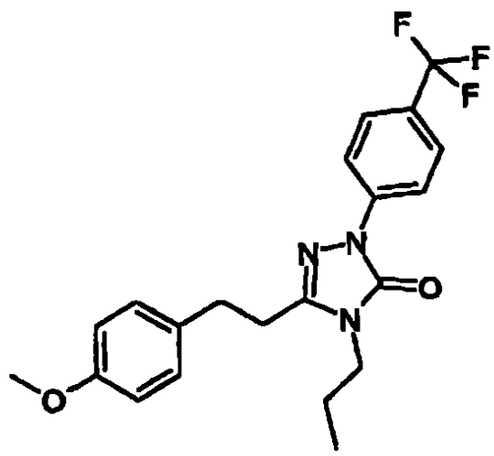
Etapa C:

Preparación de



A una solución de éster metílico del ácido 3-(4-metoxifenil)-N-propilpropionimídico (3,0 g, 12,77 mmoles) en cloruro de metileno (10 ml) se añadió 4-trifluorometilfenilhidrazina (2,25 g, 12,77 mmoles) en cloruro de metileno (10 ml) y se agita la mezcla de reacción durante una noche a 45°C. El análisis de HPLC y TLC reveló la presencia de considerable material de partida. La mezcla de reacción se calentó a reflujo durante una noche sin ningún cambio apreciable. El disolvente de reacción se evaporó y se sustituyó con 1,2-dicloroetano (20 ml). La mezcla de reacción se agitó a 84°C durante 72 horas. Se inactivó la mezcla de reacción con agua y se extrajo con acetato de etilo. Los extractos orgánicos reunidos se lavaron con agua, salmuera, se secaron y se evaporaron hasta sequedad para proporcionar el producto bruto (5,3 g) que se llevó a la siguiente etapa sin posterior purificación: EMES *m/z* (intensidad relativa) 378,0 ($M - H^+$, 50).

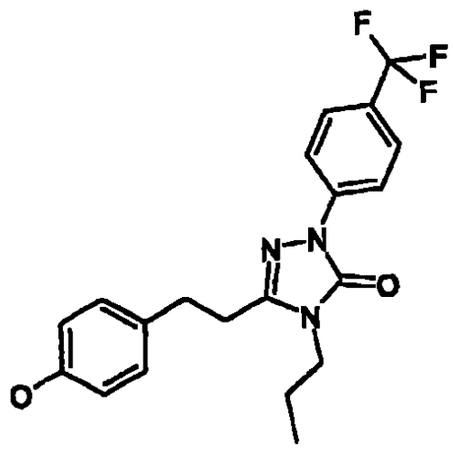
Etapa D: Preparación de 5-[2-(4-metoxifenil)etil]-4-propil-2-(4-trifluorometilfenil)-2,4-dihidro-[1,2,4]triazol-3-ona



A una solución del intermedio de hidrazina bruto de la etapa C (5,3 g) en THF anhidro (25 ml) se añadió carbonildiimidazol (2,5 g, 15,38 mmoles) y la mezcla de reacción se agita a temperatura ambiente durante una noche. Se evaporó el disolvente y se purificó el residuo mediante cromatografía ultra - rápida en gel de sílice (gradiente de acetato de etilo en hexanos) produciendo el compuesto del título (1,52 g). ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,18 (d, 2 H, J = 8,0 Hz), 7,65 (d, 2 H, J = 8,0 Hz), 7,18 (d, 2 H, J = 7,8 Hz), 7,83 (d, 2 H, J = 8,0 Hz), 3,80 (s, 3 H), 3,55 (t, 2 H, J = 8,0 Hz), 3,08 (t, 2 H, J = 8,0 Hz), 2,82 (m, 2 H), 1,65 (m, 2 H), 0,96 (s, 3 H); EMES *m/z* (intensidad relativa) 406,2 (M + H^+, 100).

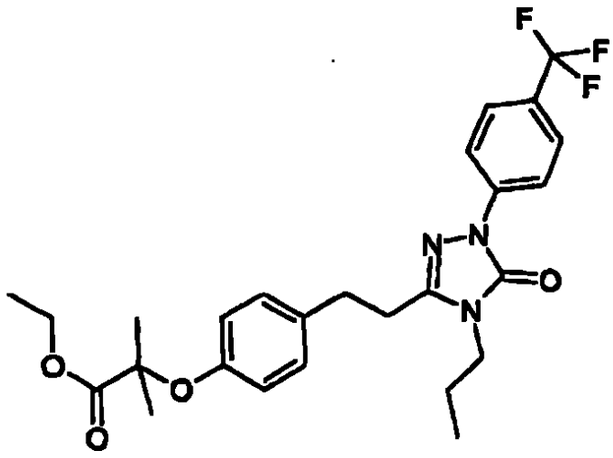
Etapa E: Preparación de 5-[2-(4-hidroxifenil)etil]-4-propil-2-(4-trifluorometilfenil)-2,4-dihidro-

[1,2,4]triazol-3-ona



A una solución de 5-[2-(4-metoxifenil)etil]-4-propil-2-(4-trifluorometilfenil)-2,4-dihidro-[1,2,4]triazol-3-ona (1,52 g, 3,75 mmoles) en cloruro de metileno (36 ml) a -78°C se añadió tribromuro de boro (0,75 ml) y se dejó calentar hasta temperatura ambiente. Después de 2 horas, se inactivó la reacción con agua y se extrajo con acetato de etilo. Las fases orgánicas reunidas se lavaron con agua, salmuera, se secaron y se evaporaron hasta sequedad para producir el producto (1,35 g, 92,5%). ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,13 (d, 2 H, J = 8,8 Hz), 7,81 (d, 2 H, J = 8,8 Hz), 7,09 (d, 2 H, J = 8,4 Hz), 6,66 (m, 2 H), 3,56 (t, 2 H), 2,89 (m, 4 H), 1,58 (m, 2 H), 0,84 (m, 3 H); EMES *m/z* (intensidad relativa) 392,2 (M + H^+, 100), 390,1 (M - H^+, 100).

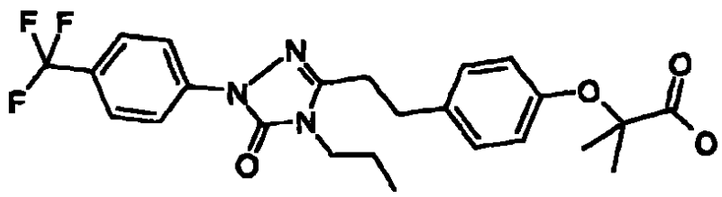
Etapa F: Preparación de éster etílico del ácido 2-metil-2-(4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)propiónico



A una solución de 5-[2-(4-hidroxifenil)etil]-4-propil-2-(4-trifluorometilfenil)-2,4-dihidro-[1,2,4]triazol-3-ona (0,10 g, 0,26 mmoles) y carbonato de cesio (0,16 g, 0,49 mmoles) en DMF anhidro (2,5 ml) se añadió 2-bromoisobutirato de etilo (81,1 mg, 60,6 ml, 0,42 mmoles). Se calentó la mezcla de reacción hasta 75°C durante una noche. Se añadió más 2-bromoisobutirato de etilo (30,3 ml) y se agitó la mezcla a 110°C durante una noche y a temperatura ambiente durante el fin de semana. Se inactivó la mezcla de reacción con agua y se extrajo con acetato de etilo. Los extractos orgánicos reunidos se lavaron con solución acuosa al 5% de cloruro de litio, agua, salmuera, se secaron y se evaporaron, La cromatografía en cromatotron (gradiente de acetato de etilo en hexanos)

proporcionó el compuesto puro (94 mg, 70,7%). ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,14 (m, 2 H), 7,65 (m, 2 H), 7,10 (m, 2 H), 6,80 (m, 2 H), 4,23 (m, 2 H), 3,53 (m, 2 H), 3,05 (m, 2 H), 2,83 (m, 2 H), 1,70 (m, 2 H), 1,57 (s, 6 H), 1,26 (m, 6 H); EMES *m/z* (intensidad relativa) 506,1 (M + H^+, 100).

Etapa G: Ácido 2-Metil-2-(4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)propiónico



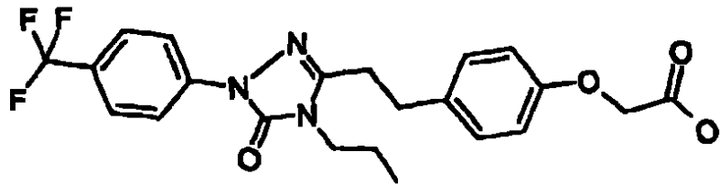
Éster etílico del ácido 2-metil-2-(4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)propiónico (94 mg, 0,19 mmoles) y solución de hidróxido sódico 2 N (2,3 ml) en etanol (5 ml) se calentó hasta 80°C durante 35 minutos. Se evaporó el disolvente, se añadió agua y se acidificó la solución con ácido clorhídrico concentrado (pH 0 - 1) y se extrajo con éter. Los extractos orgánicos reunidos se lavaron con agua, salmuera, se secaron y se evaporaron hasta sequedad para proporcionar el compuesto puro (82 mg, 92,3%): ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,06 (d, 2 H, J = 8,3 Hz), 7,59 (d,

2 H, J = 8,3 Hz), 7,09 (d, 2 H, J = 6,4 Hz), 6,83 (d, 2 H, J = 8,3 Hz), 3,45 (t, 2 H, J = 7,4 Hz), 3,02 (d, 2 H, J = 7,3 Hz), 2,79 (m, 2 H), 1,60 (m, 2 H), 1,52 (s, 6 H), 0,87 (t, 3 H, J = 7,8 Hz); EMES *m/z* (intensidad relativa) 476,1 (M - H^+, 50).

Los siguientes compuestos se prepararon mediante un procedimiento sustancialmente similar:

Ejemplo 134

Ácido (4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético

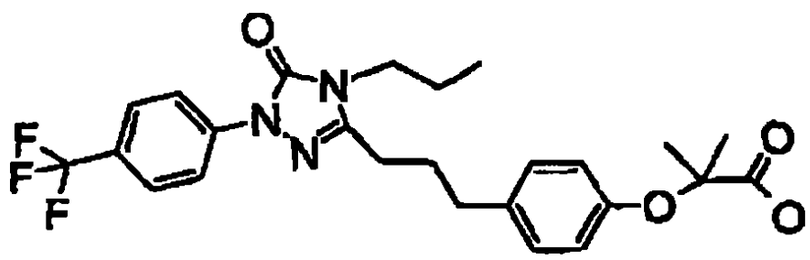


^1H - RMN ($CDCl_3$, 400 MHz), δ 8,08 (d, 2 H, J = 8,3 Hz), 7,60 (d, 2 H, J = 8,3 Hz), 7,12 (d, 2 H, J = 8,8 Hz), 6,82 (d, 2 H, J = 8,8 Hz), 4,60 (s, 2 H), 3,48 (t, 2 H, J = 7,4 Hz), 3,03 (d, 2 H, J = 7,4 Hz), 2,80 (t, 2 H, J = 7,4 Hz), 1,60 (m, 2 H), 0,88 (t, 3 H, J = 7,3 Hz); EMES *m/z* (intensidad relativa) 450,2 (M + H^+, 80).

Ejemplo 135

Ácido 2-metil-2(4-{2-[5-oxo-4-propil-1-(4-

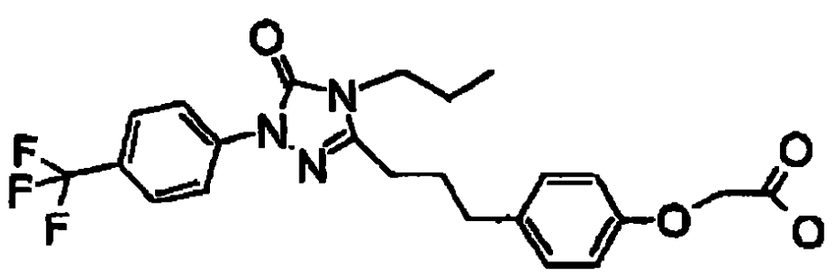
trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)propiónico



^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,12 (d, 2 H, J = 8,8 Hz), 7,80 (d, 2 H, J = 8,81 Hz), 7,12 (d, 2 H, J = 8,31 Hz), 6,74 (d, 2 H, J = 8,8 Hz), 3,56 (m, 2 H), 2,64 (m, 4 H), 1,96 (m, 2 H), 1,60 (m, 2 H), 1,45 (s, 6 H), 0,85 (t, 3 H, J = 7,33 Hz); EMES *m/z* (intensidad relativa) 492,15 (M + H^+).

Ejemplo 136

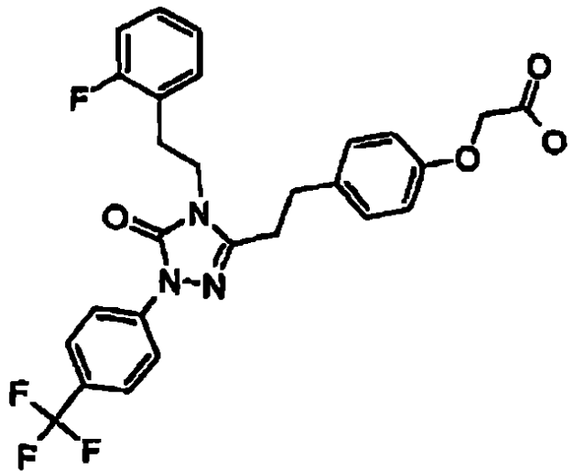
Ácido (4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)acético



^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,12 (d, 2 H, J = 8,8 Hz), 7,80 (d, 2 H, J = 8,8 Hz), 7,14 (d, 2 H, J = 8,31 Hz), 6,82 (d, 2 H, J = 8,32 Hz), 4,60 (s, 2 H), 3,56 (t, 2 H, J = 7,33 Hz), 2,64 (m, 4 H), 1,96 (m, 2 H), 1,60 (m, 2 H), 0,85 (t, 3 H, J = 7,34 Hz); EMES *m/z* (intensidad relativa) 464,14 ($M + H^+$).

Ejemplo 137

Ácido (4-{2-[4-[2-(2-fluorofenil)etil]-5-oxo-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)acético

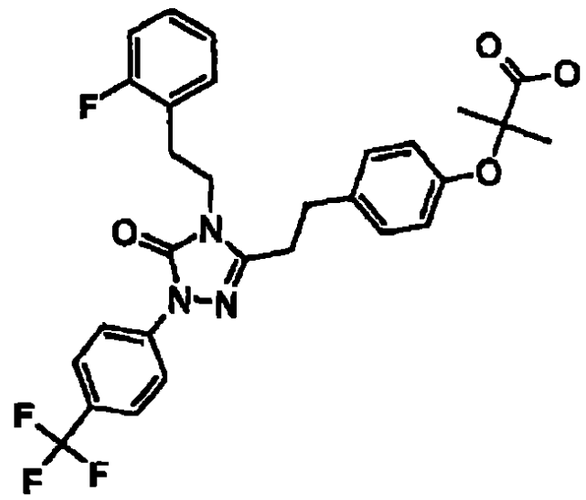


^{1}H - RMN (DMSO - d_6, 400 MHz), δ 2,48 - 2,52 (m, 2 H), 2,75 - 2,79 (m, 2 H), 2,96 (m, 2 H), 3,85 (m, 2 H), 4,44 (s, 2 H), 6,78 (d, J = 7,82 Hz, 2 H), 7,06 - 7,14 (m, 4 H), 7,24

- 7,28 (m, 2 H), 7,80 (d, J = 8,32 Hz, 2 H), 8,10 (d, J = 8,32 Hz, 2 H); EM (ES *m/z*) $C_{27}H_{23}F_4N_3O_4$: 529,99 (M^+ + 1), 528,01 (M^+ - 1).

Ejemplo 138

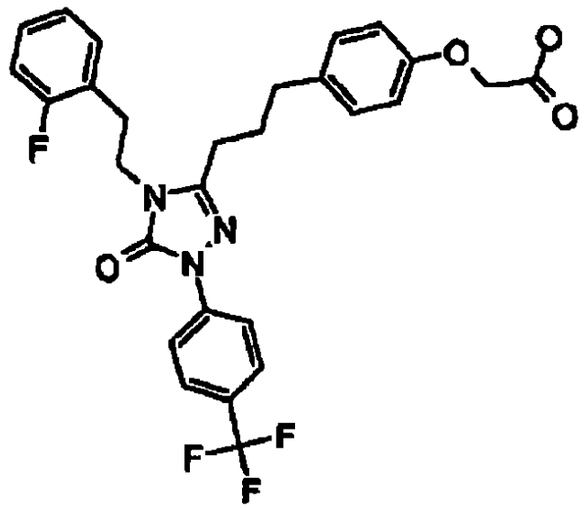
Ácido 2-(4-{2-[4-[2-(2-fluorofenil)etil]-5-oxo-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)-2-metilpropiónico



^{1}H - RMN (DMSO - d_6, 400 MHz), δ 1,54 (s, 6 H), 2,62 (t, J = 7,33 Hz, 2 H), 2,87 (t, J = 7,34 Hz, 2 H), 3,05 (m, 2 H), 3,93 (m, 2 H), 6,82 (d, J = 8,32 Hz, 2 H), 7,15 - 7,23 (m, 4 H), 7,33 - 7,37 (m, 2 H), 7,89 (d, J = 8,32 Hz, 2 H), 8,18 (d, J = 8,31 Hz, 2 H); EM (ES, *m/z* $C_{29}H_{27}F_4N_3O_4$: 558,05 (M^+ + 1), 556,07 (M^+ - 1).

Ejemplo 139

Ácido (4-{3-[4-[2-(2-fluorofenil)etil]-5-oxo-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)acético

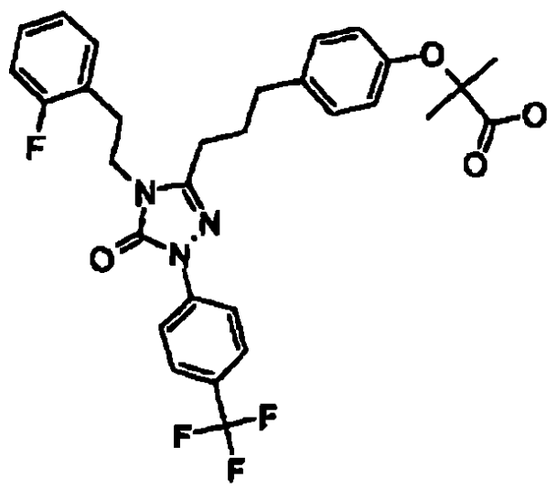


^{1}H - RMN (DMSO - d_6, 400 MHz), δ 1,76 - 1,80 (m, 2 H), 2,23 (t, J = 7,82 Hz, 2 H), 2,51 (t, J = 7,34 Hz, 2 H), 2,97 (t, J = 6,85 Hz, 2 H), 3,83 (t, J = 6,85 Hz, 2 H), 4,61 (s, 2 H), 6,81 (d, J = 8,80 Hz, 2 H), 7,07 - 7,13 (m, 4 H), 7,22 - 7,26 (m, 2 H), 7,80 (d, J = 8,80 Hz, 2 H), 8,10 (d, J = 8,82 Hz, 2 H); EM (ES, *m/z* $C_{28}H_{25}F_4N_3O_4$: 544,24 (M^+ + 1), 542,21 (M^+ - 1).

Ejemplo 140

Ácido 2-(4-{3-[4-[2-(2-fluorofenil)etil]-5-oxo-1-(4-

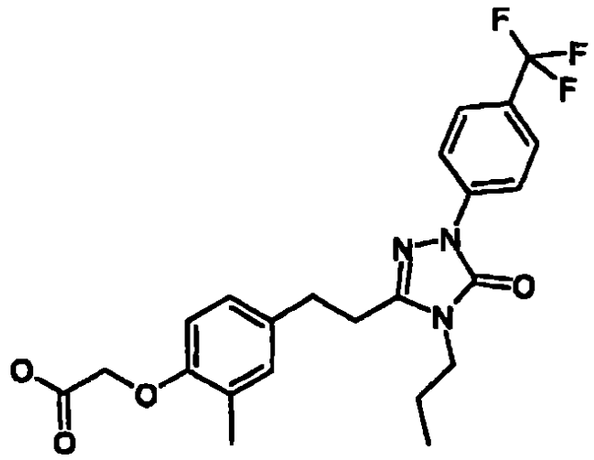
trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)-2-metilpropopiónico



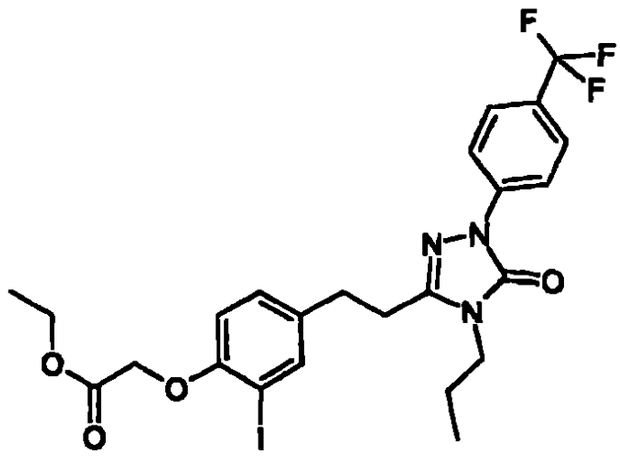
^{1}H - RMN (DMSO - d_6, 400 MHz), δ 1,46 (s, 6 H), 1,78 (m, 2 H), 2,24 (t, J = 7,83 Hz, 2 H), 2,51 (t, J = 7,82 Hz, 2 H), 2,97 (t, J = 6,36 Hz, 2 H), 3,83 (t, J = 6,80 Hz, 2 H), 6,74 (d, J = 8,32 Hz, 2 H), 7,05 - 7,11 (m, 4 H), 7,24 (m, 2 H), 7,79 (d, J = 8,80 Hz, 2 H), 8,10 (d, J = 8,32 Hz, 2 H); EM (ES, *m/z* $C_{30}H_{29}F_4N_3O_4$: 572,20 (M^+ + 1), 570,30 (M^+ - 1).

