Delegatura de Propiedad Industrial
División de Nuevas Creaciones

PCT

CSA674086

SOLICITUD

PATENTE DE INVENCIÓN

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"

07-123805

21. **EXPEDIENTE NO.**

54. **TÍTULO** ACIDOS BENZOILAMINO-INDAN-2-CARBOXILICOS SUSTITUIDOS Y COMPUESTOS RELACIONADOS

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** SANOFI-AVENTIS

DOMICILIO PARIS, FRANCIA

74. **APODERADO** LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-123805- -00000-0000
Fecha: 2009-11-03 16:25:13 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 664

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **SANOFI-AVENTIS**
sociedad constituida y existente bajo las leyes de Francia.

Dirección: 174 avenue de France,
75013 Paris,
Francia

Domicilio: Paris,
Francia

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número _____

3 REPRESENTANTE O APODERADO

Nombre: LUZ CLEMENCIA DE PÁEZ
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual _____
Número 35.456.344 T. P. 23.555

4 INVENTOR (ES) (72)

1. **Thomas J. CAULFIELD**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

2. **Jennifer CLEMENS**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

3. **Robert S. FRANCIS**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

4. **Brian S. FREED**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

5. **Stanly JOHN**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

6. **Tieu-Binh LE**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

7. **Brian PEDGRIFT**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

8. **Antonio D. RAMOS**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

9. **Gerard ROSSE**
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

10. **Martin SMRCINA**
1580 E. Hanley Blvd.,
Tucson,
Arizona 85737,
Estados Unidos de América

11. **David S. THORPE**
1580 E. Hanley Blvd.,
Tucson,
Arizona 85737,
Estados Unidos de América,

12. **William WIRE**
1580 E. Hanley Blvd.,
Tucson,
Arizona 85737,
Estados Unidos de América

13. Jianhong ZHAO
55 Corporate Drive,
Bridgewater,
New Jersey 08807,
Estados Unidos de América

(5) **PCT (86)**
Solicitud Internacional No. PCT/US2008/065711 Fecha: 4 de junio de 2008
Publicación Internacional No. WO 2008/151211 A1 Fecha: 11 de diciembre de 2008

(6) **Título (54)**
ÁCIDOS BENZOILAMINO-INDAN-2-CARBOXÍLICOS SUSTITUIDOS Y COMPUESTOS RELACIONADOS

(7) **Clasificación Internacional (51)** C07D 333/068 C07C 235/54
A61K 31/33 A61P 11/06

(8) **Prioridad** SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	5 de junio de 2007	60/942,169

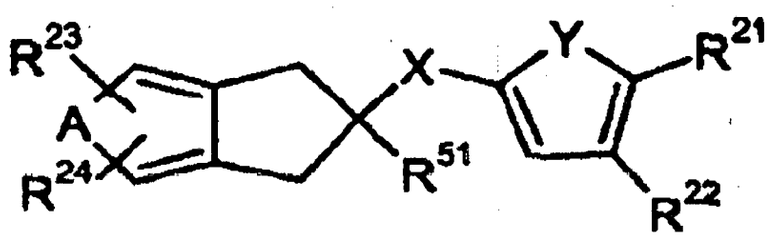
(9) **Comprobante de pago No.:** 09-75,153 **Fecha:** 5 de octubre de 2009
Comprobante de pago No.: 09-70,532 **Fecha:** 21 de septiembre de 2009

(10) **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 540.000.oo.
- ☒ Comprobante de pago por 24 reivindicaciones adicionales después de la decimoquinta reivindicación por $600.000.oo.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar 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 12x12
- ☐ 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.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



12 Solicito la concesión de la patente,

NOMBRE: LUZ CLEMENCIA DE PÁEZ

FIRMA : Luz Clemencia de Páez

C.C. 35.456.344 de Usaquén T.P. 23.555

JGG

4

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2008/151211 A1
   Descripción:
   Páginas 303 en el idioma original
   Páginas 318 en español
   Reivindicaciones: Número (s) 39
   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ **Forma PCT/IB/306.** Notificación de la inscripción del cambio de nombre y direcciones de los inventores Thomas J. Caulfield, Martin Smrcina, David S. Thorpe y William Wire.

4. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

ME-43

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 9 - COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

14475
7804

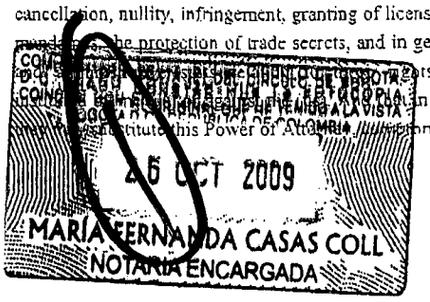
Yo (nosotros), abajo firmado (s)/I (we), the undersigned
SANOFI-AVENTIS
domiciliado (s) en/of 174, avenue de France
F-75013 Paris, Francia, hereby ratify the patent application No. 05.057.645 filed by EMILIO FERRERO on June 14, 2005 and

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ [illegible] the protection of trade secrets, and in general the civil, penal, [illegible] actions and suits [illegible] in all the above matters [illegible] this Power of Attorney, [illegible] compromise, conciliate, admit



© CAVELIER ABOGADOS

6

promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this _____

en/in _____

por/by _____

Firma / Signature

Sanofi-Aventis Dr. Markus Jacobi

Vu pour certification matérielle de la signature de M. Markus JACOBI apposée ci-dessus.

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. - République Française
   Le présent acte public
2. - a été signé par Me Koenig
3. - agissant en qualité de NOTAIRE
4. - est revêtu du sceau de l'Etude

ATTESTE

5. - à Paris le 21 JUIN 2005
6. - Par le Procureur Gal près la Cour d'Appel
8. - Sous N° 81902/2005
9. - Sceau Le signature

COUR D'APPEL DE PARIS
LE PROCUREUR GÉNÉRAL

NOTARIA SESENTA Y UNO DEL CIRCULO DE BOGOTA D.C.
HAGO CONSTAR: QUE LA FOTOCOPIA
CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
26 OCT 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

© CAVELIER ABOGADOS

K. L. ASSOCIÉS
Notaires
20, rue de la Paix
75002 PARIS
Tél. 01 55 04 70 00 - Fax 01 40 20 42 43

CERTIFICAT NOTARIE (SOCIETE)

Le Notaire soussigné certifie : que la signature qui précède de :
Markus JACOBI

Est authentique et que le signataire occupe actuellement le poste de Directeur Operations Brevets Europe
De la société sanofi-aventis,
et que ladite société fonctionne et est régie par le droit français
que la société est sise174 avenue de France, 75013 PARIS, France
et que le signataire est habilité à octroyer le présent pouvoir.

Tous les faits susmentionnés sont connus du Notaire qui a examiné les documents correspondants et les certifie.

Etabli et signé à Paris
Le 20/06/05

Le Notaire
(signature – cachet)

Alain KOENIG
NOTAIRE
20 rue de la Paix - 75002 PARIS Cedex 01

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Pays :
   Le présent acte public
2. a été signé par
3. agissant en qualité de
4. est revêtu du sceau/cachet de/du

Attesté

5. à
6. le
7. par
8. N°
9. Sceau/cachet :
10. Signature :

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. DIGO CONSTAR: QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. COLOMBIA
26 OCT 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. - République Française
   Le présent acte public
2. - a été signé par Me Koenig
3. - agissant en qualité de notaire
4. - est revêtu du sceau de A.en E.T.U.D.E.

ATTESTE

5. - à Paris le 21 JUIN 2005
7. - Par le Procureur Gal près la Cour d'Appel
8. - Sous N° 91903
9. - Sceau
   Le. signature

COUR D'APPEL DE PARIS
PROCUREUR GÉNÉRAL

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
26 OCT 2009
MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

Traducción Oficial No. 20050708 de un documento escrito en Francés y en INGLES, el cual, para su identificación se sella con el sello de María Eugenia Sanint Traductora Oficial según Resolución 1448 del Ministerio de Justicia.

LEGALIZACIONES

Escritas en FRANCES, al pie de un PODER escrito en ESPAÑOL, otorgado por **SANOFI- AVENTIS**, a favor de EMILIO FERRERO, GONZALO PERDOMO, LUZ CLEMENCIA PAEZ Y GERMAN CAVELIER (por el cual se ratifica la solicitud de patente NO. 05.057.645 presentada por EMILIO FERRERO el 14 de junio de 2005.)

(Firma Ilegible)
Dr. Markus Jacobi
Sanofi-Aventis

Visto para la certificación material de la firma del Sr. Markus Jacobi, puesta anteriormente.
(Firma Ilegible)
.L. ASSOCIES
Notarios
20, rue de la Paix
75002 PARIS

Sello del Notario

CERTIFICADO NOTARIAL (SOCIEDAD)

El Notario suscrito certifica que la firma puesta anteriormente de:

Marcus Jacobi

es auténtica, y que el signatario ocupa actualmente el cargo de Director de Operaciones Patentes Europa, de la sociedad Sanofi-Aventis, y que la dicha sociedad funciona y está regida por el derecho francés; que la sociedad tiene su sede en el 174, avenue de France, 75013, PARIS, Francia, y que el signatario está habilitado para otorgar el presente poder.

Todos los hechos mencionados anteriormente son de conocimiento del Notario, quien examinó los documentos correspondientes y los certifica.

Dado y firmado en París, hoy, 20 de junio de 2005.

El Notario
(Firma – sello)

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION [illegible] 671 DEL
DEL MINISTERIO DE JUSTICIA

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION [illegible] 1448 DEL
5 DE SEPT. [illegible] 30
del Ministerio de Justicia

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA, D.C. DEJO CONSTANCIA QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 OCT 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

(Ilegible)
Alain Koenig
NOTARIO
20, rue de la Paix, París

APOSTILLA
(Convenio de La Haya del 5 de octubre de 1961)

1. País: República Francesa

   El presente Documento Público

2. Fue firmado por el Abogado Koenig

3. Quien actúa en calidad de NOTARIO

4. Lleva el sello de SU DESPACHO

Certifica

5. En París 6. El 21 de junio de 2005

7. Por el Procurador General ante el Tribunal de Primera Instancia

8. Bajo el Número 81903

9. Sello/Estampilla:

   Sello del Tribunal de Primera Instancia de París.

10- Firma: (Ilegible)

ES TRADUCCIÓN FIEL Y COMPLETA.
Traductora : Maria Eùgenia Sanint
Bogotá, 8 de julio de 2005

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION No. 671 DEL
DEL MINISTERIO DE JUSTICIA

MARIA EUGENIA SANINT
TRADUCTORA OFICIAL
RESOLUCION 1318 DEL
30 DE SE... 30.
del Ministerio de Justicia

COMO NOTARIA ENCARGADA DEL CIRCULO DE BOGOTA, D.C. HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
BOGOTA D.C. REPUBLICA DE COLOMBIA
26 OCT 2009
MARÍA FERNANDA CASAS COLL
NOTARIA ENCARGADA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

María Eugenia Samint

COMPARECIO(S) CON C.C. No.(s)

Y ESCRIBIO(S) AUTENTICA(S)

SANTAFE DE BOGOTA 12 JUL 2005

NOTARIA SEXTA
PABLO MEJIA DAVALOS
Roberto Soto Escobar

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2005 JUL 12 P 1:28

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

449243

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

COMO NOTARIA SEXTA (E) DEL CIRCULO DE BOGOTA D.C. DOY FE Y HAGO CONSTAR: QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

BOGOTA D.C. REPUBLICA DE COLOMBIA

26 OCT 2009

MARIA FERNANDA CASAS COLL
NOTARIA ENCARGADA

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 December 2008 (11.12.2008)

PCT

(10) International Publication Number
WO 2008/151211 A1

(51) International Patent Classification:
C07D 333/68 (2006.01) *C07C 323/62* (2006.01)
C07D 333/78 (2006.01) *A61K 31/33* (2006.01)
C07C 233/63 (2006.01) *A61K 31/16* (2006.01)
C07C 235/54 (2006.01) *A61P 11/06* (2006.01)
C07C 235/84 (2006.01) *A61P 19/02* (2006.01)
C07C 311/15 (2006.01) *A61P 29/00* (2006.01)
C07C 317/14 (2006.01)

(21) International Application Number:
PCT/US2008/065711

(22) International Filing Date: 4 June 2008 (04.06.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/942,169 5 June 2007 (05.06.2007) US

(71) Applicant *(for all designated States except US)*: **SANOFI-AVENTIS** [FR/FR]; 174 avenue de France, F-75013 Paris (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CAULFIELD, Thomas, J.** [US/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **CLEMENS, Jennifer** [US/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **FRANCIS, Robert S.** [US/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **FREED, Brian S.** [US/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **JOHN, Stanly** [US/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **LE, Tieu-Binh** [US/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **PEDGRIFT, Brian** [GB/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **RAMOS, Antonio D.** [US/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **ROSSE, Gerard** [CH/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US). **SMRCINA, Martin** [CZ/US]; 1580 E. Hanley Blvd., Tucson, Arizona 85737 (US). **THORPE, David S.** [US/US]; 1580 E. Hanley Blvd., Tucson, Arizona 85737 (US). **WIRE, William** [US/US]; 1580 E. Hanley Blvd., Tucson, Arizona 85737 (US). **ZHAO, Jianhong** [CN/US]; 55 Corporate Drive, Bridgewater, New Jersey 08807 (US).

(74) Agents: **LIN, Jiang** et al.; Sanofi-Aventis U.S. Inc., Route 202-206, P.O. Box 6800, Bridgewater, NJ 08807-0800 (US).

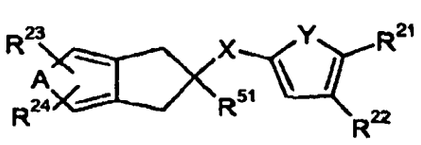
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

(54) Title: SUBSTITUTED BENZOYLAMINO-INDAN-2-CARBOXYLIC ACIDS AND RELATED COMPOUNDS



(57) **Abstract:** The present invention relates to A compound of the formula Ia wherein in any of its stereoisomers forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof, wherein the substituents are as described herein. The inventive compounds have CXCR5 inhibitory activity are particularly useful in treating or preventing various inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, Crohn's Disease, associated with the modulation of the human CXCR5 receptor.

WO 2008/151211 A1

SUBSTITUTED BENZOYLAMINO-INDAN-2-CARBOXYLIC ACIDS AND RELATED COMPOUNDS

FIELD OF THE INVENTION

The present invention is directed to substituted benzoylamino-indan-2-carboxylic acids and related compounds and intermediates thereto, their preparation including stereoselective synthetic processes to intermediates, pharmaceutical compositions containing the compounds, and the use of the compounds or compositions thereof having the ability to block the CXCR5 receptor and inhibit B cell function associated with receptor activation. The compounds having CXCR5 inhibitory activity are particularly useful in treating or preventing various inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, Crohn's Disease, associated with the modulation of the human CXCR5 receptor.

BACKGROUND OF THE INVENTION

CXCR5 is a non-promiscuous chemokine receptor belonging to the family of G-Coupled Protein receptors (GPCRs). Specifically, the CXCR5 receptor interacts with its CXCL13 ligand - which is constitutively expressed on stromal cells, such as follicular dendritic cells, and in lymphoid tissues. The CXCL13 ligand specifically attracts B cells and a small subset of T cells called B helper follicular T cells (T_{FH}). When the CXCR5/CXCL13 interaction is blocked by an antagonist, patients with Rheumatoid Arthritis (RA) and other autoimmune or inflammatory diseases in which the up-regulation of CXCR5 and/or its ligand CXCL13 are responsible for the pathogenesis or exacerbation of the disease, can be treated. While B cell depletion therapy with anti-CD20 monoclonal antibody (Rituximab) has shown as efficacious in the treatment of RA, blocking of B cells, such as CXCR5-expressing cells, is known to be of therapeutic benefit in experimental murine models of arthritis.

Furthermore, CXCR5 and/or CXCL13 is known to be up-regulated in patients with Rheumatoid Arthritis [*Arthritis Res Ther.* 2005;7(2):R217-29. Epub 2004 Dec 16.], Sjogren's syndrome [*Arthritis Rheum.* 2001 Nov;44(11):2633-41.], myasthenia gravis [*J Neuroimmunol.* 2005 Dec 30;170(1-2):172-8. Epub 2005 Oct 7] and multiple sclerosis [*Brain.* 2006

Jan;129(Pt 1):200-11. Epub 2005 Nov 9]. A linkage between CXCR5 and pancreatic carcinoma [*Cancer Res.* 2006 Oct 1;66(19):9576-82.] is also known. By blocking the receptor/ligand interaction with a CXCR5 antagonist, therapeutic benefits can be realized in the diseases mentioned above, and in other diseases in which B cell infiltration (or other lymphocyte subsets expressing the CXCR5 receptor) is responsible for the pathogenesis of the disease [*Front Biosci.* 2007 Jan 1;12:2194-2006, *J Rheumatol Suppl.* 2006 May;77:3-11].

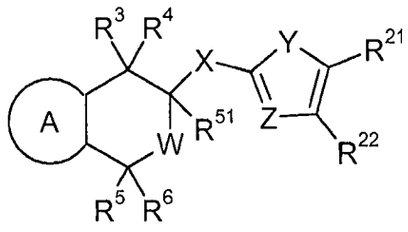
Infiltration of lymphocytes into tertiary ectopic germinal centers (GCs) is known to correlate well with increased disease severity and tolerance breakdown. By using *in vivo* murine models, such as $CXCR5^{-/-}$ and $CXCL13^{-/-}$ mice, for example, the absence of either the receptor or the ligand, results in an altered GC fine architecture caused by changed T and B cell localization. These mice are known to be protected against developing severe collagen-induced arthritis (CIA). Thus, since CXCR5 is selectively expressed on mature B cells, which are linked to the pathogenesis of RA, an antagonist that capable of blocking this receptor can modulate the arthritogenic response in affected individuals. Presently, Rheumatoid arthritis treatment with anti-CD20 antibodies has shown to be clinically effective; such as with patients on B cell directed therapy, who have shown long-lasting improvements in clinical signs and symptoms. The selective targeting of CXCR5, which is only expressed on mature B cells and B helper T cells is, therefore, not expected to affect B cell development or immuno-compromise the patient

Thus, an unmet need exists for CXCR5 antagonists for treatment of Rheumatoid Arthritis and other inflammatory, autoimmune diseases and cancers caused by the interaction of B cells expressing CXCR5 in response to CXCL13 expression.

SUMMARY OF THE INVENTION

The present invention is directed to antagonist compounds of the formula I, which have been found to block B cell migration in response to a ligand gradient, without peripheral B cell depletion. These compounds, therefore, provide a safety profile for the long-term treatment of inflammatory diseases.

The present invention relates to novel compounds of the formula I:



(I)

wherein:

ring A is a benzene ring or a monocyclic 5-membered or 6-membered aromatic heterocyclic ring comprising 1 or 2 identical or different hetero ring members chosen from the group consisting of N, N(R^1), O and S, which rings can all be substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S(O)$_m$-, cyano and nitro;

W is chosen from the group consisting of a bond or CH2;

X is chosen from the group consisting of N(R^7)C=O, N(R^7)S(O)$_m$, N(R^7)CR^8(R^9), C=ON(R^7), S(O)$_m$N(R^7), CR^8(R^9)N(R^7), CR^8(R^9)N(R^7)C=O, CR^8(R^9)N(R^7) S(O)$_m$;

Y is chosen from the group consisting of N(R^{11}), S, O, C(R^{12})=C(R^{13}), N=C(R^{14}) and C(R^{15})=N;

C(R^{12})=C(R^{13}) can be a 5-7 membered carbocycle or heterocycle with any substitution;

Z is chosen from the group consisting of N and C(R^{16});

R^1 is chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^3 and R^4 are independently of each other chosen from the group consisting of hydrogen, (C_1-C_4)-alkyl;

R^5 and R^6 are independently of each other chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^7 is chosen from the group consisting of hydrogen, (C_1-C_4)-alkyl and (C_1-C_6)-cycloalkyl;

R^8 and R^9 are independently of each other chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl or together as (C_1-C_6)-cycloalkyl;

R^{11} is chosen from the group consisting of hydrogen, (C_1-C_{10})-alkyl, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_1-C_{10})-alkyl-$S(O)_m$-, (C_1-C_{10})-alkylcarbonyl-, amino, (C_1-C_{10})-alkylamino, di((C_1-C_{10})-alkyl)amino;

R^{12}, R^{15} and R^{16} are independently of each other chosen from the group consisting of hydrogen, halogen, (C_1-C_{10})-alkyl, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_1-C_{10})-alkyl-$S(O)_m$-, cyano, (C_1-C_{10})-alkylcarbonyl-, amino, (C_1-C_{10})-alkylamino, di((C_1-C_{10})-alkyl)amino and nitro;

R^{13}, R^{14} , R^{21} and R^{22} are independently of each other chosen from the group consisting of hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino and nitro;

provided that the total number of C, N, O and S atoms which is present in any one of the groups R^{13}, R^{14} , R^{21} and R^{22}, does not exceed 4;

R^{51} is chosen from the group consisting of $COOR^{52}$, $CONR^{53}(R^{54})$, and 5-6 membered heterocycles containing 3 or more heteroatoms;

R^{52} is chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^{53} is chosen from the group consisting of hydrogen, hydroxyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl, cyano and R^{55}-SO_2-;

R^{54} is chosen from the group consisting of hydrogen, (C_1-C_4)-alkyl, (C_1-C_2)-alkylcarbonyl-, (C_1-C_3)-alkyl-$S(O)_m$-;

R^{55} is chosen from the group consisting of (C_1-C_4)-alkyl and phenyl;

R^{61} is chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^{62} is chosen from the group consisting of hydrogen and (C_1-C_4)-alkyl;

heteroaryl is a monocyclic 5-membered or 6-membered aromatic heterocyclic ring which comprises 1, 2 or 3 identical or different hetero ring members chosen from the group consisting of N, N(R^{61}), O and S;

heterocyclyl is a monocyclic 4-membered to 7-membered heterocyclic ring which comprises 1 or 2 identical or different hetero ring members chosen from the group consisting of N, N(R^{62}), O, S, SO and SO_2 but two hetero ring members from the series consisting of N(R^{62}), O and S cannot be present in adjacent ring positions, which ring is saturated or partially unsaturated and can be substituted by one or more identical or different substituents chosen from the group consisting of (C_1-C_4)-alkyl;

m is an integer chosen from the group consisting of 0, 1 and 2, where all numbers m are independent of each other and can be identical or different;

all phenyl and heteroaryl groups in the compound of the formula Ia can independently of each other be substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkylsulfonyl and cyano;

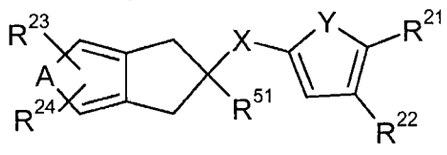
all alkyl groups in the compound of the formula Ia can independently of each other be substituted by one or more fluorine atoms;

in any of its stereoisomeric forms or a mixture of stereoisomeric forms in any ratio, or a physiologically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The contents of each of the patent documents and other references cited herein are herein incorporated by reference in their entirety.

In a particular embodiment, the present invention includes the compound of formula Ia wherein:



(Ia)

wherein:

A is CH=CH or S;

R^{23} is hydrogen, halogen, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkyloxy, $(C_1\text{-}C_4)$-alkyl-S-, or nitro;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, $(C_1\text{-}C_4)$-alkyl, $(C_1\text{-}C_4)$-alkyloxy, $(C_1\text{-}C_4)$-alkyl-S-, or nitro when A is S;

X is N(H)C=O, $N(H)S(O)_2$, C=ON(H), or $S(O)_2N(H)$;

Y is $N(R^{11})$, S, O, $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, or fused optionally substituted 5-7 membered carbocyclyl;

R^{11} is hydrogen, $(C_1\text{-}C_{10})$-alkyl, hydroxy-$(C_1\text{-}C_{10})$-alkyl-, $(C_1\text{-}C_{10})$-alkyloxy, $(C_1\text{-}C_{10})$-alkyl-$S(O)_m$-, $(C_1\text{-}C_{10})$-alkylcarbonyl-, phenyl, amino, $(C_1\text{-}C_{10})$-alkylamino, or di($(C_1\text{-}C_{10})$-alkyl)amino;

R^{12} is hydrogen, halogen, $(C_1\text{-}C_{10})$-alkyl, $(C_2\text{-}C_{10})$-alkenyl, $(C_3\text{-}C_6)$-cycloalkyloxy, $(C_3\text{-}C_{10})$-cycloalkenyloxy, $(C_3\text{-}C_6)$-cycloalkyl, $(C_3\text{-}C_{10})$-cycloalkenyl, $(C_3\text{-}C_6)$-cycloalkyl[$(C_1\text{-}C_4)$-alkyl or $(C_2\text{-}C_4)$-alkenyl], $(C_3\text{-}C_6)$-cycloalkyl$(C_1\text{-}C_4)$-alkyloxy, hydroxy-$(C_1\text{-}C_{10})$-alkyl-, $(C_1\text{-}C_{10})$-alkyloxy, $(C_2\text{-}C_{10})$-alkenyloxy, $(C_1\text{-}C_{10})$-alkyl-S-, cyano, $(C_1\text{-}C_{10})$-alkylcarbonyl-, phenyl, or nitro;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

R^{14} is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro, provided that the total number of C, N, O and S atoms which is present in R^{14} does not exceed 4;

$R^{15}$is hydrogen, halogen, (C_1-C_{10})-alkyl, (C_2-C_{10})- alkenyl, (C_3-C_6)-cycloalkyl, (C_3-C_6)-cycloalkenyl, (C_3-C_6)-cycloalkyl[(C_1-C_4)-alkyl or (C_2-C_4)-alkenyl], hydroxy-(C_1-C_{10})-alkyl-, cyano, (C_1-C_{10})-alkylcarbonyl-, phenyl, amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]((C_1-C_{10})-alkyl)amino or nitro;

R^{21} is hydrogen when Y is $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, and is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{21} does not exceed 4;

R^{22} is hydrogen, halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, or is hydrogen, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{22} does not exceed 4;

R^{51} is COOH or $CONH(R^{53})$;

R^{53} is R^{55}-SO_2- or tetrazolyl;

R^{55} is (C_1-C_4)-alkyl or phenyl optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-sulfonyl and cyano; and

m is 0, 1, or 2;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{23} is hydrogen, halogen, (C_1-C_4)-alkyl, or (C_1-C_4)-alkyloxy;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, or (C_1-C_4)-alkyl when A is S;

X is N(H)C=O, N(H)S(O)$_2$, or C=ON(H);

Y is C(R^{12})=C(R^{13}), or C(R^{15})=N, or fused optionally substituted 5-6 membered carbocyclyl;

R^{12} is (C_1-C_6)-alkyl, (C_3-C_6)-alkenyl, (C_4-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkenyl, (C_3)-cycloalkyl[(C_2)-alkyl or (C_2)-alkenyl], (C_3)-cycloalkyl(C_1)-alkyloxy, (C_3-C_4)-alkyloxy, (C_3)-alkenyloxy, (C_1-C_3)-alkyl-S-, or (C_3)-alkylcarbonyl-, phenyl;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

$R^{15}$is (C_1-C_6)-alkyl, (C_2-C_6)- alkenyl, or [(C_2-C_3)-alkyl or (C_3)-alkenyl]((C_1)-alkyl)amino;

R^{21} is hydrogen when Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$;

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$;

R^{51} is COOH;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

A is CH=CH.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{23} is hydrogen or halogen.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{24} is hydrogen or halogen when A is CH=CH;

Another particular embodiment according to the invention is the compound according to formula Ia wherein

X is N(H)C=O.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

Y is $C(R^{12})=C(R^{13})$.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

Y is $C(R^{15})=N$.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

Y is fused optionally substituted 5-6 membered carbocyclyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_4-C_6)-alkyl, or more particularly isobutyl or propyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_{3-5})-alkenyl, or more particularly penten-1-yl, isobutene-1-yl or propen-1-yl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_4)-cycloalkyloxy (cyclobutyloxy).

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_5-C_6)-cycloalkyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_5-C_6)-cycloalkenyl, or more particularlycyclopenten-1-yl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_3)-cycloalkyl[(C_2)-alkyl or (C_2)-alkenyl], or more particularly cyclopropylethyl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_3)-cycloalkyl(C_1)-alkyloxy (cyclopropylmethyl).

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is $(C_3$-$C_4)$-alkyloxy.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is (C_3)-alkenyloxy.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{12} is phenyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is halogen, or (C_1)-alkyl.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is (C_1)-alkyl wherein the alkyl is optionally substituted by 1-3 fluorine atoms, or more particularly trifluoromethylyl..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is (C_1)-alkyl (methyl).

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is (C_1)-alkyl that is substituted by 2-3 fluorine atoms.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{13} is halogen.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

$R^{15}$is [(C_2-C_3)-alkyl or (C_3)-alkenyl]((C_1-C_{10})-alkyl)amino.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{15} is (C_2-C_3)-alkyl(C_1)-alkyl)amino, or more particularly isopropylmethylamino..

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{21} is hydrogen.

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is C(R^{12})=C(R^{13}).

Another particular embodiment according to the invention is the compound according to formula Ia wherein

R^{51} is COOH.

Specific embodiments of the present invention are selected from the group consisting of

2-(2-Allyloxy-3-mcthyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

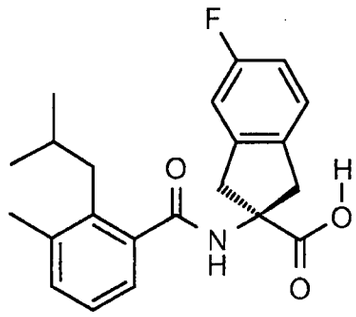
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid
2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid,
2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid,
2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid,
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,
5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid
5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid,
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid,
5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid,
5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid,
2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,
2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid,
2-[2-(-1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-[2-(1-Ethyl-butyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopentyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
2-(2-Isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[2-(-2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,

2-[2-(2-Cyclopropyl-ethyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid,
2-(3-Methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,
2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,
5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
5,6-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5,6-Difluoro-2-(3-methyl-2-propenyl-benzoylamino)-indan-2-carboxylic acid,
5,6-Difluoro-2-(3-methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,
5-Bromo-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,
2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid,
2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid,
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid,
2-(3-Cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid,
2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid,
2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid,
2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid,
2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid,
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[2-(Allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,

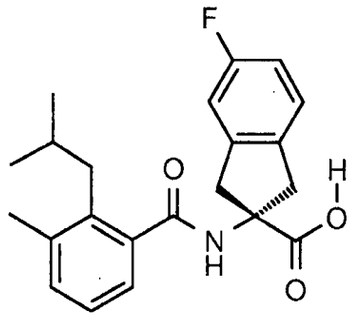
2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid,
4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,5-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid
4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,7-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5-Chloro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid
5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid
2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid,
2-Cyclobutoxy-N-(2-methanesulfonylaminocarbonyl-indan-2-yl)-3-methyl-benzamide,
2-Cyclobutoxy-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,
2-Cyclopent-1-enyl-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,
2-Cyclobutoxy-3-methyl-N-[2-(1H-tetrazol-5-yl)-indan-2-yl]-benzamide, and
2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid, or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

Another particular embodiment according to the invention is the compound of the following structure



Another particular embodiment according to the invention is the compound of the following structure



Another particular embodiment according to the invention is a compound selected from Example 232, 150, 231, 149, 136, 158, 152, 159, 144, 397, 135, 161, 155, 132, 139, 125, 329, 262, 154, 143, 160, 163, 21, 87, 212, 103, 352, 395, 392, or 388.

Another particular embodiment according to the invention is a pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to formula Ia wherein and at least one of a pharmaceutically acceptable excipient and pharmaceutically acceptable carrier.

Another particular embodiment according to the invention is a method for the treatment of a patient suffering from, or subject to, a physiological condition that can be ameliorated by the administration of a pharmaceutically effective amount of an inhibitor of a CXCR5 receptor to the patient comprising administering the compound according to formula Ia to said patient.

Another particular embodiment according to the invention is the method of treatment wherein the physiological condition is an inflammatory disease.

Another particular embodiment according to the invention is the method of treatment the physiological condition is rheumatoid arthritis.

Another particular embodiment according to the invention is the method of treatment the physiological condition is asthma.

Another particular embodiment according to the invention is the method of treatment with the administering of the compound of claim 1 and another therapeutic agent is administered at the same time or sequentially.

Another particular embodiment according to the invention is a process for producing a compound according to formula Ia as described herein.

The present invention is also directed to a pharmaceutical composition comprising a compound of formula 1, and method for using the compound of formula I or formula Ia for preventing and or treating inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, Crohn's Disease, associated with the modulation of the human CXCR5 receptor in a patient.

The invention is also directed to a process for preparing a compound that is an intermediate useful in preparing a compound of formula I or formula Ia.

Another aspect of the invention are methods of treating or preventing a physiological condition or a disease state a patient in need thereof, comprising administering to said patient a pharmaceutically effective amount of one or more compounds of formula I or formula Ia.

The amount of the compounds of formula I or formula Ia or other compounds capable of physiological condition or a disease state in any of the foregoing applications can be a pharmaceutically effective amount, a subclinical effective amount, or combinations thereof, so long as the final combination physiological condition or a disease state comprises a pharmaceutically effective amount of compounds that is effective in preventing and or treating inflammatory diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, Crohn's Disease, associated with the modulation of the human CXCR5 receptor. in a patient.

List of Abbreviations

As used throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN	acetonitrile
AIBN	2,2'-azobisisobutyronitrile
BOC or Boc	*tert*-butyl carbamate
BOP	benzotriazol-1-yl-oxytris (dimethylamino) phosphonium
n-Bu_3SnH	tri-n-butyltin hydride
t-Bu	tert-butyl
Cbz	benzyl carbamate
$CsCO_3$	cesium carbonate
DAST	(diethylamino) sulfur trifluoride (Et_2NSF_3)
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane (CH_2CI_2) or methylenechloride
DIC	1,3-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	4-(N,N-dimethylamino)pyridine
DMP reagent	Dess-Martin Periodinane reagent
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide HCl
eq	equivalent(s)
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
FMOC	9-fluorenylmethoxycarbonyl
HATU	O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF_6
HOAt	1-hydroxy-7-azabensotriazole
HOBT	1-hydroxybenzotriazole
HOSu	N-hydroxysuccinamide
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate

HPLC	high performance liquid chromatography
LAH	lithium aluminum anhydride
$MgSO_4$	magnesium sulfate
Me	methyl
MeI	methyliodide
MeOH	methanol
MeOC(O)	methyl chloroformate
MOMCI	methoxymethylchloride
MOM	methoxymethyl
MS	mass spectroscopy
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium bicarbonate
$Na_2C_4H_4O_6$	sodium tartrate
NMR	nuclear magnetic resonance
PTC	phase transfer catalyst
iPrOH	iso-propanol
P	Polymer bond
$KMnO_4$	potassium permanganate
K_2SO_4	potassium carbonate
PyBOP	benzotriazole-1-yl-oxytris-pyrrolidino-phosphonium hexafluorophosphate
Na_2SO_4	Sodium sulfate
TBD	1,5,7-triazabicyclo[4.4.0]-dec-5-ene
RP-HPLC	reverse phase-high pressure liquid chromatography
RT	room temperature
TBSCI	*tert*-butyldimethylsilyl chloride
TCA	trichloroacetic acid
TFA	trifluoroacetic acid
Tf_2O	triflate anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography

Definitions

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Acid bioisostere" means a group which has chemical and physical similarities producing broadly similar biological properties to a carboxy group (see Lipinski, Annual Reports in Medicinal Chemistry, "Bioisosterism In Drug Design" 21, 283 (1986); Yun, Hwahak Sekye, "Application of Bioisosterism To New Drug Design" 33, 576-579, (1933); Zhao, Huaxue Tongbao, "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design" 34-38, (1995); Graham, Theochem, "Theoretical Studies Applied To Drug Design ab initio Electronic Distributions In Bioisosteres" 343, 105-109, (1995)). Exemplary acid bioisosteres include -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydoxy-1-methylpyrazolyl and the like.