Ejemplo 141

Ácido 2-metil-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético



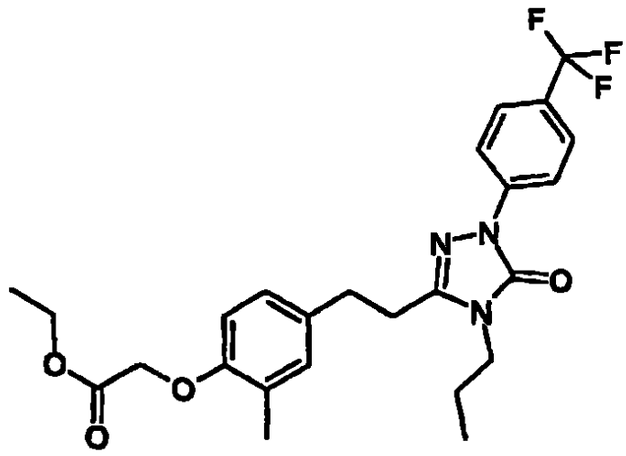
Etapa A: Preparación de éster etílico del ácido (2-yodo-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético



Se agitó a temperatura ambiente una mezcla de éster etílico del ácido (4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-

il]etil}fenoxi)acético (180 mg, 0,38 mmoles), yodo (105 mg, 0,42 mmoles), sulfato de plata (131 mg, 0,42 mmoles) y etanol. Después de 3,5 horas se añadieron más yodo (86 mg) y sulfato de plata (106 mg) y se agitaron durante otras 0,5 horas. Se inactivó la mezcla de reacción con agua y se extrajo con acetato de etilo. Se lavaron los extractos orgánicos reunidos con agua, salmuera, se secaron y se evaporaron hasta sequedad para proporcionar el producto (217 mg, 95%). ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,15 (d, 2 H, J = 8,4 Hz), 7,73 (s, 1 H), 7,67 (d, 2 H, J = 8,4 Hz), 7,18 (m, 1 H), 6,67 (d, 1 H, J = 8,0 Hz), 4,66 (s, 2 H), 4,26 (c, 2 H, J = 7,6 Hz), 3,68 (t, 2 H, J = 7,3 Hz), 3,05 (t, 2 H, J = 7,4 Hz), 2,82 (t, 2 H, J = 7,3 Hz), 1,7 (m, 2 H), 1,29 (d, 3 H, J = 7,6 Hz), 0,96 (d, 3 H, J = 7,6 Hz); EMES, *m/z* (intensidad relativa) 604,2 ($M + H^+$, 100).

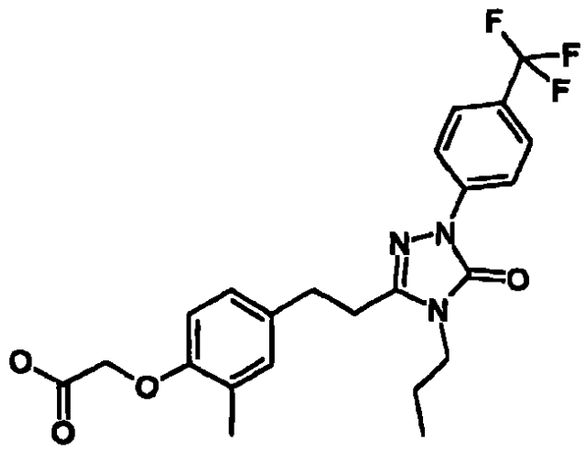
Etapa B: Preparación de éster etílico del ácido 2-metil-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético



Se desgasificó una mezcla del ácido 2-yodo-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético (182 mg, 0,3 mmoles), ácido metilborónico (53,9 mg, 0,9 mmoles) y fluoruro de cesio (136,7 mg, 0,9 mmoles) en dioxano (3 ml) y se llenó con nitrógeno por tres veces, después se añadió complejo [1,1'bis(diefenilfosfino)ferroceno]dicloropaladio (II) con diclorometano (1:1) (36 mg, 0,04 mmoles) y se calentó la mezcla de reacción a 80°C. Después de 4 horas se filtró la mezcla de reacción a través de celite y se evaporó. La cromatografía ultra - rápida en gel de sílice (gradiente de acetato de etilo en hexanos) produjo el compuesto puro (73 mg, 49,3%): ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,16 (d, 2 H, J = 8,4 Hz), 7,66 (d, 2 H, J = 8,8 Hz), 7,05 (s, 1 H), 7,00 (m, 1 H), 6,64 (d, 1 H, J = 8,0 Hz), 4,62 (s, 2 H), 4,25 (m, 2 H), 3,56 (t, 2 H, J = 8,0 Hz), 3,02

(t, 2 H, J = 8,4 Hz), 2,83 (t, 2 H, J = 8,4 Hz), 2,29 (s, 3 H), 1,7 (m, 2 H), 1,29 (t, 3 H, J = 6,8 Hz), 0,95 (t, 3 H, J = 7,2 Hz); EMES, *m/z* (intensidad relativa) 492,2 (M + H^+, 75).

Etapa C: Preparación de ácido 2-metil-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético



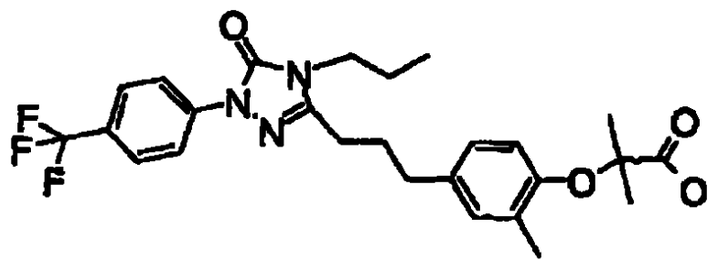
Se calentó una mezcla de éster etílico del ácido 2-metil-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético (70 mg, 0,14 mmoles) y solución de hidróxido sódico 2 N (1,6 ml) en etanol (3,3 ml) a 75°C durante 45 minutos. Se evaporó el disolvente, se añadió agua y se acidificó la solución con ácido clorhídrico concentrado (pH 0 - 1), se extrajo con éter. Se lavaron los extractos orgánicos reunidos con agua, salmuera, se secaron y se evaporaron hasta sequedad

para proporcionar el compuesto puro (60 mg, 96,4%): ^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,09 (d, 2 H, J = 8,8 Hz), 7,60 (d, 2 H, J = 8,8 Hz), 6,99 (s, 1 H), 6,94 (m, 1 H), 6,60 (d, 1 H, J = 8,4 Hz), 4,61 (s, 2 H), 3,48 (t, 2 H, J = 8,0 Hz), 2,98 (t, 2 H, J = 8,4 Hz), 2,76 (t, 2 H, J = 7,2 Hz), 2,21 (s, 3 H), 1,62 (m, 2 H), 0,88 (t, 3 H, J = 7,6 H); EMES, *m/z* (intensidad relativa) 464,2 (M + H^+, 40), 462,1 (M - H^+, 100).

Los siguientes compuestos se prepararon mediante un procedimiento sustancialmente similar:

Ejemplo 142

Ácido 2-metil-2-(2-metil-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}fenoxi)propiónico

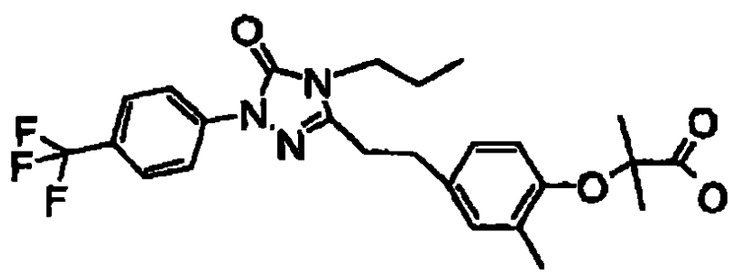


^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,15 (m, 2 H), 7,80 (m, 2 H), 6,99 (s, 1 H), 6,94 (m, 1 H), 6,62 (m, 1 H), 3,56 (m,

2 H), 2,62 (m, 4 H), 2,10 (s, 3 H), 1,98 (m, 2 H), 1,60 (m, 2 H), 1,45 (s, 6 H), 0,85 (m, 3 H); EMES, *m/z* 506,3 ($M + H^+$).

Ejemplo 143

Ácido 2-metil-2-(2-metil-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)propiónico

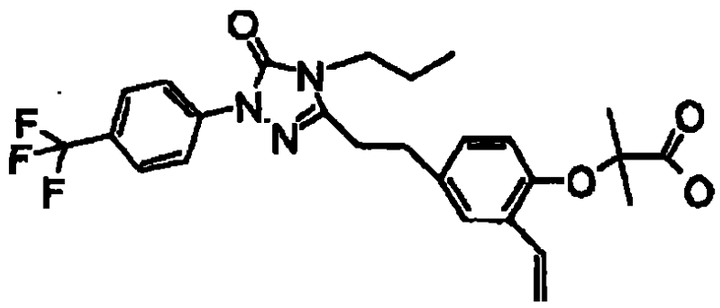


^1H - RMN ($CDCl_3$, 400 MHz), δ 8,13 (d, 2 H, J = 8,8 Hz), 7,82 (d, 2 H, J = 9,3 Hz), 7,1 (m, 1 H), 7,0 (m, 1 H), 6,62 (m, 1 H), 3,58 (m, 2 H), 2,91 (s, 4 H), 2,12 (s, 3 H), 1,59 (m, 2 H), 1,46 (s, 6 H), 0,85 (m, 3 H); EMES, *m/z* 492,3 ($M + H^+$).

Ejemplo 144

Ácido 2-metil-2-(2-vinil-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-

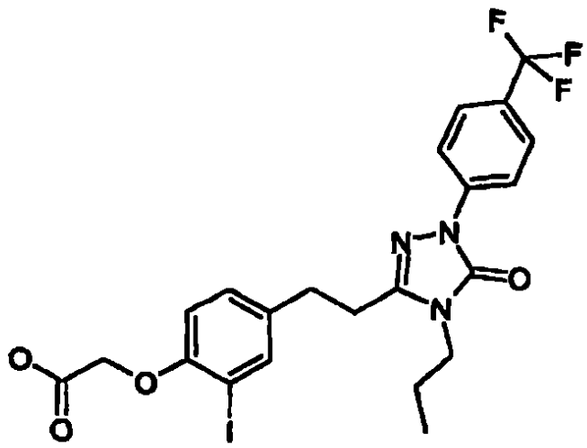
il]etil}fenoxi)propiónico



^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,13 (d, 2 H, J = 8,32 Hz), 7,81 (d, 2 H, J = 8,8 Hz), 7,51 (d, 1 H, J = 2,44 Hz), 7,13 (m, 1 H), 6,96 (m, 1 H), 6,69 (m, 1 H), 5,78 (m, 1 H), 5,23 (m, 1 H), 3,58 (t, 2 H, J = 7,34 Hz), 2,96 (m, 4 H), 1,60 (m, 2 H), 1,46 (s, 6 H), 0,84 (t, 3 H, J = 7,3 Hz); EMES, *m/z* 504,03 ($M + H^+$).

Ejemplo 145

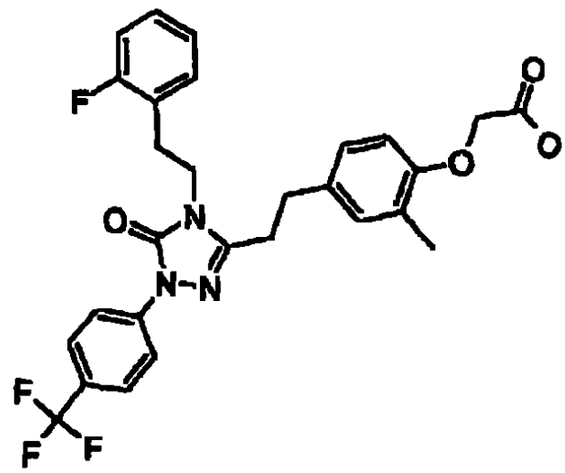
Ácido (2-yodo-4-{2-[5-oxo-4-propil-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}fenoxi)acético



^{1}H - RMN ($CDCl_3$, 400 MHz), δ 8,08 (d, 2 H, J = 8,4 Hz), 7,69 (s, 1 H), 7,61 (d, 2 H, J = 8,8 Hz), 7,11 (d, 1 H, J = 8,4 Hz), 6,65 (d, 1 H, J = 8,0 Hz) 4,63 (s, 2 H), 3,51 (t, 2 H, J = 7,6 Hz), 3,01 (t, 2 H, J = 7,6 Hz) 2,77 (t, 2 H, J = 7,2 Hz), 1,63 (m, 2 H), 0,89 (t, 3 H, J = 7,2 Hz); EMES, *m/z* (intensidad relativa) 576,0 (M + H^+, 100), 574,0 (M - H^+, 100).

Ejemplo 146

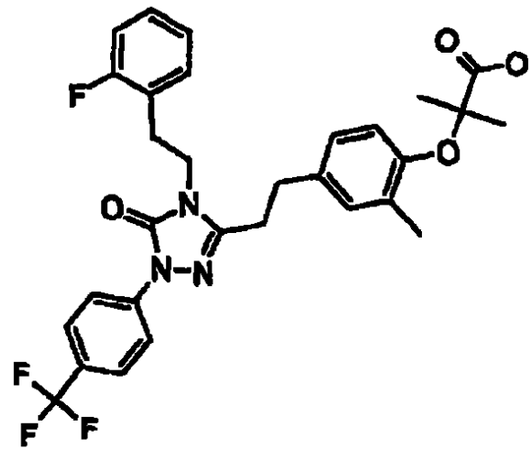
Ácido (4-{2-[4-[2-(2-fluorofenil)etil}-5-oxo-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil}-2-metilfenoxi)acético



^{1}H - RMN (DMSO - d_6, 400 MHz), δ 2,15 (s, 3 H), 2,47 - 2,51 (m, 2 H), 2,75 (t, J = 7,34 Hz, 2 H), 2,97 (t, J = 6,36 Hz, 2 H), 3,85 (t, J = 6,36 Hz, 2 H), 4,63 (s, 2 H), 6,70 (d, J = 8,32 Hz, 1 H), 6,91 - 6,96 (m, 2 H), 7,08 - 7,14 (m, 2 H), 7,24 - 7,29 (m, 2 H), 7,81 (d, J = 8,31 Hz, 2 H), 8,10 (d, J = 8,31 Hz, 2 H); EM (ES, *m/z*: $C_{28}H_{25}F_4N_3O_4$: 544,01 (M^+ + 1), 542,05 (M^+ - 1).

Ejemplo 147

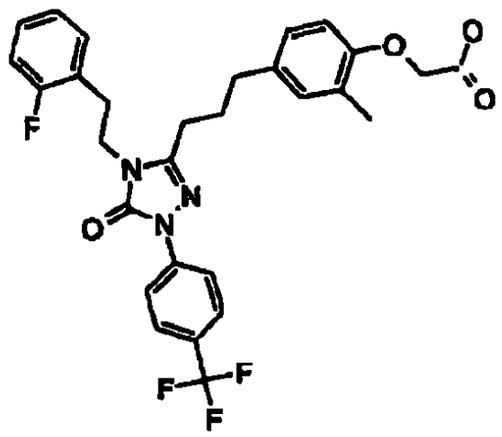
Ácido 2-(4-{2-[4-[2-(2-fluorofenil)etil}-5-oxo-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]etil)-2-metilfenoxi)-2-metilpropiónico



^{1}H - RMN (DMSO - d_6, 400 MHz), δ 1,46 (s, 6 H), 2,12 (s, 3 H), 2,50 - 2,52 (m, 2 H), 2,74 (t, J = 7,83 Hz, 2 H), 2,96 (t, J = 6,85 Hz, 2 H), 3,84 (t, J = 6,85 Hz, 2 H), 6,59 (d, J = 7,83 Hz, 1 H), 6,88 (d, J = 8,31 Hz, 1 H), 6,97 (s, 1 H), 7,10 - 7,12 (m, 2 H), 7,25 - 7,29 (m, 2 H), 7,81 (d, J = 8,30 Hz, 2 H), 8,10 (d, J = 8,30 Hz, 2 H); EM (ES, *m/z*: $C_{30}H_{29}F_4N_3O_4$: 571,97 (M^+ + 1), 570,00 (M^+ - 1).

Ejemplo 148

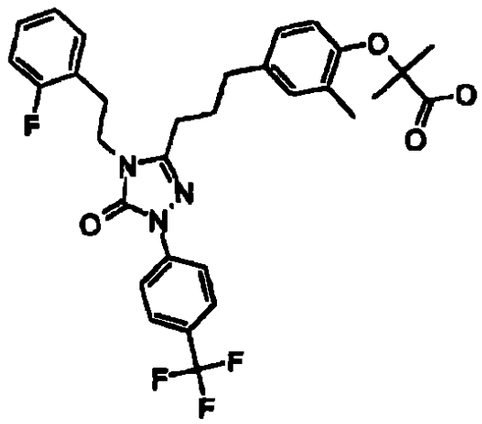
Ácido (4-{3-[4-[2-(2-fluorofenil)etil)-5-oxo-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}-2-metilfenoxi)acético



^{1}H - RMN (DMSO - d_6, 400 MHz), δ 1,76 - 1,80 (m, 2 H), 2,15 (s, 3 H), 2,23 (t, J = 7,82 Hz, 2 H), 2,45 - 2,48 (m, 2 H), 2,96 (t, J = 6,36 Hz, 2 H), 3,83 (t, J = 6,85 Hz, 2 H), 4,63 (s, 2 H), 6,70 (d, J = 8,32 Hz, 1 H), 6,90 (d, J = 7,83 Hz, 1 H), 6,95 (s, 1 H), 7,07 - 7,12 (m, 2 H), 7,22 (m, 2 H), 7,80 (d, J = 8,80 Hz, 2 H), 8,10 (d, J = 8,32 Hz, 2 H); EM (ES, *m/z*: $C_{29}H_{27}F_4N_3O_4$: 558,23 (M^+ + 1), 556,23 (M^+ - 1).

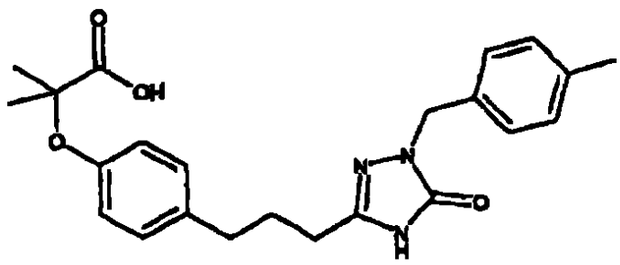
Ejemplo 149

Ácido 2-(4-{3-[4-[2-(2-fluorofenil)etil}-5-oxo-1-(4-trifluorometilfenil)-4,5-dihidro-1H-[1,2,4]triazol-3-il]propil}-2-metilfenoxi)-2-metilpropiónico



^{1}H - RMN (DMSO - d_6, 400 MHz), δ 1,46 (s, 6 H), 1,76 - 1,80 (m, 2 H), 2,11 (s, 3H), 2,23 (t, J = 7,82 Hz, 2 H), 2,45 (t, J = 7,82 Hz, 2 H), 2,96 (t, J = 6,36 Hz, 2 H), 3,83 (t, J = 6,85 Hz, 2 H), 6,60 (d, J = 8,31 Hz, 1 H), 6,86 (dd, J_1 = 8,31 Hz, J_2 = 1,96 Hz, 1 H), 6,96 (d, J = 1,96 Hz, 1 H), 7,07 - 7,11 (m, 2 H), 7,21 - 7,26 (m, 2 H), 7,79 (d, J = 8,80 Hz, 2 H), 8,10 (d, J = 8,80 Hz, 2 H); EM (ES, *m/z*: $C_{31}H_{31}F_4N_3O_4$: 586,2 (M^+ + 1), 584,2 (M^+ - 1).

Ejemplo 150



Preparación de la forma IV polimorfa

El compuesto del título (5,75 g) se reúne con acetato de etilo (30 ml) y se calienta a reflujo en forma de suspensión. Adicionalmente se añade acetato de etilo (19 ml) y se obtiene la solución de reflujo. Se enfría la solución y se produce la cristalización. Se enfría la suspensión hasta 0°C y se mantiene a esa temperatura durante 1 hora, después se filtra y la torta del filtro se aclara con acetato de etilo frío. Se secan los cristales obtenidos a vacío a 60°C durante una noche para proporcionar el compuesto del título en la forma IV polimorfa deseada: 5,45 g, 94,5%. p. f. 129,4 - 130,3 °C.

Forma IV

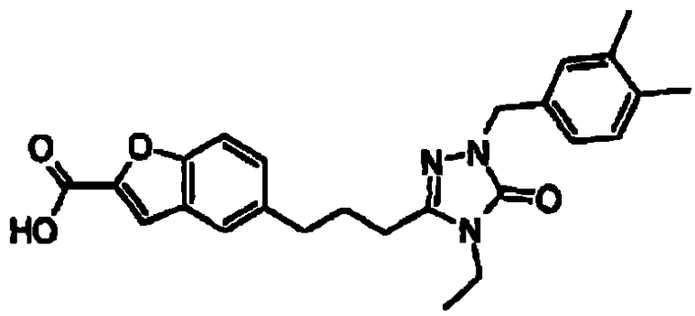
° de Ángulo Theta 2	valor d Amstrong	% de intensidad
6,863	12,87	4,7
7,993	11,135	25,7
13,225	6,689	49,9
13,746	6,437	12,5
15,023	5,893	1,2
15,97	5,545	33,9
16,669	5,314	4,3
17,005	5,21	3,1
17,327	5,114	23,1

781

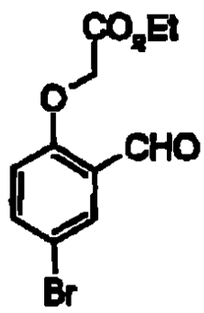
17,925	4,944	12
19,598	4,526	30,5
20,132	4,407	2
20,453	4,339	3,2
20,764	4,274	100
21,714	4,089	2
21,954	4,045	2,2
22,736	3,908	2,4
24,055	3,697	32,5
24,538	3,625	3,2
24,803	3,587	5,5
25,498	3,491	5
26,667	3,34	7,4
27,83	3,203	3,4
28,333	3,147	1,6
28,739	3,104	6,5
29,503	3,025	0,8
30,193	2,9575	4,2
30,552	2,9236	1,4
30,894	2,8921	0,8
32,905	2,7197	1,1
33,296	2,6887	1
34,198	2,6198	2,7

Ejemplo 151

Preparación de



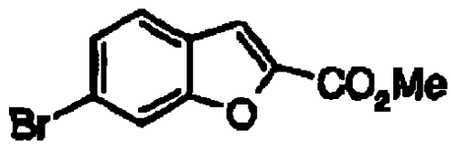
Etapa A: Preparación de



A una solución de 5-bromosalicilaldehído (3,15 g, 15,6 mmoles) en DMF (10 ml) a temperatura ambiente se añadió K_2CO_3 (5,0 g, 36,2 mmoles) y bromoacetato de etilo (2,6 ml, 23,4 mmoles). Se agitó la mezcla a temperatura ambiente durante una hora. Se diluyó la mezcla con éter dietílico (20 ml) y se añadió HCl 1 N hasta pH 3 - 4. Se separó la fase orgánica y se lavó con agua y salmuera. Se secó la fase orgánica sobre $MgSO_4$ y se retiró el disolvente a presión reducida para proporcionar el compuesto del

título. $C_{11}H_{11}BrO_4$. (MMP: 287,11); EM: m/z (M^+ + 1) 288,1.