"Acidic functional group" means a moiety bearing an acidic hydrogen. Exemplary acid functional groups include carboxyl (-C(O)OH), -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl or 3-hydroxy-3cyclobutene-1,2-dione, imidazolyl mercapto, and the like, and an appropriate hydroxy such as an aromatic hydroxy, e.g., hydroxyphenyl, hydroxyheteroaryl such as 3,5-dioxo-1,2,4-oxadiazolidinyl 3-hydroxisoxazolyl or 3-hydoxy-1methylpyrazolyl.

"Acid protecting group" means an easily removable group that is known in the art to protect an acidic hydrogen of a carboxyl group against undesirable reaction during synthetic procedures, e.g., to block or protect the acid functionality while the reactions involving other functional sites of the compound are carried out, and to be selectively removable. Such acid protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups, as described in U.S. Pat. No. 3,840,556 and 3,719,66, the disclosures of which are hereby incorporated herein by reference. For suitable acid protecting

groups, see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and sons, 1991. Acid protecting group also includes hydrogenation labile acid protecting group as defined herein. Exemplary acid protecting groups include esters such as substituted and unsubstituted C_{1-8} lower alkyl, e.g., methyl, ethyl, *t*-butyl, methoxymethyl, methylthiomethyl, 2,2,2-trichloroethyl and the like, tetrahydropyranyl, substituted and unsubstituted phenylalkyl such as benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like, cinnamyl, dialkylaminoalkyl, e.g., dimethylaminoethyl and the like, trimethylsilyl, substituted and unsubstituted amides and hydrazides, e.g., amides and hydrazides on N,N-dimethylamine, 7-nitroindole, hydrazine, N-phenylhydrazine and the like, acyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like, aroyloxyalkyl such as benzoyloxyethyl and the like, alkoxycarbonylalkyl such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl and the like, alkoxycarbonyloxyalkyl such as *t*-butyloxycarbonyloxymethyl and the like, alkoxycarbonylaminoalkyl such as *t*-butyloxycarbonylaminomethyl and the like, alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like, acylaminoalkyl such as acetylaminomethyl and the like, heterocyclylcarbonyloxyalkyl such as 4-methylpiperazinyl-carbonyloxymethyl and the like, dialkylaminocarbonyalkyl such as dimethylaminocarbonyl-methyl and the like, (5-(lower alkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl such as (5-*t*-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like, and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

"Acid labile amine protecting group" means an amine-protecting group as defined herein that is readily removed by treatment with acid while remaining relatively stable to other reagents. A preferred acid labile amine-protecting group is BOC.

"Aliphatic" means alkyl, alkenyl or alkynyl as defined herein.

"Aliphatic group substituent(s)" means substituents attached to an aliphatic group as defined herein inclusive or aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH,-C(O)-CH_2OH,-C(O)-CH_2SH,-C(O)-NH-CN-sulfo, phosphono, alkysulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, tetrazolyl,

arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3,5-dioxo-1,2,4-oxadiazolidinyl or 3-hydroxy-1-methylpyrazolyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, methylene (H_2C=), oxo (O=), thioxo (S=), Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$-, $Y^1Y^2NSO_2$-, or $Y^3SO_2NY^1$- wherein R^2 is as defined herein, Y^1 and Y^2 are independently hydrogen, alkyl, aryl or heteroaryl, and Y^3 is alkyl, cycloalkyl aryl or heteroaryl, or for where the substituent is Y^1Y^2N-, then one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl. Acidic/amide aliphatic group substituents are carboxy (acid), -C(O)-NHOH, $-C(O)CH_2OH$, $-C(O)-CH_2SH$, -C(O)-NH-CN, sulfo?), phosphono?), alkysulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3,5-dioxo-1,2,4-oxadiazolidinyl or 3-hydroxy-1-methylpyrazolyl and Y^1Y^2NCO-. Non-acidic polar aliphatic group substituents are hydroxy, oxo (O=), thioxo (S=), acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue, heteroaroyl or its thioxo analogue, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, thiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-. Exemplary aliphatic groups bearing an aliphatic group substituent include methoxymethoxy, methoxyethoxy, ethoxyethoxy, (methoxy-, benzyloxy-, phenoxy-, or ethoxy-) carbonyl(methyl or ethyl), benzyloxycarbonyl, pyridylmethyloxy-carbonylmethyl, methoxyethyl, ethoxymethyl, *n*-butoxymethyl, cyclopentylmethyloxyethyl, phenoxypropyl, phenoxyallyl, trifluoromethyl, cyclopropyl-methyl, cyclopentylmethyl, carboxy(methyl or ethyl), 2-phenethenyl, benzyloxy, 1- or 2-

naphthyl- methoxy, 4-pyridyl-methyloxy, benzyloxyethyl, 3-benzyloxyallyl, 4-pyridylmethyl-oxyethyl, 4- pyridylmethyloxyallyl, benzyl, 2-phenethyl, naphthylmethyl, styryl, 4-phenyl-1,3-pentadienyl, phenyl-propynyl, 3-phenylbut-2-ynyl, pyrid-3-ylacetylenyl and quinolin-3-ylacetylenyl, 4- pyridyl-ethynyl, 4-pyridylvinyl, thienylethenyl, pyridylethenyl, imidazolyl-ethenyl, pyrazinylethenyl, pyridylpentenyl, pyridylhexenyl and pyridylheptenyl, thienyl-methyl, pyridylmethyl, imidazolylmethyl, pyrazinylmethyl, tetrahydropyranylmethyl, tetrahydropyranyl- methoxymethyl, and the like.

"Acyl" means an H-CO- or (aliphatic or cyclyl)-CO- group wherein the aliphatic group is as herein described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl, palmitoyl, acryloyl, propynoyl, cyclohexylcarbonyl, and the like.

"Alkenoyl" means an alkenyl-CO- group wherein alkenyl is as defined herein.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain that may be straight or branched. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylbut-2-enyl, *n*-pentenyl, heptenyl, octenyl, cyclohexylbutenyl, decenyl, and the like. "Substituted alkenyl" means an alkenyl group as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary alkenyl aliphatic group substituents include halo or cycloalkyl groups.

"Alkenyloxy" means an alkenyl-O- group wherein the alkenyl group is as herein described. Exemplary alkenyloxy groups include allyloxy, 3-butenyloxy, and the like.

"Alkoxy" means an alkyl-O- group wherein the alkyl group is as herein described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, heptoxy, and the like.

"Alkoxycarbonyl" means an alkyl-O-CO- group, wherein the alkyl group is as herein defined. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, *t*-butyloxycarbonyl, and the like.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain, more preferred is lower alkyl as defined herein. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain that may be straight or branched. "Substituted alkyl" means an alkyl group as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different, and are as defined herein.

"Alkylsulfinyl" means an alkyl-SO- group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulfonyl" means an alkyl-SO_2- group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl groups is lower alkyl.

"Alkylsulfonylcarbamoyl" means an alkyl-SO_2-NH-C(=O)- group wherein the alkyl group is as herein described. Preferred alkysulfonylcarbamoyl groups are those wherein the alkyl group is lower alkyl.

"Alkylthio" means an alkyl-S- group wherein the alkyl group is as herein described. Exemplary alkylthio groups include methylthio ethylthio *i*-propylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about r carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain that may be straight or branched. The alkynyl group may be substituted by one or more halo. Exemplary alkynyl groups include

ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl, decynyl, and the like. "Substituted alkynyl" means alkynyl as defined above which is substituted with one or more "aliphatic group substituents" (preferably 1 to 3) which may be the same or different, and are as defined herein.

"Amine protecting group" means an easily removable group that is known in the art to protect a nitrogen moiety of an amino group against undesirable reaction during synthetic procedures and to be selectively removable. The use of amine protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, for example, T.W. Greene and P.G.M. Wuts, Protective groups in Organic synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Amine protecting group also includes "acid labile amine protecting group" and "hydrogenation labile amine protecting group". Exemplary amine protecting groups are acyl, including formyl, acetyl, chloroacetyl, trichloroacetyl, o-nitrophenylacetyl, o-nitrophenoxy-acetyl, trifluoroacetyl, acetoacetyl, 4-chlorobutyryl, isobutyryl, o-nitrocinnamoyl, picolinoyl, acylisothiocyanate, aminocaproyl, benzoyl and the like, and acyloxy including methoxy-carbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycarbonyl, 2-trimethylsilylethoxy-carbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 1,1-dimethyl-propynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-nitrobenzyloxycarbonyl, 2,4-dichloro-benzyloxycarbonyl, and the like.

"Amide protecting group" means an easily removable group that is known in the art to protect a nitrogen moiety of an amide group against undesirable reaction during synthetic procedures and to be selectively removable after its conversion to the amide. The use of amide protecting groups is well known in the art for protecting groups against undesirable reactions during a synthetic procedure and many such protecting groups are known for example, T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2nd edition, John Wiley & Sons, New York (1991), incorporated herein by reference. Amide protecting group also includes "acid labile amide protecting group" and "hydrogenation labile amide protecting group". Exemplary amide protecting groups are o-nitrocinnamoyl, picolinoyl, aminocaproyl, benzoyl and the like, and acyloxy including methoxy-carbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trifluoroethoxycaronyl, 2-trimethylsilyethoxy-carbonyl, vinyloxycarbonyl, allyloxycarbonyl, *t*-butyloxycarbonyl (BOC), 1,1-dimethyl-propynyloxycarbonyl, benzyloxycarbonyl (CBZ), p-

nitrobenzyloxycarbonyl, 2,4-dichloro-benzyloxycarbonyl, and the like.

"Amino acid" as defined herein is selected from the group consisting of natural and unnatural amino acids. Amino acid is also meant to include amino acids having L or D stereochemistry at the α-carbon. Preferred amino acids are those possessing an α-amino group. The amino acids may be neutral, positive or negative depending on the substituents in the side chain. "Neutral amino acid" means an amino acid containing uncharged side chain substituents. Exemplary neutral amino acids include alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine and cysteine. "Positive amino acid" means an amino acid in which the side chain substituents are positively charged at physiological pH. Exemplary positive amino acids include lysine, arginine, and histidine "Negative amino acid" means an amino acid in which the side chain substituents bear a net negative charge at physiological pH. Exemplary negative amino acids include aspartic acid and glutamic acid. Exemplary natural amino acids are isoleucine, proline, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, lysine, arginine histidine, aspartic acid and glutamic acid. "Unnatural amino acid" means an amino acid for which there is no nucleic acid codon. Exemplary unnatural amino acids include, for example, the D-isomers of the natural α-amino acids as indicated above; Aib (aminobutyric acid), βAib (3-amino-isobutyric acid) Nva (norvaline), β-Ala, Aad (2-aminoadiphic acid), βAad (3-aminoadipic acid), Abu (2-aminobutyric acid), Gaba (γ-aminobutyric acid), Acp (6-aminocaproic acid), Dbu (2,4-diaminopropionic acid), α-aminopimelic acid, TMSA (trimethylsilyl-Ala), alle (alloisoleucine), Nle (norleucine), *teri*-Leu, Cit (citrulline), Orn, Dpm (2,2'-diaminopimelic acid), α -or β- Nal, Cha (cyclohexyl-Ala), hydroxyproline, Sar (sarcosine), and the like; cyclic amino acids; N^a-alkylated amino acids such as MeGly. (Na-methylglycine), EtGly (N^a-ethylglycine) and EtAsn (Na-ethylasparagine); and amino acids in which the α-carbon bears two side-chain substituents. The names of natural and unnatural amino acids and residues thereof used herein follow the naming conventions suggested by the IUPAC Commission on the Nomenclature of Organic chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature as set out in "Nomenclature of a-Amino Acids (Recommendations, 1974)" Biochemistry, 14(2), (1975). To the extent that the names and abbreviations of amino acids and residues thereof employed in this specification and appended claims differ from those noted, differing names and abbreviations will be made clear.

"Amino acid protecting group" mean a group that protects an acid or amine moiety of the amino acid or other reactive moiety on the side chain of an amino acid, e.g., hydroxy or thiol. For examples of "corresponding protected derivatives" of amino acid side chains, see T.W. Green and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Protecting groups for an acid group in an amino acid are described herein, for example in the sections "acidic functional group" and "hydrogenation labile acid protecting group". Protecting groups for an amine group in an amino acid are described herein, for example in the sections "amine protecting group", "acid labile amine protecting group" and "hydrogenation labile amine protecting group".

"Amino acid residue" means the individual amino acid units incorporated into the compound of the invention.

"Amino acid side chain" means the substituent found on the carbon between the amino and carboxy groups in α-amino acids. Exemplary amino acid side chains include isopropyl, methyl, and carboxymethyl for valine, alanine, and aspartic acid, respectively.

"Amino acid equivalent" means an amino acid that may be substituted for another amino acid in the peptides according to the invention without any appreciable loss of function. In making such changes, substitutions of like amino acids are made on the basis of relative similarity of side chain substituents, for example regarding size, charge, hydrophilicity, hydropathicity and hydrophobicity as described herein.

"Aromatic group" means aryl or heteroaryl as defined herein. Exemplary aromatic groups include phenyl, halo substituted phenyl, azaheteroaryl, and the like.

"Aroyl" means an aryl-CO-group wherein the aryl group is as herein described. Exemplary aroyl groups include benzoyl, 1-and 2-naphthoyl, and the like.

"Aryl" means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms, preferably of about 6 to 10 carbon atoms. Encompassed by aryl are fused cycloalkenylaryl, fused cycloalkylaryl, fused heterocyclenylaryl and fused heterocyclylaryl as

defined herein when bonded through the aryl moiety thereof. The aryl is optionally substituted with one or more "ring group substituents" (preferably 1 to 3 substituents which may be the same or different, and are as defined herein. A "Substituted aryl" means an aryl group which is substituted as defined above. Exemplary aryl groups include phenyl or naphthyl, or substituted phenyl or substituted naphthyl.

"Aryldiazo" means an aryl-diazo-group wherein the aryl and diazo groups are as defined herein.

"Arylene" means an optionally substituted 1,2-, 1,3-, 1,4-, bivalent aryl group, wherein the aryl group is as defined herein. "Substituted arylene" means an arylene group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary arylene groups include optionally substituted phenylene, naphthylene and indanylene. A particular arylene is optionally substituted phenylene.

"Aryloxy" means an aryl-O- group wherein the aryl group is as defined herein. Exemplary aryloxy groups include phenoxy and 2-naphtyloxy.

"Aryloxycarbonyl" means an aryl-O-CO- group wherein the aryl group is as defined herein. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfonyl" means an aryl-SO_2- group wherein the aryl group is defined herein.

"Arylsulfonylcarbamoyl" means an aryl-SO_2-NH-C(=O)-group wherein the aryl group is herein described. An exemplary arylsulfonylcarbamoyl group is phenylsulfonylcarbamoyl.

"Arylsulfinyl" means an aryl-SO –group wherein the aryl group is as defined herein.

"Arylthio" means an aryl-S- group wherein the aryl group is as herein described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Basic nitrogen atom" means a sp^2 or sp^3 hybridized nitrogen atom having a non-bonded pair of electrons which is capable of being protonated. Exemplary basic nitrogen atoms include optionally substituted imino, optionally substituted amino and optionally substituted amidino groups.

"Carboxy" means an HO(O)C- (carboxylic acid) group.

"Coupling agent" means a compound that reacts with the hydroxyl moiety of a carboxy moiety thereby rendering it susceptible to nucleophilic attack. Exemplary coupling agents include DIC, EDCI, DCC, and the like.

"Cycloalkenyl" means an optionally substituted non aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which contains at least one carbon-carbon double bond and which can be optionally fused by an aromatic group as defined herein. "Fused (aromatic) "cycloalkenyl" means fused arylcycloalkenyl and fused heteroarylcycloalkenyl as defined herein bonded through the cycloalkenyl moiety thereof. Preferred sizes or the rings of the ring system are about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". "Substituted cycloalkenyl" means an cycloalkenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are defined herein. Exemplary monocyclic cycloalkenyl include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. An exemplary multicyclic cycloalkenyl is norbornylenyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, preferably of about 5 to about 10 carbon atoms, and which can be optionally fused by an aromatic group as defined herein. Preferred sizes of the rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". "Fused (aromatic) cycloalkyl" means fused arylcycloalkyl and fused heteroarylcycloalkyl as defined herein bonded through the cycloalkyl moiety thereof. "Substituted cycloalkyl" means a cycloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably1 to 3) which may be the same or different and are as defined herein. Exemplary monocyclic cycloalkyl include cyclopentyl, cyclohexyl,

cycloheptyl, and the like. Exemplary multicyclic cycloalkyl include 1-decalin, norbornyl, adamant-(1- or 2-)yl, and the like.

"Cycloalkylene" means a bivalent cycloalkyl group as defined herein having about 4 to about 8 carbon atoms. Preferred ring sizes of the cycloalkylene include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". The points of binding on the cycloalkylene group include 1,1-, 1,2-, 1,3-, or 1,4- binding patterns, and where applicable the stereochemical relationship of the points of binding is either cis or trans. Exemplary monocyclic cycloalkylene groups include (1,1-, 1,2-, or 1,3-)cyclohexylene and (1,1- or 1,2-)cyclopentylene. "Substituted cycloalkylene" means an cycloalkylene group as defined above which is substituted with one or more "ring group substitutes" (preferably 1 to 3) which may be the same or different and are as defined herein.

"Cyclic" or "Cyclyl" means cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl as defined herein. The term "lower" as used in connection with the term cyclic is the same as noted herein regarding the cycloalkyl, cycloalkenyl, heterocyclyl or heterocyclenyl.

"Cyclyloxy" means a cyclyl-O- group wherein the cyclyl group is as herein described. Exemplary cycloalkoxy groups include cyclopentyloxy, cyclohexyloxy, quinuclidyloxy, pentamethylenesulfidoxy, tetrahydropyranyloxy, tetrahydrothiophenyloxy, pyrrolidinyloxy, tetrahydrofuranyloxy, or 7-oxabicyclo[2.2.1]heptanyloxy, hydroxytetrahydropyranyloxy, hydroxy-7-oxabicyclo[2.2.1]heptanyloxy, and the like.

"Cyclylsulfinyl" means a cyclyl-S(O)- group wherein the cyclyl group is as herein described.

"Cyclylsulfonyl" means a cyclyl-$S(O)_2$- group wherein the cyclyl group is as herein described.

"Cyclylthio" means a cyclyl-S- group wherein the cyclyl group is as herein described.

"Diazo" means a bivalent -N=N- radical.

"Displaceable moiety" means a group that where associated with L as defined herein is subject to being displaced by nucleophilic attack by a mono- or di-substituted amine moiety with or

without the presence of an agent that facilitates said attack, e.g., coupling agent. Exemplary displaceable moieties include hydroxy, aliphatic oxy, halo, N-oxysuccinimide, acyloxy, and the like.

"Effective amount" is means an amount of a compound/composition according to the present invention effective in producing the desired therapeutic effect.

"Fused arylcycloalkenyl" means a fused aryl and cycloalkenyl as defined herein. Preferred fused arylcycloalkenyls are those wherein the aryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkenyl as a variable may be bonded through any atom of the ring system thereof capable of such. "Substituted fused arylcycloalkenyl" means a fused arylcycloalkenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary fused arylcycloalkenyl include 1,2-dihydronaphthylene, indene, and the like.

"Fused arylcycloalkyl" means a fused aryl and cycloalkyl as defined herein. Preferred fused arylcycloalkyls are those wherein the aryl thereof is phenyl and the cycloalkyl consists of about 5 to about 6 ring atoms. A fused arylcycloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. "Substituted fused arylcycloalkyl" means a fused arylcycloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. Exemplary fused arylcycloalkyl includes 1,2,3,4-tetrahydro-naphthylene, and the like.

"Fused arylheterocyclenyl" means a fused aryl and heterocyclenyl as defined herein. Preferred fused arylheterocyclenyls are those wherein the aryl thereof is phenyl and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heterocyclenyl portion of the fused arylheterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused arylheterocyclenyl" means a fused arylheterocyclenyl group as defined above which is substituted with one or more "ring group

substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused arylheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl portion of the fused arylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclenyl include 3H-indolinyl, IH-2-oxoquinolyl, 2H-l-oxoisoquinolyl, 1,2-dihydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, and the like.

"Fused arylheterocyclyl" means a fused aryl and heterocyclyl as defined herein. Preferred fused arylheterocyclyls are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or ilia as a prefix before heterocyclyl portion of the fused arylheterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused arylheterocyclyl" means a fused arylheterocyclyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused arylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl portion of the fused arylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4- tetrahydroquinoline, 1H -2,3-dihydroisoindol- 2-yl, 2,3-dihydrobenz[f]isoindol-2-y1, 1,2,3,4- tetrahydrobenz[g]-isoquinolin-2-yl, and the like.

"Fused heteroarylcycloalkenyl" means a fused heteroaryl and cycloalkenyl as defined herein. Preferred fused heteroarylcycloalkenyls are those wherein the heteroaryl thereof is phenyl and the cycloalkenyl consists of about 5 to about 6 ring atoms. A fused heteroaryl-cycloalkenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before heteroaryl portion of the fused heteroarylcycloalkenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused heteroarylcycloalkenyl" means a fused heteroarylcycloalkenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 30 which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylcycloalkenyl may be a basic nitrogen atom.

The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkenyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcycloalkenyls include 5,6- dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5- dihydro-1H -benzimidazolyl, 4,5-di -hydrobenzoxazolyl, and the like.

"Fused heteroarylcycloalkyl" means a fused heteroaryl and cycloalkyl as defined herein. Preferred fused heteroarylcycloalkyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the cycloalkyl consists of about 5 to about.6 ring atoms. A fused heteroarylcycloalkyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or ilia as a prefix before heteroaryl portion of the fused heteroarylcycloalkyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted fused heteroarylcycloalkyl" means a fused heteroarylcycloalkyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused heteroarylcycloalkyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcycloalkyl include 5,6,7,8- tetrahydroquinolinyl, 5,6,7,8-tetra-hydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8- tetrahydroquinazolyl, 4,5,6,7 -tetrahydro-1H -benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, lH-4-oxa-1,5- diazanaphthalen-2-onyl, 1,3-dihydroimidizole-[4,5]-pyridin-2-onyl, and the like.

"Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl as defined herein. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclenyl as a variable may be bonded through any atom of the ring system thereof capable of such. The designation of the aza, oxa or thia as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom "Substituted fused heteroarylheterocyclenyl" means a fused heteroarylheterocyclenyl group as defined above which is substituted with one *or* more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of a fused

heteroarylazaheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heteroaryl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide. The nitrogen or sulfur atom of the heteroaryl or heterocyclyl portion of the fused heteroarylheterocyclyl may also be optionally oxidized to the corresponding N-oxide, S- oxide or S,S-dioxide. Exemplary fused heteroarylheterocyclenyl include 7,8-dihydro[1, 7]naphthyridinyl, 1 ,2-dihydro[2,7]-naphthyridinyl, 6,7 -dihydro- 3H -imidazo [4,5- c]pyridyl, 1,2-dihydro-l,5-naphthyridinyl, 1 ,2-dihydro-l ,6-naphthyridinyl, 1 ,2-dihydro-l, 7 -naphthyridinyl, 1 ,2-dihydro-l ,8-naphthyridinyl. 1,2-dihydro-2,6-naphthyridinyl, and the like.

"Halo or halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo, and more preferred are fluoro or chloro.

"Heteroaroyl" means an heteroaryl-CO- group wherein the heteroaryl group is as herein described. Exemplary heteroaroyl groups include thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl, l- and 2-naphthoyl, pyridinoyl, and the like.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferably the ring system includes 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. Encompassed by heteroaryl are fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl and fused heteroarylheterocyclyl as defined herein when bonded through the heteroaryl moiety thereof. "Substituted heteroaryl" means a heteroaryl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The designation of the aza, oxa or thia as a prefix before heteroaryl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. A nitrogen atom of an heteroaryl may be a basic nitrogen atom and may also be optionally oxidized to the corresponding N-oxide. Exemplary heteroaryl and substituted heteroaryl groups include pyrazinyl, thienyl, isothiazolyl, oxazolyl, pyrazolyl, furazanyl, pyrrolyl, 1,2,4-thiadiazolyl, pyridazinyl, quinoxalinyl, phthalazinyl, imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazolyl, , benzofurazanyl, azaindolyl, benzimidazolyl,

benzothienyl, thienopyridyl, thienopyrimidyl, pyrrolopyridyl. imidazopyridyl, benzoazaindolyl, 1,2,4-triazinyl, benzthiazolyl, furanyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl, triazolyl, and the like. A preferred heteroaryl group is pyrazinyl.

"Heteroaryldiyl" means a bivalent radical derived from a heteroaryl, wherein the heteroaryl is as described herein. An exemplary heteroaryldiyl radical is optionally substituted pyridinediyl.

"Heteroarylsulfonylcarbamoyl" means a heteroaryl-SO_2-NH-C(=O)- group wherein the heteroaryl group is as herein described.

"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic hydrocarbon ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur atoms, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. Preferably, the ring includes 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". Encompassed by heterocyclenyl are fused arylheterocyclenyl and fused heteroarylheterocyclenyl as defined herein when bonded through the heterocyclenyl moiety thereof. The designation of the aza, oxa or thia as a prefix before heterocyclenyl define that at least a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. "Substituted heterocyclenyl" means a heterocyclenyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein. The nitrogen atom of an heterocyclenyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic azaheterocyclenyl groups include 1,2,3,4-tetrahydrohydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetra-hydropyridine, 1,4,5,6-tetrahydro-pyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Exemplary oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuranyl, and fluorodihydro-furanyl. An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl.

Exemplary monocyclic thiaheterocyclenyl rings include dihydrothiophenyl and dihydrothiopyranyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which one or more of the carbon atoms in the ring system is/are hetero element(s) other than carbon, for example nitrogen, oxygen or sulfur. Preferably, the ring system contains from 1 to 3 heteroatoms. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". Encompassed by heterocyclyl are fused arylheterocyclyl and fused heteroarylheterocyclyl as defined herein when bonded through the heterocyclyl moiety thereof. The designation of the aza, oxa or thia as a prefix before heterocyclyl define that at least a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. "Substituted heterocyclyl" means a heterocyclyl group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein The nitrogen atom of an heterocyclyl may be a basic nitrogen atom. The nitrogen or sulfur atom of the heterocyclyl may also be optionally oxidized to 20 the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

"Heterocyclylene" means a bivalent heterocyclyl group as defined herein having about 4 to about 8 carbon atoms. Preferred ring sizes of the heterocyclylene include about 5 to about 6 ring atoms; and such preferred ring sizes are also referred to as "lower". The points of binding on the cycloalkylene group include 1,1-, 1,2-, 1,3-, or 1,4- binding patterns, and where applicable the stereochemical relationship of the points of binding is either cis or trans. Exemplary heterocyclylene groups include (1,1-, 1,2- or 1,3-)piperidinylene and (1,1- or 1,2-)tetrahydrofuranylene. "Substituted heterocyclylene" means a heterocyclylene group as defined above which is substituted with one or more "ring group substituents" (preferably 1 to 3) which may be the same or different and are as defined herein.

"Hydrate" means a solvate wherein the solvent molecule(s) is/are H_2O.

"N -oxide" means a moiety of the following structure.

"Patient" includes both human and other mammals.

"Pharmaceutically acceptable ester" refers to esters that hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof, Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Exemplary esters include formates, acetates, propionates, butyrates, acrylates, ethylsuccinates, and the like.

"Pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formula, for example by hydrolysis in blood. Functional groups that may be rapidly transformed, by metabolic cleavage, in vivo form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as alkanoyl (such as acetyl, propanoyl, butanoyl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds of this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion is provided in Design of Prodrugs, H. Bundgaard, ed., Elsevier (1985); Methods in Enzymology; K. Widder et al, Ed., Academic Press, 42, 309-396 (1985); A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bandaged, ed., Chapter 5; "Design and Applications of Prodrugs" 113-191 (1991);

Advanced Drug Delivery Reviews, H. Bundgard, 8 , 1-38, (1992); J. Pharm. Sci., 77.,285 (1988); Chem. Pharm. Bull., N. Nakeya et al, 32, 692 (1984); Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, 14 A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, E.B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, which are incorporated herein by reference.

"Pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts, and base addition salts, of compounds of the present invention. These: salts can be prepared *in situ* during the final isolation and purification of the compounds. In particular, acid addition salts can be prepared by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Exemplary acid addition salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactiobionate, sulfamates, malonates, salicylates, propionates, methylene-bis-ß-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamates and laurylsulfonate salts, and the like. See, for example S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977) which is incorporated herein by reference. Base addition salts can also be prepared by separately reacting the purified compound in its acid form with a suitable organic or inorganic base and isolating the salt thus formed. Base addition salts include pharmaceutically acceptable metal and amine salts. Suitable metal salts include the sodium, potassium, calcium, barium, zinc, magnesium, and aluminum salts. The sodium and potassium salts are preferred. Suitable inorganic base addition salts are prepared from metal bases which include sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide and the like. Suitable amine base addition salts are prepared from amines which have sufficient basicity to form a stable salt, and preferably include those amines which are frequently used in medicinal chemistry because of their low toxicity and acceptability for medical use. ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'- dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, triethylamine,

dibenzylamine, ephenamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, basic amino acids, e.g., lysine and arginine, and dicyclohexylamine, and the like.

"Ring group substituents" mean substituents attached to aromatic or non-aromatic ring systems inclusive of aryl, heteroaryl, hydroxy, alkoxy, cyclyloxy, aryloxy, heteroaryloxy, acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or its thioxo analogue heteroaroyl or its thioxo analogue, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, halo, nitro, cyano, carboxy (acid), -C(O)-NHOH -C(O)-$CH_2$0H, -C(O)-CH_2SH -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl. heteroarylsulfonylcarbamoyl, 3-hydroxy-3-cyclobutene-l,2-dione, 3,5-dioxo-l,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl,3-hydoxy-1-methylpyrazoly, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl. cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, cyclylthio, arylthio, heteroarylthio, cyclyl, aryldiazo, heteroaryldiazo, thiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-, wherein Y^1, Y^2 and Y^3 are independently hydrogen, alkyl, aryl or heteroaryl. or for where the substituent is Y^1Y^2N-, then one of Y^1 and Y^2 may be acyl, cyclylcarbonyl, aroyl, heteroaroyl, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl or heteroaryloxycarbonyl, as defined herein and the other of Y^1 and Y^2 is as defined previously, or for where the substituent is $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$-, Y^1 and Y^2 may also be taken together with the N atom through which Y^1 and Y^2 are linked to form a 4 to 7 membered azaheterocyclyl or azaheterocyclenyl. When a ring system is saturated or partially saturated, the "ring group substituents" further include, methylene (H2C=), oxo (O=) and thioxo (S=). Acidic/amide ring group substituents are carboxy (acid). -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, phosphono, alkylsulfonylcarbamoyl, tetrazolyl, arylsulfonylcarbamoyl, N-methoxycarbamoyl, heteroarylsulfonylcarbamoyl, 3-hydroxy-3- cyclobutene-l,2-dione, 3,5-dioxo-l,2,4-oxadiazolidinyl or hydroxyheteroaryl such as 3-hydroxyisoxazolyl, 3-hydoxy-l-methylpyrazoly and Y^1Y^2NCO-. Non-acidic polar ring group substituents are hydroxy, oxo (O=), thioxo (S=), acyl or its thioxo analogue, cyclylcarbonyl or its thioxo analogue, aroyl or

its thioxo analogue, heteroaroyl or its thioxo analogue, alkoxycarbonyl, cyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, acyloxy, cyclylcarbonyloxy, aroyloxy, heteroaroyloxy, alkylsulfonyl, cyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, cyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, thiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- or $Y^1Y^2NSO_2$.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, methanolates, and the like.

Pharmacology

Experimental Methods and or Assays Used for Determining Activity:

FLIPR Assay – human CXCR5:

Changes in the intracellular Ca^{2+} are measured in RBL cell line stably transfected with human CXCR5 DNA. 9,000 cells/well are plated and incubated at 37°C, 5% CO_2 20h prior to the assay. On the following day, cells are washed once with assay buffer containing Hank's (Invitrogen, 14025-092) plus 20mM HEPES, pH 7.4 and loaded with dye by incubating for 30min at 37°C with 2 μM fluo-4/AM (Molecular Probes, F14202) in assay buffer plus 2.5mM probenecid. Cells are washed 3 times with assay buffer, then compounds in assay buffer plus 0.1% BSA are added into cells. Cells are washed 3 additional times with assay buffer, then stimulated with 10nM human CXCL13 (R&D, 801-CX/CF). Changes of intracellular Ca^{2+} are recorded using the 384-B FLIPR (Molecular Devices).

FLIPR Assay – murine CXCR5

Changes in the intracellular Ca^{2+} are measured in RBL cell line stably transfected with murine CXCR5 DNA. 9,000 cells/well are plated and incubated at 37°C, 5% CO_2 20h prior to

the assay. On the following day, cells are washed once with assay buffer containing Hank's (Invitrogen, 14025-092) plus 20mM HEPES, pH 7.4 and loaded with dye by incubating for 30min at 37°C with 2 μM fluo-4/AM (Molecular Probes, F14202) in assay buffer plus 2.5mM probenecid. Cellsare washed 3 times with assay buffer, then compounds in assay buffer plus 0.1% BSA are added into cells. Cells are washed 3 additional times with assay buffer, then stimulated with 6nM murine CXCL13 (R&D, 470-BC). Changes of intracellular Ca^{2+} are recorded using the 384-B FLIPR (Molecular Devices).

GTPγS Assay:

The [^{35}S]-GTPγS binding assay for CXCR5 is performed using membranes prepared from RBL cell line stably transfected with human CXCR5 DNA. 2.5 μM GDP, test compound at the desired concentration (or DMSO in the controls), 10μM un-labeled GTPγS (or buffer in controls) and 7.5μg cell membrane/well are mixed together (plate shaker) for 15min at RT. 750nM human CXCL13 and 400pM [^{35}S]-GTPγS are added and the plate shaken for 5min at RT. 1.134mg/well spa beads are then added and the plate shaken for 45min at RT. The reaction is stopped by centrifugation at 230g for 10 minutes and radioactivity measured on a Wallac Microbeta Trilux beta counter.

Chemotaxis Assay:

Wells in the assay plate are pre-coated with 150 μl RPMI (no phenol red) containing 1% BSA for 2h at room temperature. Pre-coating buffer is discarded and wells washed twice with CTX assay buffer (see below). CXCR5^{+} HS Sultan cells (ATCC cat# CRL 1484) are added to the upper chamber of the transwell plate (Millipore Cat#MAMI C5S 10) at 0.6 x10^{5} cells / well and incubated with test compound for 15min at RT. CXCL13 ligand at 100nM (R&D, cat# 801-cx/cf) or **CTX**-buffer (RPMI no phenol red supplemented with 0.02% BSA, 1mM Na pyruvate) is added to the lower chamber. The two chambers are assembled and incubated at 37°C for 2h. The upper chamber is subsequently removed and cells in lower chamber are counted after adding colorimetric reagent (Promega Cat# G3581) and reading OD_{490}. CXCR5 specific migration = total migrated cell -spontaneous migrated cells (wells containing CTX buffer without ligand).

Experimental data below is a representation of inhibitory activity as indicated by IC_{50} values for the Examples herein. The particular embodiments below are exemplary and do not limit the equivalents pertaining thereto.

Table I

EXAMPLE	IC50
5	2.4
	0.493
18	3.65
7	0.844
	0.425
	0.105
38	0.675
9	0.47
11	2.93
13	1.08
24	ND
26	ND
44	~13
42	5.45
52	>30
46	19.6
119	>30
36	>30
56	>30
58	>30
48	>30
121	ND
29	~24
75	2.85
79	ND
87	0.298
81	~9.5
54	>30
77	ND
93	18.2
91	~27
89	17.35
97	0.537
103	0.38
99	~7.8
85	6.1
95	14.75
112	>30
111	~20.5
108	>30
109	>30
107	~30
116	>30
115	~10.15
113	>30

117	>30
123	19.3
125	0.099
127	2.3
129	15.25
132	0.056
21	0.268
135	0.033
130	3.87
133	0.533
32	~16
34	~13
138	8.2
143	0.232
146	0.446
144	0.023
141	1.05
139	0.097
60	>30
149	0.011
62	~30
152	0.013
64	>30
154	0.2
152	0.013
397	0.026
136	0.014
232	0.007
161	0.045
155	0.047
132	0.056
150	0.015
231	0.030
158	0.015
395	0.009
388	0.005
392	0.038
159	0.017

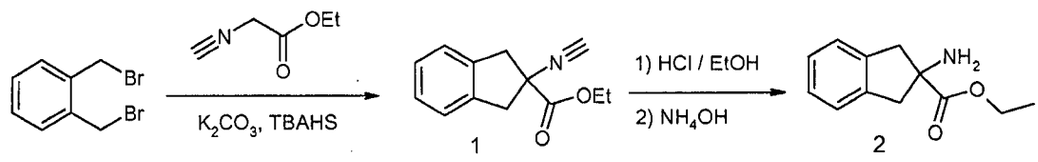
Preparation of Compounds of the Invention

The starting materials and intermediates of compounds of the invention may be prepared by the application or adaptation of known methods described below, their obvious chemical equivalents, or, for example, as described in literature by R.C. Larock in Comprehensive Organic Transformations, VCH publishers (1989).

Purification by HPLC refers to preparative high performance liquid chromatography using the following conditions: [C18 column, 10 micron particle size, gradient elution: 20-100% CH_3CN (0.1% TFA) in H_2O (0.1% TFA)].

EXAMPLES

EXAMPLE 1



Isocyano-indan-2-carboxylic acid ethyl ester (1) :

To a solution of ethyl isocyanoacetate (4.29g, 37.9mmol) in anhydrous ACN (400mL) is added anhydrous K_2CO_3 (K_2SO_4, 31.4g, 227mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.57g, 7.58mmol), and 1,2-bis-bromomethyl-benzene (10.0g, 37.9mmol). The resulting heterogeneous mixture is stirred at 75°C overnight. The reaction mixture is cooled down to RT and filtered to remove the unwanted salts. The filter cake is washed with ACN (20mL) and the filtrate is concentrated *in vacuo*. The residue is dissolved in ethyl ether (150mL) and washed with water (1 x 10mL) and brine (3 x 10mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (400g silica gel; gradient elution: 20-100% EtOAc in heptane) to give a pure product as white solid (8.0g, 49%).

^1H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.25 (s, 4H)

LC/MS (ES+) m/z = 449.25

EXAMPLE 2

2-Amino-indan-2-carboxylic acid ethyl ester (2):

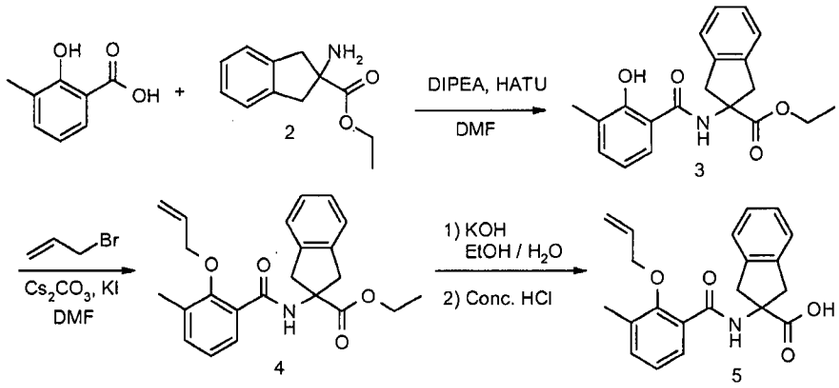
To a solution of 2-isocyano-indan-2-carboxylic acid ethyl ester (1) (8.0g, 37.2mmol) in absolute EtOH (200mL) is added concentrated HCl (5mL) dropwise. The resulting solution is stirred at RT for 5h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride salt

is dissolved in water (100mL) and extracted with of ethyl ether (3 x 5mL) to remove unwanted organic impurities. The aqueous layer is brought to pH=10 by addition of NH_4OH solution and then extracted with EtOAc (3 x 50mL). The combined EtOAc layer is washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (4.7g, 62%).

^1H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.16-7.23 (m, 4H)

LC/MS (EZ+) m/z = 206.08

EXAMPLE 3



2-(2-Hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3):

To a solution of 2-hydroxy-3-methyl-benzoic acid (3.65g, 24mmol), 2-amino-indan-2-carboxylic acid ethyl ester (5.00g, 24mmol), HATU [O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium PF_6] (11.0g, 29mmol) in anhydrous DMF (30mL) is added DIPEA (8.30mL, 50mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (400g silica gel, gradient clution: 10-80% EtOAc in heptane) to give a pure product (3) as white solid (5.5g, 67%).

^1H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 2.23(s, 3H), 3.40(d, 2H), 3.74(d, 2H), 4.25(q, 2H), 6.70(t, 1H), 6.84(s, 1H), 7.15-7.25(m, 6H), 12.21(s, 1H)

LC/MS (ES+) m/z = 340.15

EXAMPLE 4

2-(2-Allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (4):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (300mg, 0.88mmol), anhydrous Cs_2CO_3 (573mg, 1.76mmol), and KI (30mg, 0.18mmol) in DMF (8mL) is added 3-bromo-propene (90μL, 1.06mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-30% EtOAc in heptane) to give a pure product (4) as white solid (303mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 2.26(s, 3H), 3.33(d, 2H), 3.75(d, 2H), 4.25(q, 2H), 5.21(d, 1H), 5.33(d, 1H), 5.86(m, 1H), 7.09(t, 1H), 7.19(br s 4H), 7.27(d, 1H), 7.88(d, 1H), 8.43(s, 1H)

LC/MS (ES+) m/z = 380.20

EXAMPLE 5

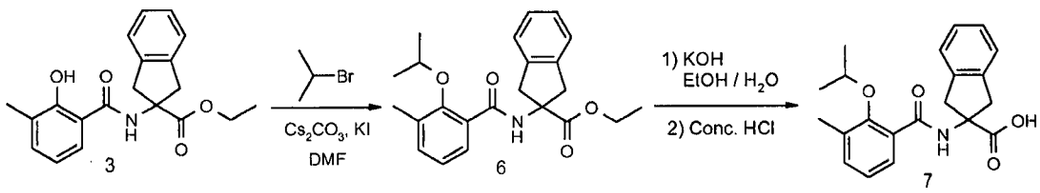
2-(2-Allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (5):

The mixture of 2-(2-allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (4) (168mg, 0.44mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (5) as white solid (150mg, 97%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 2.26(s, 3H), 3.34(d, 2H), 3.77(d, 2H), 4.23(d, 2H), 5.20(d, 1H), 5.32(d, 1H), 5.84(m, 1H), 7.10(t, 1H), 7.16-7.23(m, 4H), 7.29(d, 1H), 7.83(dd, 1H), 8.57(s, 1H)

LC/MS (ES+) m/z = 352.15

EXAMPLE 6



2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (6):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (300mg, 0.88mmol), anhydrous Cs_2CO_3 (573mg, 1.76mmol), and KI (30mg, 0.18mmol) in DMF (10mL) is added 2-bromo-propane (330μL, 3.52mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (6) as white solid (174mg, 52%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.03(d, 6H), 1.24(t, 3H), 2.25(s, 3H), 3.34(d, 2H), 3.77(d, 2H), 4.21(m, 1H), 4.25(q, 2H), 7.07(t, 1H), 7.17-7.26(m, 5H), 7.85(dd, 1H), 8.31(s, 1H)
LC/MS (ES+) m/z = 382.18

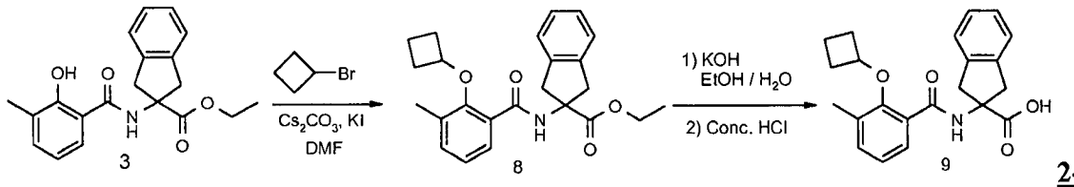
EXAMPLE 7

2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (7):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (6) (265mg, 0.69mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (6mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and the solution acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (7) as white solid (244mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.98(d, 6H), 2.24(s, 3H), 3.41(d, 2H), 3.85(d, 2H), 4.14(m, 1H), 7.08(t, 1H), 7.18-7.30(m, 5H), 7.88(d, 1H), 8.52(s, 1H)
LC/MS (ES+) m/z = 354.16

EXAMPLE 8



2-

(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (8):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (400mg, 1.18mmol), anhydrous Cs_2CO_3 (769mg, 2.36mmol), and KI (40mg, 0.24mmol) in DMF (10mL) is added bromo-cyclobutane (130μL, 1.42mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (8) as white solid (320mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 1.18-1.34(m, 1H), 1.41-1.52(m, 1H), 1.87-2.07(m, 4H), 2.26(s, 3H), 3.36(d, 2H), 3.78(d, 2H), 4.22 - 4.29(m, 1H), 4.24(q, 2H), 7.07(t, 1H), 7.17-7.27(m, 5H), 7.86(dd, 1H), 8.33(s, 1H)

LC/MS (ES+) m/z = 394.19

EXAMPLE 9

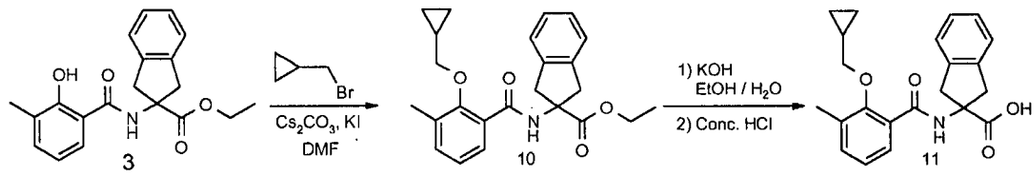
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (9):

The mixture of 2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (8) (250mg, 0.64mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and the solution acidified with conc. HCl until pH~3 to yield a precipitate. The precipitate is filtered to give a pure product (9) as white solid (190mg, 81%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.24(m, 1H), 1.45(m, 1H), 1.87-2.01(m, 4H), 2.26(s, 3H), 3.40(d, 2H), 3.81(d, 2H), 4.26(m, 1H), 7.08(t, 1H), 7.18-7.29(m, 5H), 7.82(dd, 1H), 8.48(s, 1H)

LC/MS (ES+) m/z = 366.16

EXAMPLE 10



2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (10):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (400mg, 1.18mmol), anhydrous Cs_2CO_3 (769mg, 2.36mmol), and KI (40mg, 0.24mmol) in DMF (10mL) is added bromomethylcyclopropane (229μL, 2.36mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (10) as white solid (330mg, 71%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.17(m, 2H), 0.50(m, 2H), 0.91(m, 1H), 1.24(t, 3H), 2.26(s, 3H), 3.36(d, 2H), 3.54(d, 2H), 3.79(d, 2H), 4.24(q, 2H), 7.08(t, 1H), 7.15-7.27(m, 5H), 7.86(dd, 1H), 8.44(s, 1H)

LC/MS (ES+) m/z = 394.18

EXAMPLE 11

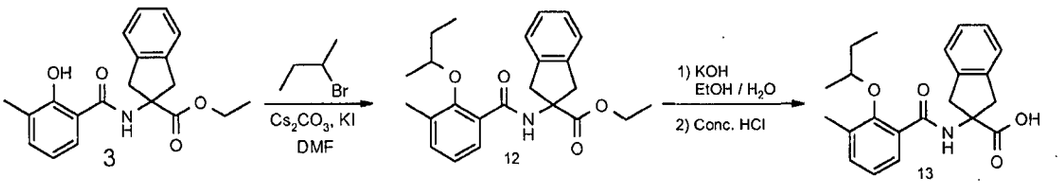
2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (11):

The mixture of 2-(2-cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (10) (240mg, 0.61mmol) and KOH (500mg, 8.93mmol) is dissolved in EtOH (6mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (11) as white solid (223mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.11(m, 2H), 0.51(m, 2H), 0.84(m, 1H), 2.26(s, 3H), 3.46(dd, 4H), 3.88(d, 2H), 7.11(t, 1H), 7.17-7.32(m, 5H), 7.89(d, 1H), 8.74(s, 1H)

LC/MS (ES+) m/z = 366.17

EXAMPLE 12



2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (12):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (400mg, 1.18mmol), anhydrous Cs_2CO_3 (574mg, 2.36mmol), and KI (40mg, 0.24mmol) in DMF (10mL) is added 2-bromobutane (508μL, 4.72mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (12) as white solid (395mg, 85%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.80(t, 3H), 0.93(d, 3H), 1.22-1.30(m, 4H), 1.48(m, 1H), 2.25(s, 3H), 3.33(dd, 2H), 3.76(dd, 2H), 3.97(m, 1H), 4.25(q, 2H), 7.01(t, 1H), 7.17-7.26(m, 5H), 7.87(dd, 1H), 8.35(s, 1H)
LC/MS (ES+) m/z = 396.19

EXAMPLE 13

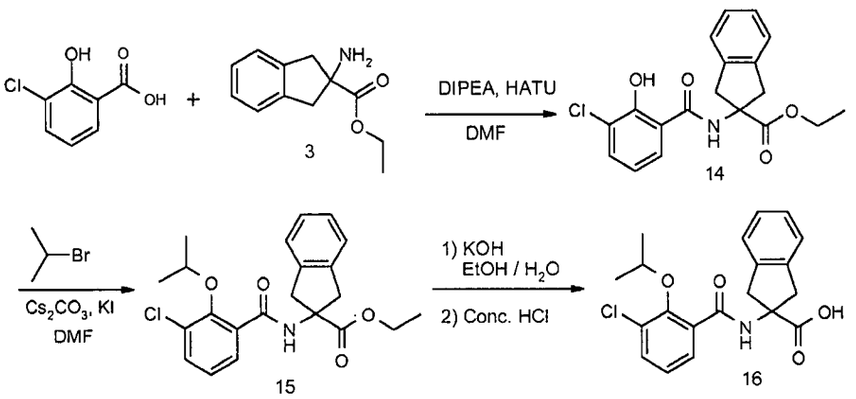
2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (13):

The mixture of 2-(2-sec-butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (12) (176mg, 0.44mmol) and KOH (500mg, 8.93mmol) is dissolved in EtOH (6mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (13) as white solid (162mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.79(t, 3H), 0.86(d, 3H), 1.18(m, 1H), 1.49(m, 1H), 2.25(s, 3H), 3.42(t, 2H), 3.86(dd, 2H), 3.91(m, 1H), 7.09(t, 1H), 7.19-7.31(m, 5H), 7.90(d, 1H), 8.59(s, 1H)

LC/MS (ES+) m/z = 368.17

EXAMPLE 14



2-(3-Chloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (14):

To a solution of 3-chloro-2-hydroxy-benzoic acid (413mg, 2.4mmol), 2-Amino-indan-2-carboxylic acid ethyl ester (500mg, 2.4mmol), HATU (1.1g, 2.9mmol) in anhydrous DMF (10mL) is added DIPEA (0.88ml, 5.3mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give a pure product (14) as white solid (420mg, 49%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.42(d, 2H), 3.73(d, 2H), 4.25(q, 2H), 6.76(t, 1H), 6.97(s, 1H), 7.23-7.29(m, 5H), 7.47(dd, 1H), 12.5(s, 1H)

LC/MS (ES+) m/z = 360.07, 362.08

EXAMPLE 15

2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (15):

To a suspension of 2-(3-chloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (14) (150mg, 0.42mmol), anhydrous Cs_2CO_3 (274mg, 0.84mmol), and KI (13mg, 0.08mmol) in DMF (7mL) is added 3-bromo-propene (237μL, 2.52mmol). The resulting reaction

suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (80g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (15) as white solid (137mg, 81%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.05(d, 6H), 1.24(t, 3H), 3.33(d, 2H), 3.76(d, 2H), 4.25(q, 2H), 4.56(m, 1H), 7.11(t, 1H), 7.19-7.26(m, 4H), 7.46(dd, 1H), 7.95(dd, 1H), 8.28(s, 1H)
LC/MS (ES+) m/z = 402.13, 404.14

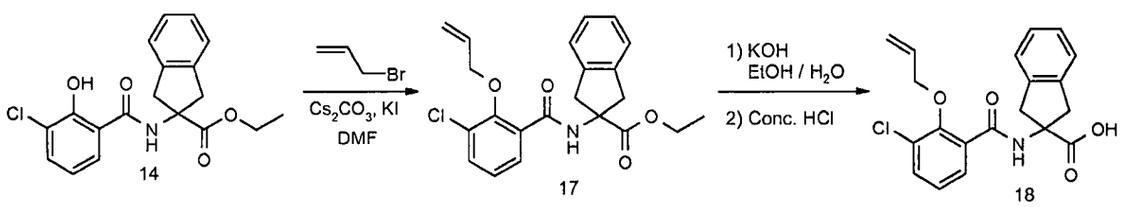
EXAMPLE 16

2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid (16):

The mixture of 2-(3-chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (15) (122mg, 0.30mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (16) as white solid (119mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.01(d, 6H), 3.40(d, 2H), 3.84(d, 2H), 4.55(m, 1H), 7.13(t, 1H), 7.19-7.26(m, 4H), 7.48(dd, 1H), 7.98(dd, 1H), 8.43(s, 1H)
LC/MS (ES+) m/z = 374.11, 376.13

EXAMPLE 17



2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid ethyl ester (17):

To a suspension of 2-(3-chloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (14) (250mg, 0.69mmol), anhydrous Cs_2CO_3 (453mg, 1.39mmol), and KI (23mg, 0.14mmol) in DMF (10mL) is added 3-bromo-propene (70μL, 0.83mmol). The resulting reaction

suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (80g silica gel, gradient elution: 10-40% EtOAc in heptane) to give a pure product (17) as white solid (160mg, 58%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 3.32(d, 2H), 3.75(d, 2H), 4.25(q, 2H), 4.41(d, 2H), 5.20-5.34(m, 2H), 5.88(m, 1H), 7.13-7.26(m, 5H), 7.49(dd, 1H), 7.97(dd, 1H), 8.36(s, 1H)
LC/MS (ES+) m/z = 402.13, 404.14

EXAMPLE 18

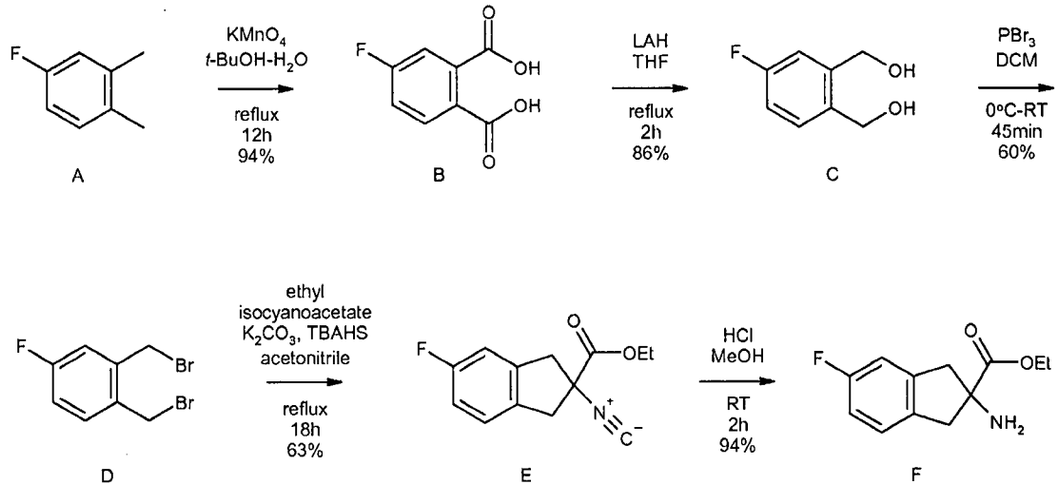
2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid (18):

The mixture of 2-(2-allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid ethyl ester (17) (140mg, 0.35mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3. After filtration, the solid is purified by HPLC to give a pure product (18) as white solid (88mg, 68%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.35(d, 2H), 3.78(d, 2H), 4.41(d, 2H), 5.21-5.34(m, 2H), 5.87(m, 1H), 7.13-7.30(m, 5H), 7.50 (dd, 1H), 7.93(dd, 1H), 8.49(s, 1H)
LC/MS (ES+) m/z = 372.09, 374.10

EXAMPLE 19

2-Amino-5-fluoroindane-2-carboxylic acid ethyl ester



Preparation of B: 4-Fluoro-1,2-dimethyl benzene **A** (50.0g, 402.7mmol) and a large excess of $KMnO_4$ (400g, 2.54mol) are dissolved in 1500mL of a water/t-butanol (70/30%, v/v) mixture. The reaction mixture is refluxed overnight. EtOH (900mL) is added to destroy unreacted $KMnO_4$ and the alcohols are distilled off. The resulting brown suspension is filtered through a celite pad. The colorless solution is concentrated and acidified with conc. HCl to pH 1. The product is filtered and the aqueous phase is extracted with EtOAc and dried over Na_2SO_4. 70.0g (94%) of white solid B is obtained after evaporation under reduced pressure.

^{1}H-NMR (400 MHz, DMSO-d6): δ 7.39 (m, 1H), 7.63 (br s, 1H), 7.99 (br s, 1H).

Preparation of C: LAH (37.5g, 989 mmol) is added to THF (850mL). The mixture is cooled in an ice bath and 4-fluorophthalic acid B (70.0g, 380 mmol) in THF (420mL) is added dropwise. After addition, the reaction mixture is refluxed for 2h. The mixture is cooled in an ice bath and water (35mL), aqueous 15% NaOH (35mL) and water (70mL) are added dropwise. The solid material is removed by filtration and washed with DCM, and the combined organic solutions are dried over Na_2SO_4 and evaporated under reduced pressure to give 51.2g (86%) of C.

^{1}H-NMR (400 MHz, $CDCl_3$) : 4.71 (t, J=4.5 Hz, 4H), 6.98 (m, 1H), 7.08 (m, 1H), 7.29 (m, 1H).

Preparation of D: To a solution of 2-hydroxy-methyl-5-fluoro-phenyl-methanol C (51.2g, 327.8 mmol) in 520mL of DCM is added phosphorous tribromide (37.3mL, 393.5 mmol) in DCM (520mL) dropwise at 0°C under a N_2 atmosphere and stirred for 45 min. The reaction mixture is quenched with water (70mL) added slowly and extracted with EtOAc, washed with water, satd. Na_2SO_4 solution and brine. The organic layer is evaporated under reduced pressure to give crude product, which is purified by silica gel 100-200 mesh column eluting with hexane to give 55.8g (60 %) of D.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.61 (m, 4H), 6.99 (m, 1H), 7.07 (m, 1H), 7.33 (m, 1H).

Preparation of E: A solution of 5-fluoro-1,2-bisbromomethylbenzene (20.4g, 72.3 mmol), ethyl isocyanoacetate (5.7mL, 51mmol), tetrabutylammonium hydrogen sulfate (6.7g, 19.7mmol) and dry K_2SO_4 (41.8g, 303mmol) in ACN (1500mL) is refluxed for 18h. After completion of reaction, the mixture is cooled and filtered. The filtrate is concentrated under reduced pressure and dissolved with EtOAc. The organic layer is washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mass obtained is purified by silica gel 100-200 mesh column eluting with 5% EtOAc-hexane to give 10.8g (63%) of E.

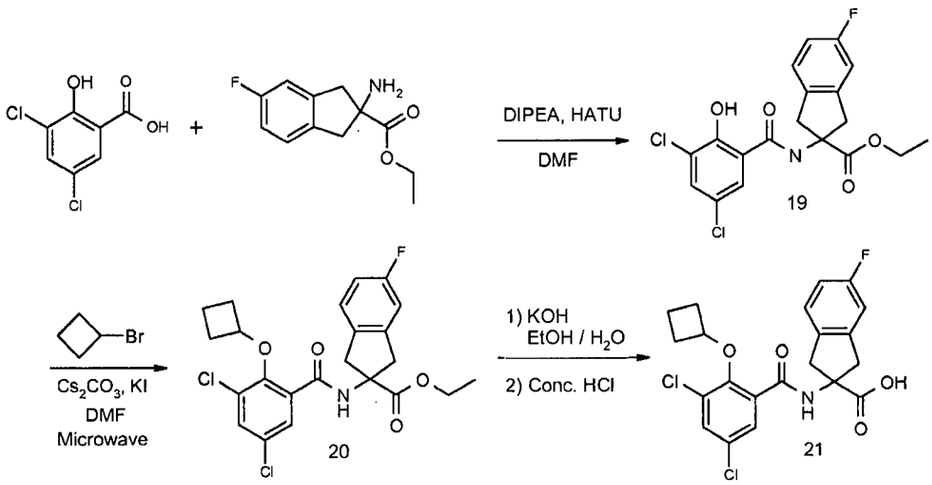
^{1}H-NMR (400 MHz, $CDCl_3$): 1.32 (m, 3 H), 3.43 (m, 2H), 3.66 (m, 2H), 4.32 (m, 2H), 6.94 (m, 2H), 7.17 (m, 1H).

Preparation of F: A methanolic solution of conc. HCl (35 %) (9.3mL in 110mL of MeOH) is added dropwise to a methanolic solution of 5-fluoro-2-isocyano-indan-2-carboxilic acid ethyl ester E (17.6g, 75.4 mmol) at RT and the mixture is stirred for 2h. The mixture is then neutralized by saturated $NaHCO_3$ solution and extracted with DCM (500mL). The organic layer is washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure to obtain 16.0g (94%) of F as yellowish semi solid.

^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (q, 3H), 1.62 (br s, 2H), 2.84 (m, 2H), 3.50 (q, 2H), 4.20 (m, 2H), 6.88 (m, 2H), 7.12 (t, J=7.6 Hz, 1H). ^{1}H-NMR (400 MHz, D_2O exchange, $CDCl_3$) : 1.26 (q, 3H), 2.83 (m, 2H), 3.49 (q, 2H), 4.20 (m, 2H), 6.88 (m, 2H), 7.12 (t, J=7 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) : 13.98, 45.14, 45.83, 61.21, 65.28, 111.82, 113.59, 125.54,

135.70, 142.44, 163.35, 176.05. IR (Neat): 1728 cm^{-1}. FIA-MS: 234 $[M+H]^+$. Qualitative GC-FID showed purity of 19 is 96.32 % (% by area normalization).

EXAMPLE 20



2-(3,5-Dichloro-2-hydroxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (19):

To a solution of 3,5-dichloro-2-hydroxy-benzoic acid (500mg, 2.42mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester F (1.08g, 4.84mmol), HATU (1.10g, 2.89mmol) in anhydrous DMF (15mL) is added DIPEA (599µl, 3.63mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give a pure product (A) as white solid (779mg, 78%).

^1H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.24(t, 3H), 3.39(dd, 2H), 3.68(dd, 2H), 4.24(q, 2H), 6.91-6.94(m, 2H), 7.14-7.18(m, 1H), 7.46(d, 1H), 7.52(d, 1H), 7.92(s, 1H), LC/MS (ES+) m/z = 412.06, 414.06

EXAMPLE 20

2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (20):

To a suspension 2-(3,5-dichloro-2-hydroxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (19) (624mg, 1.51mmol), anhydrous Cs_2CO_3 (984mg, 3.02mmol), and KI (50mg, 0.30mmol) in DMF (20mL) is added bromocyclobutane (711μL, 7.55mmol). The resulting reaction suspension is covered with argon and ran in a microwave reaction: 110°C, 2h. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-50% EtOAc in heptane) to give a pure product (20) as white solid (365mg, 52%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.23-1.38(m, 4H), 1.51-1.55(m, 1H), 1.94-2.07(m, 4H), 3.32(t, 2H), 3.73(dd, 2H), 4.26(q, 2H), 4.58(m, 1H), 6.88-6.96(m, 2H), 7.18(br s, 1H), 7.47(s, 1H), 7.93(s, 1H), 8.27(s, 1H),
LC/MS (ES+) m/z = 466.12, 468.12

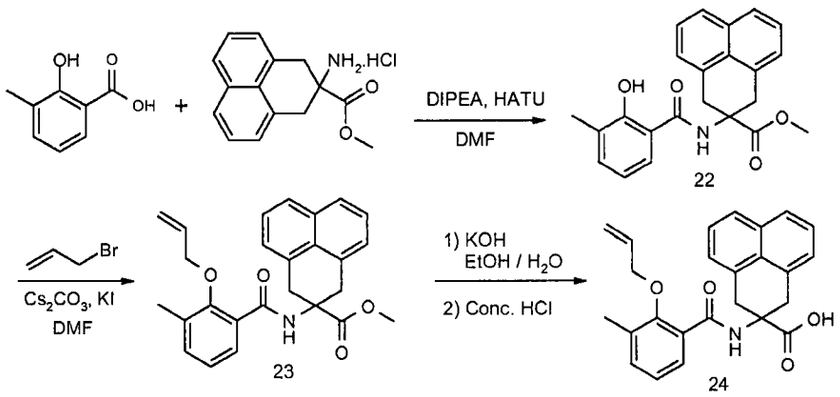
EXAMPLE 21

2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid (21):

The mixture of 2-(3,5-dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (20) (300mg, 0.64mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 6h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3. The precipitate is filtered to give a pure product (21) as white solid (200mg, 71%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.32(m, 1H), 1.50(m, 1H), 1.92-2.09(m, 4H), 3.36(t, 2H), 3.75(dd, 2H), 4.56(m, 1H), 6.91-6.96(m, 2H), 7.16-7.20(m, 1H), 7.48(dd, 1H), 7.90(dd, 1H), 8.37(s, 1H),
LC/MS (ES+) m/z = 438.09, 440.08

EXAMPLE 22



2-(2-Hydroxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (22):

To a solution of 2-hydroxy-3-methyl-benzoic acid (1.12g, 7.4mmol), 2-amino-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (2.05g, 7.4mmol), HATU (3.38g, 8.9mmol) in anhydrous DMF (28mL) is added DIPEA (4.89mL, 29.6mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (300g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give the pure product (22) as white solid (353mg, 13%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.18(s, 1H), 3.70(s, 4H), 3.85(s, 3H), 6.30(s, 1H), 6.48(t, 1H), 6.58(d, 1H), 7.13(d, 1H), 7.33(d, 2H), 7.44(t, 2H), 7.75(d, 2H), 12.08(s, 1H)

LC/MS (ES+) m/z = 376.14

EXAMPLE 23

2-(2-Allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid ethyl ester (23):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (22) (175mg, 0.47mmol), anhydrous Cs_2CO_3 (306mg, 0.94mmol), and KI (15.6mg, 0.09mmol) in DMF (8mL) is added 3-bromo-propene (199μL, 2.35mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The

residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (23) as white solid (107mg, 55%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.08(s, 3H), 3.68-3.73(m, 6H), 3.84(s, 3H), 5.02-5.11(m, 2H), 5.28-5.40(m, 1H), 6.70(t, 1H), 7.16(dd, 1H), 7.28(dd, 1H), 7.39(t, 2H), 7.69(d, 2H), 7.79(dd, 1H), 8.10(s, 1H)
LC/MS (ES+) m/z = 416.23

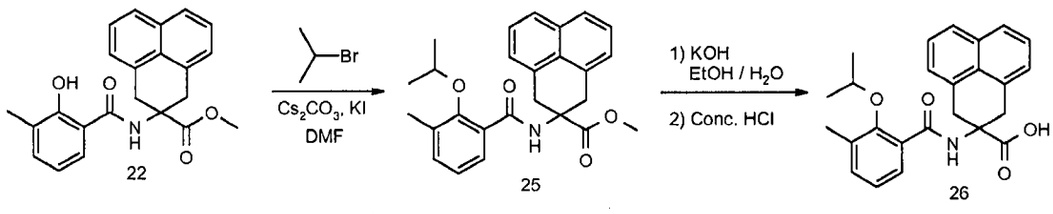
EXAMPLE 24

2-(2-Allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid (24):

The mixture of 2-(2-allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid ethyl ester (23) (107mg, 0.26mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out from the water. The precipitate is filtered to give a pure product (24) as white solid (98mg, 94%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 2.09(s, 3H), 3.71-3.74(m, 6H), 5.06-5.11(m, 2H), 5.28-5.41(m, 1H), 7.01(t, 1H), 7.18(dd, 1H), 7.30(dd, 1H), 7.41(t, 2H), 7.70(d, 2H), 7.75(dd, 1H), 8.20(s, 1H)
LC/MS (ES+) m/z = 402.16

EXAMPLE 25



2-(2-Isopropoxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (25):

To a suspension of 2-(2-hydroxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (22) (175mg, 0.47mmol), anhydrous Cs_2CO_3 (306mg, 0.94mmol), and KI (16mg, 0.09mmol) in DMF (8mL) is added 2-bromo-propane (220μL, 2.35mmol). The

resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give the pure product (25) as white solid (143mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.51(d, 6H), 2.10(s, 3H), 3.71(s, 4H), 3.81(s, 3H), 3.81-3.89(m, 1H), 6.98(t, 1H), 7.16(dd, 1H), 7.31(d, 2H), 7.41(t, 2H), 7.71(d, 2H), 7.82(dd, 1H), 8.04(s, 1H)

LC/MS (ES+) m/z = 418.23

EXAMPLE 26

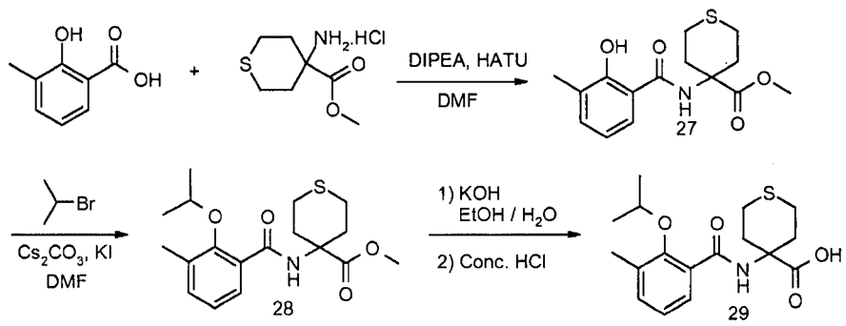
2-(2-Allyloxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid (26):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-2,3-dihydro-1H-phenalene-2-carboxylic acid methyl ester (25) (143mg, 0.34mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (26) as white solid (127mg, 93%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.49(d, 6H), 2.10(s, 3H), 3.71(s, 4H), 3.81(m, 1H), 6.99(t, 1H), 7.16(d, 1H), 7.33(d, 2H), 7.42(t, 2H), 7.72(d, 2H), 7.79(dd, 1H), 8.12(s, 1H)