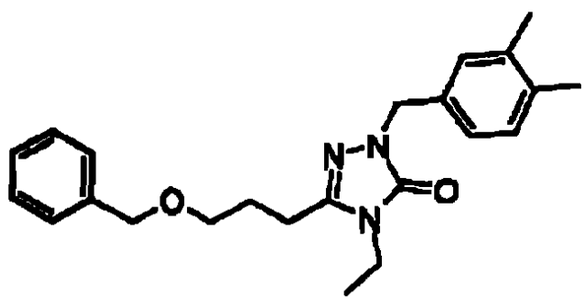
Etapa B: Preparación de



A una solución MeONa (preparado a partir de 88 mg de Na (3,8 mmoles) en 10 ml de MeOH) se añadió una solución del producto de la etapa A en metanol (1 ml) a temperatura ambiente. Se calentó la mezcla a reflujo durante 10 minutos en un baño precalentado a 80°C. Después, se dejó que la mezcla de reacción se enfriara hasta temperatura ambiente y el compuesto del título precipita con la solución en forma de un sólido blanco. Se filtró el sólido y se secó a vacío.

$C_{10}H_7BrO_3$. (MMP: 255,07); EM: m/z (M^+ + 1) 256.

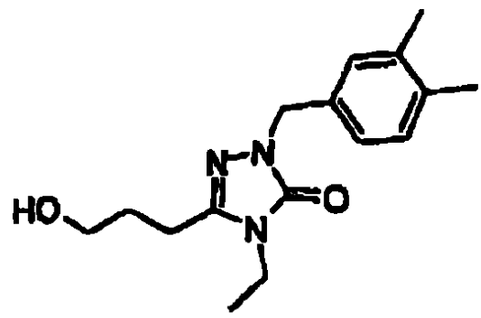
Etapa C: Preparación de



A una solución del producto preparado en el ejemplo 38, etapa D (11,3 g, 0,0436 moles) en metiletilcetona (300 ml) se añadió cloruro de 3,4-dimetilbencilo (16,0 ml, 0,1089 moles) seguido de polvo de carbonato potásico (30,1 g, 0,1382 moles). Se agitó la mezcla resultante a 80 - 85°C en un tubo de secado durante 48 horas. Se enfrió la mezcla de reacción hasta temperatura ambiente y después se repartió entre acetato de etilo (300 ml) y solución acuosa saturada de NH_4Cl (300 ml). Se extrajo la fase acuosa con acetato de etilo (200 ml) y se secó la fase orgánica reunida sobre Na_2SO_4 y se filtró. La evaporación del disolvente proporcionó el producto bruto, que se purificó en una columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano para proporcionar el compuesto del título en forma de un aceite incoloro.

$C_{23}H_{29}N_3O_2$. (MMP: 379,51); EM: m/z (M^+ + 1) = 380,2.

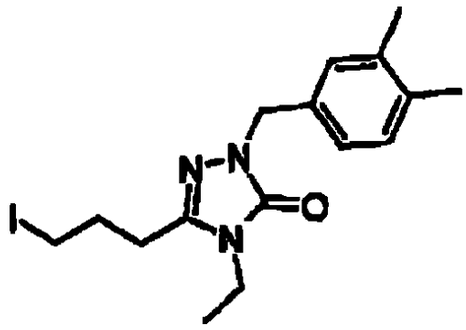
Etapa D: Preparación de



A una solución del producto de la etapa C (16,0 g, 0,0421 moles) en etanol (400 ml) a temperatura ambiente se añadió paladio, 10% en carbono activado (4,2 g). Se agitó la mezcla bajo atmósfera de nitrógeno (globo) durante 3 horas y después se filtró mediante un tampón de celite. La evaporación del disolvente proporcionó el compuesto del título que se utilizó en la etapa E sin purificación adicional.

$C_{16}H_{23}N_3O_2$. (MMP: 289,38); EM: m/z (M^+ + 1) = 290,2.

Etapa E: Preparación de

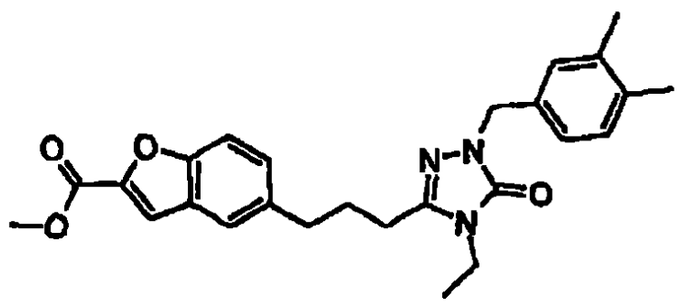


A una solución de trifenilfosfina (8,1 g, 31,0 mmoles) e imidazol (2,1 g, 31,0 mmoles) en una mezcla 3:1 de Et_2O-CH_3CN (160 ml) a 0°C en atmósfera de nitrógeno, se añadió yodo (7,8 g, 31,0 mmoles) en pequeñas porciones con agitación vigorosa. Se calentó la mezcla resultante a temperatura ambiente y se agitó durante 30 minutos.

Después se enfrió la mezcla hasta 0°C y se añadió una solución del producto de la etapa D (6,0 g, 20,7 mmoles) en una mezcla 1:1 de Et_2O-CH_3CN (40 ml). Se agitó la reacción a 0°C durante 15 minutos y a temperatura ambiente durante 30 minutos y después se vertió en HCl 0,5 N (200 ml). Se extrajo la fase acuosa dos veces con una mezcla 1:1 de Et_2O-hexanos (300 ml) y se secó la fase orgánica reunida cobre Na_2SO_4 y se filtró. La evaporación del disolvente proporcionó un producto bruto, que se purificó en una columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano para proporcionar el compuesto del título en forma de un aceite amarillo.

$C_{16}H_{22}IN_3O$. (MMP: 399,28); EM: m/z (M^+ + 1) = 400,2.

Etapa F: Preparación de

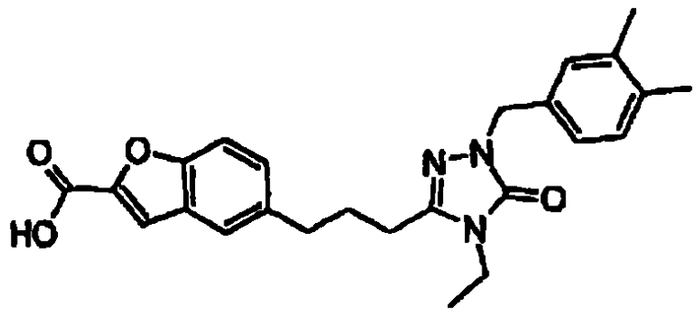


A una suspensión agitada de polvo de cinc (0,968 g, 14,7 mmoles) en THF anhidro (5 ml) bajo atmósfera de nitrógeno a 60°C se añadió 1,2-dibromoetano (63 µl, 0,7 mmoles).

Después de 15 minutos de vigorosa agitación, se dejó enfriar la suspensión hasta temperatura ambiente y se añadió clorotrimetilsilano (78 µl, 0,6 mmoles). Se agitó la mezcla durante 30 minutos y después se añadió gota a gota una solución del producto de la etapa E (0,98 g, 2,46 mmoles) en THF anhidro (5 ml). Se volvió a calentar la mezcla hasta 60°C y después se agitó durante 10 minutos. Se añadió una solución de la etapa B (0,210 g, 0,82 mmoles), $Pd(dba)_2$ (0,0237 g, 0,04 mmoles) y tri-o-tolilfosfina (0,025 g, 0,082 mmoles) en THF anhidro (2,5 ml) y la solución resultante se mantuvo a 60°C durante 2 horas. Después la reacción se enfrió a temperatura ambiente y se vertió en una mezcla 1:1 de AcOEt y HCl 0,5 N (40 ml). Se separaron las fases y se extrajo la fase acuosa con acetato de etilo (20 ml). Se lavaron las fases orgánicas reunidas con HCl 0,5 N (20 ml), se secaron sobre Na_2SO_4 y se filtraron. La evaporación del disolvente proporcionó un producto bruto que se purificó en una columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano para proporcionar el compuesto del título en forma de un aceite incoloro.

$C_{26}H_{29}N_3O_4$. (MMP: 447,54); EM: m/z ($M^+ + 1$) = 448,2.

Etapa G: Preparación de

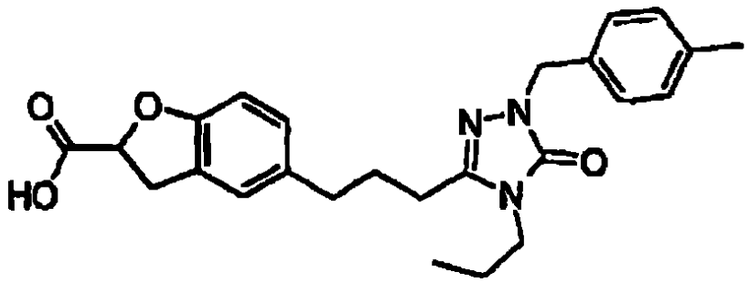


A una solución del producto de la etapa F (0,235 g, 0,52 mmoles) en THF (10,5 ml) a temperatura ambiente se añadió una solución de LiOH 1 N (4,2 ml, 4,2 mmoles). Se agitó la mezcla durante una noche y se separaron las fases. Se lavó la fase acuosa con éter dietílico (3 x 10 ml) y se enfrió hasta 0°C. Después se ajustó el pH hasta 1 - 2 mediante adición de HCl 1 N, se extrajo la fase acuosa con AcOEt (2 x 20 ml). Se secó la fase orgánica reunida sobre Na_2SO_4, se filtró y se concentró hasta sequedad para proporcionar el compuesto del título.

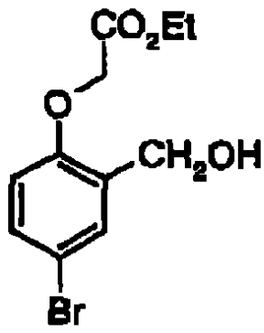
$C_{25}H_{27}N_3O_4$. (MMP: 433,51); EM: m/z (M^+ + 1) = 434,2.

Ejemplo 152

Preparación de



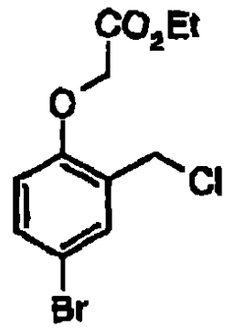
Etapa A: Preparación de



A una solución del producto de la etapa A del ejemplo 151 (2,5 g, 8,7 mmoles) en EtOH (10 ml) a 0°C se añadió en una porción $NaBH_4$ (0,394 g, 10,4 mmoles). Se agitó la mezcla durante 90 minutos permitiendo que la temperatura se elevara. Después se añadió acetona (1 ml) y se retiró el disolvente a vacío. Se disolvió el aceite obtenido en CH_2Cl_2 (20 ml) y se lavó con salmuera (20 ml). Se separaron las fases y la orgánica se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente produjo el compuesto del título en forma pura.

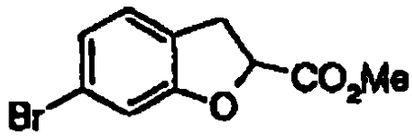
$C_{11}H_{11}BrO_4$. (MMP: 289,11); EM: m/z (M^+ + 1) = 290,1.

Etapa B: Preparación de



A una solución de $SOCl_2$ (0,7 ml, 10,3 mmoles) y piridina (3 gotas) en CH_2Cl_2 (10 ml) a temperatura ambiente se añadió gota a gota una solución del producto de la etapa A (2,5 g, 8,6 mmoles) en CH_2Cl_2 (5 ml). Se calentó la mezcla de reacción a 50°C durante 2 horas, después se dejó enfriar y se lavó con una solución acuosa saturada de $NaHCO_3$ (10 ml). Se separaron las fases y la fase acuosa se extrajo con CH_2Cl_2 (2 x 10 ml). Se reunieron las fases orgánicas, se secaron sobre Na_2SO_4 y se filtraron. La evaporación del disolvente produjo el compuesto del título en forma pura. $C_{11}H_{12}BrClO_3$. (MMP: 307,57); EM: m/z (M^+ + 1) = 307,0.

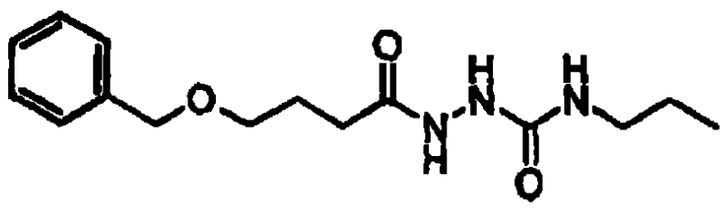
Etapa C: Preparación de



A una solución del producto de la etapa B (1,83 g, 5,9 mmoles) en N-metil-2-pirrolidinona (6 ml) a 0°C bajo atmósfera de N_2 se añadió en una porción NaH (aceite mineral al 60%, 0,283 g, 7 mmoles). Se agitó la mezcla de reacción a temperatura ambiente durante un día, después se añadieron algunas gotas de MeOH. Se diluyó la mezcla en AcOEt (20 ml) y HCl al 10% (20 ml). Se separaron las fases y se lavó la fase orgánica con HCl al 10% (2 x 20 ml) y finalmente con salmuera (20 ml). Se secó la fase orgánica sobre Na_2SO_4 y se filtró. La evaporación del disolvente produjo el compuesto del título.

$C_{10}H_9BrO_3$. (MMP: 257,09); EM: m/z (M^+ + 1) = 257,0.

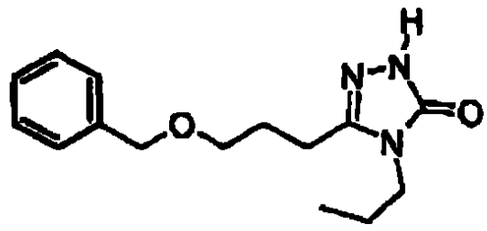
Etapa D: Preparación de



A una solución del producto de la etapa B del ejemplo 38 (82,2 g, 0,423 mmoles) en THF (400 ml) se añadió gota a gota una solución de isocianato de propilo (Aldrich 47,6 ml, 0,508 moles) en THF (400 ml) y se agitó la mezcla a temperatura ambiente durante una hora. La evaporación del disolvente produjo el compuesto del título en forma de un polvo blanquecino que se usó en la etapa E sin purificación adicional.

$C_{15}H_{23}N_3O_3$. (MMP: 293,37); EM: m/z (M^+ + 1) = 294,2.

Etapa E: Preparación de

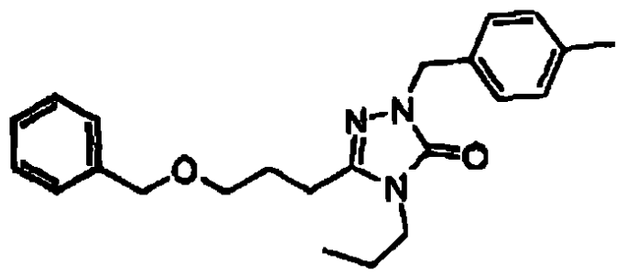


Una suspensión del producto de la etapa D (124,0 g, 0,423 mmoles) en una solución de KOH (28,5 g, 0,508 moles) en agua (570 ml) (1,2 equivalentes de solución acuosa al 5% de KOH) se calentó a 110°C durante una hora (tan pronto como se elevó la temperatura desapareció la suspensión). Al mismo tiempo, una TLC mostró que no quedaba nada del material de partida y se enfrió la reacción hasta temperatura ambiente. Después se ajustó el pH hasta pH = 6 - 7 mediante la adición de HCl 1 N y se extrajo con AcOEt

(3 x 500 ml). Se secaron las fases orgánicas reunidas sobre Na_2SO_4, se filtraron y se evaporaron para proporcionar el compuesto del título en forma de un sólido blanco.

$C_{15}H_{21}N_3O_2$. (MMP: 275,35); EM: m/z (M^+ + 1) = 276,2.

Etapa F: Preparación de

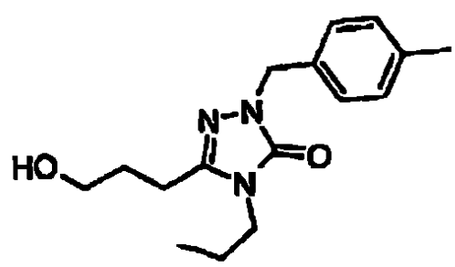


A una solución del producto de la etapa E (11,5 g, 0,0418 mmoles) en metiletilcetona (300 ml) se añadió bromuro de 4-metilbencilo (11,6 g, 0,0616 moles) seguido de polvo de carbonato potásico (28,9 g, 0,209 moles). Se agitó la mezcla resultante a 80 - 85°C en tubo de secado durante 24 horas. Se enfrió la mezcla de reacción hasta temperatura ambiente y después se repartió entre acetato de etilo (300 ml) y solución acuosa saturada de NH_4Cl (300 ml). Se extrajo la fase acuosa con acetato de etilo (200 ml) y las fase orgánica reunida se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente proporcionó un producto bruto que se purificó en columna de gel de sílice eluyendo

con acetato de etilo al 50% en hexano para proporcionar el compuesto del título en forma de un aceite incoloro.

$C_{23}H_{29}N_3O_2$. (MMP: 379,51); EM: m/z (M^+ + 1) = 380,2.

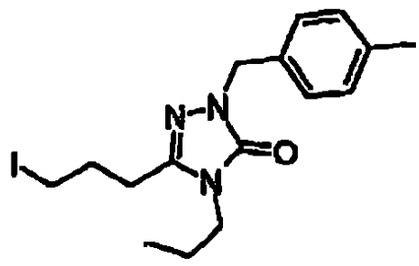
Etapa G: Preparación de



A una solución del producto de la etapa F (10,0 g, 0,0263 moles) en etanol (500 ml) a temperatura ambiente, se añadió paladio, 10% sobre carbono activo (2,6 g). Se agitó la mezcla bajo atmósfera de nitrógeno (globo) durante 3 horas y después se filtró mediante un tampón de celite. La evaporación del disolvente proporcionó el compuesto del título en forma de un sólido blanco que se utilizó en la etapa H sin purificación adicional.

$C_{16}H_{23}N_3O_2$. (MMP: 289,38); EM: m/z (M^+ + 1) = 290,2.

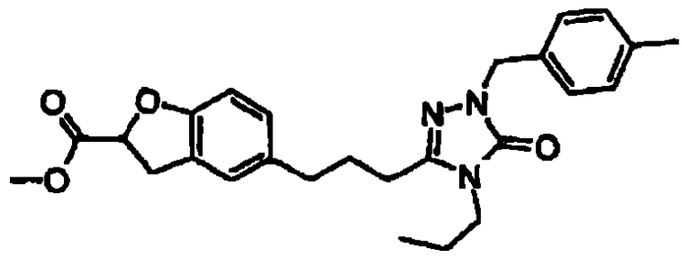
Etapa H: Preparación de



A una solución de trifenilfosfina (10,3 g, 39,4 mmoles) e imidazol (2,7 g, 39,4 mmoles) en una mezcla 3:1 de Et_2O-CH_3CN (200 ml) a 0°C bajo atmósfera de nitrógeno, se añadió en pequeñas porciones yodo (10,0 g, 39,4 mmoles) con agitación vigorosa. Se calentó la mezcla resultante a temperatura ambiente y se agitó durante una hora. Después la mezcla se enfrió hasta 0°C y se añadió una mezcla 1:1 de Et_2O-CH_3CN (50 ml). Se agitó la reacción a 0°C durante 15 minutos y a temperatura ambiente durante 1 hora y después se vertió en HCl 0,5 N (100 ml). Se extrajo la fase acuosa dos veces con una mezcla 1:1 de Et_2O-hexanos (200 ml) y la fase orgánica reunida se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente proporcionó un producto bruto que se purificó en columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano para proporcionar el compuesto del título en forma de un aceite amarillo.

$C_{16}H_{22}IN_3O$. (MMP: 399,28); EM: m/z (M^+ + 1) = 400,2.

Etapa I: Preparación de

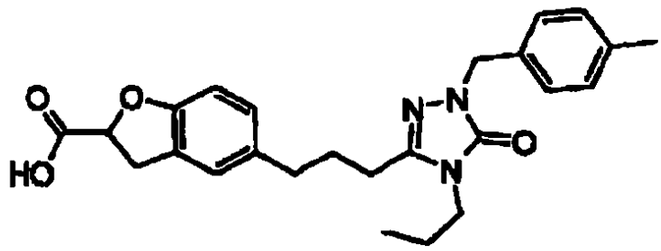


A una suspensión agitada de polvo de cinc (0,411 g, 6,3 mmoles) en THF anhidro (1,5 ml) bajo atmósfera de nitrógeno a 60°C se añadió 1,2-dibromoetano (27 µl, 0,31 mmoles). Después de 15 minutos de agitación vigorosa se dejó que la suspensión se enfriara hasta temperatura ambiente y se añadió clorotrimetilsilano (33 µl, 0,26 mmoles). Se agitó la mezcla durante 30 minutos y después se añadió gota a gota una solución del producto de la etapa H (0,42 g, 1,05 mmoles) en THF anhidro (1,5 ml). Se volvió a calentar la mezcla hasta 60°C y después se agitó durante 10 minutos. Se añadió una solución del producto de la etapa C (0,285 g, 1,05 mmoles), $Pd(dba)_2$, (0,030 g 0,052 mmoles) y tri-o-tolilfosfina (0,032 g, 0,105 mmoles) en THF anhidro (2,5 ml) y la solución resultante se mantuvo a 60°C durante 2 horas. Después la reacción se enfrió a temperatura ambiente y se vertió en una mezcla 1:1 de AcOEt y HCl 0,5 N (50 ml). Se separaron las fases y se extrajo la fase acuosa con acetato de etilo (2 x 20 ml).