LC/MS (ES+) m/z = 404.17

EXAMPLE 27



4-(2-hydroxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (27):

To a solution of HCl salt of 4-amino-tetrahydro-thiopyran-4-carboxylic acid methyl ester (529mg, 2.5mmol), 2-hydroxy-3-methyl-benzoic acid (380mg, 2.5mmol), HATU (1.14g, 3.0mmol) in anhydrous DMF (20mL) is added DIPEA (1.66mL, 10mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 10-80% EtOAc in heptane) to give a pure product (27) as white solid (102mg, 13%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.41(m, 4H), 2.72-2.80(m, 4H), 3.74(s, 3H), 6.36(s, 1H), 6.78(t, 1H), 7.25-7.30(m, 2H), 12.00(s, 1H)

LC/MS (ES+) m/z = 310.17

EXAMPLE 28

4-(2-Isopropoxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (28):

To a suspension of 4-(2-hydroxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (27) (98mg, 0.32mmol), anhydrous Cs_2CO_3 (208mg, 0.64mmol), and KI (11mg, 0.06mmol) in DMF (5mL) is added 2-bromopropane (150μL, 1.6mmol). The resulting reaction suspension is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (80g silica gel, gradient elution: 5-40% EtOAc in heptane) to give a pure product (28) as white solid (92mg, 81%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35(d, 6H), 2.33(s, 3H), 2.33-2.40(m, 4H), 2.63-2.69(m, 2H), 2.76-2.81(m, 2H), 3.76(s, 3H), 4.39(m, 1H), 7.10(t, 1H), 7.31(d, 1H), 7.84(dd, 1H), 8.28(s, 1H)

LC/MS (ES+) m/z = 352.13

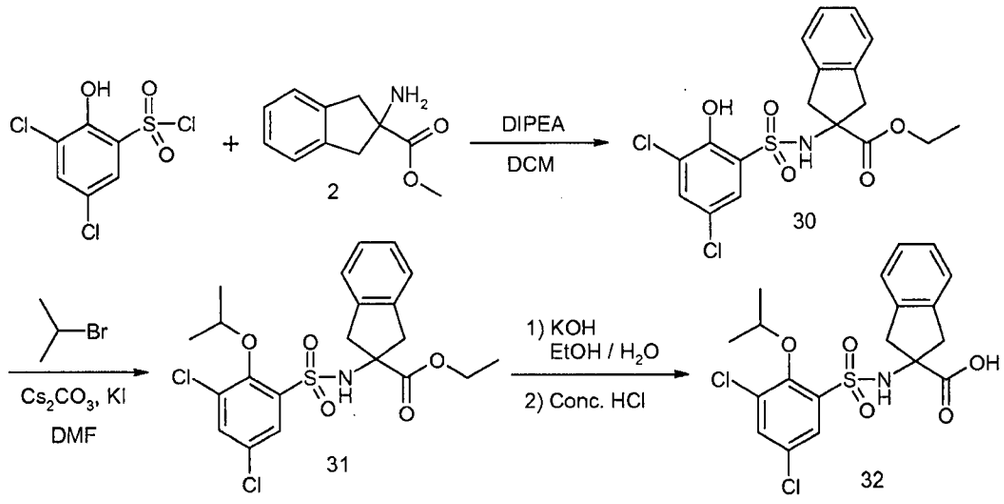
EXAMPLE 29

4-(2-Isopropoxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid (29):

The mixture of 4-(2-isopropoxy-3-methyl-benzoylamino)-tetrahydro-thiopyran-4-carboxylic acid methyl ester (28) (75mg, 0.21mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (29) as a pale yellow solid (68mg, 94%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.32(d, 6H), 2.33(s, 3H), 2.41-2.43(m, 4H), 2.64-2.74(m, 4H), 4.37(m, 1H), 7.11(t, 1H), 7.33(d, 1H), 7.86(dd, 1H), 8.42(s, 1H), 9.07(br s, 1H)
LC/MS (ES+) m/z = 338.11

EXAMPLE 30



2-(3,5-Dichloro-2-hydroxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (30):

To a solution of 2-amino-indan-2-carboxylic acid ethyl ester (3.14g, 15.3mmol) and 3,5-dichloro-2-hydroxy-benzenesulfonyl chloride (1g, 3.82mmol) in anhydrous DCM (dichloromethane, 20mL) is added DIPEA (631μL, 3.82mmol). The resulting solution is stirred at RT for 1 hour. The reaction solution is diluted in DCM (50mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (30) as white solid (450mg, 27%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 3.25(d, 2H), 3.57(d, 2H), 4.18(q, 2H), 5.60(s, 1H), 7.04-7.07(m, 2H), 7.14-7.17(m, 2H), 7.43(d, 1H), 7.49(d, 1H), 8.30(br s, 1H)
LC/MS (ES+) m/z = 447.04, 449.04, 430.01

EXAMPLE 31

2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (31):

To a suspension of 2-(3,5-dichloro-2-hydroxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (30) (226mg, 0.53mmol), anhydrous Cs_2CO_3 (300mg, 0.92mmol), and KI (15mg, 0.09mmol) in DMF (15mL) is added 2-bromopropane (432μL, 4.60mmol). The resulting reaction suspension is filled with argon and run in a microwave reaction: 110°C, 2.5h. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-60% EtOAc in heptane) to give a pure product (31) as a white semi-solid (248mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.23(t, 3H), 1.27(d, 6H), 3.19(d, 2H), 3.50(d, 2H), 4.10(q, 2H), 5.12(m, 1H), 5.75(s, 1H), 6.98-7.01(m, 2H), 7.12-7.15(m, 2H), 7.47(dd, 1H), 7.58(dd, 1H),
LC/MS (ES+) m/z = 494.0

EXAMPLE 32

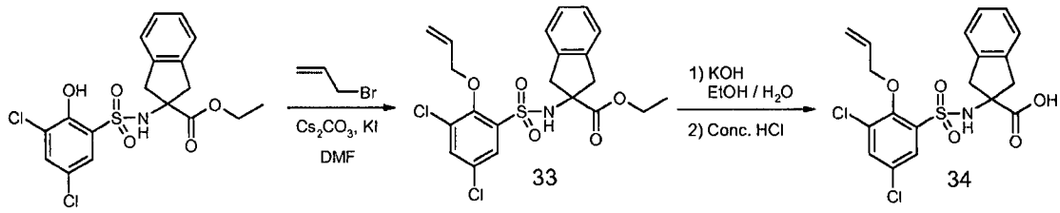
2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid (32):

The mixture of 2-(3,5-dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (31) (248mg, 0.52mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (32) as white solid (230mg, 100%).

^{1}H NMR (CDOD, 300MHz): δ 1.27(d, 6H), 3.23(d, 2H), 3.48(d, 2H), 5.05(m, 1H), 6.98-7.01(m, 2H), 7.08-7.12(m, 2H), 7.44(d, 1H), 7.60(d, 1H)

LC/MS (ES-) m/z = 442.08, 444.08

EXAMPLE 33



2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (33):

To a suspension of 2-(3,5-dichloro-2-hydroxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (10) (200mg, 0.46mmol), anhydrous Cs_2CO_3 (300mg, 0.92mmol), and KI (15mg, 0.09mmol) in DMF (15mL) is added 3-bromo-propene (390μL, 4.6mmol). The resulting reaction suspension is filled in argon and run in a microwave reaction: 110°C, 2h. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (20mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-60% EtOAc in heptane) to give a pure product (33) as white solid (162mg, 75%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22(t, 3H), 3.21(d, 2H), 3.52(d, 2H), 4.09(q, 2H), 4.55(d, 2H), 5.36(dd, 2H), 5.68(s, 1H), 6.05(m, 1H), 6.99-7.02(m, 2H), 7.12-7.14(m, 2H), 7.52(d, 1H), 7.58(d, 1H)

LC/MS (ES-) m/z = 468.10, 470.10

EXAMPLE 34

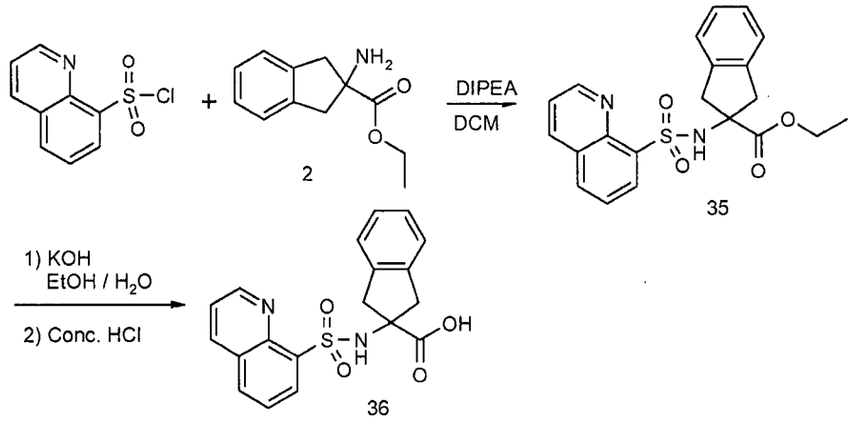
2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid (34):

The mixture of 2-(2-allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid ethyl ester (33) (143mg, 0.30mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3.

After filtration, the solid is purified by HPLC to give a pure product (34) as white solid (91mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.24(d, 2H), 3.58(d, 2H), 4.53(d, 2H), 5.36(dd, 2H), 5.72(s, 1H), 6.03(m, 1H), 7.02-7.04(m, 2H), 7.13-7.17(m, 2H), 7.34(d, 1H), 7.60(d, 1H)
LC/MS (ES+) m/z = 459.03, 461.02, 442.00

EXAMPLE 35



2-(Quinoline-8-sulfonylamino)-indan-2-carboxylic acid ethyl ester (35):

To a solution of quinoline-8-sulfonyl chloride (400mg, 1.76mmol), 2-amino-indan-2-carboxylic acid ethyl ester (361mg, 1.76mmol) in anhydrous DCM (8mL) is added DIPEA (291μL, 1.76mmol). The resulting solution is stirred at RT overnight. The reaction solution is diluted with DCM (40mL), washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (35) as white solid (245mg, 35%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.08(t, 3H), 3.20(d, 2H), 3.46(d, 2H), 3.94(q, 2H), 6.74-6.78(m, 2H), 6.86-6.90(m, 2H), 7.32(s, 1H), 7.39(dd, 1H), 7.64(t, 1H), 8.01(dd, 1H), 8.18(dd, 1H), 8.34(dd, 1H), 8.67(dd, 1H),
LC/MS (ES+) m/z = 397.11

EXAMPLE 36

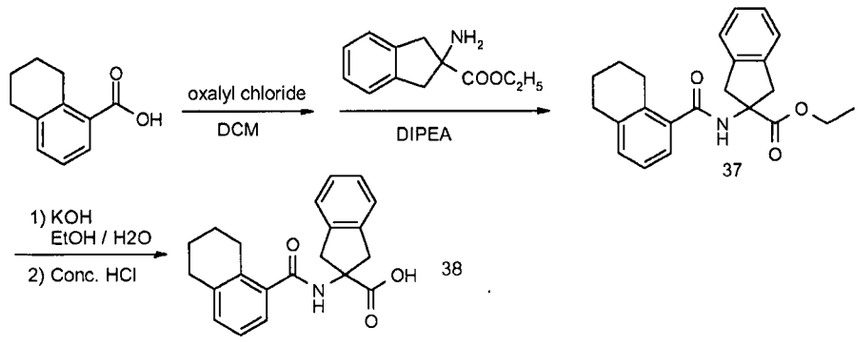
2-(Quinoline-8-sulfonylamino)-indan-2-carboxylic acid (36):

The mixture of 2-(quinoline-8-sulfonylamino)-indan-2-carboxylic acid ethyl ester (35) (210mg, 0.53mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (36) as white solid (195mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.18(d, 2H), 3.46(d, 2H), 6.66-6.69(m, 2H), 6.81-6.84(m, 2H), 7.40(dd, 1H), 7.65(t, 1H), 8.02(d, 1H), 8.18(dd, 1H), 8.34(dd, 1H), 8.64(dd, 1H)

LC/MS (ES+) m/z = 369.10

EXAMPLE 37



2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (37):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (500mg, 2.84mmol) in DCM (10mL) is added oxalyl chloride (0.50mL, 5.68mmol) dropwise. The resulting solution is stirred at RT for 2h. After the removal of DCM and excess oxalyl chloride, the residue, 2-amino-indan-2-carboxylic acid ethyl ester (583mg, 2.84mmol) and DIPEA (1.88mL, 11.3mmol) are dissolved in DCM (20mL). The resulting solution is stirred overnight. The reaction solution is diluted with DCM (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give the pure product (37) as white solid (610mg, 59%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.74(m, 4H), 2.76(m, 2H), 2.84(m, 2H), 3.34(d, 2H), 3.75d, 2H), 4.72(q, 2H), 6.20(s, 1H), 7.02-7.12(m, 3H), 7.18-7.25(m, 4H)
LC/MS (ES+) m/z = 364.18

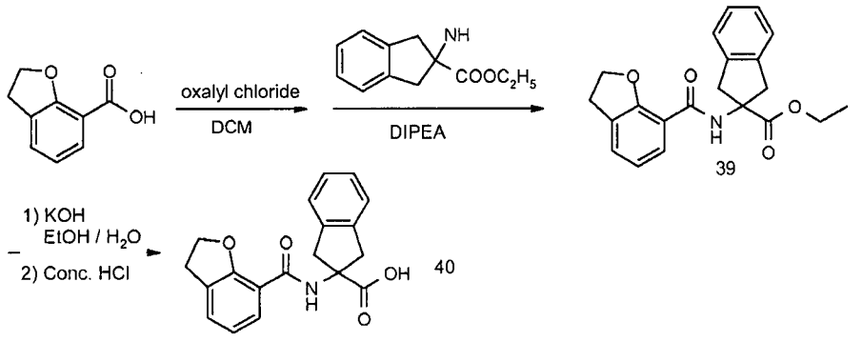
EXAMPLE 38

2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (38):

The mixture of 2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (37) (400mg, 1.1mmol) and KOH (1g, 17.8mmol) is dissolved in EtOH (10mL) and water (2mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (38) as white solid (300mg, 82%).

^{1}H NMR (CD_3OD, 300MHz): δ 1.74(m, 4H), 2.76(m, 2H), 3.38(d, 2H), 3.68(d, 2H), 4.85(s, 1H), 7.02-7.08(m, 3H), 7.14-7.23(m, 4H)
LC/MS (ES+) m/z = 336.15

EXAMPLE 39



2-[(2,3-Dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (39):

To a solution of 2,3-dihydro-benzofuran-7-carboxylic acid (394mg, 2.4mmol) in DCM (10mL) is added oxalyl chloride (0.85mL, 9.6mmol). The resulting solution is stirred at RT for 2h. After the removal of DCM and excess oxalyl chloride, the residue, 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.4mmol) and DIPEA (3.17mL, 19.2mmol) are dissolved in DCM (20mL). The resulting solution is stirred at RT overnight. The reaction solution is diluted with DCM (40mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The

organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (39) as white solid (635mg, 75%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.23(t, 3H), 3.22(t, 2H), 3.40(d, 2H), 3.77(d, 2H), 4.26(q, 2H), 4.67(t, 2H), 6.93(t, 1H), 7.17-7.30(m, 6H), 7.87(d, 1H), 8.18(s, H)
LC/MS (ES+) m/z = 352.12

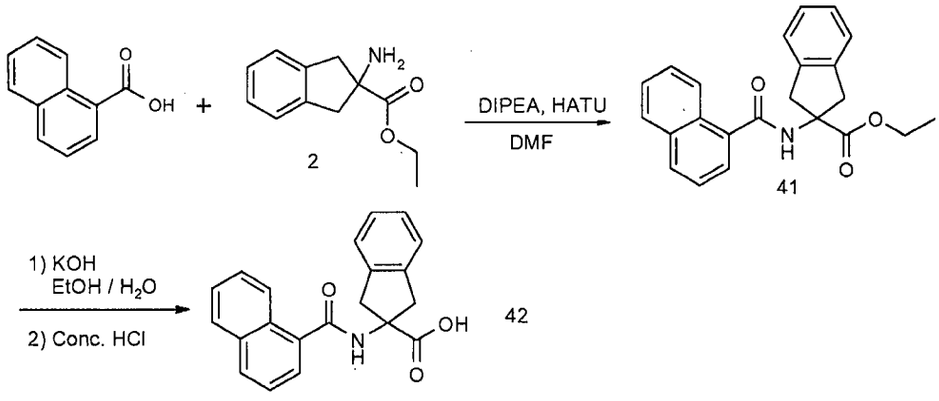
EXAMPLE 40

2-[(2,3-Dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid (40):

The mixture of 2-[(2,3-Dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (39) (250mg, 0.71mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (40) as white solid (200mg, 87%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.22(t, 2H), 3.40(d, 2H), 3.82(d, 2H), 4.68(t, 2H), 6.94(t, 1H), 7.17-7.25(m, 4H), 7.30(d, 1H), 7.83(d, 1H), 8.28(s, 1H)
LC/MS (ES+) m/z = 324.11

EXAMPLE 41



2-[(Naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (41):

To a solution of naphthalene-1-carboxylic acid (300mg, 1.74mmol), 2-amino-indan-2-carboxylic acid ethyl ester (357mg, 1.74mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (8mL) is added DIPEA (431μL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (41) as white solid (383mg, 61%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.30(t, 3H), 3.40(d, 2H), 3.77(d, 2H), 4.29(q, 2H), 6.59(s, 1H), 7.20-7.24(m, 4H), 7.34(t, 1H), 7.46-7.52(m, 3H), 7.79-7.85(m, 2H), 8.28-8.31(m, 1H)
LC/MS (ES+) m/z = 360.19

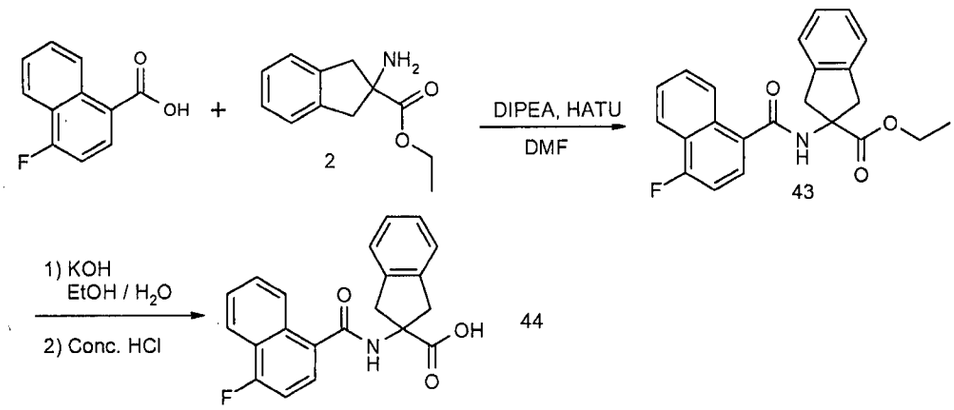
EXAMPLE 42

2-[(Naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (42):

The mixture of 2-[(naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (41) (220mg, 0.61mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (42) as white solid (196mg, 97%).

^{1}H NMR ($CDCl_3$ +drops of CD_3OD, 300MHz): δ 3.47(d, 2H), 3.82(d, 2H), 6.93(m, 1H), 7.19-7.28(m, 4H), 7.37-7.50(m, 4H), 7.81-7.89(m, 2H), 8.23-8.27(m, 1H)
LC/MS (ES+) m/z = 332.11

EXAMPLE 43



2-[(4-Fluoro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (43):

To a solution of 4-fluoro-naphthalene-1-carboxylic acid (232mg, 1.22mmol), 2-amino-indan-2-carboxylic acid ethyl ester (250mg, 1.22mmol), HATU (696mg, 1.83mmol) in anhydrous DMF (8mL) is added DIPEA (302µL, 1.83mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (43) as white solid (340mg, 74%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.31(t, 3H), 3.42(d, 2H), 3.80(d, 2H), 4.31(q, 2H), 6.53(s, 1H), 7.03(dd, 1H), 7.19-7.26(m, 4H), 7.47-7.82(m, 3H), 8.07-8.10(m, 1H), 8.31-8.35(m, 1H)
LC/MS (ES+) m/z = 378.12

EXAMPLE 44

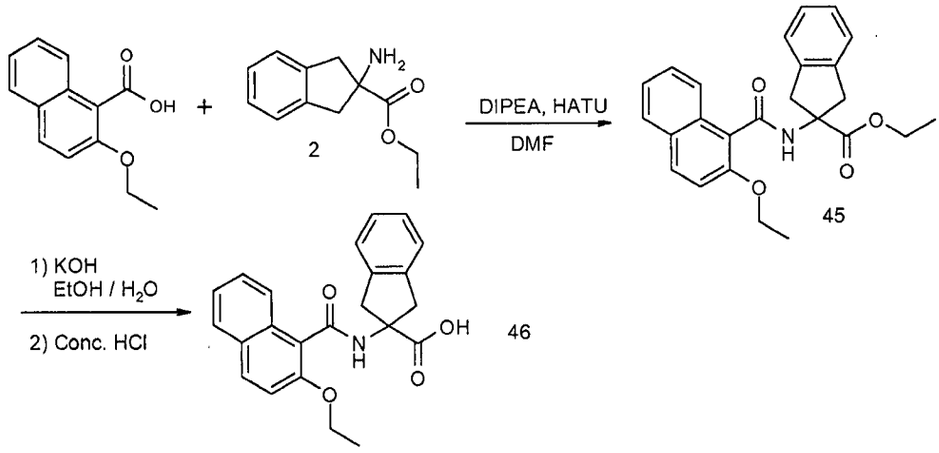
2-[(4-Fluoro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (44):

The mixture of 2-[(4-fluoro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (43) (180mg, 0.48mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 6h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (44) as white solid (174mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.46(d, 2H), 3.81(d, 2H), 6.99-7.06(m, 2H), 7.19-7.26(m, 4H), 7.48-7.54(m, 3H), 8.06-8.09(m, 1H), 8.24-8.28(m, 1H)

LC/MS (ES+) m/z = 350.09

EXAMPLE 45



2-[(2-Ethoxy-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (45):

To a solution of 2-ethoxy-naphthalene-1-carboxylic acid (335mg, 1.55mmol), 2-amino-indan-2-carboxylic acid ethyl ester (318mg, 1.55mmol), HATU (886mg, 2.33mmol) in anhydrous DMF (8mL) is added DIPEA (385μL, 2.33mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (45) as white solid (420mg, 67%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.12(t, 3H), 1.35(t, 3H), 3.40(d, 2H), 3.76(d, 2H), 3.98(q, 2H), 4.32(q, 2H), 6.73(s, 1H), 7.19 (d, 1H), 7.16-7.23(m, 4H), 7.29-7.34(m, 1H), 7.42-7.48(m, 1H), 7.73(dd, 2H), 8.16(d, 1H)

LC/MS (ES+) m/z = 404.18

EXAMPLE 46

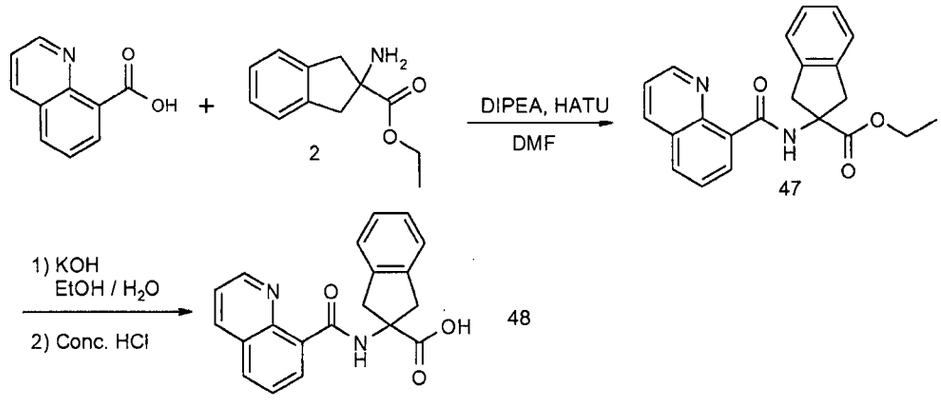
2-[(2-Ethoxy-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (46):

The mixture of 2-[(2-ethoxy-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (45) (270mg, 0.67mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL)

and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH ~ 4. The precipitate is filtered to give a pure product (46) as white solid (170mg, 68%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.18(t, 3H), 3.47(d, 2H), 3.82(d, 2H), 4.04(q, 2H), 7.09(s, 1H), 7.15-7.37 (m, 7H), 7.47(t, 1H), 7.78(dd, 2H), 8.07(d, 1H)
LC/MS (ES+) m/z = 376.19

EXAMPLE 47



2-[(Quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (47):

To a solution of quinoline-8-carboxylic acid (421mg, 2.43mmol), 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.43mmol), HATU (1.39g, 3.65mmol) in anhydrous DMF (15mL) is added DIPEA (603μL, 3.65mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (47) as white solid (281mg, 32%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.54(d, 2H), 3.86(d, 2H), 4.27(q, 2H), 7.17-7.27(m, 4H), 7.44(dd, 1H), 7.65(t, 1H), 7.94(dd, 1H), 8.24(dd, 1H), 8.80-8.84(m, 2H), 12.00(s, 1H)
LC/MS (ES+) m/z = 361.13

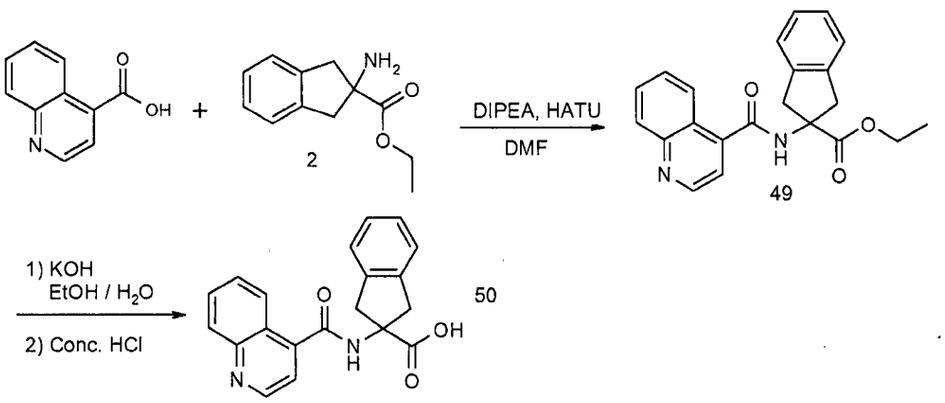
EXAMPLE 48

2-[(Quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid (48):

The mixture of 2-[(quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (47) (190mg, 0.53mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give the pure product (48) as white solid (152mg, 86%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.50(d, 2H), 3.83(d, 2H), 7.17-7.24(m, 4H), 7.44-7.49(m, 1H), 7.64(t, 1H), 7.98(d, 1H), 8.28(dd, 1H), 8.69(d, 1H), 8.83(s, 1H)
LC/MS (ES+) m/z = 333.08

EXAMPLE 49



2-[(Quinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (49):

To a solution of quinoline-4-carboxylic acid (301mg, 1.74mmol), 2-amino-indan-2-carboxylic acid ethyl ester (357mg, 1.74mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (8mL) is added DIPEA (431μL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-70% EtOAc in heptane) to give a pure product (49) as a pale yellow solid (370mg, 59%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.34(t, 3H), 3.48(d, 2H), 3.82(d, 2H), 4.34(q, 2H), 6.86(s, 1H), 7.21-7.29(m, 5H), 7.51-7.56(m, 1H), 7.65-7.71(m, 1H), 7.98(d, 1H), 8.18(d, 1H), 8.73(d, 1H)

LC/MS (ES+) m/z = 361.14

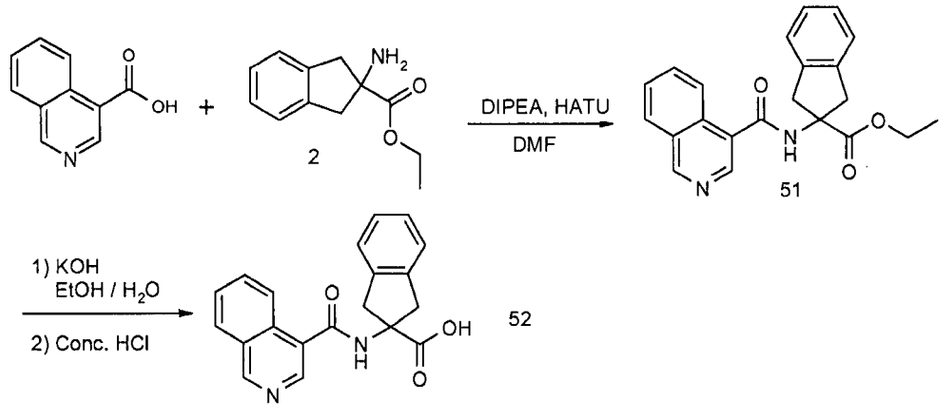
EXAMPLE 50

2-[(Quinoline-4-carbonyl)-amino]-indan-2-carboxylic acid (50):

The mixture of 2-[(quinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (49) (220mg, 0.61mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~4. The precipitate is filtered to give a pure product (50) as a pale yellow solid (98mg, 48%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.49(d, 2H), 3.83(d, 2H), 7.20-7.28(m, 4H), 7.50(d, 1H), 7.61(t, 1H), 7.79(t, 1H), 8.13(d, 1H), 8.24(d, 1H), 8.86(d, 1H)
LC/MS (ES+) m/z = 333.13

EXAMPLE 51



2-[(Isoquinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (51):

To a solution of isoquinoline-4-carboxylic acid (211mg, 1.22mmol), 2-amino-indan-2-carboxylic acid ethyl ester (250mg, 1.22mmol), HATU (696mg, 1.83mmol) in anhydrous DMF (8mL) is added DIPEA (302μL, 1.83mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (51) as white solid (359mg, 82%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 3.49 (d, 2H), 3.79(d, 2H), 4.28(q, 2H), 6.96(s, 1H), 7.20-7.27(m, 4H), 7.57-7.62(m, 1H), 7.76-7.82(m, 1H), 7.86(d, 1H), 8.12(d, 1H), 8.54(d, 1H), 9.22(d, 1H)

LC/MS (ES+) m/z = 361.15

EXAMPLE 52

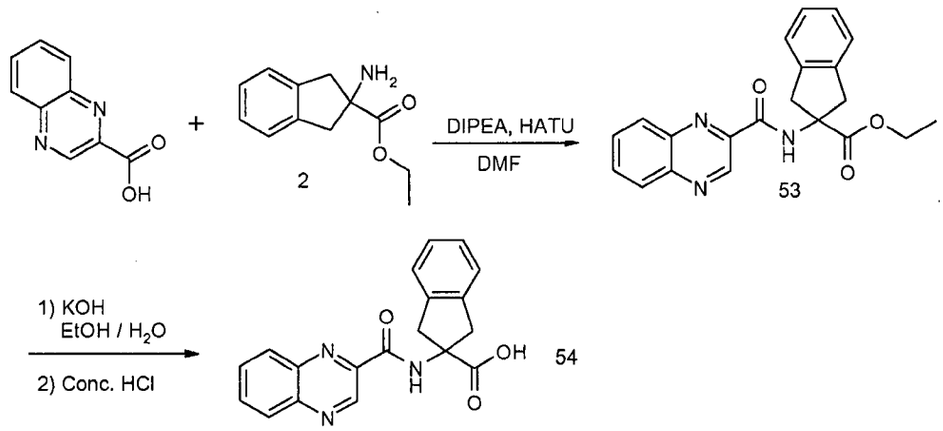
2-[(Isoquinoline-4-carbonyl)-amino]-indan-2-carboxylic acid (52):

The mixture of 2-[(isoquinoline-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (51) (200mg, 0.55mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (52) as white solid (170mg, 93%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 3.38(d, 2H), 3.53(d, 2H), 7.19-7.27(m, 4H), 7.64(t, 1H), 7.83(t, 1H), 7.94(d, 1H), 8.09(d, 1H), 8.40(s, 1H), 8.71(d, 1H), 9.22(d, 1H)

LC/MS (ES+) m/z = 333.06

EXAMPLE 53



2-[(Quinoxaline-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (53):

To a solution of quinoxaline-5-carboxylic acid (400mg, 2.3mmol), 2-amino-indan-2-carboxylic acid ethyl ester (471mg, 2.3mmol), HATU (1.3g, 3.45mmol) in anhydrous DMF (15mL) is added DIPEA (570μL, 3.45mmol). The resulting solution is stirred at RT overnight.

After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-40% EtOAc in heptane) to give a pure product (56) as an orange solid (605mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 3.55(d, 2H), 3.84(d, 2H), 4.28(q, 2H), 7.21-7.29(m, 4H), 7.79-7.89(m, 2H), 8.08-8.18(m, 2H), 8.46(s, 1H), 9.64(s, 1H)
LC/MS (ES+) m/z = 361.12

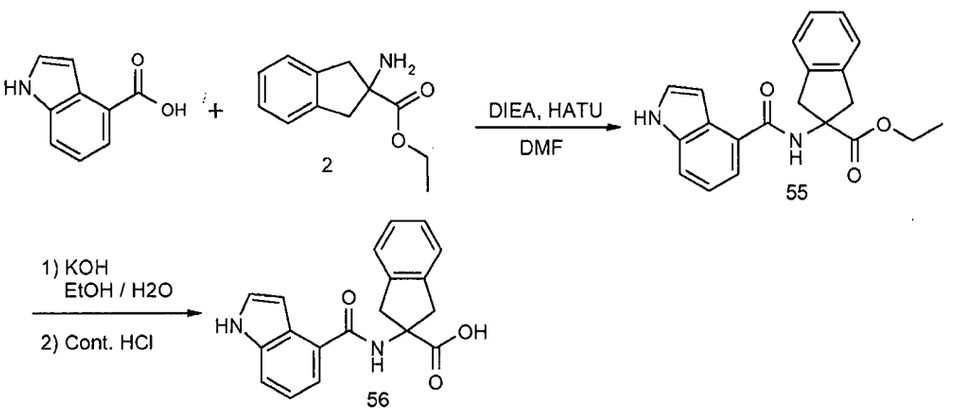
EXAMPLE 54

2-[(Quinoxaline-2-carbonyl)-amino]-indan-2-carboxylic acid (54):

The mixture of 2-[(quinoxaline-5-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (56) (480mg, 1.33mmol) and KOH (1g, 18mmol) is dissolved in EtOH (13mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (40mL) and acidified with conc. HCl dropwise until no more precipitate formed. The precipitate is filtered to give a pure product (54) as a brown solid (444mg, 100%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 3.58(d, 2H), 3.86(d, 2H), 7.21-7.30(m, 4H), 7.81-7.90(m, 2H), 8.10-8.18(m, 2H), 8.58(s, 1H), 9.61(s, 1H)
LC/MS (ES+) m/z = 361.12

EXAMPLE 55



2-[(1H-Indole-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (55):

To a solution of 1H-indole-4-carboxylic acid (250mg, 1.55mmol), 2-amino-indan-2-carboxylic acid ethyl ester (318mg, 1.55mmol), HATU (886mg, 2.33mmol) in anhydrous DMF (8mL) is added DIPEA (385μL, 2.33mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-60% EtOAc in heptane) to give a pure product (55) as white solid (278mg, 52%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.46(d, 2H), 3.78(d, 2H), 4.26(q, 2H), 6.78(m, 1H), 7.14-7.25(m, 6H), 7.46-7.49(m, 2H), 8.65(s, 1H)
LC/MS (ES+) m/z = 349.14

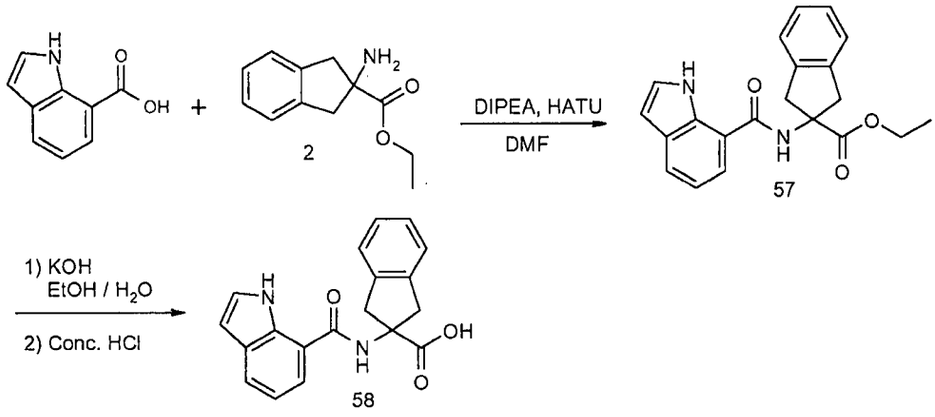
EXAMPLE 56

2-[(1H-Indole-4-carbonyl)-amino]-indan-2-carboxylic acid (56):

The mixture of 2-[(1H-indole-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (55) (200mg, 0.57mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (56) as white solid (162mg, 89%).

^{1}H NMR ($CDCl_3$ = CD_3OD, 300MHz): δ 3.50(d, 2H), 3.80(d, 2H), 6.68(m, 1H), 7.15-7.29(m, 6H), 7.46 (d, 1H), 7.53(dd, 1H), 9.79(s, 1H)
LC/MS (ES+) m/z = 321.15

EXAMPLE 57



2-[(1H-Indole-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (57):

To a solution of 1H-indole-7-carboxylic acid (250mg, 1.55mmol), 2-Amino-indan-2-carboxylic acid ethyl ester (318mg, 1.55mmol), HATU (886mg, 2.33mmol) in anhydrous DMF (8mL) is added DIPEA (385µL, 2.33mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-60% EtOAc in heptane) to give a pure product (57) as white solid (378mg, 70%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22(t, 3H), 3.44(d, 2H), 3.78(d, 2H), 4.25(q, 2H), 6.53(t, 1H), 6.93(s, 1H), 7.03(t, 1H), 7.18-7.27(m, 5H), 7.32(d, 1H), 7.77(d, 1H), 10.25(s, 1H)
LC/MS (ES+) m/z = 349.21

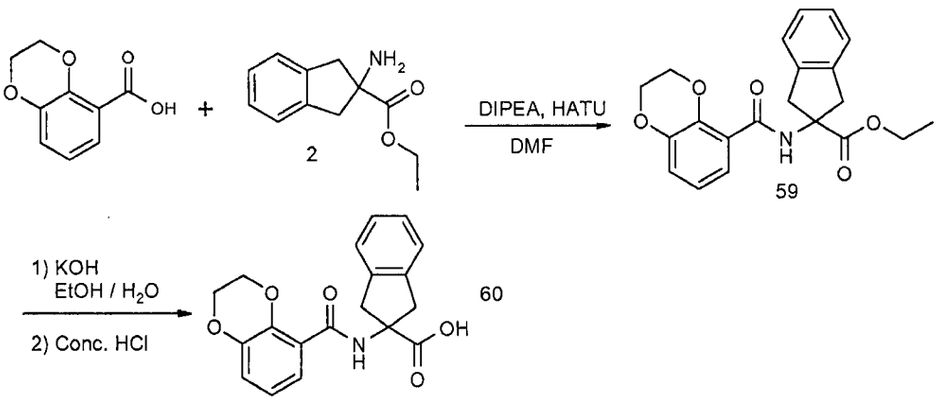
EXAMPLE 58

2-[(1H-Indole-7-carbonyl)-amino]-indan-2-carboxylic acid (58):

The mixture of 2-[(1H-indole-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (57) (220mg, 0.63mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (58) as an off white solid (186mg, 92%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.50(d, 2H), 3.79(d, 2H), 6.54(m, 2H), 7.06(t, 1H), 7.19-7.31(m, 5H), 7.42(d, 1H), 7.78(d, 1H), 10.25(s, 1H)
LC/MS (ES+) m/z = 325.15

EXAMPLE 59



2-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (59):

To a solution of 2,3-dihydro-benzo[1,4]dioxine-5-carboxylic acid (351mg, 1.95mmol), 2-amino-indan-2-carboxylic acid ethyl ester (400mg, 1.95mmol), HATU (1.11g, 2.93mmol) in anhydrous DMF (8mL) is added DIPEA (484μL, 2.93mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (59) as white solid (650mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.39(d, 2H), 3.74(d, 2H), 4.21- 4.33(m, 6H), 6.90(t, 1H), 6.98(dd, 1H), 7.17-7.24(m, 4H), 7.69(dd, 1H), 8.25(s, 1H)
LC/MS (ES+) m/z = 368.15

EXAMPLE 60

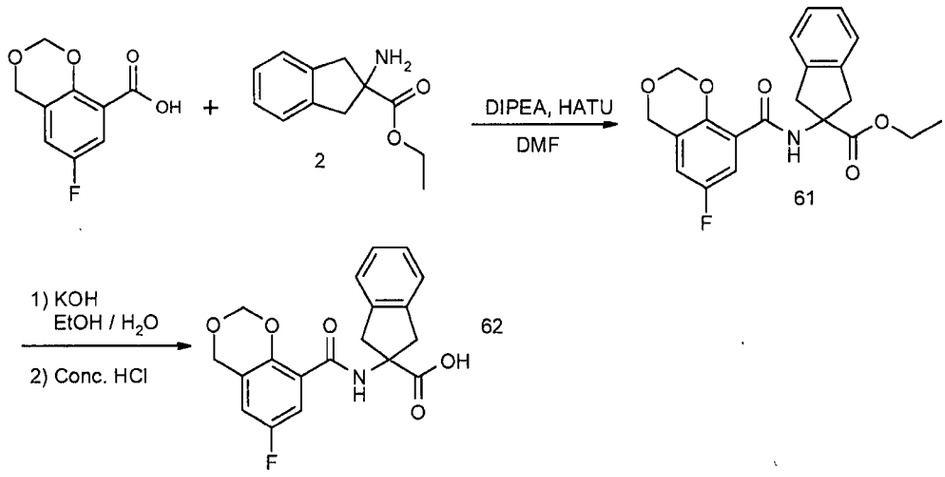
2-[(2,3-Dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-indan-2-carboxylic acid (60):

The mixture of 2-[(2,3-dihydro-benzo[1,4]dioxine-5-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (59) (495mg, 1.35mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After

concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (60) as white solid (440mg, 96%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 3.40(d, 2H), 3.78(d, 2H), 4.26- 4.33(m, 4H), 6.91(t, 1H), 7.49(dd, 1H), 7.18-7.25(m, 4H), 7.65(dd, 1H), 8.39(s, 1H)
LC/MS (ES+) m/z = 340.11

EXAMPLE 61



2-[(6-Fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (61):

To a solution of 6-fluoro-4H-benzo[1,3]dioxine-8-carboxylic acid (386mg, 1.95mmol), 2-amino-indan-2-carboxylic acid ethyl ester (400mg, 1.95mmol), HATU (1.11g, 2.93mmol) in anhydrous DMF (8mL) is added DIPEA (484μL, 2.93mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (61) as white solid (720mg, 6%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 3.38(d, 2H), 3.74(d, 2H), 4.24(q, 2H), 4.90(s, 2H), 5.27(s, 2H), 6.79(dd, 1H), 7.17-7.24(m, 4H), 7.74(dd, 1H), 8.25(s, 1H)
LC/MS (ES+) m/z = 386.11

EXAMPLE 62

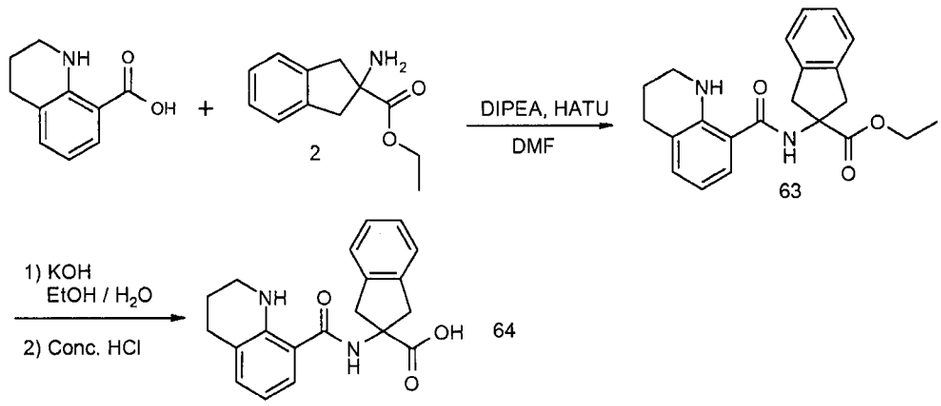
2-[(6-Fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-amino]-indan-2-carboxylic acid (62):

The mixture of 2-[(6-fluoro-4H-benzo[1,3]dioxine-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (61) (560mg, 1.45mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. After the filtration, the solid is purified by HPLC to give a pure product (62) as white solid (520mg, 100%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 3.39(d, 2H), 3.75(d, 2H), 4.92(s, 2H), 5.30(s, 2H), 6.85(dd, 1H), 7.18-7.25(m, 4H), 7.64(dd, 1H), 8.49(s, 1H)

LC/MS (ES-) m/z = 356.10

EXAMPLE 63



2-[(1,2,3,4-Tetrahydro-quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (63):

To a solution of 1,2,3,4-tetrahydro-quinoline-8-carboxylic acid (173mg, 0.97mmol), 2-amino-indan-2-carboxylic acid ethyl ester (200mg, 0.97mmol), HATU (553mg, 1.46mmol) in anhydrous DMF (20mL) is added DIPEA (241μL, 1.46mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (63) as white solid (300mg, 85%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 1.87(m, 2H), 2.74(t, 2H), 3.31-3.36(m, 4H), 3.73(d, 2H), 4.24(q, 2H), 6.38(t, 2H), 6.50(s, 1H), 6.95(d, 1H), 7.09(d, 1H), 7.17-7.24(m, 4H), 7.67(br s, 1H)

LC/MS (ES+) m/z = 365.18

EXAMPLE 64

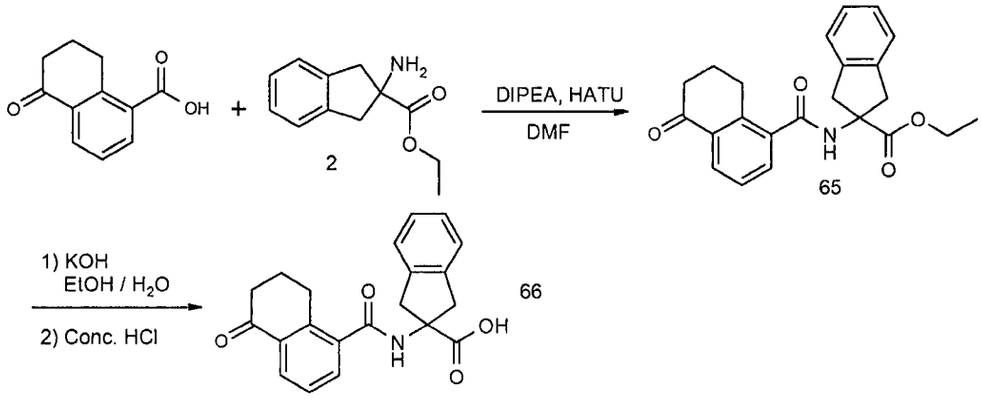
2-[(1,2,3,4-Tetrahydro-quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid (64):

The mixture of 2-[(1,2,3,4-tetrahydro-quinoline-8-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (63) (259mg, 0.71mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (15mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl dropwise until precipitate falls out of the water. After the filtration, the solid is washed by water and collected. The filtrate is acidified with conc. HCl carefully again to see if more precipitate comes out or not. The combined solid is dried *in vacuo* to give a pure product (64) as a yellow solid (205mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.87(m, 2H), 2.74(t, 2H), 3.40-3.45(m, 4H), 3.81(d, 2H), 6.36(t, 1H), 6.48(s, 1H), 6.98(t, 2H), 7.18-7.26(m, 4H)

LC/MS (ES+) m/z = 337.17

EXAMPLE 65



2-[(5-Oxo-5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (65):

To a solution of 5-oxo-5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (430mg, 2.26mmol), 2-amino-indan-2-carboxylic acid ethyl ester (464mg, 2.26mmol), HATU (1g, 2.70mmol) in anhydrous DMF (20mL) is added DIPEA (446μL, 2.70mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (65) as white solid (828mg, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.30(t, 3H), 2.09(m, 2H), 2.63(t, 2H), 3.07(t, 2H), 3.38(d, 2H), 3.77(d, 2H), 4.29(q, 2H), 6.31(t, 2H), 7.20-7.26(m, 4H), 7.30(d, 1H), 7.50(dd, 1H), 8.05(dd, 1H)

LC/MS (ES+) m/z = 378.13

EXAMPLE 66

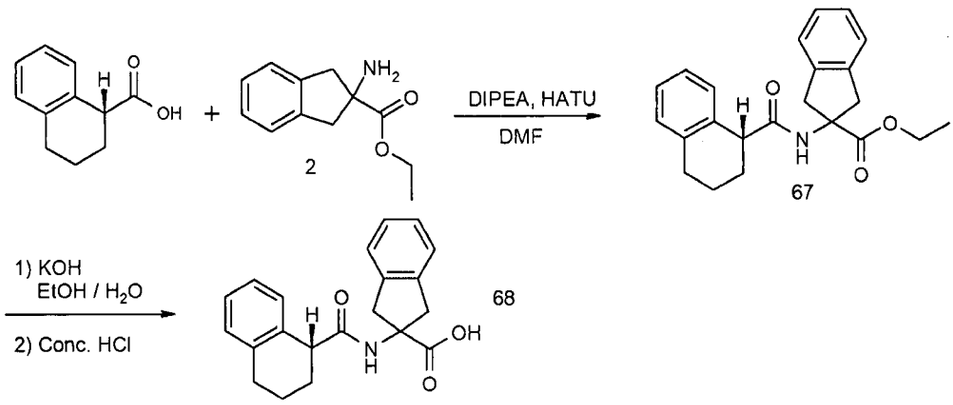
2-[(5-Oxo-5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (66):

The mixture of 2-[(5-oxo-5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (65) (250mg, 0.66mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the solid is purified by HPLC to give a pure product (66) as white solid (150mg, 65%).

^{1}H NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 1.98(m, 2H), 2.60(t, 2H), 2.97(t, 2H), 3.34(d, 2H), 3.58(d, 2H), 7.15-7.25(m, 4H), 7.38(d, 1H), 7.48(t, 1H), 7.94 (dd, 1H), 9.02(s, 1H)

LC/MS (ES+) m/z = 350.16

EXAMPLE 67



2-[((R)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (67):

To a solution of (R)-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid (300mg, 1.7mmol), 2-amino-indan-2-carboxylic acid ethyl ester (349mg, 1.7mmol), HATU (760mg, 2.0mmol) in anhydrous DMF (10mL) is added DIPEA (330μL, 2mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (67) as white solid (615mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 1.57-2.00(m, 3H), 2.17-2.26(m, 1H), 2.76(m, 2H), 3.10(dd, 2H), 3.57-3.68(m, 3H), 4.19(q, 2H), 5.87(s, 1H), 7.03-7.18 (m, 8H)

LC/MS (ES+) m/z = 364.16

EXAMPLE 68

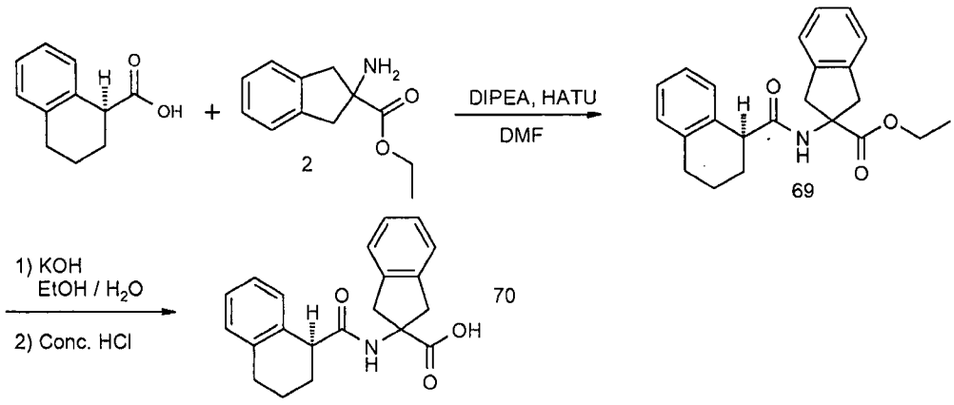
2-[((R)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (68):

The mixture of 2-[((R)-1,2,3,4-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (67) (440mg, 1.21mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (68) as white solid (391mg, 96%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.65-1.73(m, 2H), 1.93-1.96(m, 1H), 2.17-2.27(m, 1H), 2.69(t, 2H), 3.12(t, 2H), 3.63-3.70(m, 3H), 5.84(s, 1H), 6.86(d, 1H), 7.00(t, 1H), 7.07(d, 1H), 7.13-7.20(m, 5H)

LC/MS (ES-) m/z = 334.14

EXAMPLE 69



2-[((S)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (69):

To a solution of (S)-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid (300mg, 1.7mmol), 2-amino-indan-2-carboxylic acid ethyl ester (349mg, 1.7mmol), HATU (760mg, 2mmol) in anhydrous DMF (8mL) is added DIPEA (330μL, 2mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (69) as white solid (615mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24(t, 3H), 1.58-2.00(m, 3H), 2.17-2.26(m, 1H), 2.76(m, 2H), 3.10(dd, 2H), 3.57-3.68(m, 3H), 4.19(q, 2H), 5.87(s, 1H), 7.05-7.26(m, 8H)
LC/MS (ES+) m/z = 364.19

EXAMPLE 70

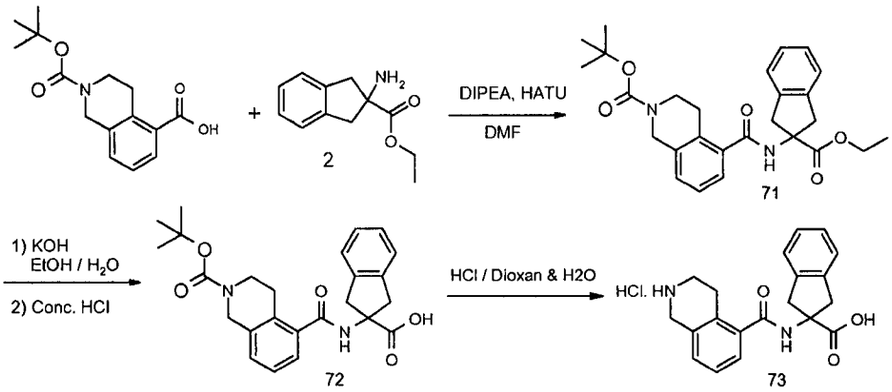
2-[((S)-1,2,3,4-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (70):

The mixture of 2-[((S)-1,2,3,4-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (69) (440mg, 1.21mmol) and KOH (800mg, 14.2mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (70) as white solid (405mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.66-1.73(m, 2H), 1.93-1.96(m, 1H), 2.20-2.22(m, 1H), 2.69(t, 2H), 3.12(t, 2H), 3.17-3.71(m, 3H), 5.82(s, 1H), 6.87(d, 1H), 7.01(t, 1H), 7.07(d, 1H), 7.13-7.21(m, 5H)

LC/MS (ES+) m/z = 336.13

EXAMPLE 71



5-(2-Ethoxycarbonyl-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (71):

To a solution of 3,4-dihydro-1H-isoquinoline-2,5-dicarboxylic acid 2-tert-butyl ester (2g, 7.2mmol), 2-amino-indan-2-carboxylic acid ethyl ester (1.5g, 7.2mmol), HATU (3.27g, 8.6mmol) in anhydrous DMF (20mL) is added DIPEA (1.42mL, 8.6mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 20mL) and brine (2 x 20mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (71) as white solid (1.02g, 30%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.48(s, 9H), 2.95(t, 2H), 3.35(d, 2H), 3.57(t, 2H), 3.75(d, 2H), 4.27(q, 2H), 4.55(s, 2H), 6.26(s, 1H), 7.14-7.26(m, 7H)
LC/MS (ES+) m/z = 465.26

EXAMPLE 72

5-(2-Carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (72):

The mixture of 5-(2-ethoxycarbonyl-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (71) (882mg, 1.78mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (15mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (50mL) and acidified with conc. HCl until no more white precipitate came out of the water. After the filtration, the solid is purified by HPLC to give a pure product (72) as white solid (680mg, 88%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.46(s, 9H), 2.84(t, 2H), 3.36(d, 2H), 3.48(t, 2H), 3.74(d, 2H), 4.49(s, 2H), 6.57(br s, 1H), 7.10-7.19(m, 7H)
LC/MS (ES+) m/z = 381.17, 437.23

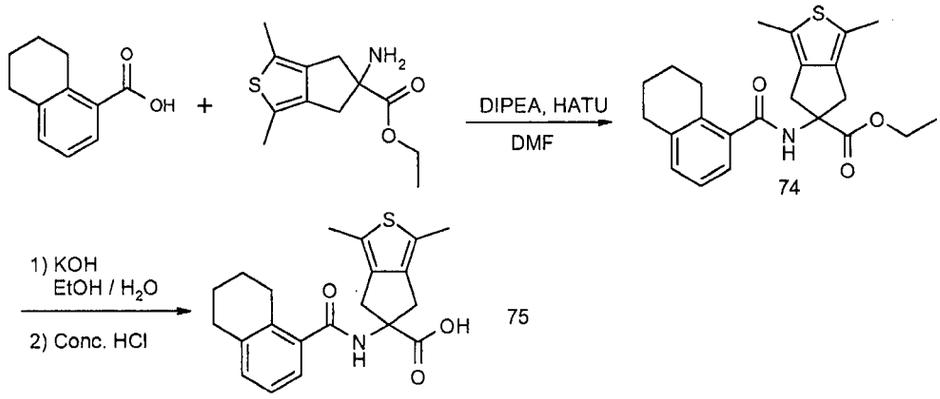
EXAMPLE 73

2-[(1,2,3,4-Tetrahydro-isoquinoline-5-carbonyl)-amino]-indan-2-carboxylic acid hydrochloride salt (73):

5-(2-Carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (72) (650mg, 1.49mmol) is dissolved in 30% solution of TFA in DCM (10mL) and the resulting solution is stirred at RT for 2h. The solution is concentrated to give a TFA salt of 2-[(1,2,3,4-tetrahydro-isoquinoline-5-carbonyl)-amino]-indan-2-carboxylic acid (670mg, 100%). This TFA salt (250mg, 0.56mmol) is dissolved in 6N aqueous solution of HCl (20mL). The resulting suspension is stirred overnight and turned into a clear solution. The solution is concentrated to give a pure product (73) as white solid (130mg, 62%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.05(t, 2H), 3.32-3.37(m, 4H), 3.57(d, 2H), 4.27(s, 2H), 7.15-7.29(m, 7H), 8.98(s, 1H), 9.42(s, 2H), 12.51(br s, 1H)
LC/MS (ES+) m/z = 337.17

EXAMPLE 74



1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (74):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (500mg, 2.84mmol), 5-amino-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (816mg, 3.41mmol), HATU (1.62g, 4.26mmol) in anhydrous DMF (15mL) is added DIPEA (704μL, 4.26mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (74) as white solid (1.10g, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.76(m, 4H), 2.25(s, 6H), 2.80(m, 4H), 2.97(d, 2H), 3.31(d, 2H), 4.26(q, 2H), 6.22(s, 1H), 7.15-7.15(m, 3H)
LC/MS (ES+) m/z = 398.16

EXAMPLE 75

1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid (75):

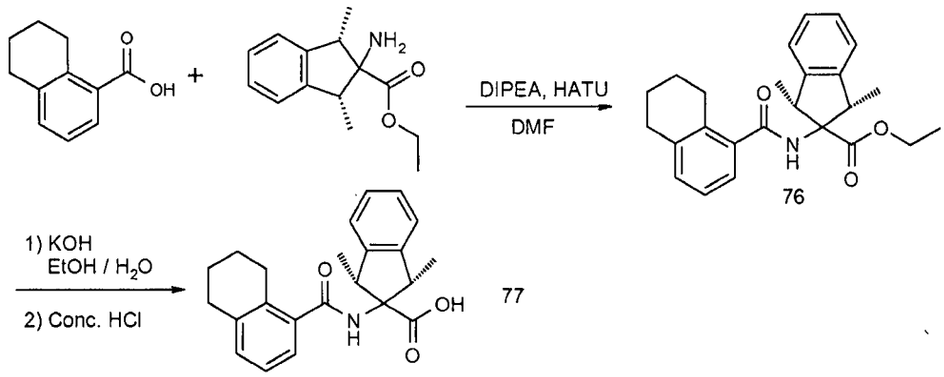
The mixture of 1,3-dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (74) (942mg, 2.37mmol) and KOH (3g, 23mmol) is dissolved in EtOH (20mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water

(20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (75) as a pale brown solid (832mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.75(m, 4H), 2.25(s, 6H), 2.75(m, 4H), 3.03(d, 2H), 3.36(d, 2H), 6.26(s, 1H), 7.08-7.16(m, 3H)

LC/MS (ES+) m/z = 370.12

EXAMPLE 76



(cis)-1,3-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (76):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), (cis)-2-Amino-1,3-dimethyl-indan-2-carboxylic acid ethyl ester (636mg, 2.72mmol), HATU (1.3g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563μL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 50-50% EtOAc in heptane) to give a pure product (76) as white solid (79mg, 9%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.32(t, 3H), 1.50(d, 6H), 1.75(m, 4H), 2.75(br s, 2H), 2.88(br s, 2H), 3.80(q, 2H), 4.31(q, 2H), 5.73(s, 1H), 7.00-7.25(m, 7H)

LC/MS (ES+) m/z = 392.22

EXAMPLE 77

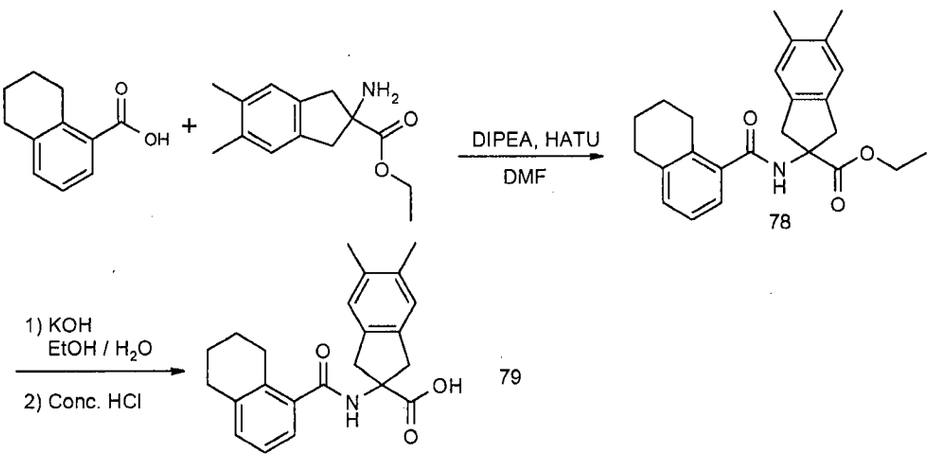
(cis)-1,3-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (77):

The mixture of (cis)-1,3-dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (76) (62mg, 1.2mmol) and KOH (300mg, 5.4mmol) is dissolved in EtOH (3mL) and water (0.3mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~ 4. The precipitate is filtered to give a pure product (77) as white solid (44mg, 75%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.51(d, 6H), 1.74(m, 4H), 2.75(br s, 2H), 2.86(br s, 2H), 3.88(q, 2H), 5.81(s, 1H), 7.01-7.26(m, 7H)

LC/MS (ES+) m/z = 364.23

EXAMPLE 78



5,6-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (78):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), 2-amino-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (636mg, 2.72mmol), HATU (1.30g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563μL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is

purified by flash column chromatography (115g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (78) as white solid (817mg, 92%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.74(m, 4H), 2.23(s, 6H), 2.75(br s, 2H), 2.84(br s, 2H), 3.25(d, 2H), 3.69(d, 2H), 4.26(q, 2H), 6.20(s, 1H), 6.99-7.11(m, 5H)
LC/MS (ES+) m/z = 392.20

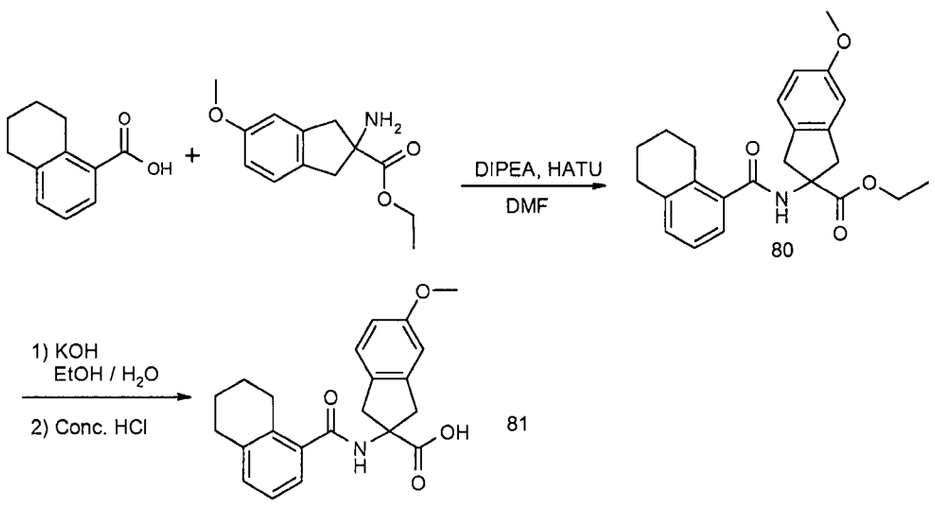
EXAMPLE 79

5,6-Dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (79):

The mixture of 5,6-dimethyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (78) (438mg, 1.11mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (79) as a pale brown solid (390mg, 97%).