Se lavaron las fases orgánicas reunidas con HCl 0,5 N (25 ml), se secaron sobre Na_2SO_4 y se filtraron. La evaporación del disolvente proporcionó un producto bruto que se purificó en columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano para proporcionar el compuesto del título en forma de un aceite incoloro.

$C_{26}H_{31}N_3O_4$. (MMP: 449,55); EM: m/z (M^+ + 1) = 450,2.

Etapa J: Preparación de



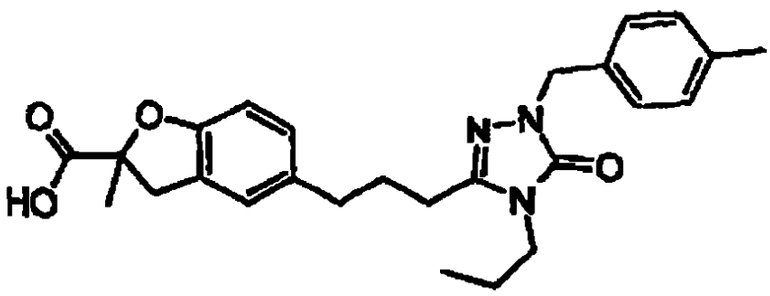
A una suspensión del producto de la etapa I (0,05 g, 0,11 mmoles) en THF (2,5 ml) a temperatura ambiente se añadió una solución de NaOH 1 N (2,5 ml, 2,5 mmoles). Se agitó la mezcla durante dos días y después se separaron las fases. Se lavó la fase acuosa con éter dietílico (4 x 5 ml) y se enfrió a 0°C. Después se ajustó el pH hasta 1 - 2 mediante adición de HCl 1 N, se extrajo la fase acuosa con AcOEt (2 x 10 ml). La fase orgánica reunida se secó sobre Na_2SO_4, se filtró y se concentró hasta sequedad para proporcionar el

compuesto del título.

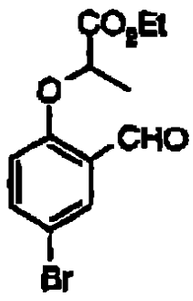
$C_{25}H_{29}N_3O_4$. (MMP: 435,53); EM: m/z (M^+ + 1) = 435,2.

Ejemplo 153

Preparación de



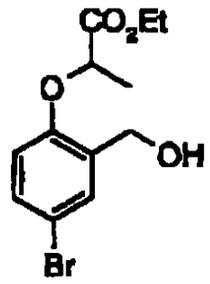
Etapa A: Preparación de



A una solución de 5-bromosalicilaldehído (2,6 g, 13 mmoles) en DMF (10 m) a temperatura ambiente se añadió K_2CO_3 (5,5 g, 39 mmoles) y 2-bromopropionato de etilo (2,6 ml, 19,5 mmoles). Se agitó la mezcla a temperatura ambiente durante dos horas. Se filtró el sólido y se lavó

el filtrado con HCl 1 N (10 ml) y H_2O (10 ml). Se secó la fase orgánica sobre Na_2SO_4 y se filtró. La evaporación del disolvente proporcionó un sólido que se suspendió en hexano (30 ml) y se filtró produciendo el compuesto del título en forma pura. $C_{12}H_{13}BrO_4$. (MMP: 301,14); EM: m/z (M^+ + 1) = 302,2.

Etapa B: Preparación de

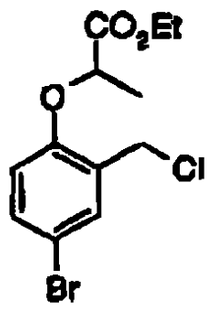


A una solución del producto de la etapa A (1,5 g, 4,98 mmoles) en EtOH (25 ml) a 0°C se añadió en una porción $NaBH_4$ (0,206 g, 5,47 mmoles). Se agitó la mezcla durante 30 minutos permitiendo que la temperatura se elevara. Después se añadió acetona (1 ml) y se retiró el disolvente a vacío. Se disolvió el aceite obtenido en CH_2Cl_2 (20 ml) y se lavó con salmuera (20 ml). Se separaron las fases y la orgánica se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente proporcionó el compuesto del título en

forma pura.

$C_{12}H_{15}BrO_4$. (MMP: 303,14); EM: m/z (M^+ + 1) = 304,2.

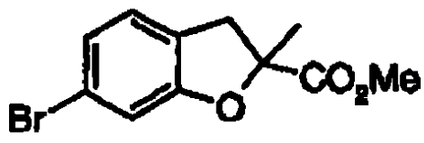
Etapa C: Preparación de



A una solución de $SOCl_2$ (0,43 ml, 5,97 mmoles) y piridina (2 gotas) en CH_2Cl_2 (5 ml) a temperatura ambiente se añadió gota a gota una solución del producto de la etapa B (1,3 g, 4,38 mmoles) en CH_2Cl_2 (3 ml). Se calentó la mezcla de reacción a 50°C durante 90 minutos, después se dejó enfriar y se lavó con solución acuosa saturada de $NaHCO_3$ (10 ml). Se separaron las fases y se extrajo la fase acuosa con CH_2Cl_2 (2 x 10 ml). Se juntaron las fases orgánicas, se secaron sobre Na_2SO_4 y se filtraron. La evaporación del disolvente proporcionó el compuesto del título en forma pura.

$C_{12}H_{14}BrClO_3$. (MMP: 321,60); EM: m/z (M^+ + 1) = 321,0.

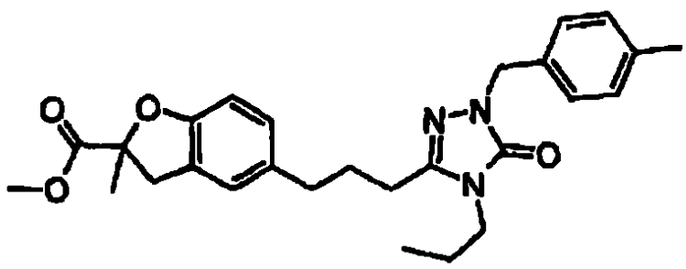
Etapa D: Preparación de



A una solución del producto de la etapa C (1,3 ml, 4 mmoles) en N-metil-2-pirrolidinona (4 ml) a 0°C bajo atmósfera de nitrógeno se añadió en una porción NaH (aceite mineral al 60%, 0,194 g, 4,85 mmoles). Se agitó la mezcla de reacción a temperatura ambiente durante un día, después se añadieron algunas gotas de MeOH. Se diluyó la mezcla en AcOEt (20 ml) y HCl al 10% (20 ml). Se separaron las fases y se lavó la fase orgánica con HCl al 10% (2 x 20 ml) y finalmente con salmuera (20 ml). La fase orgánica se secó sobre Na_2SO_4 y se filtró. La evaporación del disolvente proporcionó el compuesto del título.

$C_{11}H_{11}BrO_3$. (MMP: 271,11); EM: m/z (M^+ + 1) = 271,0.

Etapa E: Preparación de

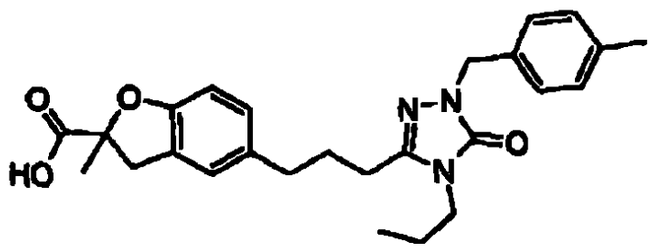


A una suspensión agitada de polvo de cinc (0,411 g, 6,3 mmoles) en THF anhidro (1,5 ml) en atmósfera de nitrógeno a 60°C se añadió 1,2-dibromoetano (27 µl, 0,31 mmoles). Después de 15 minutos de agitación vigorosa se dejó que la suspensión se enfriara hasta temperatura ambiente y se añadió clorotrimetilsilano (33 µl, 0,26 mmoles). Se agitó la mezcla durante 30 minutos y después se añadió gota a gota una solución del producto de la etapa H del ejemplo 152 (0,42 g, 1,05 mmoles) en THF anhidro (1,5 ml). Se volvió a calentar la mezcla hasta 60°C y después se agitó durante 10 minutos. Se añadió una solución del producto de la etapa D (0,271 g, 1,0 mmoles), $Pd(dba)_2$, (0,030 g 0,052 mmoles) y tri-o-tolilfosfina (0,032 g, 0,105 mmoles) en THF anhidro (2,5 ml) y la solución resultante se mantuvo a 60°C durante 2 horas. Después la reacción se enfrió a temperatura ambiente y se vertió en una mezcla 1:1 de AcOEt y HCl 0,5 N (50 ml). Se separaron las fases y se extrajo la fase acuosa con acetato de etilo (2 x 20 ml). Se separaron las fases y la fase acuosa se extrajo con acetato de etilo (2 x 20 ml). Se lavaron las fases orgánicas reunidas con HCl 0,5 N (25 ml) se secaron sobre Na_2SO_4 y se filtraron. La evaporación del disolvente proporcionó un producto bruto que se purificó en columna de gel de sílice eluyendo con acetato de etilo al 50% en hexano para proporcionar el compuesto del título en forma

de un aceite incoloro.

$C_{27}H_{33}N_3O_4$. (MMP: 463,58); EM: m/z (M^+ + 1) = 464,2.

Etapa F: Preparación de

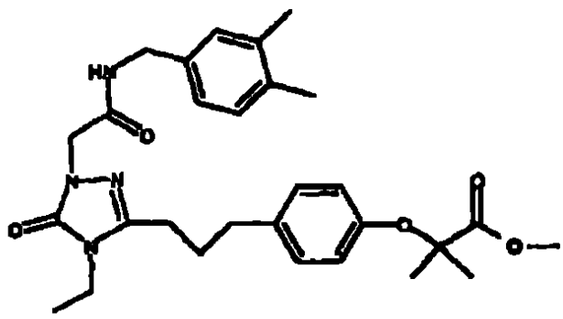


A una solución del producto de la etapa D (0,05 g, 0,10 mmoles) en THF (2 ml) a temperatura ambiente se añadió una solución de de NaOH 1 N (2ml, 2mmoles). Se agitó la mezcla durante tres días y después se separaron las fases. Se lavó la fase acuosa con éter dietílico (3 x 10 ml) y se enfrió hasta 0°C. Después se ajustó el pH hasta 1 - 2 mediante la adición de HCl 1 N, se extrajo la fase acuosa con AcOEt (2 x 10 ml). Se secó la fase orgánica reunida sobre Na_2SO_4, se filtró y se concentró hasta sequedad para proporcionar el compuesto del título.

$C_{26}H_{31}N_3O_4$. (MMP: 449,55); EM: m/z (M^+ + 1) = 450,2.

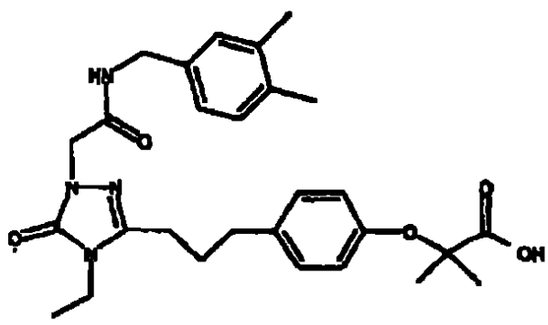
Ejemplo 154

Etapa A:



Una solución en THF del ácido descrito en la etapa B del ejemplo 127 (0,300 g, 0,0007 moles) se trató con EDC (0,212 g, 0,0011 moles) y HOAt (0,095 g, 0,0007 moles). Se añadió un equivalente de 3,4-dimetilbencilamina (0,10 ml, 0,0007 moles) y se agitó la reacción durante una noche. Se concentró el disolvente y se volvió a disolver el residuo en cloruro de metileno y se extrajo con agua. La purificación mediante cromatografía ultra - rápida (acetato de etilo al 100%) proporcionó la amida deseada. $C_{29}H_{38}N_4O_5$. (MMP: 522,65); Espectroscopía de Masas: m/z (MH^+) = 523,3.

Etapa B:

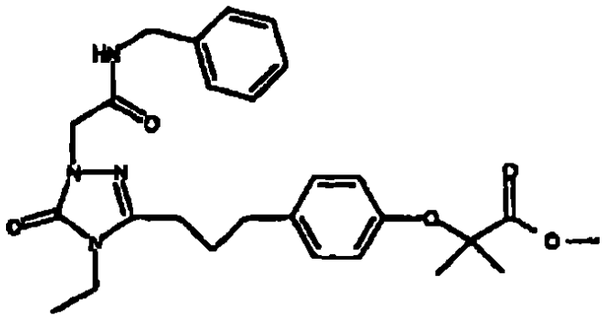


La amida de la etapa A (0,260 g, 0,0005 moles) se disolvió en dioxano (3 ml) y agua (3 ml) después se trató con LiOH (0,012 g, 0,0005 moles). Se agitó la reacción durante dos horas. Se añadió agua a la mezcla y se extrajo la fase con éter. Se acidificó la fase acuosa con HCl 1 N y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, después se concentró para producir el producto deseado en forma de una espuma blanca.

$C_{28}H_{36}N_4O_5$. (MMP: 508,62); espectroscopía de masas: m/z (MH^+) = 509,4.

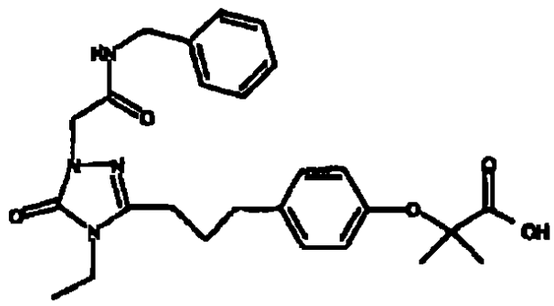
Ejemplo 155

Etapa A:



Una solución en THF del ácido descrito en la etapa B del ejemplo 127 (0,300 g, 0,0007 moles) se trató con EDC (0,212 g, 0,0011 moles) y HOAt (0,095 g, 0,0007 moles). Se añadió un equivalente de bencilamina (0,076 ml, 0,0007 moles) y se agitó la reacción durante una noche. Se concentró el disolvente y se volvió a disolver el residuo en cloruro de metileno y se extrajo con agua. La purificación mediante cromatografía ultra - rápida (acetato de etilo al 100%) proporcionó la amida deseada. $C_{27}H_{34}N_4O_5$. (MMP: 494,60); espectroscopía de masas: m/z (MH^+) = 495,2.

Etapa B:

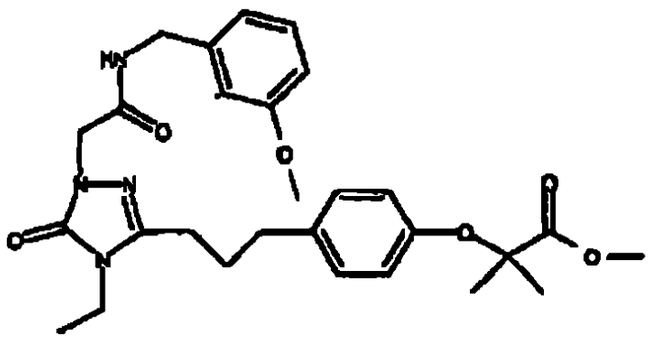


La amida de la etapa A (0,176 g, 0,00035 moles) se disolvió en dioxano (3 ml) y agua (3 ml) después se trató con LiOH (0,0085 g, 0,00035 moles). Se agitó la reacción durante dos horas. Se añadió agua a la mezcla y se extrajo la fase con éter. Se acidificó la fase acuosa con HCl 1 N y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, después se concentró para producir el producto deseado en forma de una espuma blanca.

$C_{26}H_{32}N_4O_5$. (MMP: 480,57); espectroscopía de masas: m/z (MH^+) = 481,4.

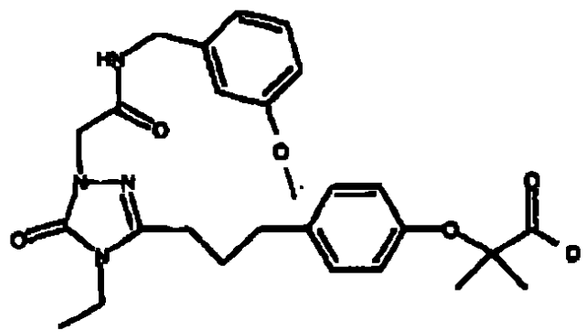
Ejemplo 156

Etapa A:



Una solución en THF del ácido descrito en la etapa B del ejemplo 127 (0,300 g, 0,0007 moles) se trató con EDC (0,212 g, 0,0011 moles) y HOAt (0,095 g, 0,0007 moles). Se añadió un equivalente de 3-metoxibencilamina (0,090 ml, 0,0007 moles) y se agitó la reacción durante una noche. Se concentró el disolvente y se volvió a disolver el residuo en cloruro de metileno y se extrajo con agua. La purificación mediante cromatografía ultra - rápida (acetato de etilo al 100%) proporcionó la amida deseada. $C_{28}H_{36}N_4O_6$. (MMP: 524,62); espectroscopía de masas: m/z (MH^+) = 525,3.

Etapa B:

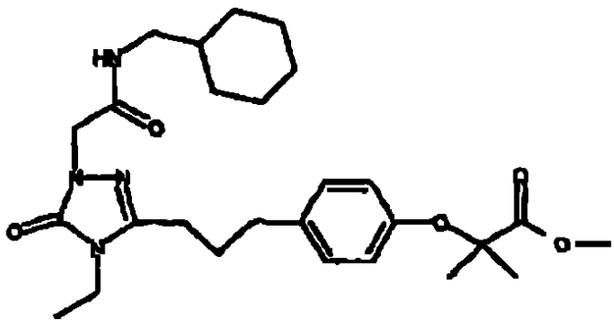


La amida de la etapa A (0,260 g, 0,00049 moles) se disolvió en dioxano (3 ml) y agua (3 ml) después se trató con LiOH (0,0012 g, 0,00049 moles). Se agitó la reacción durante dos horas. Se añadió agua a la mezcla y se extrajo la fase con éter. Se acidificó la fase acuosa con HCl 1 N y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, después se concentró para producir el producto deseado en forma de una espuma blanca.

$C_{27}H_{34}N_4O_6$. (MMP: 510,59); espectroscopía de masas: m/z (MH^+) = 511,3.

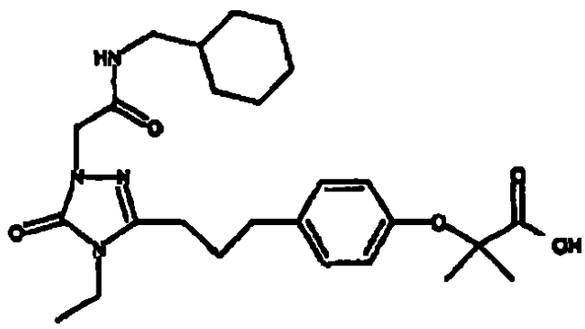
Ejemplo 156

Etapa A:



Una solución en THF del ácido descrito en la etapa B del ejemplo 127 (0,300 g, 0,0007 moles) se trató con EDC (0,212 g, 0,0011 moles) y HOAt (0,095 g, 0,0007 moles). Se añadió un equivalente de 3-metoxibencilamina (0,091 ml, 0,0007 moles) y se agitó la reacción durante una noche. Se concentró el disolvente y se volvió a disolver el residuo en cloruro de metileno y se extrajo con agua. La purificación mediante cromatografía ultra - rápida (acetato de etilo al 100%) proporcionó la amida deseada. $C_{27}H_{40}N_4O_5$. (MMP: 500,6); espectroscopía de masas: m/z (MH^+) = 501,4.

Etapa B:



La amida de la etapa A (0,290 g, 0,00058 moles) se disolvió en dioxano (3 ml) y agua (3 ml) después se trató con LiOH (0,0013 g, 0,00058 moles). Se agitó la reacción durante dos horas. Se añadió agua a la mezcla y se extrajo la fase con éter. Se acidificó la fase acuosa con HCl 1 N y se extrajo con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4, después se concentró para producir el producto deseado en forma de sólido blanco.

$C_{26}H_{38}N_4O_5$. (MMP: 486,62); Espectroscopía de Masas: m/z (MH^+) = 487,4.

Ensayos biológicos

Estudios de unión y contrasfección

La pureza *in vitro* de los compuestos que modulan los receptores PPARα se determinaron mediante los procedimientos detallados más adelante. La unión a DNA

dependiente (unión ABCD) se llevó a cabo utilizando tecnología de análisis de centelleo por proximidad (abreviadamente SPA) con receptores PPAR. Se utilizaron agonistas PPARα marcados con tritio como radioligandos para generar curvas de desplazamiento y los valores de CI_{50} con compuestos de la invención. Los ensayos de cotransfección se llevaron a cabo en células CV - 1. El plásmido localizador contenía un acilCoAoxidasa (abreviadamente AOX) PPRE y promotor TK hacia abajo del cDNA localizador de luciferasa. Los PPARs apropiados se expresaron constitutivamente usando plásmidos que contenían el promotor CMV. Para PPARα, era una inconveniente la interferencia por PPARγ endógenos en las células CV - 1. Con el fin de eliminar tal interferencia, se utilizó un sistema quimérico GAL4 en el que el dominio de unión al DNA del PPAR transfectado se sustituyó con el de GAL4 y se utilizó el elemento de respuesta de GAL4 en lugar del AOX PPRE. La eficiencia de la cotransfección se determinó en relación a las moléculas de referencia de agonistas PPARα. Las eficiencias se determinaron mediante un ajuste por ordenador a una curva de concentración - respuesta, o en algunos casos a una única concentración alta de agonista (10 μM).