^{1}H NMR ($CDCl_3$ + drops CD_3OD, 300MHz): δ 1.73(m, 4H), 2.23(s, 6H), 2.74-2.80(m, 4H), 3.29(d, 2H), 3.69(d, 2H), 6.60(s, 1H), 6.99-7.08(m, 5H)
LC/MS (ES+) m/z = 364.23

EXAMPLE 80



5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (80):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), 2-amino-5-methoxy-indan-2-carboxylic acid ethyl ester (639mg, 2.72mmol), HATU (1.3g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563μL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (52) as white solid (622mg, 70%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.28(t, 3H), 1.74(m, 4H), 2.75(br s, 2H), 2.84(br s, 2H), 3.27(dd, 2H), 3.69(dd, 2H), 3.78(s, 3H), 4.25(q, 2H), 6.26(s, 1H), 6.72-6.76(m, 2H), 7.01-7.11(m, 4H),

LC/MS (ES+) m/z = 394.21

EXAMPLE 81

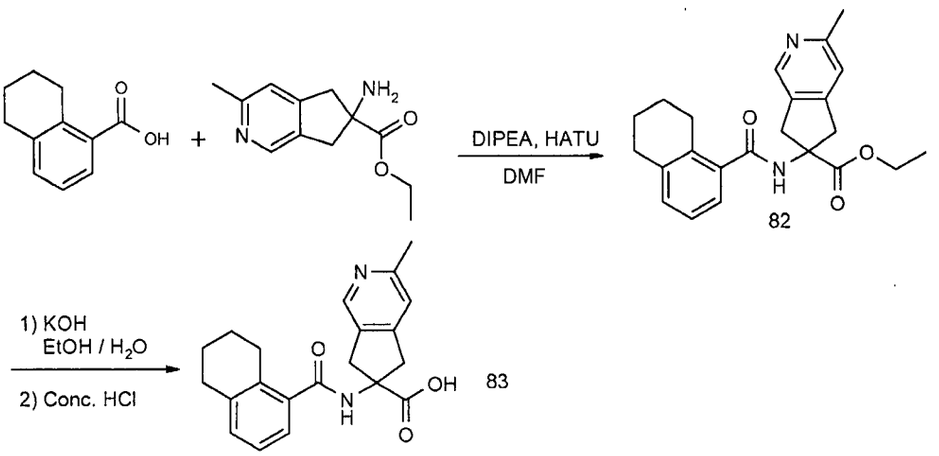
5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (81):

The mixture of 5-methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (80) (458mg, 1.2mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (81) as a pale brown solid (448mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.72(m, 4H), 2.75-2.78(m, 4H), 3.32(dd, 2H), 3.78(dd, 2H), 3.78(s, 3H), 6.45(s, 1H), 6.73-6.77(m, 2H), 7.03-7.11(m, 4H),

LC/MS (ES+) m/z = 366.20

EXAMPLE 82



3-Methyl-6-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-6,7-dihydro-5H-[2]pyrindine-6-carboxylic acid ethyl ester (82):

To a solution of 1,2,3,4-tetrahydro-quinoline-8-carboxylic acid (240mg, 1.36mmol), 6-amino-3-methyl-6,7-dihydro-5H-[2]pyrindine-6-carboxylic acid ethyl ester (not pure, 300mg, 1.36mmol), HATU (608mg, 1.60mmol) in anhydrous DMF (10mL) is added DIPEA (264μL, 1.60mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (40mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a product (82) as a colorless oil (100mg, 19%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.75(br s, 4H), 2.76(br s, 2H), 3.68(s, 2H), 3.86(q, 2H), 4.26(q, 2H), 7.02-7.12(m, 3H), 7.32(s, 1H), 7.52(s, 1H), 8.51(s, 1H)
LC/MS (ES+) m/z = 379.22

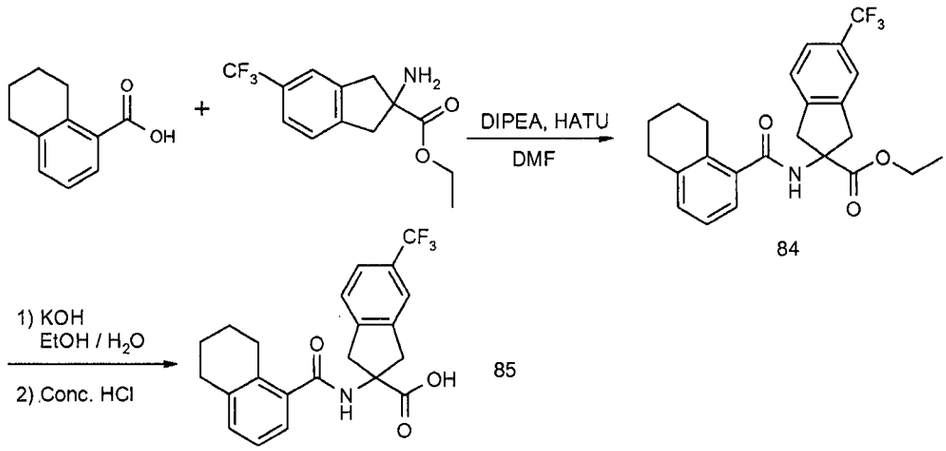
EXAMPLE 83

3-Methyl-6-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-6,7-dihydro-5H-[2]pyrindine-6-carboxylic acid (83):

The mixture of 3-methyl-6-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-6,7-dihydro-5H-[2]pyrindine-6-carboxylic acid ethyl ester (82) and KOH (1g, 17.9mmol) in EtOH (5mL) and water (0.3mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl dropwise until no more precipitate came out of the water. After the filtration, the solid is purified by HPLC to give a pure product (83) as colorless oil (20mg, 22%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.77(br s, 4H), 2.79(br s, 2H), 3.69(m, 2H), 3.88(q, 2H), 7.06-7.15(m, 3H), 7.53(s, 1H), 8.56(s, 1H)
LC/MS (ES+) m/z = 351.11

EXAMPLE 84



2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (84):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (306mg, 1.74mmol), 2-amino-5-trifluoro-indan-2-carboxylic acid ethyl ester (583mg, 2.13mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (15mL) is added DIPEA (431μL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (80mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (84) as white solid (589mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.75(m, 4H), 2.76(br s, 2H), 2.83(br s, 2H), 3.44(dd, 2H), 3.74(dd, 2H), 4.26(q, 2H), 6.35(s, 1H), 7.02-7.12(m, 3H), 7.32(d, 1H), 7.46(br s, 2H) LC/MS (ES+) m/z = 432.17

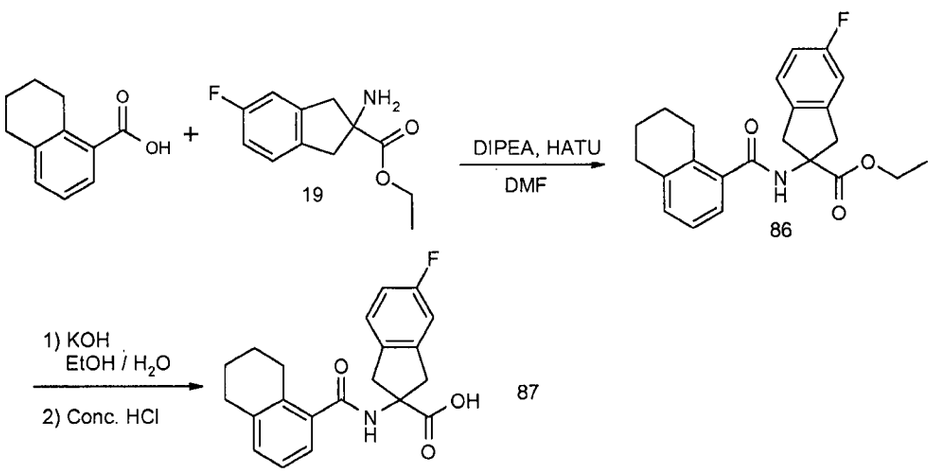
EXAMPLE 85

2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid (85):

The mixture of 2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (84) (437mg, 1.0mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (50mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (85) as white solid (408mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.74(m, 4H), 2.78(m, 4H), 3.49(dd, 2H), 3.76(dd, 2H), 6.69(s, 1H), 7.03-7.13(m, 3H), 7.32(d, 1H), 7.47(dd, 2H)
LC/MS (ES+) m/z = 404.15

EXAMPLE 86



5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (86):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (400mg, 2.27mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (610mg, 2.72mmol), HATU (1.30g, 3.41mmol) in anhydrous DMF (15mL) is added DIPEA (563μL, 3.41mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (86) as white solid (345mg, 40%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.28(t, 3H), 1.75(m, 4H), 2.76(br s, 2H), 2.83(br s, 2H), 3.33(dd, 2H), 3.69(dd, 2H), 4.25(q, 2H), 6.29(s, 1H), 6.85-6.93(m, 2H), 7.02-7.16(m, 4H)
LC/MS (ES+) m/z = 382.16

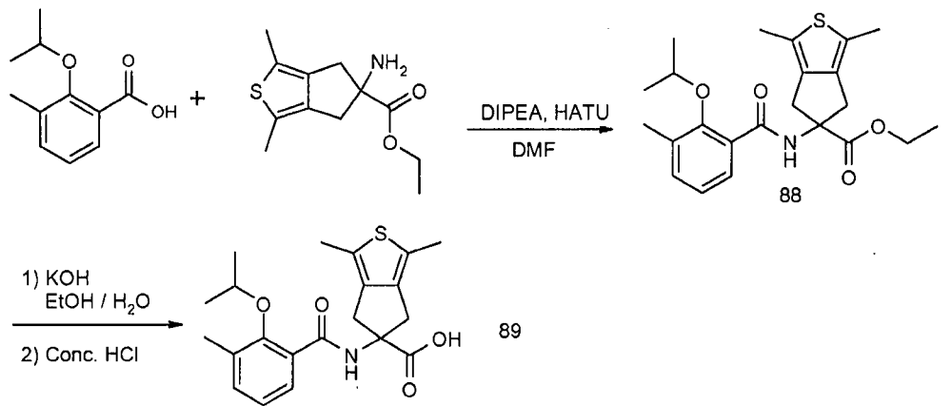
EXAMPLE 87

5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (87):

The mixture of 5-fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (86) (190mg, 0.50mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (87) as a pale brown solid (178mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.75(m, 4H), 2.76-2.81(m, 4H), 3.40(dd, 2H), 3.72(dd, 2H), 6.65(s, 1H), 6.86-6.94(m, 2H), 7.03-7.18(m, 4H)
LC/MS (ES+) m/z = 382.16

EXAMPLE 88



5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (88):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (300mg, 1.54mmol), 5-amino-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (443mg, 1.85mmol), HATU (878g, 2.31mmol) in anhydrous DMF (10mL) is added DIPEA (382μL,

2.31mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (88) as a pale yellow solid (599mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.09(d, 6H), 1.23(t, 3H), 2.25(s, 6H), 2.28(s, 3H), 2.98(d, 2H), 3.33(d, 2H), 4.20-4.24(m, 3H), 7.08(t, 1H), 7.28(d, 1H), 7.87(d, 1H), 8.37(s, 1H)
LC/MS (ES+) m/z = 416.17

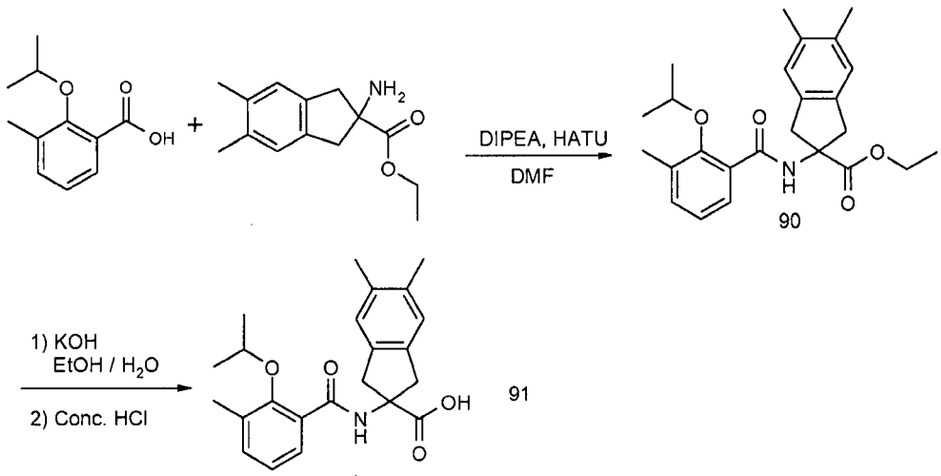
EXAMPLE 89

5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid (89):

The mixture of 5-(2-isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid ethyl ester (88) (448mg, 1.08mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (89) as a brown solid (360mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.06(d, 6H), 2.26(s, 6H), 2.28(s, 3H), 3.09(d, 2H), 3.43(d, 2H), 4.17(m, 1H), 7.12(t, 1H), 7.32(d, 1H), 7.91(d, 1H), 8.61(s, 1H)
LC/MS (ES+) m/z = 388.14

EXAMPLE 90



2-(2-Isopropoxy-3-methyl-benzoylamino)-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (90):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (300mg, 1.54mmol), 2-amino-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (432mg, 1.85mmol), HATU 878g, 2.31mmol) in anhydrous DMF (10mL) is added DIPEA (382μL, 2.31mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5-40% EtOAc in heptane) to give a pure product (90) as white solid (591mg, 94%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.08(d, 6H), 1.24(t, 3H), 2.22(s, 6H), 2.24(s, 3H), 3.25(d, 2H), 3.70(d, 2H), 4.20-4.28(m, 3H), 7.00-7.08(m, 3H), 7.24(d, 1H), 7.83(d, 1H), 8.27(s, 1H)
LC/MS (ES+) m/z = 410.21

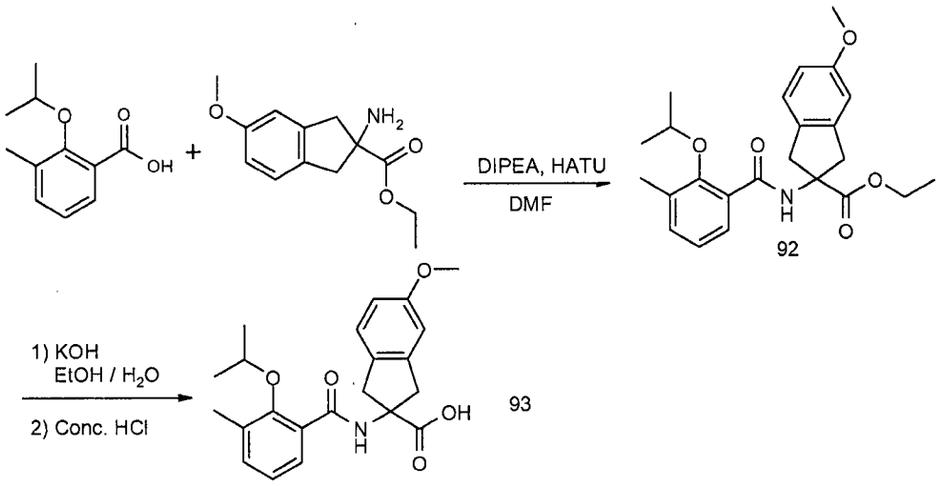
EXAMPLE 91

2-(2-Isopropoxy-3-methyl-benzoylamino)-5,6-dimethyl-indan-2-carboxylic acid (91):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-5,6-dimethyl-indan-2-carboxylic acid ethyl ester (90) (440mg, 1.07mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give the pure product (91) as a pale brown solid (374mg, 92%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.02(d, 6H), 2.22(s, 6H), 2.25(s, 3H), 3.34(d, 2H), 3.80(d, 2H), 4.14(m, 1H), 7.01(s, 2H), 7.09(t, 1H), 7.29(d, 1H), 7.87(dd, 1H), 8.52(s, 1H)
LC/MS (ES+) m/z = 382.19

EXAMPLE 92



2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid ethyl ester (92):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (300mg, 1.54mmol), 2-amino-5-methoxy-indan-2-carboxylic acid ethyl ester (435mg, 1.85mmol), HATU (878g, 2.31mmol) in anhydrous DMF (10mL) is added DIPEA (382μL, 2.31mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (92) as a pale yellow oil (569mg, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.07(d, 6H), 1.24(t, 3H), 2.25(s, 3H), 3.28(d, 2H), 3.72(dd, 2H), 3.78(s, 3H), 4.21-4.25(m, 3H), 6.73-6.78(m, 2H), 7.04-7.13(m, 2H), 7.26(d, 1H), 7.85(d, 1H), 8.32(s, 1H)
LC/MS (ES+) m/z = 412.18

EXAMPLE 93

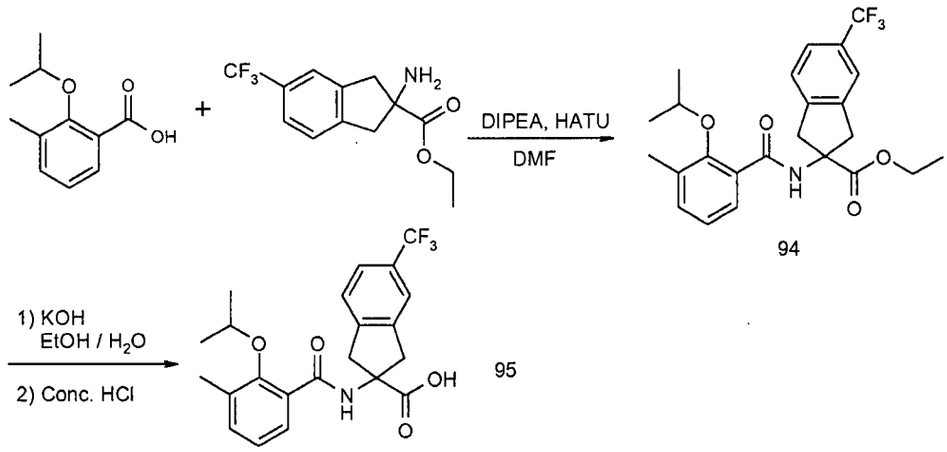
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid (93):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid ethyl ester (92) (410mg, 1mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (93) as white solid (400mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.02(m, 6H), 2.25(s, 3H), 3.34(d, 2H), 3.78(s, 3H), 3.80(dd, 2H), 4.16(m, 1H), 6.73-6.78(m, 2H), 7.05-7.14(m, 2H), 7.27-7.30(m, 1H), 7.88(dd, 1H), 8.51(s, 1H)

LC/MS (ES+) m/z = 384.17

EXAMPLE 94



2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (94):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (377mg, 1.94mmol), 2-amino-5-trifluoro-indan-2-carboxylic acid ethyl ester (650mg, 2.38mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480μL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column

chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (94) as white solid (842mg, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.06(d, 6H), 1.24(t, 3H), 2.26(s, 3H), 3.43(d, 2H), 3.78(dd, 2H), 4.16-4.29(m, 1H), 4.25(q, 2H), 7.08(t, 1H), 7.26-7.35(m, 2H), 7.47(d, 2H), 7.85(dd, 1H), 8.39(s, 1H)
LC/MS (ES+) m/z = 450.18

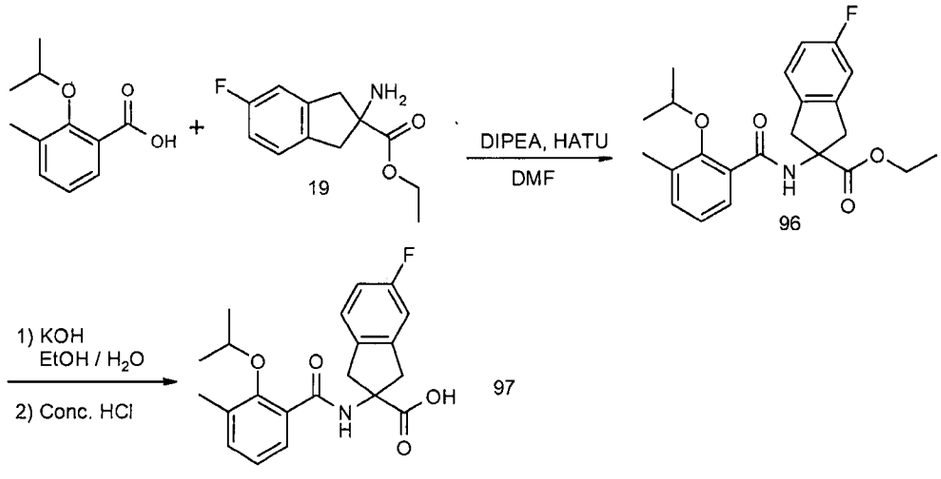
EXAMPLE 95

2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid (95):

The mixture of 2-(2-isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid ethyl ester (94) (690mg, 1.5mmol) and KOH (1.5g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved. The resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~4. The precipitate is filtered to give a pure product (95) as a pale brown solid (495mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.99(d, 6H), 2.25(s, 3H), 3.48(d, 2H), 3.89(d, 2H), 4.15 (m, 1H), 7.10(t, 1H), 7.29-7.37(m, 2H), 7.49(d, 2H), 7.88(dd, 1H), 8.57(s, 1H)
LC/MS (ES+) m/z = 422.15

EXAMPLE 96



5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (96):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (400mg, 2.06mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (554mg, 2.47mmol), HATU 1.17g, 3.09mmol) in anhydrous DMF (10mL) is added DIPEA (511μL, 3.09mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (96) as white solid (709mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.07(m, 6H), 1.24(t, 3H), 2.26(s, 3H), 3.32(t, 2H), 3.72(dd, 2H), 4.23(m, 3H), 6.85-6.94(m, 2H), 7.05-7.28((m, 3H), 7.85(dd, 1H), 8.36(s, 1H)
LC/MS (ES+) m/z = 400.18

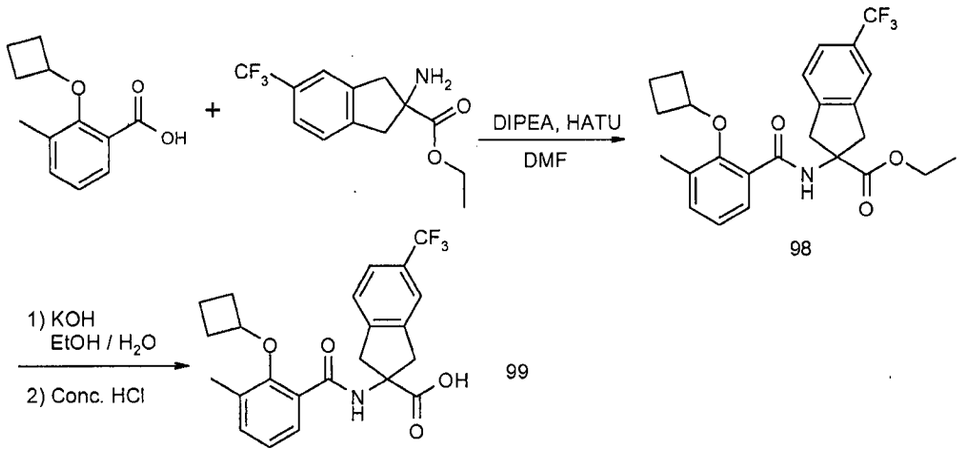
EXAMPLE 97

5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (97):

The mixture of 5-fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (96) (544mg, 1.36mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (97) as white solid (460mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.02(m, 6H), 2.26(s, 3H), 3.38(dd, 2H), 3.82(dd, 2H), 4.16(m, 1H), 6.87-6.95(m, 2H), 7.07-7.31((m, 3H), 7.88(dd, 1H), 8.56(s, 1H)
LC/MS (ES+) m/z = 372.16

EXAMPLE 98



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid ethyl ester (98):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (400mg, 1.94mmol), 2-amino-5-trifluoro-indan-2-carboxylic acid ethyl ester (650mg, 2.38mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480μL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-60% EtOAc in heptane) to give a pure product (98) as white solid (800mg, 89%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 1.26-1.38(m, 1H), 1.45-1.55(m, 1H), 1.89-2.17(S, 3H), 2.27(s, 3H), 3.44(dd, 2H), 3.80(dd, 2H), 4.22-4.35(m, 3H), 7.08(t, 1H), 7.27(d, 1H), 7.34(d, 1H), 7.47(d, 2H), 7.85(d, 1H), 8.41(s, 1H)
LC/MS (ES+) m/z = 462.18

EXAMPLE 99

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid (99):

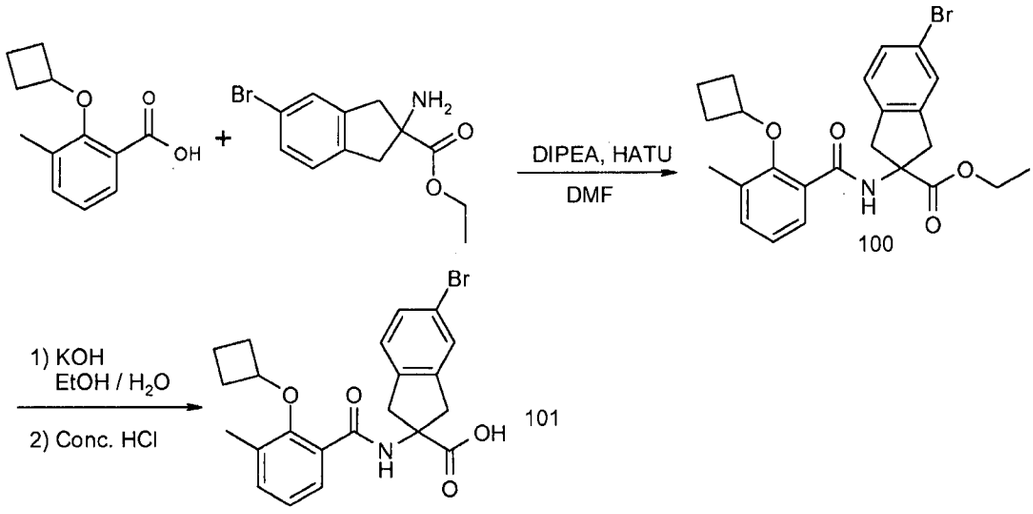
The mixture of 2-(2-cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid ethyl ester (98) (648mg, 1.4mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more

precipitate formed. The precipitate is filtered to give a pure product (99) as a pale brown solid (595mg, 98%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.32(m, 1H), 1.41-1.51(m, 1H), 1.85-2.08(S, 3H), 2.25(s, 3H), 3.48(dd, 2H), 3.89(dd, 2H), 4.26(m, 1H), 7.09(t, 1H), 7.26-7.36(m, 2H), 7.49(d, 2H), 7.87(dd, 1H), 8.55(s, 1H)

LC/MS (ES+) m/z = 434.16

EXAMPLE 100



5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (100):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (250mg, 1.21mmol), 2-amino-5-bromo-indan-2-carboxylic acid ethyl ester (344mg, 1.21mmol), HATU (551mg, 1.45mmol) in anhydrous DMF (10mL) is added DIPEA (240μL, 1.45mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (100) as a colorless oil (520mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.22-1.40(m, 4H), 1.48-1.63(m, 1H), 1.90-2.12(m, 4H), 2.27(s, 3H), 3.44(dd, 2H), 3.72(dd, 2H), 4.21-4.35(m, 3H), 7.05-7.12(m, 2H), 7.26-7.27(m, 3H), 7.85(dd, 1H), 8.38(s, 1H)

LC/MS (ES+) m/z = 472.14, 474.13

EXAMPLE 101

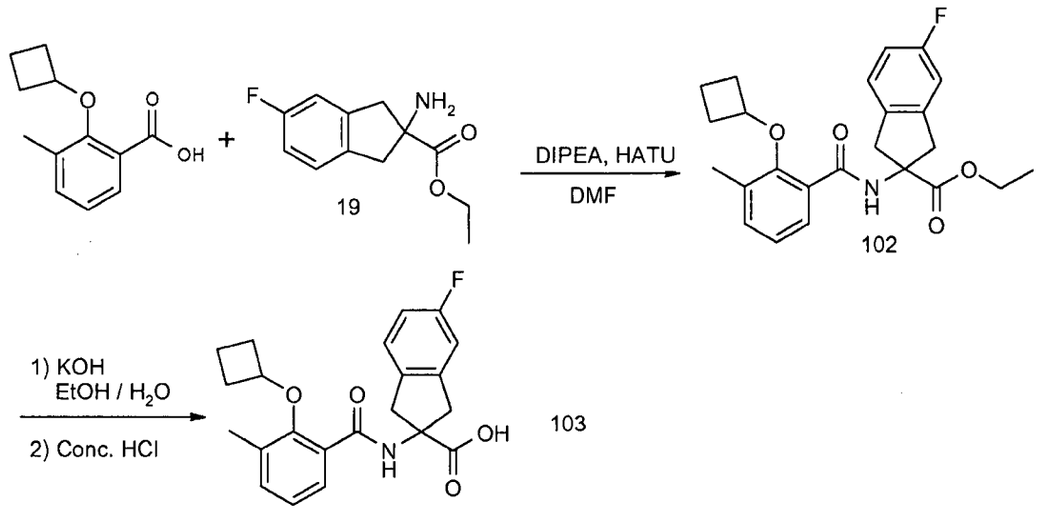
5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (101):

The mixture 5-bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (100) (442mg, 0.94mmol) and KOH (700mg, 12mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (101) as white solid (390mg, 93%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(m, 1H), 1.49(m, 1H), 1.83-2.00(m, 4H), 2.22(s, 3H), 3.31-3.61(m, 4H), 4.33(m, 1H), 7.04 (t, 1H), 7.21(d, 1H), 7.28-7.37(m, 3H), 7.46(s, 1H), 8.67(s, 1H), 12.65(s, 1H)

LC/MS (ES+) m/z = 444.07, 446.06

EXAMPLE 102



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (102):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (400mg, 1.94mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (523mg, 2.33mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (18mL) is added DIPEA (480μL, 2.91mmol). The resulting solution is stirred

at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 5%-40% EtOAc in heptane) to give a pure product (102) as white solid (681mg, 85%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21- 4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.19(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)

LC/MS (ES+) m/z = 412.19

EXAMPLE 103

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid (103):

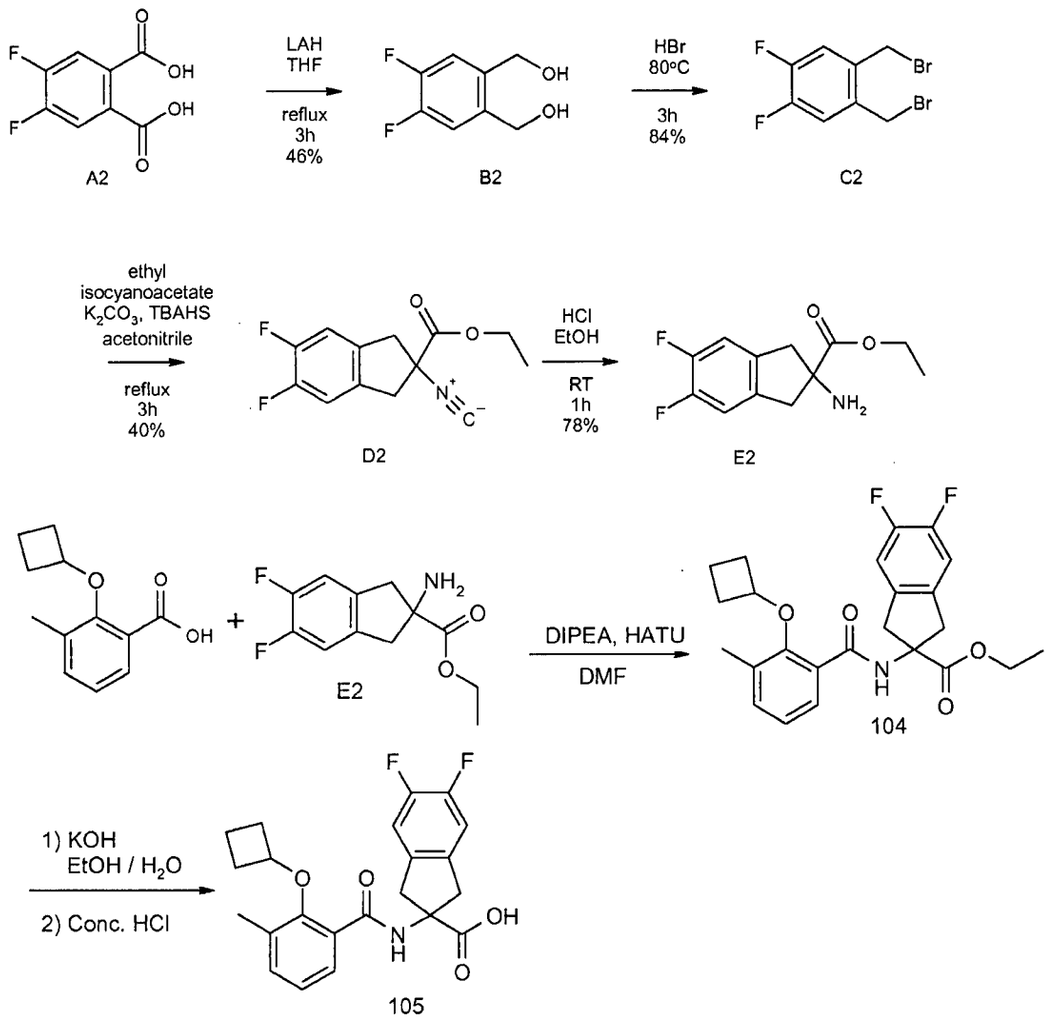
The mixture of 2-(2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (102) (510mg, 1.24mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (103) as white solid (469mg, 99%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)

LC/MS (ES+) m/z = 384.15

Example 104

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid ethyl ester (104):



Preparation of B2: To a suspension of LAH (375mg, 9.9 mmol) in THF (5mL) is added a solution of 4,5-difluorophthalic acid **A2** (1g, 4.95 mmol) in THF (15mL), dropwise at 0°C. The resulting mixture is refluxed for 3 hr following which it is cooled to 0°C and quenched by slow addition of EtOAc. The reaction mass is filtered through a pad of celite and the filter bed is washed with methanol. The combined filtrate is concentrated to yield crude product that is purified over silica eluting with 5% MeOH in DCM to yield B2 (400mg, 46%).

^{1}H-NMR (400 MHz, $CDCl_3$): 4.69 (s, 4H), 7.19 (t, J = 9.2 and 2 Hz, 2H); FIA-MS: m/z 173 (M + H).

Preparation of C2: A stirred suspension of B2 (1g, 5.74 mmol) in aq. HBr (47%, 10mL) is stirred at 80°C for 3h. The progress of the reaction is monitored by tlc. After complete

consumption of starting material, the reaction mixture is cooled to RT and extracted with DCM. The combined organics is washed with brine, dried and concentrated to give C2 (1.4g, 84%). The dibromide is rather unstable and is immediately utilized for the next step.

^{1}H-NMR (400 MHz, $CDCl_3$): 4.59 (s, 4H), 7.19 (t, J = 9 and 2 Hz, 2H); FIA-MS: m/z 201 (M + H).

Preparation of D2: A mixture of dibromide C2 (5.5g, 18.33 mmol), ethylcyanoacetate (2.07g, 18.33 mmol), K_2CO_3 (14g, 106.3 mmol) and tetrabutylammonium hydrogensulfate (1.8g, 5.33 mmol) in CH_3CN (150mL) is refluxed for 3h. The reaction mixture is cooled to RT, filtered and concentrated. The residue is dissolved in ether, washed with water, brine, dried, concentrated to get a sticky mass that is purified over silica eluting with 10% EtOAc in hexanes to yield D2 (1.8g, 40%).

^{1}H-NMR (400 MHz, $CDCl_3$): 1.32 (t, J = 7.2 and 3 Hz, 3H), 3.40 (d, J = 16.3 Hz, 2H), 3.60 (d, J = 16.3 Hz, 2H), 4.30 (q, J = 7.2 and 2 Hz, 2H), 7.04 (t, J = 8.6 and 2 Hz, 2H).

Preparation of E2: To a stirred solution of D2 (2g, 7.96 mmol) in EtOH (50mL) is added conc HCl (1mL) and reaction mixture is stirred at RT for 1h. The reaction mixture is concentrated, diluted with water and extracted with ether. The organic layer is discarded and the aqueous layer is brought to pH 9-10 by using aq. ammonia solution maintaining internal temperature below 10°C. The resulting solution is extracted with EtOAc (3 x 50mL). The combined organics is washed with water, brine, dried, and concentrated to get a sticky mass that is purified over silica eluting with 10% EtOAc in hexanes to yield E2 (1.5g, 78%) as off-white solid of mp 69-71°C.

^{1}H-NMR (400 MHz, $CDCl_3$): 1.26 (t, J = 7.1and 3 Hz, 3H), 2.80 (d, J = 15.9 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 6.99 (t, J = 8.8 and 2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): 175.7, 150.7, 150.5, 148.2, 148.1, 136.3, 136.26, 136.22, 113.24, 113.17, 113.11, 113.05, 65.2, 61.2, 45.2, 13.8; FIA-MS: m/z 242 (M + H); HPLC purity: 94.28% (qualitative).

Preparation of 104:

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (250mg, 1.21mmol), 2-amino-5,6-difluoro-indan-2-carboxylic acid ethyl ester E2 (292mg, 1.21mmol), HATU (551mg, 1.45mmol) in anhydrous DMF (10mL) is added DIPEA (240μL, 1.45mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (50mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10%-70% EtOAc in heptane) to give a pure product (104A) as white solid (420mg, 81%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.25(t, 3H), 1.30-1.41(m, 1H), 1.52-1.62(m, 1H), 1.96-2.16(m, 4H), 2.28(s, 3H), 3.34(d, 2H), 3.70(d, 2H), 4.21- 4.39(m, 3H), 6.99-7.11(m, 3H), 7.28(d, 1H), 7.85(dd, 1H), 8.43(s, 1H)
LC/MS (ES+) m/z = 430.22

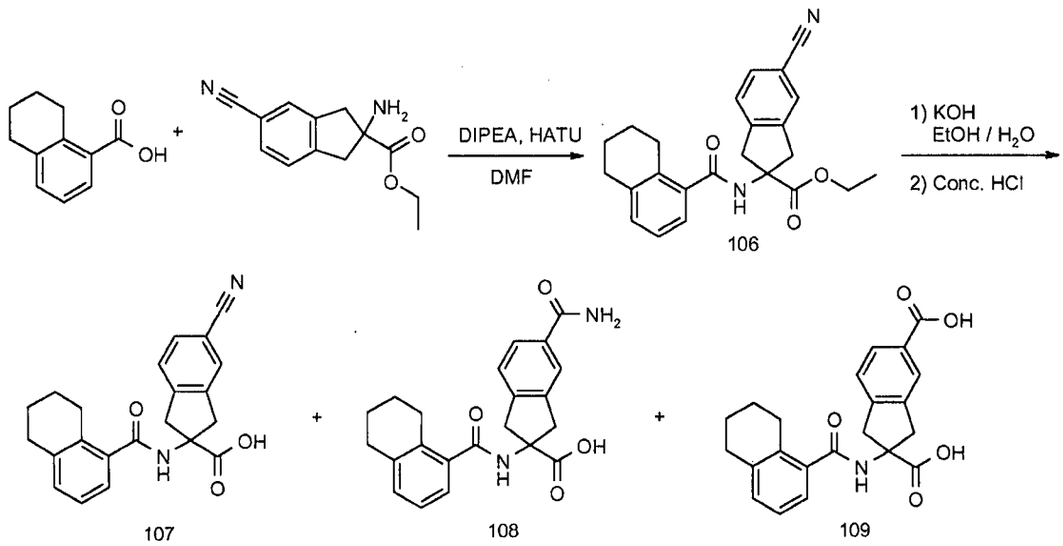
EXAMPLE 105

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid (105):

The mixture 2-(2-cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid ethyl ester (104) (367mg, 0.85mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the solid is purified by HPLC to give a pure product (105) as white solid (300mg, 88%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.28(m, 1H), 1.48(m, 1H), 1.85-2.00(m, 4H), 2.21(s, 3H), 3.34(d, 2H), 3.51(d, 2H), 4.33(m, 1H), 7.02(t, 1H), 7.28-7.34(m, 4H), 8.69(s, 1H)
LC/MS (ES+) m/z = 430.22

EXAMPLE 106



5-Cyano-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (106):

To a solution of 5,6,7,8-tetrahydro-naphthalene-1-carboxylic acid (306mg, 1.74mmol), 2-amino-5-cyano-indan-2-carboxylic acid ethyl ester (601mg, 2.61mmol), HATU (992mg, 2.61mmol) in anhydrous DMF (15mL) is added DIPEA (431μL, 2.61mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (70mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-80% EtOAc in heptane) to give a pure product (106) as white solid (473mg, 70%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.74(m, 4H), 2.76(br s, 2H), 2.82(br s, 2H), 3.47(dd, 2H), 3.72(t, 2H), 4.25(q, 2H), 6.47(s, 1H), 7.03-7.12(m, 3H), 7.31(d, 1H), 7.49(d, 2H)

LC/MS (ES+) m/z = 389.18

EXAMPLES 107, 108, 109

5-Cyano-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (107):

5-Carbamoyl-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (108):

and 2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2,5-dicarboxylic acid (109):

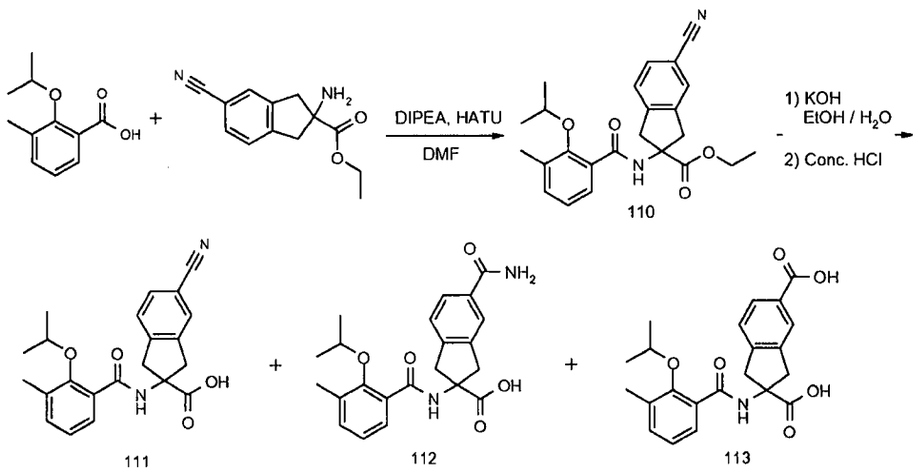
The mixture of 5-cyano-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (106) (320mg, 0.82mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved. The resulting reaction solution is heated up to 50°C and stirred at this temperature overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~2. After filtration, the solid is purified by HPLC to give 3 pure products: (107) as white solid (44mg, 15%), (108) as white solid (154mg, 50%) and (109) as white solid (28mg, 9%).

(107): ^{1}H NMR (CD_3OD, 300MHz): δ 1.75(m, 4H), 2.77(br s, 4H), 3.49(dd, 2H), 3.75(t, 2H), 7.04-7.12(m, 3H), 7.41(d, 1H), 7.54-7.59(m, 2H), 8.87(s, 1/3H)
LC/MS (ES+) m/z = 361.15

(108): ^{1}H NMR (CD_3OD, 300MHz): δ 1.74(m, 4H), 2.76(m, 4H), 3.44(d, 2H), 3.73(dd, 2H), 7.04-7.11 (m, 3H), 7.32(d, 1H), 7.72(d, 2H), 8.87(s, 1/2H)
LC/MS (ES+) m/z = 379.17

(109): ^{1}H NMR (CD_3OD, 300MHz): δ 1.74(m, 4H), 2.77(m, 4H), 3.45(dd, 2H), 3.74(t, 2H), 7.04-7.09(m, 3H), 7.33(d, 1H), 7.88(d, 2H), 8.88(s, 1/2H)
LC/MS (ES+) m/z = 380.16

EXAMPLE 110



5-Cyano-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (110):

To a solution of 2-isopropoxy-3-methyl-benzoic acid (377mg, 1.94mmol), 2-amino-5-cyano-indan-2-carboxylic acid ethyl ester (670mg, 2.91mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480μL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-70% EtOAc in heptane) to give a pure product (110) as a white semisolid (680mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.12(m, 6H), 1.23(t, 3H), 2.27(s, 3H), 3.47(dd, 2H), 3.77(t, 2H), 4.21- 4.26(m, 3H), 7.08(t, 1H), 7.28-7.35(m, 2H), 7.51(d, 2H), 7.84(d, 1H), 8.47(s, 1H)
LC/MS (ES+) m/z = 407.19

EXAMPLE 111, 112, 113

5-Cyano-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (111):

5-Carbamoyl-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (112):

2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2,5-dicarboxylic acid (113):

The mixture of 5-cyano-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (110) (527mg, 1.3mmol) and KOH (1.3g, 23mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely

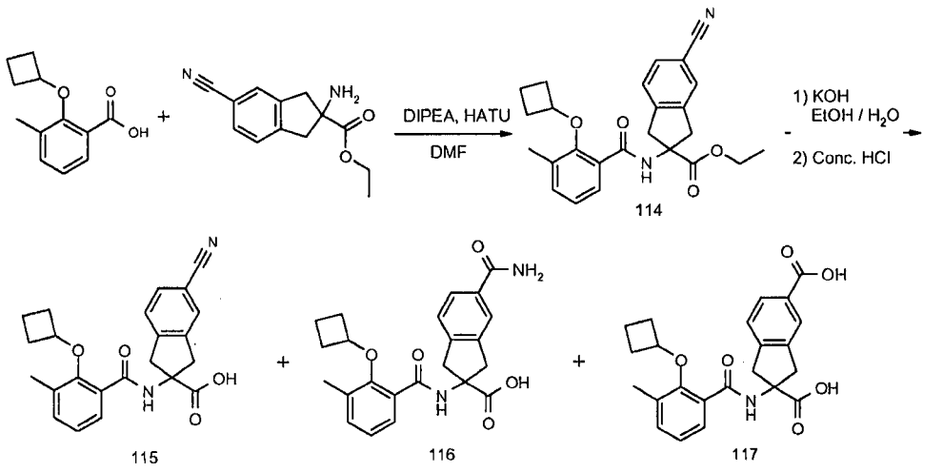
dissolved. The resulting reaction solution is heated up to 50°C and stirred at this temperature overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~2. After filtration, the solid is purified by HPLC to give 3 pure products: (111) as white solid (37mg, 8%), (112) as white solid (295mg, 57%) and (113) as white solid (62mg, 12%).

(111): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.06(m, 6H), 2.27(s, 3H), 3.49(dd, 2H), 3.90(dd, 2H), 4.19(m, 1H), 7.11(t, 1H), 7.34(t, 2H), 7.53(d, 2H), 7.88(dd, 1H), 8.65(s, 1H)
LC/MS (ES+) m/z = 379.16

(112): ^{1}H NMR ($CDCl_3$ + drops of D3OD, 300MHz): δ 1.08(dd, 6H), 2.26(s, 3H), 3.43(dd, 2H), 3.80(dd, 2H), 4.20(m, 1H), 7.08(t, 1H), 7.28-7.32(m, 2H), 7.67-7.77(m, 2H), 7.79(dd, 1H), 8.58(s, 1/4H)
LC/MS (ES+) m/z = 397.18

(113): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.04(m, 6H), 2.26(s, 3H), 3.45(dd, 2H), 3.81(t, 2H), 4.18(m, 1H), 7.08(t, 1H), 7.27-7.32(m, 2H), 7.80(d, 1H), 7.92(dd, 2H), 8.53(s, 1H)
LC/MS (ES+) m/z = 398.16

EXAMPLE 114



5-Cyano-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (114):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (400mg, 1.94mmol), 2-amino-5-cyano-indan-2-carboxylic acid ethyl ester (670mg, 2.91mmol), HATU (1.11g, 2.91mmol) in anhydrous DMF (15mL) is added DIPEA (480μL, 2.91mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-60% EtOAc in heptane) to give a pure product (114) as a white semisolid (682mg, 84%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.30-1.43(m, 1H), 1.51-1.65(m, 1H), 1.98-2.12(m, 4H), 2.28(s, 3H), 3.47(dd, 2H), 3.78(t, 2H), 4.22- 4.33(m, 3H), 7.08(t, 1H), 7.27-7.35(m, 2H), 7.51(d, 2H), 7.85(d, 1H), 8.47(s, 1H)
LC/MS (ES+) m/z = 419.19

EXAMPLES 115, 116, 117

5-Cyano-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (115):

5-Carbamoyl-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (116):

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2,5-dicarboxylic acid (117):

The mixture of 5-cyano-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (114) (530mg, 1.3mmol) and KOH (1.3g, 23mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved. The resulting reaction solution is heated up to 50°C and stirred at this temperature overnight. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until pH~2. After filtration, the obtained solid is purified by HPLC to give three pure products: (115) as white solid (167mg, 33%), (116) as white solid (239mg, 45%) and (117) as white solid (21mg, 4%).

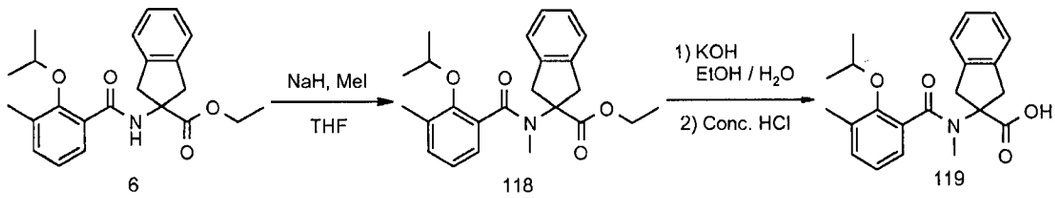
(115): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.24-1.39(m, 1H), 1.46-1.56(m, 1H), 1.89-2.13(m, 4H), 2.10(s, 3H), 3.47(dd, 2H), 3.89(dd, 2H), 4.29(m, 1H), 7.09(t, 1H), 7.26-7.36(m, 2H), 7.52(d, 2H), 7.85(d, 2H), 8.60(s, 1H)

LC/MS (ES+) m/z = 391.13

(116): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.22-1.38(m, 1H), 1.46-1.56(m, 1H), 1.92-2.09(m, 4H), 2.26(s, 3H), 3.47(dd, 2H), 3.82(dd, 2H), 4.30(m, 1H), 7.08(t, 1H), 7.27-7.32(m, 2H), 7.66-7.72(m, 2H), 7.81(d, 1H), 8.57(s, 1H)
LC/MS (ES+) m/z = 409.14

(117): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.22-1.35(m, 1H), 1.42-1.52(m, 1H), 1.87-2.06(m, 4H), 2.26(s, 3H), 3.47(dd, 2H), 3.83(dd, 2H), 4.28(m, 1H), 7.08(t, 1H), 7.27-7.33(m, 2H), 7.82(d, 1H), 7.93(d, 2H), 8.53(s, 1H)
LC/MS (ES+) m/z = 410.17

EXAMPLE 118



6 118 119

2-[(2-Isopropoxy-3-methyl-benzoyl)-methyl-amino]-indan-2-carboxylic acid ethyl ester (118):

To a solution of NaH (sodium hydride, 60% dispersion, 86.0mg, 2.15mmol)) in anhydrous THF (20mL) is added dropwise the solution of 2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (6) (410mg, 1.07mmol) in THF (5mL) at 0°C. After stirring for 20min, methyl iodide (452μL, 7.26mmol) is added dropwise and the resulting suspension is warmed up to RT and continued stirring overnight. After being quenched by saturated aqueous solution of ammonium chloride (5mL), the reaction mixture is diluted in EtOAc (50mL). The organic layer is separated, washed with water (1 x 5mL) and brine (2 x 5mL), dried over anhydrous Na_2SO_4 and concentrated in *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-30% EtOAc in heptane) to give the pure product (118) as a colorless oil (240mg, 57%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.18(br d, 6H), 1.28(t, 3H), 2.24(s, 3H), 2.85(s, 3H), 3.44(d, 2H), 3.62(br d, 1H), 4.02(br d, 1H), 4.18-4.36(m, 3H), 7.00(t, 1H), 7.09(d, 1H), 7.18-7.20(m, 5H)

LC/MS (ES+) m/z = 396.21

EXAMPLE 119

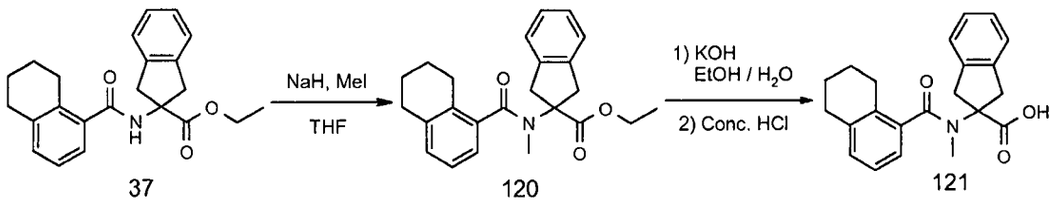
2-[(2-Isopropoxy-3-methyl-benzoyl)-methyl-amino]-indan-2-carboxylic acid (119):

The mixture of 2-[(2-isopropoxy-3-methyl-benzoyl)-methyl-amino]-indan-2-carboxylic acid ethyl ester (118`) (200mg, 0.51mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (119) as a pale orange solid (170mg, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.15(br d, 6H), 2.24(s, 3H), 2.86(s, 3H), 3.46(d, 2H), 3.74(br d, 1H), 4.02(br d, 1H), 4.26(m, 1H), 6.99(t, 1H), 7.15-7.26(m, 6H), 8.79(br s, 1H)

LC/MS (ES+) m/z = 368.20

EXAMPLE 120



37 120 121

2-[Methyl-(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (120):

To a solution of NaH (sodium hydride, 60% dispersion, 124mg, 3.08mmol) in anhydrous THF (20mL) is added dropwise the solution of 2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (37) (280mg, 0.77mmol) in THF (5mL) at 0°C. After stirring for 20min, methyl iodide (377μL, 6.05mmol) is added dropwise and the resulting suspension is warmed up to RT and continued stirring overnight. After being quenched by saturated ammonium chloride aqueous solution (5mL), the reaction mixture is diluted in EtOAc (50mL). The organic layer is separated, washed with water (1 x 5mL) and brine (2 x 5mL), dried over anhydrous Na_2SO_4 and concentrated in *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-30% EtOAc in heptane) to give a pure product (120) as a colorless semisolid (250mg, 86%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.76(br s, 4H), 2.47(br s, 1H), 2.76(br s, 2H), 2.82(s, 3H), 2.82(br s, 1H), 3.45(d, 2H), 3.83(d, 2H), 4.24(m, 2H), 6.92(d, 1H), 7.05-7.08(m, 2H), 7.17-7.23(m, 4H)

LC/MS (ES+) m/z = 378.22

EXAMPLE 121

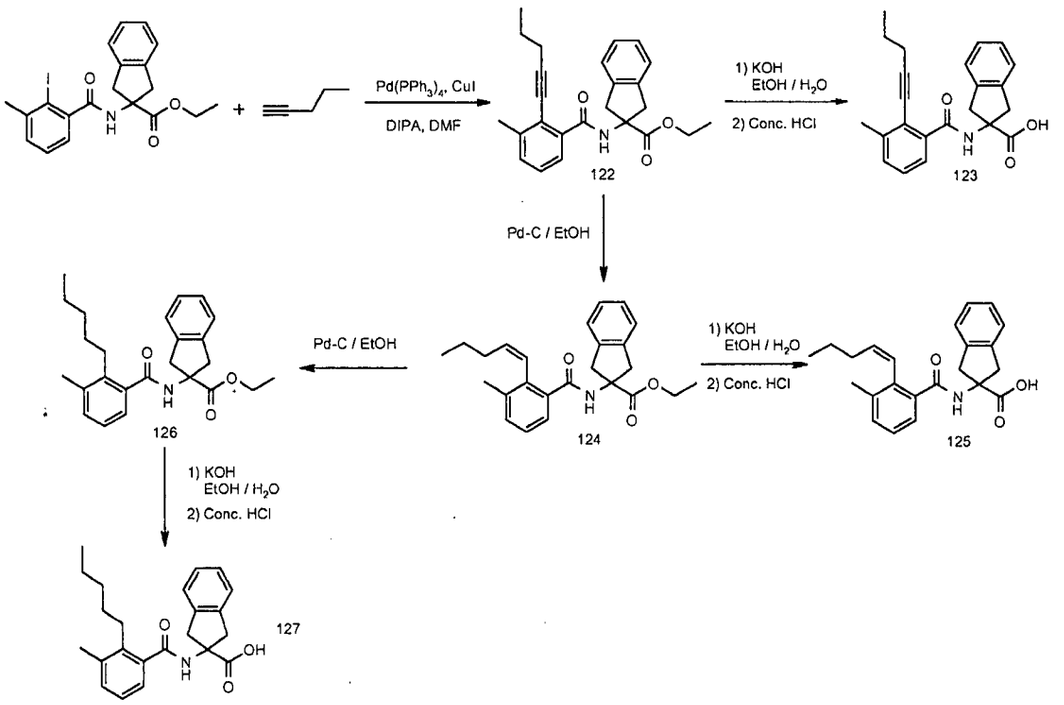
2-[Methyl-(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid (121):

The mixture of 2-[methyl-(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (120) (226mg, 0.60mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (5mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~ 3. The precipitate is filtered to give a pure product (121) as a pale orange solid (150mg, 72%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.74(br s, 4H), 2.45(br s, 1H), 2.76-2.84(m, 3H), 2.85(s, 3H), 3.48(d, 2H), 3.90(d, 2H), 4.24(m, 2H), 6.96-7.26(m, 7H)

LC/MS (ES+) m/z = 350.16

EXAMPLE 122



2-(3-Methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (122):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (693mg, 1.54mmol) in anhydrous DMF (5mL) and DIPA (diisopropylamine, 10mL) is added $Pd(PPh_3)_4$ (89mg, 7.7%mmol), CuI (29mg, 0.154mmol) and pent-1-yne (1.5mL, 15.4mmol). The resulting solution is covered in argon and run in a microwave reaction: 110°C, 35minutes. After the removal of DMF and DIPA *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 0%-40% EtOAc in heptane) to give a pure product (122) as a pale yellow solid (144mg, 24%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.99(t, 3H), 1.25(t, 3H), 1.51(m, 2H), 2.14(t, 1H), 2.39(s, 3H), 3.35(d, 2H), 3.77(d, 2H), 4.25(q, 2H), 7.17-7.30(m, 6H), 7.84(d, 1H), 8.21(s, 1H)

LC/MS (ES+) m/z = 390.18

EXAMPLE 123

2-(3-Methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid (123):

The mixture of 2-(3-methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (122) (180mg, 0.46mmol) and KOH (1g, 18mmol) is dissolved in EtOH (8mL) and water

(1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~4. After filtration, the solid is purified by HPLC to give a pure product (123) as white solid (114mg, 69%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.99(t, 3H), 1.53(m, 2H), 2.14(t, 1H), 2.40(s, 3H), 3.39(d, 2H), 3.82(d, 2H), 7.18-7.32(m, 6H), 7.83(d, 1H), 8.39(s, 1H)
LC/MS (ES+) m/z = 362.17

EXAMPLE 124

2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (124):

To a solution of 2-(3-methyl-2-pent-1-ynyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (122) (300mg, 0.77mmol) in absolute EtOH (18mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 30mg, 1.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product as white solid (168mg, 56%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.72(t, 3H), 1.13-1.30(m, 5H), 1.64(m, 2H), 2.16(s, 3H), 3.29(d, 2H), 3.69(d, 2H), 4.25(q, 2H), 5.56(dt, 1H), 6.29(d, 1H), 6.78(s, 1H), 7.17-7.26(m, 6H), 7.57(d, 1H)
LC/MS (ES+) m/z = 392.12

EXAMPLE 125

2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid (125):

The mixture of 2-[3-methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (124) (69mg, 0.18mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 5h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~4. The precipitate is filtered to give a pure product (125) as white solid (42mg, 64%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.73(t, 3H), 1.11-1.25(m, 2H), 1.62(q, 2H), 2.16(s, 3H), 3.33(d, 2H), 3.72(d, 2H), 5.54(dt, 1H), 6.25(d, 1H), 7.01(s, 1H), 7.18-7.28(m, 6H), 7.57(d, 1H)

LC/MS (ES+) m/z = 364.18

EXAMPLE 126

2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (126):

To a solution of 2-[3-methyl-2-((Z)-pent-1)-enyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (124) (92mg, 0.23mmol) in absolute EtOH (10mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 30mg, 1.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (126) as white solid (80mg, 89%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.88(t, 3H), 1.26-1.33(m, 7H), 1.42-1.47(m, 2H), 2.29(s, 3H), 2.64-2.69(m, 2H), 3.34(d, 2H), 3.74(d, 2H), 4.28(q, 2H), 6.18(s, 1H), 7.02-7.26(m, 7H)

LC/MS (ES+) m/z = 394.23

EXAMPLE 127

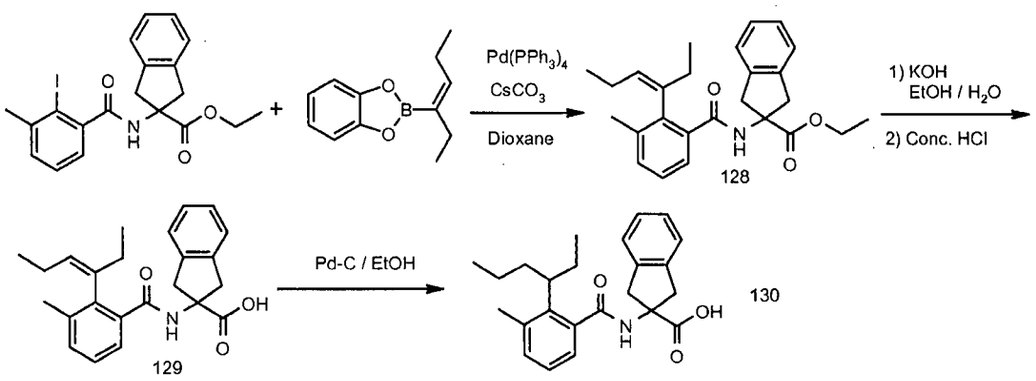
2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid (127):

The mixture of 2-(3-methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (126) (68mg, 0.17mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (127) as a pale brown solid (63mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.88(t, 3H), 1.26-1.30(m, 4H), 1.41-1.43(m, 2H), 2.30(s, 3H), 2.62-2.67(m, 2H), 3.40(d, 2H), 3.83(d, 2H), 6.22(s, 1H), 7.01-7.07(m, 2H), 7.17-7.26(m, 5H)

LC/MS (ES+) m/z = 366.20

EXAMPLE 128



2-[2-(-1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (128):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.89mmol) and 2-(1-Ethyl-but-1-enyl)-benzo[1,3,2]dioxaborole (709μL, 3.56mmol) in dioxane (15mL) is added $Pd(PPh_3)_4$ (103mg, 8.9%mmol) and 2M aqueous solution of $CsCO_3$ (1.34mL, 2.67mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 2h. After concentration *in vacuo*, the residue is purified by flash column chromatography (120g silica gel, gradient elution: 5%-50% EtOAc in heptane) to give a pure product (128) as a brown semi-solid (530mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.71(t, 3H), 0.99(t, 3H), 1.27(t, 3H), 1.75-2.05(m, 3H), 2.11-2.25(m, 1H), 2.21(s, 3H), 3.11(d, 1H), 3.33(d, 1H), 3.37(dd, 2H), 4.25(q, 2H), 5.54(t, 1H), 7.16-7.27(m, 6H), 7.66(d, 1H)

LC/MS (ES+) m/z = 406.25

EXAMPLE 129

2-[2-(-1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (129):

The mixture of 2-[2-(-1-ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (128) (503mg, 1.24mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (10mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (40mL) and acidified with conc. HCl until pH~3. The precipitate is filtered to give a pure product (129) as a brown solid (452mg, 97%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.68(t, 3H), 0.99(t, 3H), 1.83(m, 2H), 1.95-2.18(m, 2H), 2.20 (s, 3H), 3.11(d, 1H), 3.39(d, 1H), 3.72(dd, 2H), 5.54(t, 1H), 7.16-7.35(m, 6H), 7.63(d, 1H)

LC/MS (ES+) m/z = 378.21

EXAMPLE 130

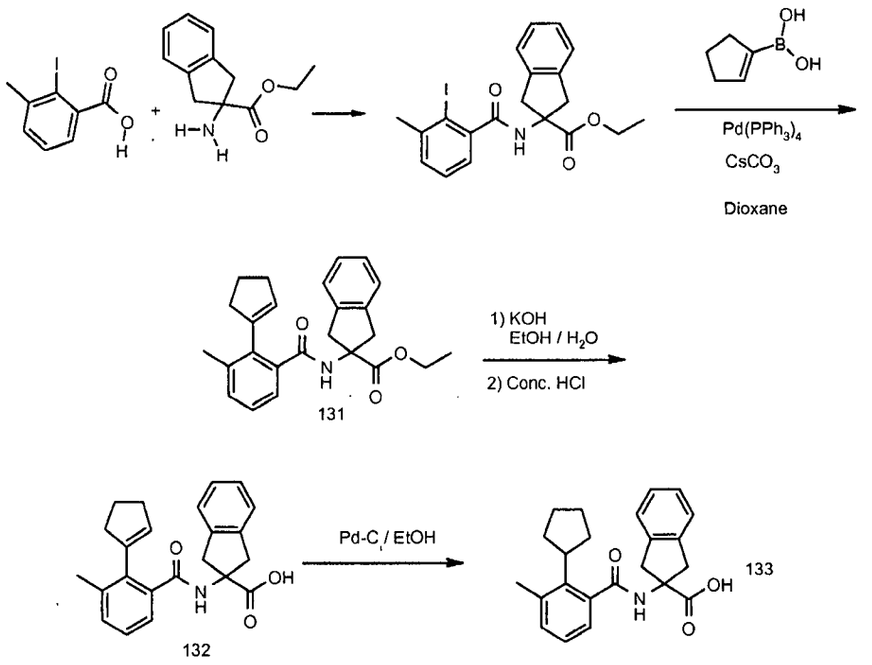
2-[2-(1-Ethyl-butyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (130):

To a solution of 2-[2-(-1-ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (129) (270mg, 0.72mmol) in absolute EtOH (15mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 46mg, 2.2%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 70°C, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (130) as white solid (75mg, 28%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.66-0.75(m, 6H), 0.83-1.26 (m, 2H), 1.56-1.69(m, 4H), 2.34(s, 3H), 2.87(m, 1H), 3.34-3.43(m, 2H), 3.72(d, 2H), 6.15(s, 1H), 7.00-7.25(m, 7H), 8.83(br s, 1H)

LC/MS (ES+) m/z = 380.22

EXAMPLE 131



2-(2-Iodo-3-methyl-benzoylamino)-indan-2-carboxylic Acid Ethyl Ester

A 100mL round bottom flask is charged with 2-Iodo-3-methylbenzoic Acid (1.92g, 7.31mmol) and dry DCM (25mL). A stirring bar is added and stirring initiated. After 5min, HTBU (2.37g, 7.31mmol) is added. After 5min, the 2-amino-indane-2-carboxylic Acid Ethyl Ester (1.50g, 7.31mmoles) is added followed by DIPEA (3.2mL, 18.37mmol). The reaction is allowed to stir for 118 hours. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/Dischloromethane) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (70 mL). This is washed with dilute aqueous HCl (3%, 2 x 30mL), saturated aqueous $NaHCO_3$ (2 x 30mL) and brine (30 mL), dried over MgSO4, filtered and evaporated *in vacuo* to provide 2.04g of white solid. This material is dissolved in DCM (15mL). This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 10 column volumes. 27mL fractions of UV active elutant were collected. Fractions 10 through 15 are combined and evaporated *in vacuo* to constant weight to give 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester 1.04g of white solid.

2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (131):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (800mg, 1.78mmol) and cyclopenten-1-ylboronic acid (796mg, 7.11mmol) in dioxane (20mL) is added $Pd(PPh_3)_4$ (412mg, 0.36mmol) and 2M aqueous solution of $CsCO_3$ (5.34mL, 10.7mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 2.7h. After concentration *in vacuo*, the residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-40% EtOAc in heptane) to give a pure product (131) as a brown solid (589mg, 85%).

^1H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.72(m, 2H), 2.19(s, 3H), 2.33-2.43(m, 4H), 3.23(d, 2H), 3.70(dd, 2H), 4.25(q, 2H), 5.57(m, 1H), 6.99(s, 1H), 7.16-7.26(m, 6H), 7.58(d, 1H)
LC/MS (ES+) m/z = 390.22

EXAMPLE 132

2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (132):

The mixture of 2-(2-cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (131) (560mg, 1.43mmol) and KOH (1g, 17.9mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until pH~3. The precipitate is filtered to give a pure product (132) as a pale yellow solid (518mg, 100%).

^1H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.73(m, 2H), 2.19(s, 3H), 2.36-2.39(m, 4H), 3.27(d, 2H), 3.73(dd, 2H), 5.57(m, 1H), 7.16-7.29(m, 6H), 7.53(d, 1H)
LC/MS (ES+) m/z = 362.17

EXAMPLE 133

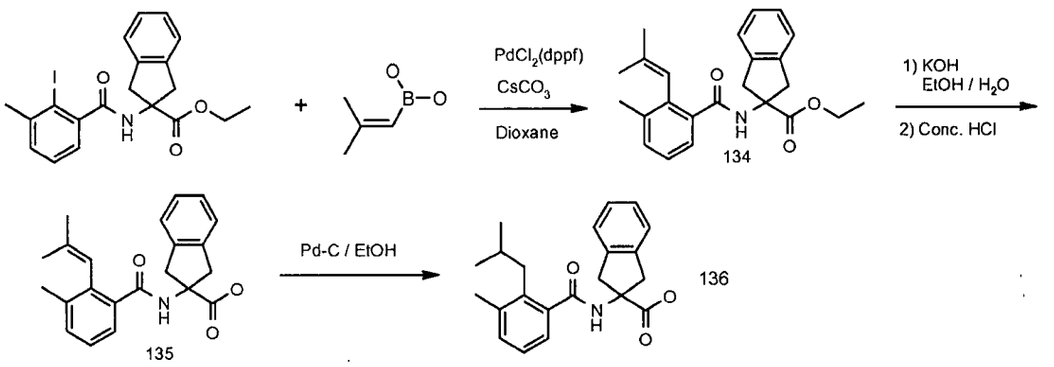
2-(2-Cyclopentyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (133):

To a solution of 2-(2-cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (132) (365mg, 1.01mmol) in absolute EtOH (15mL) is added the catalyst, Pd-C (50% wetted powder, 10%Pd, 192mg, 9%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 50°C, overnight. The catalyst is removed by

the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (133) as white solid (184mg, 50%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.55-1.77(m, 8H), 2.33(s, 3H), 3.22(m, 1H), 3.27(d, 2H), 3.77(dd, 2H), 6.22(m, 1H), 7.101-7.26(m, 7H)
LC/MS (ES+) m/z = 364.22

EXAMPLE 134



2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (134):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.89mmol) and 2,2-dimethyethylenelboronic acid (133mg, 1.34mmol) in dioxane (15mL) is added $PdCl_2$(dppf) ([1,1'-bis(diphenylphosphine)ferrocene]-dichloropalladium(II), 73mg, 8.9%mmol) and 2M aqueous solution of $CsCO_3$ (1.34mL, 2.67mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 2h. After concentration *in vacuo*, the residue is purified by flash column chromatography (120g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (134) as a pale yellow solid (523mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.30(s, 3H), 1.65(s, 3H), 2.14(s, 3H), 3.24(br d, 2H), 3.70(br d, 2H), 4.25(q, 2H), 6.10(s, 1H), 7.02(s, 1H), 7.17-7.26(m, 6H), 7.69(d, 1H)
LC/MS (ES+) m/z = 378.22

EXAMPLE 135

2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (135):

The mixture 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (134) (283mg, 0.75mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. The precipitate is filtered to give a pure product (135) as white solid (250mg, 95%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.28(t, 3H), 1.68(s, 3H), 2.14(s, 3H), 3.28(d, 2H), 3.74(d, 2H), 6.09(s, 1H), 7.17-7.29(m, 6H), 7.66(d, 1H)
LC/MS (ES+) m/z = 350.19

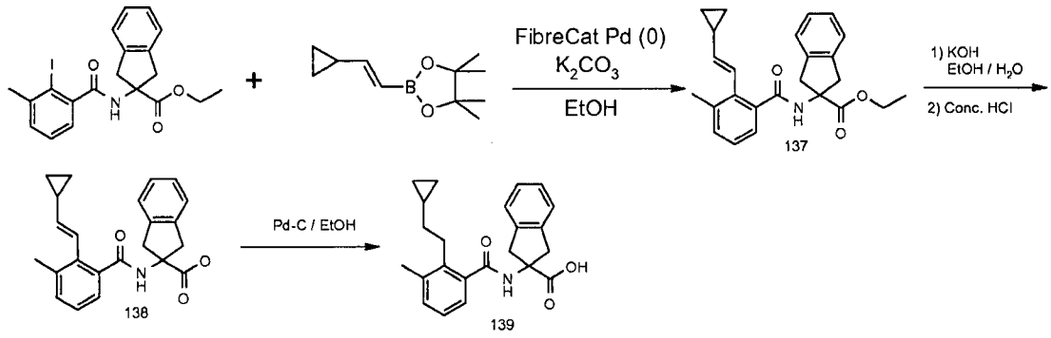
EXAMPLE 136

2-(2-Isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (136):

To a solution of 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (135) (120mg, 0.34mmol) in acetic acid (15mL) is added the catalyst, Pd-C (5wt.%Pd, 72mg, 3.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 95°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed by EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (136) as white solid (65mg, 54%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.80(d, 6H), 1.75-1.78(m, 1H), 2.30(s, 3H), 2.68(d, 2H), 3.38(d, 2H), 3.76(d, 2H), 6.53(s, 1H), 7.03-7.25(m, 7H)
LC/MS (ES+) m/z = 352.15

EXAMPLE 137



2-[2-(-2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (137):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (600mg, 1.34mmol) and 2-(2-cyclopropyl-vinyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (1.11mL, 5.36mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0), (4.84%Pd, 285mg, 0.13mmol) and 2M aqueous solution of K_2SO_4 (2.68mL, 5.36mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (137) as white solid (250mg, 49%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.47-0.50(m, 2H), 0.76-0.82(m, 2H), 1.29(t, 3H), 1.45(m, 1H), 2.27(s, 3H), 3.32(d, 2H), 3.72(d, 2H), 4.27(q, 2H), 5.30(dd, 1H), 6.45(dd, 1H), 6.52(s, 1H), 7.09-7.23(m, 6H), 7.39(d, 1H)

LC/MS (ES+) m/z = 390.20

EXAMPLE 138

2-[2-(-2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (138):