Estos estudios se llevaron a cabo con el fin de evaluar la capacidad de los compuestos de la invención

para unirse a y/o activar diversos factores de transcripción nuclear, particularmente huPPARα ("hu" indica "humano"). Estos estudios proporcionan datos *in vitro* concernientes a la eficacia y selectividad de los compuestos de la invención. Además, los datos de unión y cotransfección de los compuestos de la invención se compararon con los correspondientes datos de los compuestos comerciales que actúan sobre huPPARα.

Los valores encontrados de eficiencia de unión y cotransfección para los compuestos de la invención y los compuestos de esta invención que son útiles para modular un receptor PPAR alfa fueron ≤100 nM ≥ 50% respectivamente.

Evaluación de reducción de triglicéridos y elevación de colesterol HDL en ratones transgénicos HuapoAI

Se realizaron diecisiete series diferentes de estudios para evaluar los compuestos de la presente invención sobre los niveles de HDL y triglicéridos en ratones que contienen apoIA humano. Para cada compuesto ensayado, ratones macho de siete a ocho semanas, transgénicos para la apoAI humana (C57BL/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME) se aclimatan en jaulas individuales durante dos semanas con una dieta Chow convencional (Purina 5001) y agua proporcionada a

discreción. Después de la aclimatación, se pesan los ratones y la dieta Chow y se asignan a grupos de ensayo (n = 5) aleatorizando el peso corporal. A los ratos se les dosifica diariamente mediante administración oral forzada durante 8 días usando una aguja curva de alimentación de 1-1/2 pulgadas, de calibre 29, (Popper & Sons). El vehículo para las muestras de control, compuestos de ensayo y la muestra de control positiva (100 mg/kg fenofibrato) fue de un 1% de carboximetilcelulosa (p/v) con un 0,25% de Tween 80 (p/v). Todos los ratones se dosifican diariamente entre 6 y 8 a.m. con un volumen de dosificación de 0,2 ml. Antes de la finalización, se pesan los animales y las dietas y se calcula el cambio de peso corporal y el consumo de alimento. Tres horas después de la última dosis, los ratones se sacrifican con CO_2 y se elimina la sangre (0,5-1,0 ml) mediante punción cardiaca. Después del sacrificio, se escinden y pesan el hígado, el corazón y la bola adiposa epididimal. Se deja coagular la sangre y se separa el suero de la sangre por centrifugación.

Se mide el colesterol y los triglicéridos colorimétricamente usando reactivos preparados en el mercado (por ejemplo, los disponibles en Sigma #339-1000 y Roche #450061 para triglicéridos y colesterol, respectivamente). Los procedimientos son una modificación

del trabajo publicado por McGowan M. W. et al., Clin Chem 29:538-542, 1983; Allain C. C. et al., Clin Chem 20:470-475, 1974. Se miden por duplicado los patrones disponibles en el mercado para triglicéridos y colesterol total, respectivamente, el control de calidad del plasma y las muestras, usando 200 µl de reactivo. Una alícuota adicional de muestra, añadida a un pocillo que contiene 200 ml de agua, proporciona un blanco para cada muestra de ensayo. Las placas se incuban a temperatura ambiente en un agitador de placas y se leyó la absorbancia a 500 nm y 540 nm del colesterol total y triglicéridos, respectivamente. Los valores del control positivo estaban siempre dentro del intervalo esperado y el coeficiente de variación de las muestras era inferior al 10%. Todas la muestras de un experimento se analizaron al mismo tiempo para minimizar la variabilidad entre los análisis.

Se separaron las lipoproteínas en suero y se cuantificó el colesterol mediante cromatografía líquida rápida de proteínas (abreviadamente CLRP) acoplada a un sistema de detección lineal. Se aplicaron las muestras a una columna de exclusión por tamaño de Superosa 6 HR (Amersham Pharmacia Biotech) y se eluyó con solución salina tamponada con fosfato - EDTA a 0,5 ml/min. Se mezcló reactivo de colesterol (Roche Diagnostics Chol/HP 704036) a 0,16 ml/min con el efluente de la columna

mediante una conexión en T y se pasó la mezcla a través de un reactor tubular acanalado de tipo id 15 m x 0,5 mm sumergido en una baño de agua a 37°C. El producto coloreado producido en presencia de colesterol se controló en la corriente del flujo a 505 nm y la tensión análoga del monitor se convirtió en una señal digital para la recogida y análisis. El cambio en tensión correspondiente al cambio en concentración de colesterol se dispuso gráficamente frente al tiempo y se calculó el área bajo la curva correspondiente a la elución de lipoproteína de densidad muy baja (abreviadamente VLDL), lipoproteína de baja densidad (abreviadamente LDL) y lipoproteína de alta densidad (abreviadamente HDL) utilizando un software de Perkin Elmer Turbochrome. Los resultados de los niveles de triglicéridos y colesterol HDL de estos estudios se indican en las siguientes tablas. Hay que destacar que los números subrayados en las siguientes tablas se refieren a los números de los estudios. Además, los valores determinados en cada estudio de los niveles de triglicéridos en los ratones de control y de los niveles de colesterol HDL en los ratones tratados con fenofibrato también se indican en las siguientes tablas.

Con el fin de identificar los compuestos que particularmente se podrían usar para reducir los triglicéridos se compararon los niveles de triglicéridos

en suero de ratones a los que se les había administrado un compuesto de la invención con los ratones que recibían el vehículo. En general, descensos de triglicéridos mayores o iguales al 30% (treinta por ciento) comparados con el control que seguían a la administración de una dosis de 30 mg/kg sugiere un compuesto que puede ser especialmente útil para reducir los niveles de triglicéridos.

El incremento en porcentaje de los niveles en suero de HDLc en ratones que recibían un compuesto de la invención se comparó con el de ratones que recibían vehículo para identificar los compuestos que pudieran ser particularmente útiles para elevar los niveles de HDL. En general, un incremento mayor o igual que 25% (veinticinco por ciento) en el nivel de HDLc que sigue a una administración de una dosis de 30 mg/kg sugiere un compuesto que puede ser específicamente útil para elevar los niveles de HDLc.

Puede ser particularmente deseable seleccionar los compuestos de esta invención que, tanto reduzcan los niveles los niveles de triglicéridos como incrementen los niveles de HDLc. Sin embargo, también pueden ser deseables los compuestos que o bien reducen los niveles de triglicéridos o incrementan los niveles de HDLc.

Evaluación de los niveles de glucosa en ratones db/db

Se estudiaron los efectos sobre glucosa en plasma de la administración de diversos niveles de dosis de cinco diferentes compuestos de la presente invención y el agonista PPAR gamma rosiglitazona (BRL49653) o el agonista PPAR alfa fenofibrato y el control a machos de ratones db/db.

Machos de ratones diabéticos (db/db) de cinco semanas de edad [por ejemplo C57B1Ks/j-m +/+ Lepr (db), Jackson Laboratory, Bar Harbor, ME] o hermanos de camada sin grasa se introdujeron 6 por jaula con alimento y agua siempre disponible. Después de un período de aclimatación de 2 semanas los animales se identificaron mediante unas muescas en la oreja, se pesaron y se extrajo sangre de la vena de la cola para determinar los niveles iniciales de glucosa. Se recogió sangre (100 µl) de animales no en ayunas envolviendo cada ratón en una toalla, cortando la punta de la cola con un escalpelo y drenando la sangre de la cola a un tubo capilar heparinizado. Se descargó la muestra en un tubo microtainer heparinizado con gel separador y se mantuvo en hielo. El plasma se obtuvo después de centrifugación a 4°C y se midió la glucosa inmediatamente. Una vez que se analizó la glucosa y triglicéridos en todas las muestras, el plasma restante se congeló hasta la terminación del experimento. Loa animales se agruparon en función de los niveles iniciales de

glucosa y pesos corporales. Al comienzo de la siguiente mañana, se les administró la dosis a los ratones mediante una sonda oral durante 7 días. En los tratamientos se ensayaron los compuestos (30 mg/kg), un agente de control positivo (30 mg/kg) o un vehículo [carboximetilcelulosa al 1% (p/v) / Tween - 20 al 0,25% (p/v); 0,3 ml/ratón)]. En el día 7, los ratones se pesaron y se extrajo sangre (vena de la cola) 3 horas después de la administración. Veinticuatro horas después de la 7ª dosis (es decir el día 8) se extrajo sangre a los animales (vena de la cola). Las muestras obtenidas de los animales conscientes en los días 0, 7 y 8 se analizaron para determinación de glucosa. Después de 24 horas de la extracción de sangre, los animales se pesaron y se les administró la dosis por última vez. Tres horas después de la administración el día 8, los animales se anestesiaron mediante inhalación de isofluorano y se extrajo sangre mediante punción cardiaca (0,5 - 0,7 ml). La sangre entera se transfirió a tubos separadores de suero, se enfriaron en hielo y se dejó que se coagularan. El suero se obtuvo después de centrifugación a 4°C y se congeló hasta el análisis de los niveles de los compuestos. Después de sacrificio mediante dislocación cervical, se retiraron el hígado, el corazón y las bolsas adiposas de epidídimo y se pesaron.

La glucosa se determinó colorimétricamente utilizando

reactivos comprados comercialmente. Según los fabricantes, los procedimientos se modificaron a partir del trabajo publicado (McGowan, M. W., Artiss, J. D., Strandberg, D. R. & Zak, B. Clin. Chem, 20: 470 - 5 (1974) y Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Resumen de los artículos de la sesión n° 129 ACS 31C (1956)); y depende de la liberación de un mol de peróxido de hidrógeno por cada mol de analito, unido con una primera reacción colorimétrica descrita por Trinder (Trinder, P. Determination of glucosa in blood using glucosa oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6: 24 (1969)). La absorbancia del producto teñido está linealmente relacionada con el analito en la muestra. Los análisis se modificaron posteriormente en los laboratorios de los autores para uso en formato de 96 pocillos. Los patrones comercialmente disponibles de glucosa, plasma del control de calidad comercialmente disponible y muestras (2 ó 5 µl/pocillo) se midieron por duplicado usando 200 µl de reactivo. Una alícuota adicional de muestra, se pipeteó a un tercer pocillo y se diluyó en 200 µl de agua y se proporcionó un blanco para cada espécimen. Las placas se incubaron a temperatura ambiente durante 18 minutos para determinación de glucosa en un agitador de palcas (DPC Micormix 5) y se leyó la absorbancia a 500 nm en un lector de placas. Las

absorbancias de las muestras se compararon con una curva estándar (100 - 800 de glucosa). Los valores de la muestra del control de calidad estaban siempre dentro del intervalo esperado y el coeficiente de variación de las muestras era inferior al 10%. Todas las muestras de un experimento se analizaron al mismo tiempo para minimizar la variabilidad entre análisis.

Los resultados de este estudio, sugieren compuestos de la presente invención que reducían significativamente los niveles de glucosa en plasma del ratón db/db al mismo tiempo que daba como resultado una ganancia en peso corporal que era menor que la observada para la rosiglitazona.

Evaluación de los efectos de los compuestos de la presente invención sobre el peso corporal de ratones A^y, masa adiposa, glucosa y niveles de insulina

Hembras de ratones A^y

Hembras de ratones A^y se enjaularon individualmente, se mantuvieron bajo condiciones estándar (22°C, 12 horas de luz, ciclo de oscuridad) y se les proporcionó acceso libre para comer y beber agua durante toda la duración del estudio. A las veintidós semanas de edad los ratones se asignaron al azar como control de vehículo y se trataron a

los grupos en función de su peso corporal y contenido en grasa corporal según se estableció mediante un análisis de densitometría DEXA (N = 6). Después se les administró a los ratones la dosificación mediante una sonda oral bien con vehículo o con un compuesto de esta invención (50 mg/kg) una hora después de la iniciación del ciclo luminoso (por ejemplo, aproximadamente a las 7 a. m.) durante 18 días. Los pesos corporales se determinaron diariamente durante todo el estudio. El día 14 los ratones se mantuvieron en cámaras metabólicas individuales para valoraciones de calorimetría indirecta de consumo de energía y utilización de combustible. El día 18 se sometió a los ratones otra vez al análisis de denstitometría DEXA para determinar la composición del cuerpo después del tratamiento.

Los resultados de la administración oral del compuesto durante 18 días en peso corporal, masa adiposa y masa magra se evaluaron y sugieren que los compuestos de esta invención pueden ser específicamente útiles para mantener un peso deseable y/o promover la deseada delgadez y masa adiposa.

Las mediciones calorimétricas indirectas revelaron una significativa reducción en el cociente respiratorio (abreviadamente RQ) en los animales tratados durante el ciclo de oscuridad [0,864 $\pm$ 0.013 (control) frente 0,803 $\pm$

0,007 (tratados); p < 0,001]. Esta reducción en RQ es indicativa de un incremento de la utilización de grasa durante el ciclo activo (oscuro) de los animales. Adicionalmente, los animales tratados mostraban índices significativamente mayores de consumo de energía que los animales control (17,40 ± 0,49 frente 13, 62 ± 0,26 kcal/kg/hr, respectivamente).

Machos de ratones KK/A^y

Machos de ratones KK/A^y se enjaularon individualmente, se mantuvieron bajo condiciones estándar (22°C, 12 horas de luz, ciclo de oscuridad) y se les proporcionó acceso libre para comer y beber agua durante toda la duración del estudio. A las veintidós semanas de edad los ratones se asignaron al azar como control de vehículo y se trataron a los grupos en función de sus niveles de glucosa en plasma. Después se les administró a los ratones la dosificación mediante una sonda oral bien con vehículo o con un compuesto de esta invención (30 mg/kg) una hora después de la iniciación del ciclo luminoso (a las 7 a. m.) durante 14 días. Los niveles de glucosa en plasma, triglicéridos e insulina se determinaron el día 14.

Los resultados de la administración oral del compuesto durante 14 días en glucosa en plasma, triglicéridos e insulina se evaluaron para identificar los

compuestos de esta invención que ser específicamente se pueden desear.

Procedimiento para dilucidar el efecto de reducción de colesterol LDL colesterol total y triglicéridos del compuesto 5 (8)

Machos de hámsteres Syrian (Harlan Sprague Dawley) que pesaban entre 80 - 120 g se sometieron a una dieta de alta grasa rica en colesterol durante dos a tres semanas antes de su utilización. Se les suministró alimento y agua a discreción durante todo el transcurso del experimento. Bajo estas condiciones los hámsteres se hicieron hipercolesterolémicos mostrando unos niveles de colesterol en plasma entre 180 - 280 mg/dl. (los hámsteres alimentados con pienso normal tenían un nivel de colesterol entre 100 - 150 mg/dl. Los hámsteres con colesterol en plasma alto (180 mg/dl y superiores) se distribuyeron al azar en grupos de tratamiento en función de su nivel de colesterol total en plasma usando el programa GroupOptimizeV211. x 1s.

Se disolvió un compuesto de esta invención en un vehículo acuoso (conteniendo CMC con Tween 80) de modo que cada hámster recibió una vez al día aproximadamente 1 ml de la solución mediante la sonda en dosis de 3 y 30 mg/kg de peso corporal. El fenofibrato (Sigma Chemical,

preparado en forma de suspensión en el mismo vehículo) se proporcionó como un control de agonista alfa conocido a una dosis de 200 mg/kg, y el control de blanco fue el vehículo solo. La dosificación se realizó diariamente por la mañana temprano durante 11 días.

Cuantificación de lípidos en plasma:

El último día del ensayo se extrajo sangre de los hámsteres (400 µl) del seno suborbital mientras se mantenían bajo anestesia con isofluorano 2 horas después de la administración de la dosis. Las muestras de sangre se recogieron en tubos microfuge heparinizados enfriados en baño de hielo. Se separaron las muestras de plasma de los glóbulos rojos mediante una centrifugación breve. Se determinaron el colesterol total y los triglicéridos mediante análisis enzimáticos llevados a cabo automáticamente en el equipo Monarca (Laboratorio de Instrumentación) siguiendo el procedimiento del fabricante. Las lipoproteínas en plasma (VLDL, LDL y HDL) se volvieron a disolver inyectando 25 µl de las muestras de plasma reunidas en un sistema FPLC eluido con solución salina tamponada con fosfato a 0,5 ml/min a través de una columna de Superosa 6 HR 10/30 (Pharmacia) mantenida a temperatura ambiente. La detección y caracterización de los lípidos en plasma aislados se realizó mediante incubación del efluente después de la columna con un

reactivo de colesterol /HP (por ejemplo, Roche Lab System; infundido a 0,12 ml/min) en un serpentín de reacción acanalado mantenido a 37°C. La intensidad del color formado era proporcional a la concentración de colesterol y se midió fotométricamente a 505 nm.

El efecto de administración de un compuesto de esta invención durante 14 días se estudia para determinar el porcentaje de reducción del nivel de LDL con referencia al grupo del vehículo. La eficacia de ciertos compuestos de esta invención para reducir el LDL es marcadamente más potente que la del fenofibrato. Pueden ser específicamente deseables los compuestos de esta invención que disminuyan el LDL en una cantidad mayor o igual que el 30% (treinta por ciento) comparados con el vehículo.

También se estudiaron los efectos de reducción del colesterol total y triglicéridos de un compuesto de esta invención. Los datos de reducción en los niveles del colesterol total y triglicéridos después del tratamiento con un compuesto de esta invención durante 14 días se compararon con el vehículo para proponer compuestos que pudieran ser particularmente deseables. El fenofibrato de control conocido no mostró eficacia significativa bajo las mismas condiciones experimentales.

Procedimiento para esclarecer el efecto de reducción de

fibrinógeno de los moduladores PPAR

Modelo de rata adiposa Zucker:

La fase de vida del estudio del estudio sobre el efecto de reducción de fibrinógeno de los compuestos de esta invención era parte de los procedimientos de la fase de vida para el estudio antidiabético de los mismos compuestos. El último día (14) del período del tratamiento, con los animales situados bajo anestesia quirúrgica, se recogieron 3 ml de sangre mediante punción cardiaca en una jeringa que contenía tampón citrato. La muestra de sangre se enfría y se centrifuga a 4°C para aislar el plasma que se almacenó a - 70°C antes del análisis de fibrinógeno.

Cuantificación de fibrinógeno en plasma de rata

Los niveles de fibrinógeno en plasma de rata se cuantificaron utilizando un sistema de análisis comercial que consiste en un instrumento de coagulación siguiendo el protocolo del fabricante. En esencia, se muestrearon 100 µl de plasma de cada espécimen y se preparó una dilución 1/20 con tampón. El plasma diluido se incubó a 37°C durante 240 segundos. Después se añaden cincuenta microlitros de una solución de trombina de reactivo de coagulación (proporcionada por el fabricante del instrumento en una concentración estándar). El instrumento

controlaba el tiempo de coagulación, una función de la concentración del fibrinógeno cuantificada con relación a las muestras estándar.

Resultados:

Los compuestos de esta invención son capaces de reducir el nivel de fibrinógeno *in vivo*. Pueden ser especialmente deseables los compuestos que reduzcan el nivel de fibrinógeno más que el vehículo.

Los efectos de reducción de colesterol y triglicéridos de los compuestos de esta invención se produjeron también en las ratas Zucker.

Procedimiento para esclarecer los efectos de antiganancia de peso corporal y antiapetito de los compuestos de esta invención

Estudio de catorce días en modelos de ratas [1] adiposas Zucker o ratas [2] ZDF:

Machos de ratas adiposas Zucker, no diabéticas (Charles River Laboratories, Wilmington, MA) o machos de ratas ZDF (Genetics Models, Inc, Indianápolis, IN) de edad y peso comparable se aclimataron durante una semana antes del tratamiento. Las ratas se alimentaron con pienso normal y agua a discreción durante todo el transcurso del

experimento.

Se disolvieron agonistas α en un vehículo acuoso de manera que cada rata recibió una vez al día aproximadamente 1 ml de la solución mediante sonda a dosis de 0,1, 0,3, 1 y 3 mg/kg de peso corporal. Los controles fueron el fenofibrato (Sigma Chemical, preparado en forma de una suspensión en el mismo vehículo) un agonista alfa conocido proporcionado a dosis de 300 mg/kg, así como el vehículo. La dosificación se realizó diariamente por la mañana temprano durante 14 días. Durante el transcurso del experimento, se controlaron peso corporal y consumo de alimento.

Utilizando este ensayo, se encontró que los compuestos de esta invención daban como resultado una reducción significativa de peso.

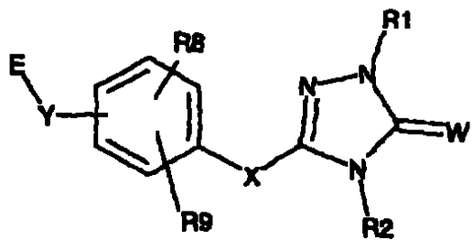
EQUIVALENTES

Aunque esta invención se ha mostrado y descrito particularmente con referencias a realizaciones preferidas de las mismas, los expertos en la técnica entenderán que se pueden realizar diversos cambios en la forma y detalles hechos en esta memoria descriptiva sin salirse del alcance de la invención comprendido por las reivindicaciones del apéndice.

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Un compuesto representado por la siguiente fórmula estructural I:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R1 se selecciona del grupo constituido por hidrógeno, un grupo, sustituido o insustituido, seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cicloalquilaril C_3-C_6-alquilo C_0-C_2, y $-CH_2$-C(O)-R17-R18, en la que R17 es O o NH y R18 es bencilo opcionalmente sustituido;

(b) W es O o S;

(c) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo

C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(d) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(e) Y es C, O, S, NH o un enlace sencillo; y

(f) E se selecciona del grupo constituido por hidrógeno, C(R3)(R4)A, A, sustituido o insustituido, seleccionado del grupo constituido por $(CH_2)_n$COOR19, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(vi) n es 0, 1, 2 o 3,

(vii) A es un grupo funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(viii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(ix) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

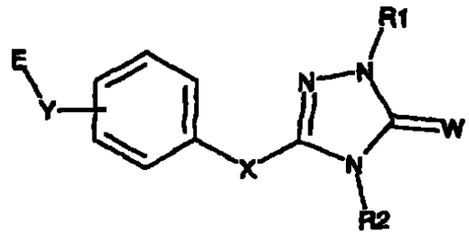
(x) R19 se selecciona del grupo constituido por hidrógeno, arilmetilo opcionalmente sustituido y alquilo C_1-C_4 opcionalmente sustituido;

(g) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

(h) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

(i) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4,

2. Un compuesto según se reivindica en la Reivindicación 1, representado por la siguiente fórmula estructura Fórmula I':



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R1 es un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_2, heteroarilalquilo C_0-C_2, cicloalquilaril C_3-C_6-alquilo C_0-C_2 o fenilo;

(b) W es O o S;

(c) R2 es H o un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_6, y cicloalquilo C_3-C_6;

(d) X es un alquileno C_2-C_5 de unión en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(e) Y es C, O, S, NH o un enlace sencillo; y

(f) E es $(CH_2)_nCOOH$ o C(R3)(R4)A, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo funcional ácido, como por ejemplo carboxilo, carboxamida, sulfonamida sustituida o insustituida, o tetrazol

sustituido o insustituido,

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4.

3. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1 o 2 en el que W es O.

4. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2 o 3 en el que E es A.

5. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2, 3 o 4 en el que A es COOH.

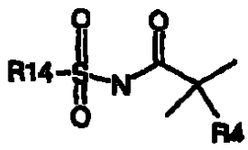
6. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2, 3, 4 o 5 en el que Y es O.

7. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2, 3, 4 o 5 en el que Y es C.

8. Un compuesto de la Reivindicación 7 en el que E se

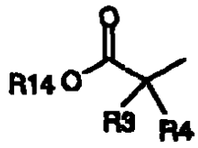
selecciona del grupo constituido por arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxialquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4.

9. Un compuesto según se reivindica en una de las reivindicaciones 1, 2, 3, 6 o 7 en el que E es un grupo de fórmula:



en la que R14 se selecciona del grupo constituido por CF_3, fenilo sustituido o insustituido, arilalquilo C_0-C_4 sustituido o insustituido y alquilo C_1-C_6.

10. Un compuesto según se reivindica en una de las reivindicaciones 1, 2, 3, 6 o 7 en el que E es un grupo de fórmula:



en la que R14 se selecciona del grupo constituido por

CF_3, fenilo sustituido o insustituido, arilalquilo C_0-C_4 sustituido o insustituido y alquilo C_1-C_6

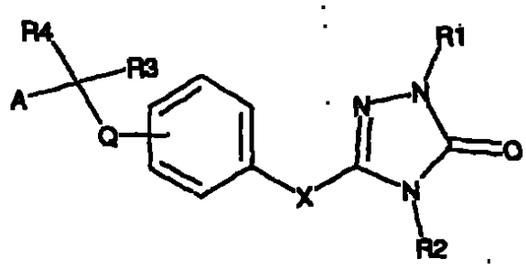
11. Un compuesto según se reivindica en una de las reivindicaciones 1, 2, 3, 4, 5, 6, 7, 8, 9 o 10 en el que X es un alquileno C_2-C_5 opcionalmente sustituido.

12. Un compuesto según se reivindica en una de las reivindicaciones 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 u 11 en el que X es propileno.

13. Un compuesto de la Reivindicación 1 que es ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico.

14. Un compuesto de la Reivindicación 13 que es ácido 2-[4-[3-[2,5-dihidro-1-[(4-metilfenil)metil]-5-oxo-1*H*-1,2,4-triazol-3-il]propil]fenoxi]-2-metil-propanoico cristalino que tiene un esquema de difracción de rayos X que comprende al menos uno de los siguientes picos: 13,2 +/- 0,2, 15,9 +/- 0,2, 20,7 +/- 0,2 y 24,1 +/- 0,2 en 2θ cuando se obtiene a partir de una fuente de radiación de cobre.

15. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2, 5, 11 o 12 que está representado por la siguiente fórmula estructural:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R1 se selecciona del grupo constituido por hidrógeno, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_8, alrilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cilcoalquilarilalquilo C_0-C_2, y $-CH_2-C(O)-R17-R18$, en la que R17 es O o NH y R18 es bencilo opcionalmente sustituido;

(b) R2 es H o un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_6, cicloalquilo C_3-C_6 y heteroarilo;

(c) X es un alquileno C_2-C_5 de unión en el que un átomo de carbono del elemento de unión puede

estar sustituido con O, NH o S;

(d) Q es C, O o S;

(e) A es un grupo funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(f) R3 es H, alquilo C_1-C_5 sustituido o insustituido, alcoxi C_1-C_5; y

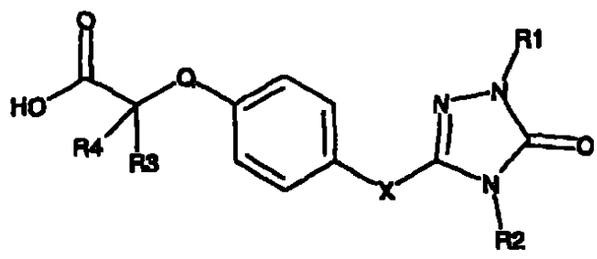
(g) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4.

16. Un compuesto según se reivindica en la Reivindicación 15 en el que A es COOH.

17. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 15 o 16 en el que R3 es metilo.

18. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 15, 16 o 17 en el que R4 es metilo.

19. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2, 11 o 12 que está representado por la fórmula estructural:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R1 se selecciona del grupo constituido por hidrógeno, un grupo sustituido o insustituido seleccionada entre alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cicloalquilaril C_3-C_6-alquilo C_0-C_2, y $-CH_2-C(O)-R17-R18$, en la que R17 es O o NH y R18 es bencilo opcionalmente sustituido;

(b) R2 es H o un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_6, cicloalquilo C_3-C_6 y heteroarilo;

(c) X es un alquileno C_1-C_5 opcionalmente sustituido en el que un átomo de carbono del

elemento de unión puede estar sustituido con O, NH o S;

(d) Q es C, O o S;

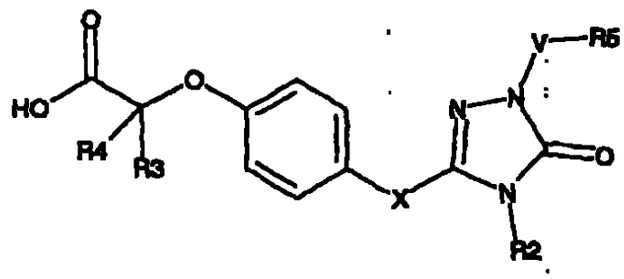
(e) R3 es H, alquilo C_1-C_5, alcoxi C_1-C_5; y

(f) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4.

20. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1-12, 15, 16, 17, 18 o 19 en el que R1 se selecciona del grupo constituido por alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4 y cicloalquilaril C_3-C_6-alquilo C_0-C_2 sustituido o insustituido.

21. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1-12, 15, 16, 17, 18, 19 o 20 en el que R1 es arilo sustituido.

22. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2, 11 o 12 que está representado por la siguiente fórmula estructural:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R2 es H o un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_6, cicloalquilo C_3-C_6 y heteroarilo;

(b) X es un alquileno C_1-C_5 opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(c) R3 es H, alquilo C_1-C_5, alcoxi C_1-C_5;

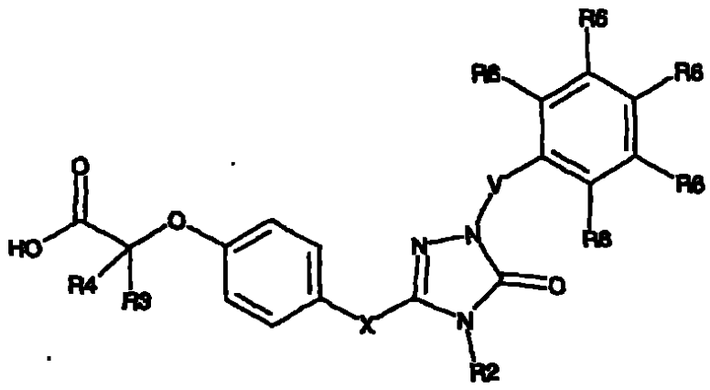
(d) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(e) V es un enlace o un grupo alquileno C_1-C_3 sustituido o insustituido; y

(f) R5 es un grupo sustituido o insustituido seleccionado entre grupos arilo, heteroarilo y

cicloalquilo.

23. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2, 11 o 12 que está representado por la siguiente fórmula estructural:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R2 es H o un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_6, cicloalquilo C_3-C_6 y heteroarilo (suprimir heteroarilo);

(b) X es un alquileno C_1-C_5 opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(c) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5;

(d) R4 es H, halo, un grupo sustituido o

insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4,

(e) V es un enlace o un grupo alquileno C_1-C_3 sustituido o insustituido; y

(f) R6 es H, OH, alquilo C_1-C_5, alcoxi, halo, haloalquilo, haloalcoxi, nitro, fenilo, ariloxi, SO2R7, SR7, ciano, benciloxi, fenoxi, alquilcarboxamido o COOH en la que R7 es alquilo o haloalquilo.

24. Un compuesto de la Reivindicación 23 en el que V es metileno.

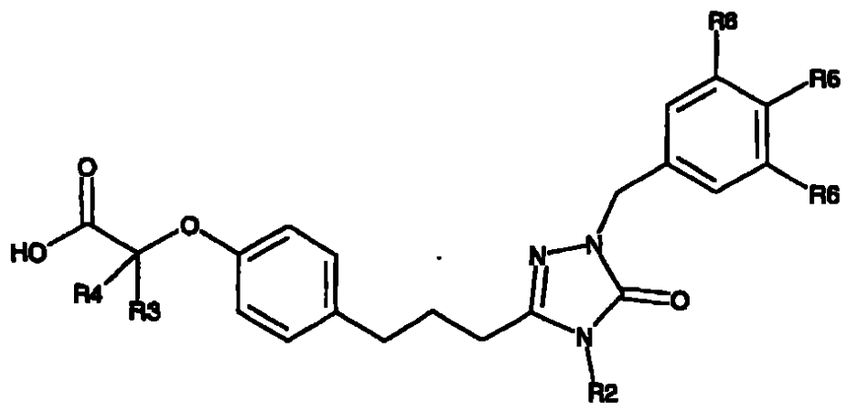
25. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 23 o 24 en el que X es propileno.

26. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 23, 24 o 25 en el que R3 es metilo.

27. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 23, 24, 25 o 26 en el que R4

es metilo.

28. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1 o 2 que está representado por la siguiente fórmula estructural:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R2 es H o un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_6, cicloalquilo C_3-C_6 y heteroarilo (suprimir heteroarilo);

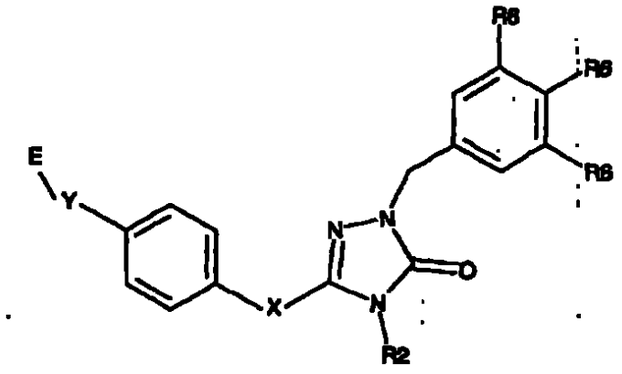
(b) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5,

(c) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6 y fenilo, o R3

y R4 se combinan para formar un cicloalquilo C_3-C_4; y

(d) R6 se selecciona independientemente del grupo constituido por H, OH, alquilo C_1-C_5, alcoxi, halo, haloalquilo, haloalcoxi, nitro, fenilo, ariloxi, SO2R7, SR7, ciano, benciloxi, fenoxi, alquilcarboxamido o COOH en la que R7 es un alquilo o haloalquilo.

29. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2 o 4-28, que está representado por la siguiente fórmula estructural:

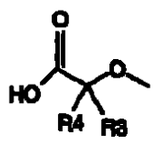


en la que R6 se selecciona independientemente del grupo constituido por H, OH, alquilo C_1-C_5, alcoxi, halo, haloalquilo, haloalcoxi, nitro, fenilo,

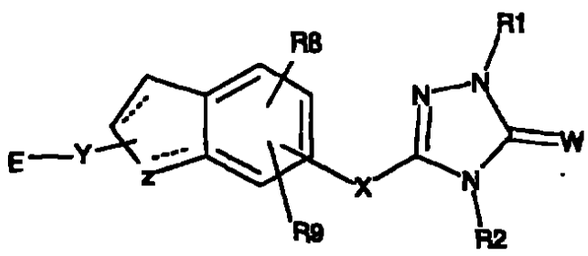
ariloxi, SO2R7, SR7, ciano, benciloxi, fenoxi, alquilcarboxamido o COOH en la que R7 es un alquilo o un haloalquilo.

30. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2 o 4-29 en el que hay dos sustituyentes R6 sustituidos independientemente seleccionados del grupo constituido por hidrógeno, alquilo C_1-C_5, Cl, F, OCH_3, CF_3 y SCF_3.

31. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 2 o 4-30 en el que EY es



32. Un compuesto representado por la siguiente fórmula estructural:



y las sales, solvatos e hidratos farmacéuticamente aceptables del mismo, en la que:

(a) R1 se selecciona del grupo constituido por hidrógeno, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cicloalquilarilo C_3-C_6-alquilo C_0-C_2, y -CH_2-C(O)-R17-R18, en la que R17 es O o NH y R18 es un bencilo opcionalmente sustituido;

(b) W es O o S;

(c) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(d) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(e) Y es C, O, S, NH o un enlace sencillo; y

(f) E se selecciona del grupo constituido por hidrógeno, C(R3)(R4)A, A, un grupo sustituido o insustituido constituido por $(CH_2)_n$COOR19, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4,

tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo, o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, arilmetilo opcionalmente sustituido y alquilo C_1-C_4 opcionalmente sustituido;

(g) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, y halo;

(h) R9 se selecciona independientemente el grupo

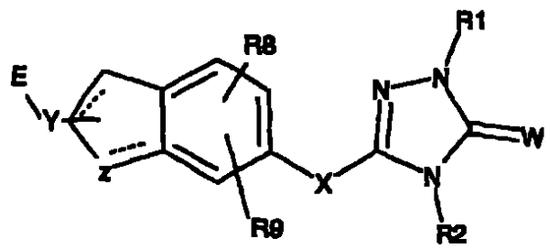
constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6 y OR10;

(i) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4;

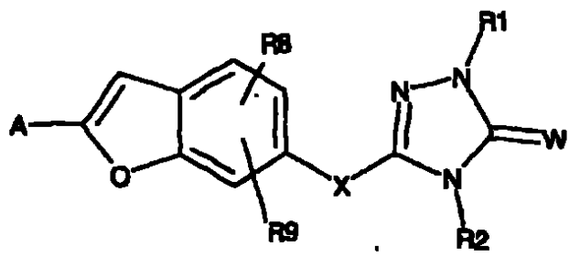
(j) Z es alquileno C_0-C_3, O, S, N, O-(alquileno C_0-C_2), S-(alquileno C_0-C_2) y N-(alquileno C_0-C_2); y

(k) - - - es un enlace opcional para formar un doble enlace.

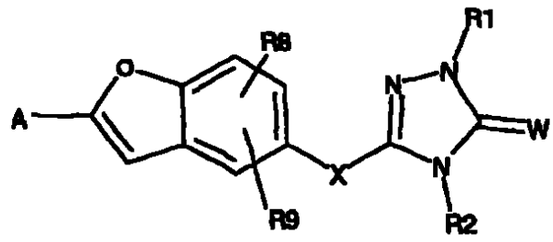
33. Un compuesto de la Reivindicación 32 que tiene la fórmula:



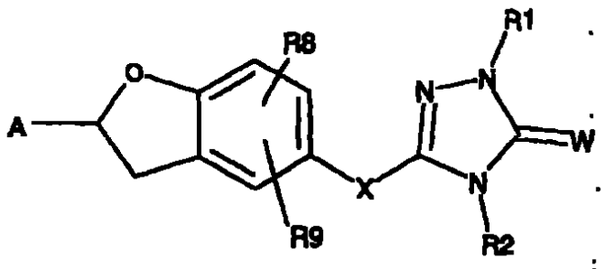
34. Un compuesto de las Reivindicaciones 32 o 33 representado por la fórmula estructural:



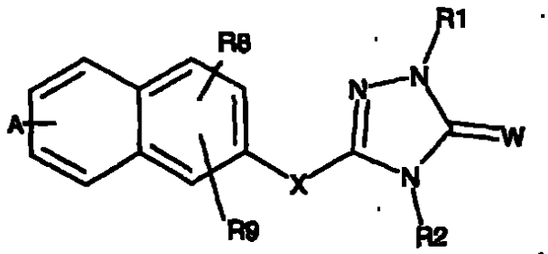
35. Un compuesto de la Reivindicación 32 representado por la fórmula estructural:



36. Un compuesto de las Reivindicaciones 32 o 33 representado por la siguiente estructura:



37. Un compuesto de las Reivindicaciones 32 o 33 representado por la siguiente estructura:



38. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 32, 33, 34, 35, 36 o 37 en el que A es COOH.

39. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 32, 33, 34, 35, 36, 37 o 38 en el que W es O.

40. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 32, 33, 34, 35, 36, 37, 38 o 39 en el que R2 es alquilo C_1-C_4.

41. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 32, 33, 34, 35, 36, 37, 38, 39 o 40 en el que X es alquileno C_2-C_3.

42. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 32, 33, 34, 35, 36, 37, 38, 39, 40 o 41 en el que R1 es fenilo o bencilo opcionalmente sustituido.

43. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 32, 33, 34, 35, 36, 37, 38, 39, 40, 41 o 42 en el que R1 es un grupo sustituido o insustituido seleccionado del grupo constituido por

alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cicloalquilaril C_3-C_6-alquilo C_0-C_2 y fenilo.

44. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1-43 en el que dicho compuesto está radiomarcardo.

45. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1-44 en el que dicho compuesto está tritiado.

46. Una composición farmacéutica, que comprende un vehículo farmacéuticamente aceptable y al menos un compuesto según se reivindica en cualquiera de las Reivindicaciones 1-45, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

47. Un procedimiento para modular el receptor activa del proliferador de peroxisoma, que comprende la etapa de conectar el receptor con al menos un compuesto según se reivindica en cualquiera de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

48. El procedimiento de la Reivindicación 47, en el

que receptor de peroxisoma activado por un proliferador es un receptor α.

49. Un procedimiento de tratamiento de la diabetes mellitus en un mamífero, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

50. Un procedimiento de prevención de la diabetes mellitus en un mamífero, que comprende la etapa de administrar al mamífero una cantidad eficaz de al menos un compuesto de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

51. El procedimiento de cualquiera de las Reivindicaciones 49 o 50 en el que el compuesto disminuye los niveles de glucosa en sangre.

52. Un procedimiento de tratamiento de enfermedades cardiovasculares en un mamífero, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de

las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

53. Un procedimiento de prevención de enfermedades cardiovasculares en un mamífero, que comprende la etapa de administrar al mamífero una cantidad eficaz de al menos un compuesto de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

54. El procedimiento de cualquiera de las Reivindicaciones 52 o 53 en el que el compuesto disminuye los triglicéridos en el mamífero.

55. El procedimiento de cualquiera de las Reivindicaciones 52, 53 o 54 en el que el compuesto disminuye las lipoproteínas de baja densidad en el mamífero.

56. El procedimiento de las Reivindicaciones 52, 53 o 54 en el que el compuesto aumenta las lipoproteínas de alta densidad en un mamífero.

57. Un procedimiento de tratamiento del síndrome X en un mamífero, que comprende la etapa de administrar

al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

58. Un procedimiento de prevención del síndrome X en un mamífero, que comprende la etapa de administrar al mamífero una cantidad eficaz de al menos un compuesto de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

59. El procedimiento de la Reivindicación 58 en el que el compuesto disminuye los niveles de glucosa en sangre.

60. El procedimiento de cualquiera de las Reivindicaciones 58 o 59 en el que el compuesto disminuye la concentración de triglicéridos en suero en el mamífero.

61. El procedimiento de cualquiera de las Reivindicaciones 58, 59 o 60 en el que el compuesto disminuye la concentración de las lipoproteínas de baja densidad en suero en el mamífero.

62. El procedimiento de cualquiera de las Reivindicaciones 58, 59, 60 o 61 en el que el compuesto aumenta la concentración de las lipoproteínas de alta densidad en suero en un mamífero.

63. Un procedimiento de tratamiento de la obesidad en un mamífero, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

64. Un procedimiento de prevención de la obesidad en un mamífero, que comprende la etapa de administrar al mamífero una cantidad terapéuticamente eficaz de al menos un compuesto de las Reivindicaciones 1-43, o una sal, solvato o hidrato farmacéuticamente aceptable del mismo.

65. El procedimiento de cualquiera de las Reivindicaciones 47-64 en el que el mamífero es un humano.

66. Un compuesto para usar en terapia para un

trastorno modulado por un receptor de peroxisoma activado por un proliferador; dicho compuesto o una sal, solvato o hidrato farmacéuticamente aceptable del mismo es un compuesto de las Reivindicaciones 1-43.

67. Uso de un compuesto para la fabricación de un medicamento para el tratamiento de una afección modulada por un receptor de peroxisoma activado por un proliferador; dicho compuesto o una sal, solvato o hidrato farmacéuticamente aceptable del mismo es un compuesto de las Reivindicaciones 1-43.

68. Todos los procedimientos descritos en la presente memoria descriptiva de preparación de los compuestos representados por la Fórmula Estructural I.

69. Un procedimiento de preparación de un triazol a partir de una semicarbazida de acilo que comprende poner en contacto dicha semicarbazida de acilo con un ácido.

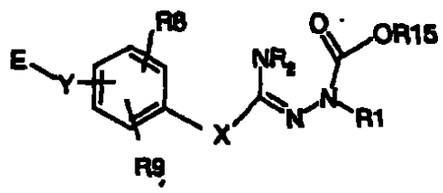
70. Un procedimiento según se reivindica en la Reivindicación 69 en el que el ácido es ácido

sulfónico.

71. Un procedimiento según se reivindica en la Reivindicación 69 en el que el ácido es clorhidrato de piridinio.

72. Un procedimiento según se reivindica en cualquiera de las Reivindicaciones 69, 70 o 71 en el que la triazalona está representada por la fórmula I.

73. Un compuesto de fórmula:



en la que

(a) R1 es hidrógeno o se selecciona del grupo constituido por un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4 y cicloalquilaril C_3-C_6-alquilo C_0-C_2;

(b) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4,

heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(c) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(d) Y es C, O, S, NH o un enlace sencillo; y

(e) E se selecciona del grupo constituido por hidrógeno, $(CH_2)_n$COOR19, C(R3)(R4)A, A, sustituido o insustituido, seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o

insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, alquilo C_1-C_4 opcionalmente sustituido y arilmetilo opcionalmente sustituido;

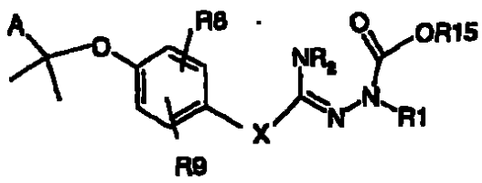
(f) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

(g) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

(h) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4; y

(i) R15 se selecciona del grupo constituido por hidrógeno y un sustituyente opcionalmente sustituido seleccionado del grupo constituido por alquilo C_1-C_4, arilo y bencilo.

74. Un compuesto de la Reivindicación 73 que tiene la fórmula:



75. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 73 y 74 en el que X es alquileno C_2-C_5.

76. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 73, 74 o 75 en el que A se selecciona del grupo constituido por COOH y alquilnitrilo C_1-C_3.

77. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 73, 74, 75 o 76 en el que R2 es alquilo C_1-C_4.

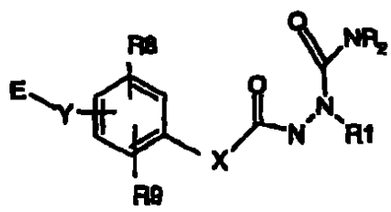
78. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 73, 74, 75, 76 o 77 en el que X es alquileno C_2-C_3.

79. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 73, 74, 75, 76, 77 o 78 en el

que R1 es fenilo o bencilo opcionalmente sustituido.

80. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 73, 74, 75, 76, 77, 78 o 79 en el que R1 es un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, cicloalquilaril C_3-C_6-alquilo C_0-C_2 y fenilo.

81. Un compuesto de fórmula:



en la que

(a) R1 es hidrógeno o se selecciona del grupo constituido por un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4 y cicloalquilaril C_3-C_6-alquilo C_0-C_2;

(b) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo

C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(c) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(d) Y es C, O, S, NH o un enlace sencillo; y

(e) E se selecciona del grupo constituido por hidrógeno, o se selecciona del grupo constituido por $(CH_2)_nCOOR19$, C(R3)(R4)A, sustituido o insustituido, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo ácido funcional seleccionado del grupo constituido por carboxilo, alquilnitrilo C1-C3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C1-C5 saturado o insaturado, alcoxi C1-C5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, alquilo C_1-C_4 opcionalmente sustituido y arilmetilo opcionalmente sustituido;

(f) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

(g) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

(h) R10 se selecciona independientemente del grupo constituido por hidrógeno y alquilo C_1-C_4.

82. Un compuesto según se reivindica en la Reivindicación 81 en la que X es alquileno C_2-C_5.

83. Un compuesto según se reivindica en cualquiera

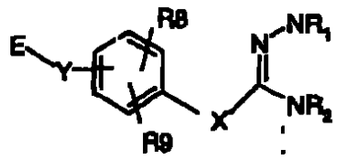
de las Reivindicaciones 81 u 82 en el que A se selecciona del grupo constituido por COOH y alquilnitrilo C_1-C_3.

84. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 81, 82 u 83 en el que R2 es alquilo C_1-C_4.

85. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 81, 82, 83 u 84 en el que X es alquileno C_2-C_3.

86. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 81, 82, 83, 84 u 85 en el que R1 es fenilo o bencilo opcionalmente sustituido.

87. Un compuesto de fórmula:



en la que

(a) R1 es hidrógeno o se selecciona del grupo constituido por un grupo sustituido o

insustituido seleccionado del grupo constituido por alquilo C_1-C_8, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4 y cicloalquilaril C_3-C_6-alquilo C_0-C_2;

(b) R2 es H o un grupo sustituido o insustituido seleccionado del grupo constituido por alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, heteroarilalquilo C_0-C_4, sulfonamida, amida, OR10 y cicloalquilo C_3-C_6;

(c) X es un alquileno C_1-C_5 de unión opcionalmente sustituido en el que un átomo de carbono del elemento de unión puede estar sustituido con O, NH o S;

(d) Y es C, O, S, NH o un enlace sencillo; y

(e) E se selecciona del grupo constituido por hidrógeno, o se selecciona del grupo constituido por $(CH_2)_nCOOR19$, C(R3)(R4)A, sustituido o insustituido, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4, y en la que

(i) n es 0, 1, 2 o 3,

(ii) A es un grupo ácido funcional seleccionado del grupo constituido por carboxilo,

alquilnitrilo C_1-C_3, carboxamida, sulfonamida sustituida o insustituida, acilsulfonamida sustituida o insustituida y tetrazol sustituido o insustituido;

(iii) R3 es H, alquilo C_1-C_5 saturado o insaturado, alcoxi C_1-C_5, y

(iv) R4 es H, halo, un grupo sustituido o insustituido seleccionado entre alquilo C_1-C_5, alcoxi C_1-C_5, cicloalquilo C_3-C_6, arilalquilo C_0-C_4 y fenilo o R3 y R4 se combinan para formar un cicloalquilo C_3-C_4;

(v) R19 se selecciona del grupo constituido por hidrógeno, alquilo C_1-C_4 opcionalmente sustituido y arilmetilo opcionalmente sustituido;

(f) R8 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4 y halo;

(g) R9 se selecciona independientemente del grupo constituido por hidrógeno, alquilo C_1-C_4, alquilenilo C_1-C_4, halo, arilo sustituido o insustituido, arilalquilo C_1-C_4 sustituido o insustituido, heteroarilo sustituido o insustituido, alilo C_1-C_6, y OR10; y

(h) R10 se selecciona independientemente del grupo

constituido por hidrógeno y alquilo C_1-C_4.

88. Un compuesto según se reivindica en la Reivindicación 87 en el que X es alquileno C_2-C_5.

89. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 87 u 88 en el que A se selecciona del grupo constituido por COOH y alquilnitrilo C_1-C_3.

90. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 87, 88 u 89 en el que R2 es alquilo C_1-C_4.

91. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 87, 88, 89 o 90, en el que X es alquileno C_2-C_3.

92. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 87, 88, 89, 90 o 91 en el que R1 es fenilo o bencilo opcionalmente sustituido.

93. Un compuesto según se reivindica en cualquiera de las Reivindicaciones 1, 3, 6, 7, 11, 12, 29, 30, 32, 33, 73, 81, 84, 85, 86, 87, 88, 91, 91, o 92 en

el que E se selecciona del grupo constituido por hidrógeno, C(R3)(R4)A sustituido o insustituido seleccionado del grupo constituido por $(CH_2)_nCOOH$, alquilo C_1-C_6, alilo C_1-C_6, arilalquilo C_0-C_4, tioalquilo C_1-C_4, tioarilo, alcoxiarilo C_1-C_4, alcoxi C_1-C_4-alquilo C_1-C_4, aminoarilo y aminoalquilo C_1-C_4.

94. Un compuesto según se describe en cualquiera de los ejemplos de la presente memoria descriptiva.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
X14174		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US01/42928	09/11/2001	10/11/2000
International Patent Classification (IPC) or national classification and IPC		
C07D249/12		
Applicant		
ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/05/2002	13.11.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Scruton-Evans, I Telephone No. +49 89 2399 8272

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US01/42928

I. Basis of the report

1. With regard to the elements of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-358 as originally filed

Claims, No.:

1-94 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-18,30,32-37,39-68,73-94(partly).

because:

☒ the said international application, or the said claims Nos. 47-65 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-18,30,32-37,39-68,73-94(partly).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-68,72-94.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,7-68,72-94
	No:	Claims	1,3-6
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-68,72-94
Industrial applicability (IA)	Yes:	Claims	1-46,66-68,72-94
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 47-65 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claims 1-18,30,32-37,39-68,73-94 were only partially searched in as far as the group Y-E is in the 4-position, chosen from CH2-C-COO or S-C-COO or O-C-COO or O-(CH2)1-3-COO or O-C-CON or COOH, and the intermediates of claims 73-92 with the corresponding group Y-E. This preliminary opinion is thus only based on the searched subject matter.

Re Item IV

Lack of unity of invention

No further search fees were paid at the search stage, and thus this opinion is based only on the first invention, claims 1-68,72-94 (see PCT/ISA Sheet 206 for the detailed non-unity analysis).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are cited in the Search Report;

D1: WO 96 35680 A (BAYER AG ;MUELLER KLAUS HELMUT (DE); KIRSTEN ROLF (DE); GESING ERN) 14 November 1996 (1996-11-14)

D2: WO 96 13264 A (DOMINIANNI SAMUEL JAMES ;FITCH LORA LOUISE (US); LILLY CO ELI (US)) 9 May 1996 (1996-05-09)

D3: EP-A-1 028 111 (YAMANOUCHI PHARMA CO LTD) 16 August 2000 (2000-08-16)

D4: WO 01 40207 A (SIERRA MICHAEL LAWRENCE ;GLAXO GROUP LTD (GB)) 7 June 2001 (2001-06-07)

D5: WO 99 08501 A (REDDY RESEARCH FOUNDATION ;REDDY CHEMINOR INC (US)) 25 February 1999 (1999-02-25)

D6: T.M.WILLSON ET AL: 'The structure-activity relationship between PPAR-gamma agonism and the antihyperglycemic activity of thiazolidinediones' JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 3, 1996, pages 665-668, XP002007700

Document D4 was published after the priority date of the present application, and until such a time as the priority document has been studied, no discussion as to its relevance will be made.

With regard to the requirement for novelty (Article 33(2) of the PCT); the end compounds of the present application are not novel with respect to D1 due tot he specific compound II-8 on page 59. D2 overlaps with the compounds of the present application in that the definition of substituted alkyl for Y-E in the present application falls within D2 (see especially the examples 7,8,9,1 in D2). D3 differs in the nature of the nature of the group X in the present application, and D5 in the nature of the heterocycle. D6 is a general document on thiazolidinediones. Article 33(2) is thus not satisfied for claims 1,3-6.

With regard to the requirement for inventive step (Article 33(39 of the PCT), the compounds of the present application are disclosed as being PPAR alpha agonists (see pages 346-358). The document D5 discloses exactly the same qualitative activity, document D1 has herbicidal activity, D2 has a hypoglycaemic activity, D3 are selective beta-3 agonists, and D6 also the same qualitative activity as the present application. It would appear that although the hypoglycaemic activity of D2 and the beta-3 agonist activity of D3 are related in part to the PPAR activity, they are not exactly the same qualitative activity, although with overlapping pharmacological uses. Thus D5 and D6 are considered to represent the closest prior arts. D6 discloses thiazolidinediones, and D5 a different class of heterocycle. Thus the man skilled in the art, faced with the problem of providing further novel compounds with the PPAR activity would have been

aware that certain modifications of the heterocycle can lead to a retention of the activity, but it cannot be said that he would have been unambiguously led to the compounds of the present application, expecting them to have the desired activity in the light of D5 and D6, but before an inventive step can be acknowledged, it must be shown that the problem has been solved in a representative manner across the scope of the claim, i.e. that all compounds falling within the scope of the claim can be reasonably expected to display the activity. Given that different activities are present in the prior arts D1-D3 for structurally similar compounds (and the overlap with D2), the doubt arises as to whether this is indeed the case, and the Applicant should clearly state on what basis the claimed scope was conceived, especially the wide variation in the various groupings on the modified feature. It would apper that the compounds of claims 32-43 are also active end products, and it must also be clear on what basis such a generalisation for these compounds is made.

For the intermediates of claims 73-93, until such a time as an inventive step has been acknowledged for the end-products, their satisfaction of Article 33(3) cannot be ascertained, but it would appear that they include the precursor to the heterocyclic ring distinguishing the application, and thus providing their scope is consistent with the end-products (see above), then they could benefit from an eventual inventive step for the end-products.

All terms such as "substituted","optionally substituted","heteoraryl" etc give rise to a very broad scope, and these should be defined according to the description.

Claim 94 is not clear (Article 6 PCT).

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(PCT Artículo 36 y regla 70)

Referencia del archivo del solicitante o agente X-14174	**PARA UNA ACCIÓN ADICIONAL**	Véase la Notificación de Transmisión del Informe de Examen Preliminar Internacional (formulario PCT/IPEA/416)
Solicitud Internacional No. PCT/US01/42928	Fecha de presentación internacional *(día/mes/año)* 09/11/2001	Fecha de prioridad *(día/mes/año)* 10/11/2000
Clasificación de Patente Internacional (IPC) o tanto clasificación nacional como IPC C07D249/12		
Solicitante ELI LILLY AND COMPANY et al.		

1. Este informe de examen preliminar internacional se ha preparado por la Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de acuerdo con el Artículo 36.
2. Este INFORME consta de un total de 6 hojas, incluyendo esta hoja de portada.
   __ Este informe también se acompaña de ANEXOS, es decir, hojas de la descripción reivindicaciones y/o dibujos que se han enmendado y son la base para este informe y/o hojas que contienen rectificaciones hechas antes de esta Autoridad (véase Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT.

3. Este informe contiene indicaciones relacionadas con las siguientes cuestiones
   - I. X. Bases de la opinión
   - II. _ Prioridad
   - III. X. Opinión sin establecer con respecto a la novedad, actividad inventiva y aplicabilidad industrial
   - IV. X. Falta de unidad de invención
   - V. X. Afirmación razonada según la Regla 35(2) con respecto a la novedad, actividad inventiva o aplicabilidad industrial; citaciones y explicaciones que apoyan dicha afirmación
   - VI. _ Algunos documentos citados
   - VII. _ Algunos defectos en la solicitud internacional
   - VIII. _ Algunas observaciones en la solicitud internacional

Fecha de presentación de la demanda 13/05/2002	Fecha de terminación de este informe 13.11.2002
Nombre y dirección de correo de la Autoridad Examinadora preliminar internacional: European Patent Office D-80298 Munich Tel 49892399-0 Tx5236656 epmu-d Fax 49892399	Funcionario autorizado Scruton-Evans, I Número de teléfono: +49 89 2399 8272

INFORME DE EXAMEN
PRELIMINAR INTERNACIONAL solicitud Internacional número: PCT/US01/16519

I. Bases del Informe

1. con respecto a los elementos de la solicitud internacional (las hojas de sustitución que se han proporcionado a la Oficina receptora en respuesta a una invitación según el artículo 14, en el presente informe se designan como "presentadas originalmente" y no se adjuntan a este informe, ya que no contienen modificaciones (normas 70.16 y 70.17):

Descripción, páginas:
1-358 como presentadas originalmente.

Reivindicaciones, No:
1-94 como presentadas originalmente

2. Con respecto al **idioma**, todos los elementos marcados anteriormente estaban disponibles o se proporcionaron a esta Autoridad en el idioma en el que se presentó la solicitud internacional, a menos que se indique otra cosa en este apartado

Estos elementos estaban disponibles o se proporcionaron a esta Autoridad en el siguiente idioma
, que es
_ el idioma de una traducción proporcionada para los fines de investigación internacional (de acuerdo con la Norma 23.1(b)

_ El idioma de publicación de la solicitud internacional (de acuerdo con la Norma 48.3(b))

_ El idioma de una traducción proporcionada para los fines de examen preliminar internacional (de acuerdo con la Norma 55.2 y/o 55.3)

3. Con respecto a cualquier **secuencia de nucleótidos y/o de aminoácidos** descrita en la solicitud internacional, el examen preliminar internacional se realizó basándose en la lista de secuencias.

_ contenida en la solicitud internacional en forma escrita.
_ presentada junto con la solicitud internacional en forma legible por ordenador.
_ proporcionada con posterioridad a esta Autoridad en forma escrita
_ proporcionada con posterioridad a esta Autoridad en forma legible por ordenador
_ se ha proporcionado la declaración de que la lista de secuencias escrita proporcionada posteriormente no va más allá de la descripción de la solicitud internacional según se presentó
_ se ha proporcionado la declaración de que la información guardada en forma legible por ordenador es idéntica a la lista de secuencias escrita.

4. Las modificaciones han dado como resultado la anulación de:

_ La descripción, páginas:
_ Las reivindicaciones, números:
_ Los dibujos, hojas

5. _ Este informe se ha establecido como si (algunas de) las modificaciones no se hubieran realizado, ya que se ha considerado que van más allá de la descripción según se presentó (norma 70.2(c))

(Cualquier hoja de sustitución que contenga tales modificaciones deberá ser mencionada en el punto 1 y adjuntarse en este informe.)

6. Observaciones adicionales en caso de que sea necesario:

INFORME DE EXAMEN
PRELIMINAR INTERNACIONAL **solicitud Internacional número: PCT/US01/16519**

III. No establecimiento de opinión con respecto a la novedad, actividad inventiva y aplicabilidad industrial.

1. Las cuestiones de si la invención reivindicada parece ser nueva, implicar una actividad inventiva (ser no evidente) o ser aplicable industrialmente no se han examinado respecto de:

_ La solicitud internacional entera

X La reivindicaciones número 1-18, 30, 32-37, 39-68, 73-94 (parcialmente)
Porque:

X dicha solicitud internacional o dichas reivindicaciones números: se refieren a la siguiente materia objeto que no requiere un examen preliminar internacional (especificar):
Véase hoja separada

_ la descripción, reivindicaciones o dibujos (indicar los elementos particulares más adelante) o dichas reivindicaciones Nos. Están tan poco claras que no puede formarse una opinión significativa (*especificar)*

_Las reivindicaciones, o dichas reivindicaciones están apoyadas tan inadecuadamente por la descripción, que no puede formarse una opinión significativa.

X No se ha establecido ningún informe de búsqueda internacional para dichas reivindicaciones números: 1-18, 30, 32-37, 39-68, 73-94 (parcialmente)

2. No puede realizarse un examen preliminar internacional significativo debido a que la lista de secuencias de nucleótidos y/o aminoácidos no cumple con la norma proporcionada en el Anexo C de las Instrucciones Administrativas:

_ la forma escrita no se ha proporcionado o no cumple con la norma.

_ la forma legible por ordenador no se ha proporcionado o no cumple con la norma

IV. Falta de unidad de la invención.

1. En respuesta a la petición para restringir o pagar tasas adicionales el solicitante ha:

_ Restringido las reivindicaciones.

_ Pagado las tasas adicionales.

_ Pagado las tasas adicionales con protesta.

X Ni las restricciones ni pago de las tasas adicionales.

2. __ Esta Autoridad considera que la solicitud de unidad de invención con las Reglas 13.1, 13.2 y 13.3 está:

_ Completa con

_ No completa por las siguientes razones:

4. Consecuentemente, las siguientes partes de la solicitud internacional fueron objeto de un Examen Preliminar Internacional estableciendo este informe:

_ Todas las partes.

X las partes relativas a las reivindicaciones número: 1-68, 72-94.

V. Declaración razonada según el Artículo 35(2) con respecto a la novedad, actividad inventiva o aplicabilidad industrial; citaciones y explicaciones que apoyan tal declaración.

1. Declaración

Novedad (N)	Sí	Reivindicaciones	2-7-68, 72-94
	No	Reivindicaciones	1, 3-6
Actividad inventiva	Sí	Reivindicaciones	
(IS)	No	Reivindicaciones	1-68, 72-94
Aplicabilidad	Sí	Reivindicaciones	1-46, 66-68, 72-
industrial (IA)	No	Reivindicaciones	94

2. Citaciones y explicaciones

Ver hoja separada.

RE Punto III

No establecimiento de opinión con respecto a la novedad, etapa inventiva y aplicabilidad industrial.

Las reivindicaciones 47-65 se refieren a la materia en cuestión considerada por esta Autoridad para ser cubierta por las disposiciones de la Regla 67.1 (iv) PCT. Consecuentemente, no se formulará opinión con respecto a la aplicabilidad industrial de la materia en cuestión de estas reivindicaciones (artículo 34(4) (a)(i) PCT)

Las reivindicaciones 1-18, 30,32-37,39-68, 73-94 se investigaron sólo parcialmente siempre que el grupo Y-E esté en la posición 4, elegido de etre CH_2-C-COO o S-C-COO o O-C-COO o O-$(CH_2)_{1-3}$-COO O O-C-CON O-COOH y los intermedios de las reivindicaciones 73-92 con el grupo correspondiente Y-E. Esta opinión preliminar está por tanto basada sólo en la materia en cuestión investigada

Re Punto IV

Falta de unidad de la invención.

No se pagaron más tasas de investigación en la etapa de investigación y por tanto esta opinión se basa sólo en la primera invención reivindicaciones 1-68, 72-94 (véase PCT/ISA Hoja 206 para el análisis detallado de no unidad)

Re Punto V

Sentencia razonada según la Regla 66.2 (a)(ii) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citaciones y explicaciones que apoyan dicha sentencia.

Los siguientes documentos se citan en el informe de investigación;

D1: WO 35680 A (BAYER AG; MUELLER KLAUS HELMUT (DE); DIRSTEN ROLF (DE); GESING ERN) 14 November 1996 (1996-11-14)

D2: WO 96 13264 A (DOMINIANNI SAMUEL JAMES; FITCH LORA LOUISE (US); LILLY CO ELI (US)) 9 May 1996 (1996-05-09)

D3: EP-a-1 028 111(YAMANOUCHI PHARMA CO LTD) 16 August 2000 (2000-08-16)

D4: WO 01 40207 A (SIERRA MICHAEL LAWRENCE; GLAXO GROUP LTD (GB)) 7 June 2001 (2001-06-07)

D5: WO 01 40207A (REDDY RESEARCH FOUNDATION; REDDY CHEMINOR INC (US)) 25 February 1999 (1999-02-25)

D6: T.M. WILLSON ET AL "The structure activity relationship beween PPAR- gamma agonism and the antihyperglycemic activity of thiazolidinediones" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no 3, 1996 oages 665-668 XP002007700

El documento D4 se publicó después de la fecha de prioridad de la presente solicitud y hasta ese momento no se harán discusiones sobre su relevancia cuando el documento de prioridad se haya estudiado.
Con respecto a los requisitos de novedad (Artículo 33 (2) de la PCT); los compuestos finales de la presente solicitud no son novedosos con respecto a D1 debido a que el compuesto específico II-8 de la página 59 de D2 se solapa con los compuestos de la presente solicitud en que la definición de alquilo sustituido para Y-E en la presente solicitud está dentro de D2 (véase especialmente los ejemplos 7,8,9,1 en D2) D3 difiere en la naturaleza del grupo X en la presente solicitud, y D5 en la naturaleza del heterociclo. D6 es un documento general sobre las tiazolididionas. Por lo tanto, el Artículo 33 (2) no se cumple en las reivindicaciones 1,3-6.
Con respecto a los requisitos par ala etapa inventiva (artículo 33(39 de la PCT)), los compuestos de la presente solicitud se describen como agonistas alfa de PPAR (véase páginas 346-358).
El documento D5 describe exactamente la misma actividad cualitativa, el documento D1 presenta actividad herbicida, el documento D2 presenta actividad hipoglucémica, el documento D3 presenta agonistas beta-3 selectivos y el documento D6 presenta también la misma actividad cualitativa que la presente solicitud. Parece que aunque la actividad hipoglucémica de D2 y la actividad beta-3 agonista de D3 están relacionadas en parte con la actividad PPAR, no son exactamente la misma actividad cualitativa aunque presenten usos farmacológicos que se solapan. Por tanto, el experto en la técnica, enfrentado al problema de proporcionar compuestos novedosos adicionales con la actividad PPAR tendría que ser consciente de que ciertas modificaciones del heterociclo pueden conducir a una retención de la actividad, pero no puede decirse que el experto haya sido conducido inequívocamente a los compuestos de la presente solicitud, esperando que los compuestos presenten la actividad deseada a la vista de D5 y D6, pero antes de poder reconocer una etapa inventiva se debe mostrar que el problema se ha solucionado de manera representativa a lo largo del alcance de la reivindicación, es decir, que pueda esperarse razonablemente que todos los compuestos que estén dentro del alcance de la reivindicación presenten la actividad. Dadas la sdiferentes actividades presentes en la técnica anterior D1-D3 para compuestos estructuralmente similares (y el solapamiento con D2), se genera la duda de si este es en efecto el caso y el solicitante debería declarar claramente en qué bases se concibió el alcance reivindicado, especialmente la amplia variación en los diversos agrupamientos en la característica modificada. Parece que los compuestos de las reivindicaciones 32-43 son también productos finales activos y debe también quedar claro en qué bases se hace una generalización tal para estos compuestos.
Par los intermedios de las reivindicaciones 73-93, hasta el momento en que se haya reconocido la etapa inventiva para los productos finales, no se puede comprobar su cumplimiento del Artículo 33(3), pero parece que incluyen el precursor del anillo heterocíclico, distinguiendo la solicitud y por parto proporcionadndo un alcance coherente con los productos finales (véase anteriormente), así ellos podrían beneficiarse de una etapa inventiva eventual para los productos finales.
Todos los términos como "sustituido","opcionalmente sustituido", "heteroarilo", etc dan lugar a una alcance muy ancho y estos deberían definirse de acuerdo con la descripción. La reivindicación 94 no está clara (artículo 6 de PCT)

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TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(PCT Artículo 18 y Reglas 43 y 44)

Referencia del archivo del solicitante o agente X-14174	**PARA UNA ACCIÓN ADICIONAL**	Véase la Notificación de Transmisión del Informe de Examen Preliminar Internacional (formulario PCT/IPA/416)
Solicitud Internacional No. PCT/US01/42928	Fecha de presentación internacional *(día/mes/año)* 09/11/2001	Fecha de prioridad *(día/mes/año)* 10/11/2000

Solicitante
ELI LILLY AND COMPANY

1. Este informe de examen preliminar internacional se ha preparado por la Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de acuerdo con el Artículo 36.
2. Este INFORME consta de un total de 6 hojas, incluyendo esta hoja de portada.
   __ Este informe también se acompaña de una copia de cada documento citado anteriormente en este informe

1. **Bases del informe**

a. con respecto al idioma la búsqueda internacional se llevo a cabo en base a la solicitud internacional en el idioma en el que fue presentada, si no se indica de otra manera bajo este punto.
   __ La búsqueda internacional se llevo a cabo en base a una traducción de la solicitud internacional proporcionada a esta autoridad.

b. **Respecto a cualquier secuencia de nucleótidos y/o aminoácidos mostrada en la solicitud internacional, la búsqueda internacional fue llevada a cabo en base a la lista de secuencia:**
   __ contenidas en la solicitud internacional de forma escrita
   __ presentada con la solicitud internacional de forma computerizada legible
   __ Proporcionada a esta autoridad posteriormente de forma escrita.
   __ Proporcionada a esta autoridad posteriormente de forma computerizada legible.
   ___ se ha proporcionado la declaración de que la lista de secuencias escrita proporcionada posteriormente no va más allá de la descripción de la solicitud internacional según se presentó
   _ se ha proporcionado la declaración de que la información guardada en forma legible por ordenador es idéntica a la lista de secuencias escrita.

2. **X Algunas reivindicaciones fueron consideradas no susceptible de búsqueda.**
3. **X No existe unidad de invención**
4. **Respecto al título,**
   __ el texto es aprobado según fue presentado por el solicitante
   X el texto ha sido establecido por la autoridad como:
   TRIAZOLE DERIVATIVES AND THEIR USE AS PEROXISOME PROLIFERATOR ACTIVATE RECEPTOR ALPHA AGONISTS
5. **Respecto al resumen**
   __ el texto es aprobado según fue presentado por el solicitante.
   X El texto ha sido establecido, según la regla 38.2 (b). por esta autoridad como aparece en la casilla III. El solicitante debe dirigir sus comentarios por correo a esta autoridad dentro del mes siguiente.
6. Las figuras de los dibujos a publicar con el resumen son las figuras
   X No hay figuras.
   __ Según sugerencia del solicitante
   __ porque el solicitante renuncia a sugerir la figura

__porque la figura caracteriza mejor esta invención.

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud internacional
PCT/US 01/42928

CASILLA I Observaciones donde ciertas reivindicaciones fueron consideradas no susceptibles de búsqueda

El informe de búsqueda Internacional no ha establecido determinadas reivindicaciones bajo el Artículo 17(2)(a) por las siguientes razones:

X . Reivindicaciones Número:
Porque describen un asunto no solicitado para la búsqueda realizada por esta autoridad, a saber:

Aunque las reivindicaciones 47-65 están dirigidas a un método de tratamiento de un ser humano o un animal, la búsqueda se ha basado y ha sido llevada a cabo en las alegaciones de los efectos del compuesto.

X Las reivindicaciones : 1-18, 30, 32-37, 39-68, 73-94(en parte)
Porque se refieren a partes de la solicitud internacional que siguen los requisitos, por lo que ninguna búsqueda significativa puede ser llevada a cabo:
Ver más información página PCT/ISA/210

__ Reivindicaciones Nos.
Porque son reivindicaciones dependientes y no están diseñadas de acuerdo con la segunda y la tercera frase de la Regla 6.4(a).

CASILLA II Observaciones falta donde la unidad de invención.

La Autoridad Internacional de Búsqueda encontró múltiples invenciones en esta solicitud
Ver hoja adicional.

1. __Puesto que todas las tasas de búsqueda fueron pagadas a tiempo por el solicitante, este informe de búsqueda internacional cubre todas las reivindicaciones susceptibles de ser sometidas a búsqueda.
2. __ Puesto que todas las reivindicaciones susceptibles de búsqueda pueden ser sometidas a ella sin ningún tipo de esfuerzo adicional que justifique otras tasas, esta autoridad no reclama el pago de tasas adicionales.
3. __ Puesto que sólo algunas de las tasas adicionales requeridas fueron pagadas a tiempo, este informe de Búsqueda Internacional solo cubre aquellas reivindicaciones por las que las tasas fueron pagadas, específicamente reivindicaciones número:
4. X Las tasas adicionales no requeridas fueron pagadas a tiempo por el solicitante. En consecuencia este Informe de búsqueda Internacional, está restringido a la invención primeramente mencionada en las reivindicaciones; cubren las reivindicaciones número:
1-68,72-94

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INFORMACIÓN DE CONTINUACIÓN DESDE EL PCT/ISA 210

Continuación de la casilla 1.2

Reivindicaciones Números: 1-18,30,32-37, 39-68, 73-94 (parcialmente)

Las presentes reivindicaciones1-18,30,32-37, 39-68, 73-94 (todas parcialmente) se refieren a un número extremadamente grande de posibles compuestos. Se ha de encontrar un apoyo dentro del significado del Artículo 6 de PCT y /o descripción dentro del significado del Artículo 5PCT, sin embargo, sólo se ha encontrado para una muy pequeña proporción de los compuestos reivindicados. En el presente caso, las reivindicaciones carecen de apoyo y la solicitud carece de descripción de manera que se hace imposible una investigación significativa sobre todo lo reivindicado. Consecuentemente, la investigación se ha llevado a cabo para aquellas partes de las reivindicaciones que parecen estar apoyadas y descritas a saber aquellas partes que se refieren a los compuestos de fórmula I en la que el grupo Y-E está en la posición 4 y se elige entre CH_2-C-COO o S-C-COO o O-C-COO o O-$(CH_2)_{1-3}$-COO o O-C-CON o COOH, es decir, aquellos grupos dentro de los cuales se incluyen todos los ejemplos de la solicitud y los intermedios de las reivindicaciones 73-92 con el correspondiente grupo Y-E.
La atención del solicitante se dirige al hecho de que las reivindicaciones o partes de las reivindicaciones, relacionadas con las invenciones respecto a los que no se ha establecido un informe de investigación internacional no necesitan ser objeto de un examen preliminar internacional (Regla 66.1(e) PCT). Se aconseja al solicitante que la norma de la EPO cuando actúa como Autoridad del Examen Preliminar Internacional normalmente es no llevar a cabo un examen preliminar sobre materia que no haya sido investigada. Este es el caso independientemente de si las reivindicaciones se corrigen o no después de la recepción del informe de investigación o durante cualquier procedimiento del Capítulo II.

Esta Autoridad de Investigación Internacional encontró múltiples (grupos de) invenciones en esta solicitud internacional, como sigue:

1. Reivindicaciones: 1-68, 72-94
   Compuestos de fórmula I, intermedios para su preparación, procesos para su preparación y el uso de dichos compuestos y sus composiciones.
2. Reivindicaciones: 69-71
   Un procedimiento de preparación de cualquier triazolona a partir de una acilsemicarbazida

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
X14174		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 01/ 42928	09/11/2001	10/11/2000
Applicant		
ELI LILLY AND COMPANY		

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 6 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, unless otherwise indicated under this item.

   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readble form.

   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☒ Unity of invention is lacking (see Box II).

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:

   TRIAZOLE DERIVATIVES AND THEIR USE AS PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR ALPHA AGONISTS

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(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ because the applicant failed to suggest a figure.

   ☐ because this figure better characterizes the invention.

   ☒ None of the figures.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/42928

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 47-65 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound

2. [X] Claims Nos.: 1-18,30,32-37,39-68,73-94 (partly)
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:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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. [X] 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.:

1-68, 72-94

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

International Application No. PCT/US 01/42928

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-18,30,32-37,39-68,73-94 (partly)

Present claims 1-18,30,32-37,39-68,73-94 (all partly) relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I wherein the group Y-E is in the 4-position and is chosen from CH2-C-COO or S-C-COO or O-C-COO or O-(CH2)1-3-COO or O-C-CON or COOH, i.e those groups under which all of the examples of the application fall and the intermediates of claims 73-92 with the corresponding group Y-E.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1-68,72-94

   Compounds of formula I, intermediates for their preparation, processes for their preparation and the use of such compounds and compositions thereof

2. Claims: 69-71

   A method of preparation of any triazolone from an acyl semicarbazide.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 01/42928 889

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D249/12 A61K31/4196 C07D401/06 C07D413/06 C07D409/06
C07D409/12 C07D417/12 C07D405/06 A61K31/4439 A61K31/427
C07C257/22 C07C281/04 C07C281/06

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 7 C07D A61K C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 35680 A (BAYER AG ;MUELLER KLAUS HELMUT (DE); KIRSTEN ROLF (DE); GESING ERN) 14 November 1996 (1996-11-14) see compound 11-8, page 59 ---	1,3-5
Y	WO 96 13264 A (DOMINIANNI SAMUEL JAMES ;FITCH LORA LOUISE (US); LILLY CO ELI (US)) 9 May 1996 (1996-05-09)	1-68, 72-94
X	see the examples, especially 7,8,9 1 ---	1,3,6
Y	EP 1 028 111 A (YAMANOUCHI PHARMA CO LTD) 16 August 2000 (2000-08-16) see the definitions of claim 1 and the examples 84,47,48,35 ---	1-68, 72-94
	-/--	

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2002	05. 07. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

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Form PCT/ISA/210 (second sheet) (July 1998)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 01 40207 A (SIERRA MICHAEL LAWRENCE ;GLAXO GROUP LTD (GB)) 7 June 2001 (2001-06-07) see the general formula ---	1-68, 72-94
Y	WO 99 08501 A (REDDY RESEARCH FOUNDATION ;REDDY CHEMINOR INC (US)) 25 February 1999 (1999-02-25) see especially claim 28 the whole document ---	1-68, 72-94
A	T.M.WILLSON ET AL: "The structure-activity relationship between PPAR-gamma agonism and the antihyperglycemic activity of thiazolidinediones" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 3, 1996, pages 665-668, XP002207708 the whole document -----	1-68, 72-94

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/42928

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9635680 A	14-11-1996	DE 19517505 A1	14-11-1996
		AU 5762996 A	29-11-1996
		CA 2220494 A1	14-11-1996
		WO 9635680 A1	14-11-1996
		EP 0824528 A1	25-02-1998
		JP 11504927 T	11-05-1999
WO 9613264 A	09-05-1996	US 5641796 A	24-06-1997
		AU 3971995 A	23-05-1996
		CA 2203277 A1	09-05-1996
		EP 0789570 A1	20-08-1997
		JP 10508030 T	04-08-1998
		WO 9613264 A1	09-05-1996
EP 1028111 A	16-08-2000	AU 9462198 A	10-05-1999
		CA 2305802 A1	29-04-1999
		EP 1028111 A1	16-08-2000
		JP 3193706 B2	30-07-2001
		NO 20001983 A	14-04-2000
		US 6346532 B1	12-02-2002
		AU 736676 B2	02-08-2001
		AU 8928898 A	06-05-1999
		BR 9804500 A	11-04-2000
		CN 1218045 A	02-06-1999
		HU 9802417 A2	30-08-1999
		WO 9920607 A1	29-04-1999
		PL 329233 A1	26-04-1999
WO 0140207 A	07-06-2001	AU 2003001 A	12-06-2001
		WO 0140207 A1	07-06-2001
WO 9908501 A	25-02-1999	AU 1120599 A	08-03-1999
		CN 1280571 T	17-01-2001
		EP 1073643 A2	07-02-2001
		WO 9908501 A2	25-02-1999
		US 6369067 B1	09-04-2002

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INF RME INTERNACIONAL DE BÚSQUEDA

Nº de expediente internacional
PCT/US 01/42928

A. CLASIFICACIÓN DEL OBJETO DE SOLICITUD
Int. Cl. [7]
C07D249/12 A61K31/4196 C07D401/06 C07D413/06 C07D409/06
C07D409/12 C07D417/12 C07D405/06 A61K31/4439 A61K31/427
C07C257/22 C07C281/04 C07C281/06
Según la clasificación internacional de Patentes (IPC) o tanto clasificación nacional e IPC

B. CAMPOS INVESTIGADOS
Material mínimo comprobado en la búsqueda (sistema de clasificación y símbolos de clasificación)
IPC 7 C07D A61K C07C

Publicaciones investigadas que, sin embargo, no forman parte del material mínimo comprobado, en la medida que pertenecen a los campos búsqueda

Base de datos electrónica consultada en la búsqueda internacional (nombre de la base de datos y conceptos de búsqueda eventualmente utilizados)
EPO-Internal, WPI Data, PAJ, BEILTEIN Data, CHEM ABS Data.

C. DOCUMENTOS CONSIDERADOS FUNDAMENTALES

Categoría*	Denominación de la publicación, si es necesario, indicándose las partes relevantes	Resp. a reivindicació
X	WO 98 35680 A (BAYER AG; MUELLER KLAUS HELMUT (DE); DIRSTEN ROLF (DE); GESING ERN) 14 november 1998 (1998-11-14) See compound II-8, page 59.	1,3-5
Y	WO 96 13284 A (DOMINIANNI SAMUEL JAMES; FITCH LORA LOUISE (US); LILLY CO ELI (US)) 9 May 1996 (1996-05-09) see examples, especially 7, 8, 9 1	1-68 72-94 1,3,6
X	EP 1 028 111 A (YAMANOUCHI PHARMA CO LTD) 16 August 2000 (2000-08-16) see definitions of claim 1 and examples 84, 47, 48, 35	1-68, 72-94
P,Y	WO 01 40207 A (SIERRA MICHAEL LAWRENCE; GLAXO GROUP LTD(GB)) 7 June 2001(2001-06-07) see the general formula	1-68, 72-94
Y	WO 99 08501 A (REDDY RESEARCH FOUNDATION; REDDY CHEMINOR INC(US)) 25 February 1999 (1999-02-25) see especially claim 28 the whole document	1-68, 72-94
A	TMWILLSON ET AL: "The structure-activity relationship between PPAR-gamma agonism and the antihyperglycemic activity of thiazolidinediones" JOURNAL OF MEDICINAL CHEMISTRY, Vol. 39, no. 3, 1996, pages 665-668, XP002007700 The whole document	1-68, 72-94

-/-

X Otras publicaciones se indican en la continuación del campo C

X Véase el anexo Familia de patentes

* Categorías especiales de las publicaciones indicadas
"A" Publicación que define el estado general de la técnica, pero que no debe considerarse especialmente relevante
"E" Documento anterior que, sin embargo, no se ha publicado antes de la fecha de solicitud internacional o incluso posteriormente a ésta.
"L" Publicación que hace dudosa la reivindicación de la prioridad o con la que se pretende comprobar la fecha de publicación de otra publicación indicada en el informe de búsqueda o que se indica por otra razón especial (según se indique).
"O" Publicación que se refiere a una descripción oral, un uso, una exposición u otras medidas
"P" Publicación que se ha publicado antes de la fecha de solicitud

"T" Publicación posterior, que se ha publicado después de la fech solicitud internacional o después de la fecha de prioridad y co que no colisiona la solicitud, indicándose sólo para la compre del principio en el que se basa la invención o de la teoría en l se basa la misma.
"X" Publicación de importancia especial; solamente en base a est publicación, la invención reivindicada no puede considerarse ni puede considerarse que la misma esté basada en una activ inventiva.
"Y" Publicación de importancia especial; no puede considerarse la invención reivindicada esté basada en una actividad invent la publicación se asocia a una o a varias otras publicaciones

Internacional, pero después de la fecha de prioridad reivindicada.	categoría y si esta asociación es evidente para un experto. "&" Publicación que es miembro de la misma familia de patentes
Fecha de la finalización de la búsqueda internacional 11 de abril de 2002	Fecha de envío del informe internacional de búsqueda 05.07.02
Nombre y dirección postal de la Autoridad Internacional de Búsqueda ISA/AU European Patent Office, P.B. 5818 Oatebtkaab 2 NL 2280 HV Rijswijk Tel (+34-70) 310-2040, Tx 31 651 epo nl Fax (+31-70) 340-3016	Empleado autorizado Scruton-Evans, I

Formulario PCT/ISA/210 (hoja 2) (julio de 1998)

INFORME INTERNACIONAL DE BÚSQUEDA

Datos respecto a publicaciones que forman parte de la misma familia de patentes

Nº de expediente internacional
PCT/US 01/42928

Documento de patente indicado en el informe de búsqueda		Fecha de publicación	Miembro(s) de la familia de patentes			Fecha de publicació
WO 9835660	A	14-11-1998	DE	19817505	A1	14-11-1998
			AU	5762998	A	25-11-1998
			CA	2220494	A1	14-11-1998
			WO	9835660	A1	14-11-1998
			EP	0924528	A1	25-02-1998
			JP	11504927	T	11-05-1999
WO 9813284	A	09-05-1998	US	564798	A	24-08-1997
			AU	3971995	A	23-05-1998
			CA	2203277	A1	09-05-1998
			EP	0789570	A1	20-08-1997
			JP	10509030	T	04-05-1998
			WO	9813284	A1	09-05-1998
EP 1028111	A	16-08-2000	AU	9462198	A	15-05-1999
			CA	2305802	A1	29-04-1999
			EP	1028111	A1	16-08-2000
			JP	3193708	B2	30-07-2001
			NO	20001963	A	14-04-2000
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			AU	736876	B2	02-08-2001
			AU	8928698	A	06-05-1999
			BR	9804500	A	11-04-2000
			CN	1218045	A	02-06-1999
			HU	9802417	A2	30-08-1999
			WO	9920607	A1	29-04-1999
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			WO	0140207	A1	07-06-2001
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			CN	1260571	T	17-01-2001
			EP	1073643	A2	07-02-2001
			WO	9908501	A2	25-02-1999
			US	6369067	B1	09-04-2002

SUPERINDUSTRIA Y COMERCIO
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Fecha (HMA): 2003-05-09 17:09:35
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

900 894

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADÓR
PATENTE DE INVENCIÓN ✓ **MODELO DE UTILIDAD**	( )	( )
- Indicación de que se solicita la concesión de una patente.	✓	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	✓	( )
- Descripción de la invención.	✓	( )
- Dibujos de ser estos pertinentes.	✓	( )
- Comprobante de Pago de las tasas establecidas.		( )
COMPLETA ( ) **INCOMPLETA**	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable: ANDREA POSSE

Fecha:

895

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Carlos R. Olarte
Apoderado
Eli Lilly and Company.

Oficio N°
07922

ASUNTO:	Radicación N°	03-39013
	Solicitud internacional	PCT/US 01/42928
	Fecha inicio fase nacional	10/06/03
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

202057