The mixture 2-[2-(-2-cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (137) (220mg, 0.56mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (138) as white solid (209mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.47-0.50(m, 2H), 0.78-0.84(m, 2H), 1.43(m, 1H), 2.26(s, 3H), 3.38(d, 2H), 3.83(d, 2H), 5.24(dd, 1H), 6.34(d, 1H), 6.68(s, 1H), 7.11-7.26(m, 6H), 7.41(d, 1H)

LC/MS (ES+) m/z = 362.17

EXAMPLE 139

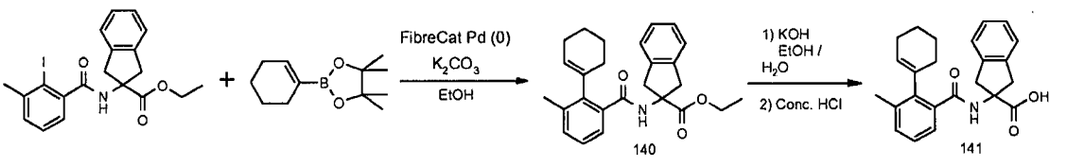
2-[2-(2-Cyclopropyl-ethyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (139):

To a solution of 2-[2-((E)-2-cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (138) (120mg, 0.33mmol) in absolute EtOH (10mL) is added the catalyst, Pd-C (5wt.%Pd, 28mg, 1.3%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed by EtOH. The combined solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (139) as white solid (30mg, 25%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.00(m, 2H), 0.35-0.41(m, 2H), 0.66(m, 1H), 1.32-1.39(m, 2H), 2.30(s, 3H), 2.76-2.82(m, 2H), 3.40(d, 2H), 3.82(d, 2H), 6.23(s, 1H), 7.03-7.04(m, 2H), 7.16-7.26(m, 4H)

LC/MS (ES+) m/z = 364.13

EXAMPLE 140



2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (140):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (491mg, 1.09mmol) and 2-cyclohex-1-enyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (937μL, 4.36mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 240mg, 0.11mmol) and 2M aqueous solution of K_2SO_4 (2.18mL, 4.36mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (140) as white solid (95mg, 22%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.55(br t, 4H), 2.01-2.34(m, 4H), 2.21(s, 3H), 3.27(br t, 2H), 3.74(br d, 2H), 4.22-4.27(m, 2H), 5.56(s, 1H), 7.16-7.29(m, 7H), 7.63(d, 1H)
LC/MS (ES+) m/z = 404.22

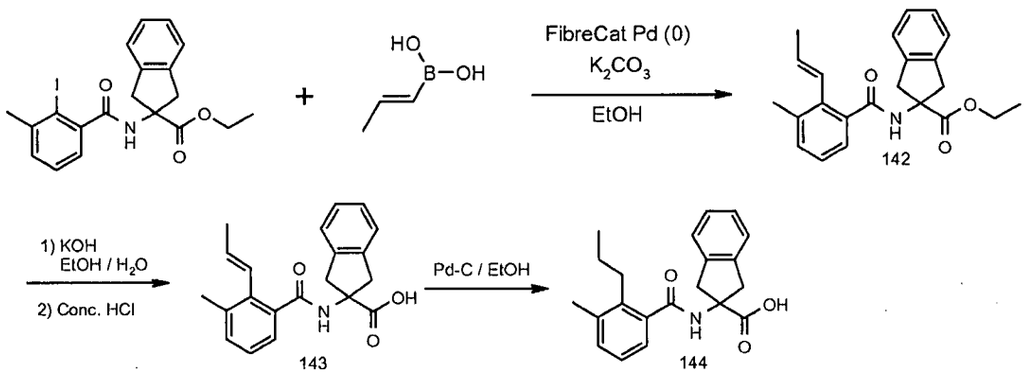
EXAMPLE 141

2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (141):

The mixture 2-(2-cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (141) (80mg, 0.20mmol) and KOH (300mg, 5.36mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (141) as white solid (71mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.41-1.56(m, 4H), 2.03-2.24(m, 4H), 2.21(s, 3H), 3.32(m, 2H), 3.83(d, 2H), 5.56(s, 1H), 7.16-7.34(m, 6H), 7.61(d, 1H)
LC/MS (ES+) m/z = 376.22

EXAMPLE 142



2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (142):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (600mg, 1.34mmol) and trans-1-propen-1-ylboronic acid (460mg, 5.36mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0), (4.84%Pd, 285mg, 0.13mmol) and 2M aqueous solution of K_2SO_4 (2.68mL, 5.36mmol). The resulting reaction mixture is covered with argon and run in a microwave

reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC and gave the pure product (142) as white solid (300mg, 63%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 1.74(dd, 3H), 2.25(s, 3H), 3.28(d, 2H), 3.71(d, 2H), 4.27(q, 2H), 5.75(dq, 1H), 6.37(d, 1H), 7.10-7.26(m, 6H), 7.36(d, 1H)
LC/MS (ES+) m/z = 364.18

EXAMPLE 143

2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid (143):

The mixture 2-[3-methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (142) (340mg, 0.94mmol) and KOH (700mg, 12.5mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (143) as white solid (315mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.75(dd, 3H), 2.25(s, 3H), 3.32(d, 2H), 3.73(d, 2H), 5.75(dq, 1H), 6.36(dd, 1H), 6.76(s, 1H), 7.10-7.24(m, 6H), 7.31(d, 1H)
LC/MS (ES+) m/z = 336.16

EXAMPLE 144

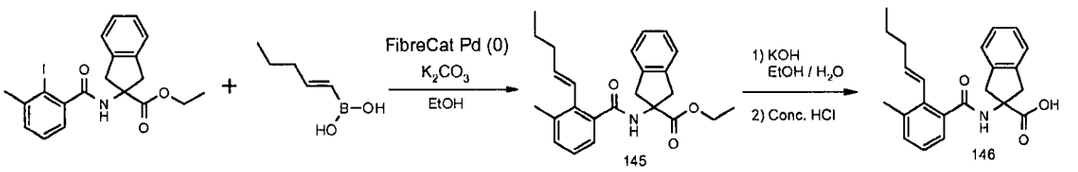
2-(3-Methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid (144):

To a solution of 2-[3-methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid (143) (220mg, 0.65mmol) in absolute EtOH (10mL) is added the catalyst, Pd-C (5wt.%Pd, 55mg, 2.6%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, room temperature, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed with EtOH. The combined solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (144) as white solid (128mg, 58%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.91(t, 3H), 1.45(m, 2H), 2.45(s, 3H), 2.61-2.66(d, 2H), 3.40 (d, 2H), 3.82(d, 2H), 6.22(s, 1H), 7.04(d, 2H), 7.17-7.26(m, 5H)

LC/MS (ES+) m/z = 338.17

EXAMPLES 145-146



2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (145):

To a solution of 2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (200mg, 0.45mmol) and trans-1-penten-1-ylboronic acid (205mg, 1.80mmol) in EtOH (10mL) and dioxane (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 96mg, 0.045mmol) and 2M aqueous solution of K_2SO_4 (0.90mL, 1.80mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (145) as white solid (107mg, 60%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.93(t, 3H), 1.28(t, 3H), 1.42(m, 2H), 2.03(q, 3H), 2.26(s, 3H), 3.29(d, 2H), 3.70(d, 2H), 4.25(q, 2H), 5.75(dt, 1H), 6.37(d, 1H), 6.43(s, 1H), 7.09-7.25(m, 6H), 7.37(d, 1H)

LC/MS (ES+) m/z = 392.0

EXAMPLE 146

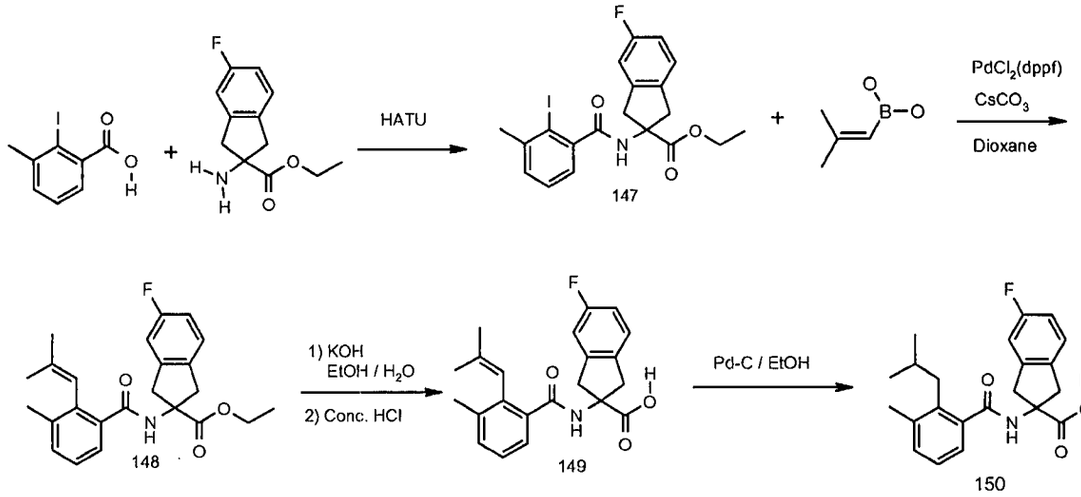
2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid (146):

The mixture 2-[3-methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (145) (170mg, 0.43mmol) and KOH (60mg, 10.7mmol) is dissolved in EtOH (8mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (146) as white solid (160mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.93(t, 3H), 1.42(m, 2H), 2.05(q, 3H), 2.26(s, 3H), 3.33(d, 2H), 3.74(d, 2H), 4.25(q, 2H), 5.73(dt, 1H), 6.35(d, 1H), 6.68(s, 1H), 7.11-7.21(m, 6H), 7.34(d, 1H)

LC/MS (ES+) m/z = 364.18

EXAMPLES 147-150



EXAMPLE 147

5-Fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (147):

To a solution of 2-iodo-3-methyl-benzoic acid (3.85g, 14.7mmol), 2-amino-5-fluoro-indan-2-carboxylic acid ethyl ester (3.00g, 13.4mmol), HATU (6.10g, 16.1mmol) in anhydrous DMF (6mL) is added DIPEA (3.30mL, 20.1mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is recrystallized from EtOAc to give a pure product (147) as white solid (3.90g, 62%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 2.44 (s, 3H), 3.45-3.67(m, 4H), 4.28 (q, 2H), 6.32 (s, 1H), 6.85-6.94(m, 2H), 7.12-7.26(m, 4H)

LC/MS (ES+) m/z = 468.03

EXAMPLE 148

5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (148):

To a solution of 5-fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.85mmol) and 2,2-dimethyethylenelboronic acid (342mg, 3.42mmol) in EtOH

(10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 186mg, 8.5%mmol) and 2M aqueous solution of K_2SO_4 (1.71mL, 3.42mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 120°C, 7h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (148) as a colorless oil (245mg, 73%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.34(d, 3H), 1.71(dd, 3H), 2.15(s, 3H), 3.25(br dd, 2H), 3.65(br dd, 2H), 4.24(q, 2H), 6.12(s, 1H), 6.86-6.92(m, 2H), 7.19-7.26(m, 4H), 7.65(d, 1H)

LC/MS (ES+) m/z = 396.18

EXAMPLE 149

5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (149):

The mixture 5-fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (148) (245mg, 0.62mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (149) as white solid (230mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.32(s, 3H), 1.73(s, 3H), 2.15(s, 3H), 3.27(t, 2H), 3.68(dd, 2H), 6.12(s, 1H), 6.86-6.93(m, 2H), 7.13-7.30(m, 4H), 7.61(d, 1H)

LC/MS (ES+) m/z = 368.10

EXAMPLE 150

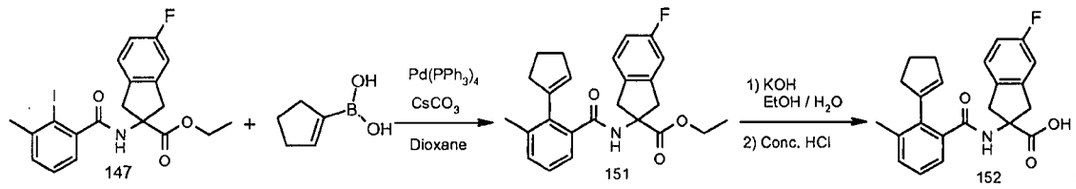
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (150):

To a solution of 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (149) (230mg, 0.63mmol) in acetic acid (10mL) is added the catalyst, Pd-C (5wt.%Pd, 134mg, 6.3%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 95°C, overnight. The catalyst is removed by filtration through a pre-

column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (150) as white solid (200mg, 86%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.81(dd, 6H), 1.78(m, 1H), 2.30(s, 3H), 2.68(d, 2H), 3.37(t, 2H), 3.69(dd, 2H), 6.88-6.93(m, 3H), 7.13-7.30(m, 4H), 7.32(s, 1H)
LC/MS (ES+) m/z = 370.19

EXAMPLE 151-152



2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (151):

To a solution of 5-fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.85mmol) and cyclopenten-1-ylboronic acid (383mg, 3.42mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 186mg, 8.5%mmol) and 2M aqueous solution of K_2SO_4 (1.71mL, 3.42mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 8h. After concentration *in vacuo*, the residue is purified HPLC to give a pure product (151) as white solid (240mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.27(t, 3H), 1.76(m, 2H), 2.20(s, 3H), 2.38-2.41(m, 4H), 3.25(dd, 2H), 3.66(dd, 2H), 4.25(q, 2H), 5.62(t, 1H), 6.87-6.93(m, 2H), 7.12-7.30(m, 4H), 7.53(d, 1H), 8.39(br s, 1H)
LC/MS (ES+) m/z = 408.22

EXAMPLE 152

2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid (152):

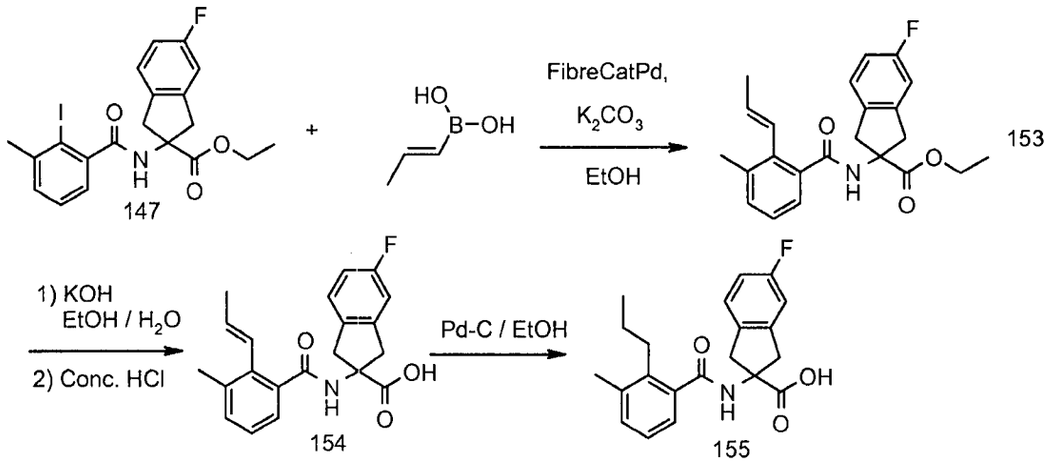
The mixture of 2-(2-cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (151) (190mg, 0.47mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is

completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate formed. The precipitate is filtered to give a pure product (152) as white solid (182mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.72(m, 2H), 2.18(s, 3H), 2.34(t, 4H), 3.20(t, 2H), 3.66(dd, 2H), 5.55(s, 1H), 6.84-6.89(m, 2H), 7.07-7.26(m, 4H), 7.56(d, 1H)

LC/MS (ES+) m/z = 380.19

EXAMPLE 153



5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (153):

To a solution of 5-fluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.85mmol) and trans-1-propen-1-ylboronic acid (294mg, 3.42mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 186mg, 8.5%mmol) and 2M aqueous solution of K_2SO_4 (1.71mL, 3.42mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 7h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (153) as white solid (165mg, 51%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.28(t, 3H), 1.75(m, 3H), 2.26(s, 3H), 3.27(dd, 2H), 3.62(dd, 2H), 4.26(q, 2H), 5.76(dq, 1H), 6.38(d, 1H), 6.44(s, 1H), 6.85-6.91(m, 2H), 7.11-7.22(m, 3H), 7.35(d, 1H)

LC/MS (ES+) m/z = 382.21

EXAMPLE 154

5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid (154):

The mixture 5-fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (153) (260mg, 0.68mmol) and KOH (600mg, 10.7mmol) is dissolved in EtOH (8mL) and water (0.2mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 2.5h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with conc. HCl until no more precipitate came out of the water. The filtered compound is purified by HPLC to give a pure product (154) as white solid (267mg, 100%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.76(m, 3H), 2.26(s, 3H), 3.31(t, 2H), 3.65(dd, 2H), 5.76(dq, 1H), 6.38(d, 1H), 6.80(s, 1H), 6.85-6.93(m, 2H), 7.10-7.22(m, 3H), 7.31(d, 1H)

LC/MS (ES+) m/z = 354.18

EXAMPLE 155

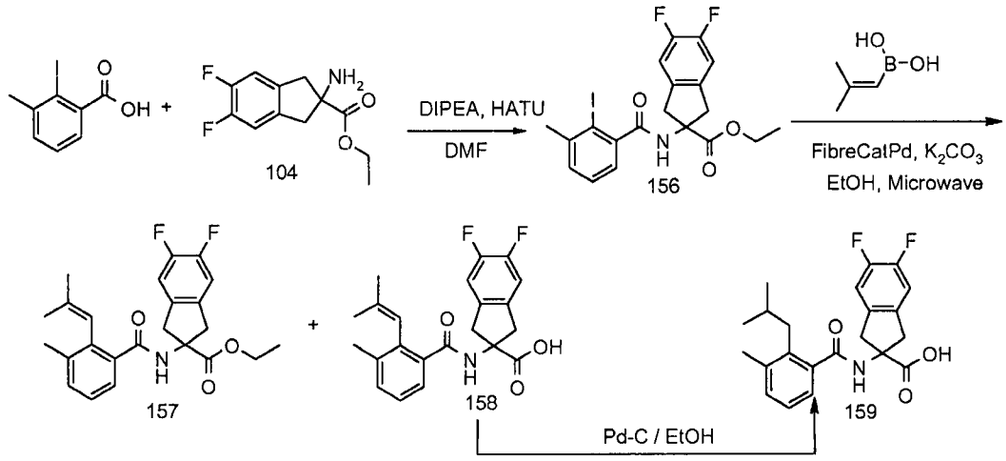
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (155):

5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid (154) (270mg, 0.76mmol) is dissolved in absolute EtOH (15mL) by heating. The resulting solution is cooled down to RT under argon and then is added the catalyst, Pd-C (5wt.%Pd, 125mg, 5.9%mmol). The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 50psi, 50°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (155) as white solid (210mg, 78%).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.92(t, 3H), 1.46(m, 2H), 2.30(s, 3H), 2.65-2.68(m, 2H), 3.36(t, 2H), 3.71(dd, 2H), 6.85-6.93(m, 2H), 7.03-7.18(m, 4H)

LC/MS (ES+) m/z = 356.14

EXAMPLE 156



5,6-Difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (156):

To a solution of 2-iodo-3-methyl-benzoic acid (1.50g, 5.75mmol), 2-amino-5,6-difluoro-indan-2-carboxylic acid ethyl ester (1.39g, 5.75mmol), HATU (2.63g, 6.90mmol) in anhydrous DMF (6mL) is added DIPEA (1.14mL, 6.90mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (200mL) and washed with water (1 x 20mL) and brine (2 x 20mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (400g silica gel, gradient elution: 10%-80% EtOAc in heptane) to give a pure product (156) as white solid (2.32g, 83%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29(t, 3H), 2.45(s, 3H), 3.48(d, 2H), 3.63(d, 2H), 4.27(q, 2H), 6.38 (s, 1H), 7.04(t, 2H), 7.10-7.13(m, 1H), 7.24-7.27(m, 2H)
LC/MS (ES+) m/z = 486.02

EXAMPLES 157 and 158

5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (157) and 5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (158):

To a solution of 5,6-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.82mmol) and 2,2-dimethyethylenelboronic acid (328mg, 3.28mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 180mg, 8.2%mmol) and 2M aqueous solution of K_2SO_4 (1.64mL, 3.28mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 120°C, 6h. After concentration *in vacuo*, the residue is purified by HPLC to give two

pure products: (157) as white solid (100mg, 29%) and (158) as white solid as well (120mg, 38%).

(157): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.26(t, 3H), 1.38(d, 3H), 1.76(s, 3H), 2.15(s, 3H), 3.27(d, 2H), 3.59(d, 2H), 4.24(q, 2H), 6.14(s, 1H), 6.98-7.31(m, 5H), 7.61(d, 1H)
LC/MS (ES+) m/z = 414.20

(158): ^{1}H NMR ($CDCl_3$, 300MHz): δ 1.34(d, 3H), 1.79(s, 3H), 2.15(s, 3H), 3.26(d, 2H), 3.75(d, 2H), 6.09(s, 1H), 7.02(t, 2H), 7.21-7.34(m, 3H), 7.77(d, 1H)
LC/MS (ES+) m/z = 386.19

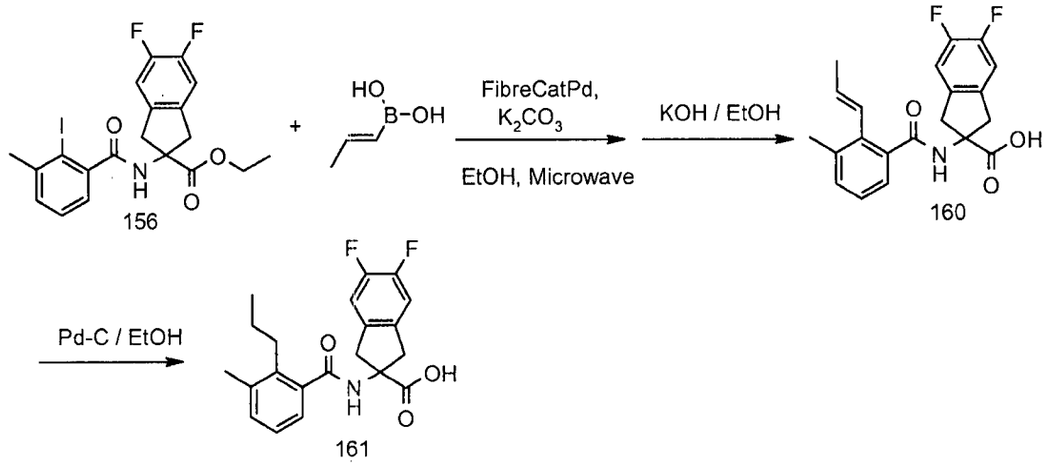
EXAMPLE 159

5,6-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (159):

5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (158) (200mg, 0.63mmol) is dissolved in acetic acid (15mL) by heating. The resulting solution is cooled down to RT and then the catalyst, Pd-C (5wt.%Pd, 134mg, 6.3%mmol) is added under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 95°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (159) as white solid (170mg, 84%).

(159): ^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.83(d, 6H), 1.80(m, 1H), 2.32(s, 3H), 2.68(d, 2H), 3.39(d, 2H), 7.00-7.20(m, 5H), 7.44(s, 1H)
LC/MS (ES+) m/z = 388.17

EXAMPLES 160-161



5,6-Difluoro-2-(3-methyl-2-propenyl-benzoylamino)-indan-2-carboxylic acid (160):

To a solution of 5,6-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.82mmol) and trans-1-propen-1-ylboronic acid (282mg, 3.28mmol) in EtOH (10mL) and dioxane (5mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 180mg, 8.2%mmol) and 2M aqueous solution of K_2SO_4 (1.64mL, 3.28mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 120°C, 5h. After concentration *in vacuo*, the residue is purified by HPLC to give a white solid (160mg), which is dissolved in EtOH (5mL) and water (0.2mL) together with KOH (600mg, 10.7mmol) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration is purified by HPLC to give a pure product (160) as white solid (127mg, 42% overall yield).

^{1}H NMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.80(dd, 3H), 2.27(s, 3H), 3.36(d, 2H), 3.63(d, 2H), 5.77(dq, 1H), 6.40(d, 1H), 7.01(t, 2H), 7.10-7.29(m, 4H)
LC/MS (ES+) m/z = 372.15

EXAMPLE 161

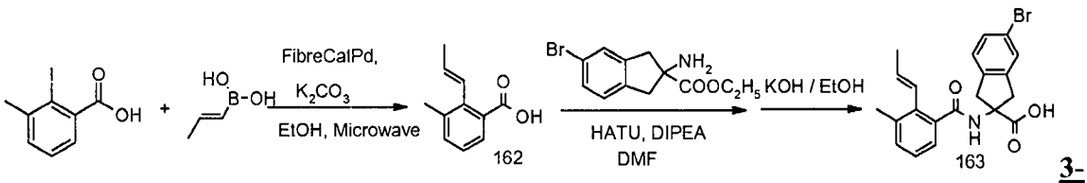
5,6-Difluoro-2-(3-methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid (161):

5,6-Difluoro-2-[3-methyl-2-(-propenyl)-benzoylamino]-indan-2-carboxylic acid (160) (110mg, 0.30mmol) is dissolved in absolute EtOH (15mL) by heating. The resulting solution is cooled to RT and catalyst, Pd-C (5wt.%Pd, 64mg, 3.0%mmol) is added under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 50°C, overnight.

The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined EtOH solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (161) as white solid (80mg, 71%).

^{1}H NMR (DMSO-d6, 300MHz): δ 0.86(q, 3H), 1.40(m, 2H), 2.27(s, 3H), 2.58(m, 2H), 3.29(d, 2H), 3.52(d, 2H), 7.00(d, 1H), 7.08(t, 1H), 7.18(d, 1H), 7.29(t, 2H), 8.87(s, 1H), 12.58(s, 1H)
LC/MS (ES+) m/z = 374.14

EXAMPLE 162



3-Methyl-2-((E)-propenyl)-benzoic acid (162):

To a solution of 2-iodo-3-methyl-benzoic acid (708mg, 2.70mmol) and trans-1-propen-1-ylboronic acid (526mg, 6.12mmol) in EtOH (10mL) is added palladium anchored homogeneous catalyst, FibreCatPd(0) (4.84% Pd, 235mg, 0.15mmol) and 2M aqueous solution of K_2SO_4 (3.06mL, 6.12mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 7h. After concentration *in vacuo*, the residue is purified by HPLC to give a pure product (162) as a pale yellow solid (500mg, 93%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.90(dd, 3H), 2.34(s, 3H), 5.68(dq, 1H), 6.67(d, 1H), 7.20(t, 1H), 7.35(d, 1H), 7.70(d, 1H)
LC/MS (ES+) m/z = 177.10, 218.13

EXAMPLE 163

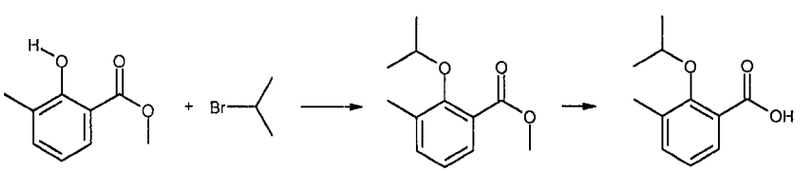
5-Bromo-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid (163):

To a solution of 3-methyl-2-((E)-propenyl)-benzoic acid (162) (470mg, 2.67mmol), 2-amino-5-bromo-indan-2-carboxylic acid ethyl ester (835mg, 2.94mmol) and HATU (1.22mg, 3.20mmol) in anhydrous DMF (12mL) is added DIPEA (529μL, 3.20mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is

purified by flash column chromatography (300g silica gel, gradient elution: 5-60% EtOAc in heptane) to give a white solid (1.12g), which is dissolved in EtOH (15mL) and water (1mL) together with KOH (1.20g, 21mmol) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (100mL) and acidified with conc. HCl until no more precipitate came out of the water. The filtered compound is purified by HPLC to give a pure product (163) as white solid (1.03g, 93% overall yield).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.74(dd, 3H), 2.25(s, 3H), 3.30(dd, 2H), 3.74(dd, 2H), 5.73(dq, 1H), 6.32(d, 1H), 6.51(s, 1H), 7.08-7.38(m, 6H)
LC/MS (ES+) m/z = 414.09, 416.09

EXAMPLE 164



164

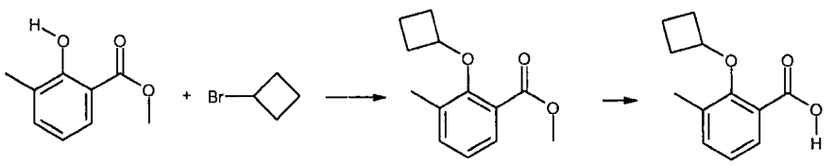
2-Isopropoxy-3-methyl-benzoic acid (164):

A 250mL round bottom flask is charged with methyl 2-hydroxy-3-methylbenzoate (10g, 60.18mmol) and dry N,N-dimethylformamide (DMF, 120mL). A stirring bar is added and stirring is initiated. After 2 minutes 2-Bromopropane (8.1mL, 86.65mmol) is added via syringe. KI (20mg, cat.) and $CsCO_3$ (44.42g, 136.32mmol) are added in order. The reaction is capped. The reaction flask is fitted with a heating mantle that is warmed to 43°C. After 4 days, tlc analysis (silica, 1:3 EtOAc:heptanes) indicates that the starting phenol is consumed and converted to a single spot as visualized by UV analysis. The heating source is removed from the reaction flask. After stirring for an additional 2h at ambient temperature, the contents of the reaction flask are filtered through a pad of Celite. The Celite pad is washed with EtOAc:heptanes (1:1, 200mL). The filtrate is transferred to a separatory funnel and washed with brine (100mL), water (100mL), saturated aqueous $NaHCO_3$ (100mL). This washing sequence is repeated (1 time) followed by a final washing with brine (50mL). The organic layer is dried over $MgSO_4$, filtered and evaporated *in vacuo*. Pumping to constant weight provided 11.88g of pale yellow oil. The 250mL flask containing the above material is charged with 1,4-dioxane (50mL) and MeOH (100mL). A stirring bar is added and stirring is initiated.

After dissolution, water (50mL) is added followed by the LiOH hydrate (5.7g, 135.8mmol). After 18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, 55mL). The contents of the flask are transferred to a separatory funnel containing EtOAc (100mL). The layers are separated. The aqueous layer is extracted with EtOAc (50mL). The combined organic extracts are washed with water (50mL) and brine (50mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Pumping to constant weight gives 10.19g (52.46mmol, 87.18 %) of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.18 (d, 6 H), 2.22, (s, 3H), 4.19 (m, 1H), 7.03 (dd, 1H), 7.38, (dd, 1H), 7.48 (dd, 1H).
LC/MS m/z=195.

EXAMPLE 165



165

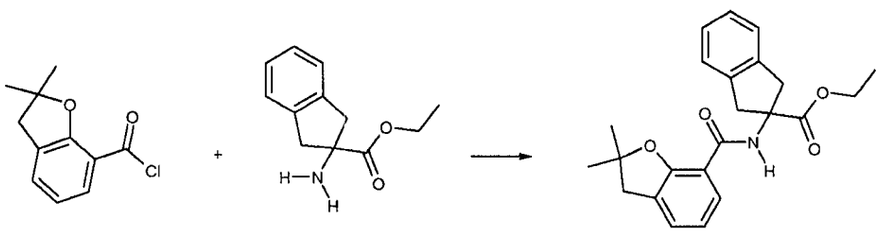
2-Cyclobutoxy-3-methyl-benzoic acid (165):

A 100mL round bottom flask is charged with methyl 2-hydroxy-3-methylbenzoate (5g, 30.09mmol) and dry N,N-dimethylformamide (DMF, 60mL). A stirring bar is added and stirring is initiated. After 2min bromocyclobutane (5g, 37.04mmoles) is added via syringe. Potassium iodide (10mg, cat.) and $CsCO_3$ (22.21g, 68.16mmol) are added in order. The reaction is capped. The reaction flask is fitted with a heating mantle that is warmed to 43°C. After 4 days, tlc analysis (silica, 1:3 EtOAc:heptanes) indicates that the starting phenol had been consumed and converted to a single spot as visualized by UV analysis. The heating source is removed from the reaction flask. After stirring for an additional 16h at ambient temperature, the contents of the reaction flask are filtered through a pad of Celite. The Celite pad is washed with EtOAc:heptanes (1:1, 200mL). The filtrate is transferred to a separatory funnel and washed with brine (50mL), water (50mL), saturated aqueous $NaHCO_3$ (50mL). This washing sequence is repeated (1x) followed by a final washing with brine (50mL). The organic layer is dried over $MgSO_4$, filtered and evaporated *in vacuo*. Pumping to constant weight gives 5.94g of pale yellow oil. The 100mL flask containing the above material is

charged with 1,4-dioxane (30mL) and MeOH (30mL). A stirring bar is added and stirring is initiated. After dissolution, water (10mL) is added followed by the LiOH hydrate (2.80g, 66.78mmol). After 18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, 30mL). The contents of the flask are transferred to a separatory funnel that contains EtOAc (80mL). The layers are separated. The aqueous layer is extracted with EtOAc (40mL). The combined organic extracts are washed with water (50mL) and brine (50mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Pumping to constant weight gives 5.3g (25.70mmol, 85.40 %) of a white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.37 (m, 1 H), 1.42 (m, 1 H), 2.02 – 2.26, (m, 4 H), 2.22 (s, 3 H) 4.35 (m, 1H), 7.03 (dd, 1H), 7.36, (dd, 1H), 7.47 (dd, 1H).
LC/MS m/z = 207.

EXAMPLE 166



2 166

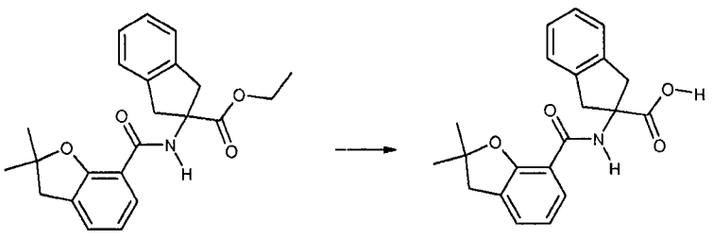
2-[(2,2-Dimethyl-2,3-dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (166):

A test tube (25 x 150 mm) containing a stirring bar and 2-amino-indane-2-carboxylic acid ethyl ester (0.5g, 2.436mmol) is charged with dry DCM (3mL). Stirring is initiated. After dissolution, the DIPEA (1.50mL, 8.6mmol) and 4-dimethylaminopyridine (2mg, 17μmol) are added. A solution of 2,2-dimethy-2,3-dihydro-1-benzofuran-7-carbonyl chloride (0.73g, 3.47mmol) in dry DCM (4mL) is added to the reaction tube. After stirring for 18h, tlc analysis (silica, 10 % CH_3OH in DCM) indicates complete consumption of the starting amine. The reaction mixture is diluted with DCM (10mL) and washed with 5% aqueous HCl (2 x 5mL) and brine (5mL), dried over $MgSO_4$ filtered and evaporated by pumping to constant weight gives 0.72g of a light brown gum. This material is purified by chromatography (silica, 0% to 20 % EtOAc in DCM) on the ISCO Companion using a 40g cartridge (silica). Fractions 17 -

22 are combined, evaporated and pumped to a constant weight to provide 0.62g (67 %) of a glassy solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.14 (t, 3 H), 1.37 (s, 6 H) 3.03, (s, 2 H), 3.43 (dd, 4H), 4.12 (q, 2H), 6.91 (dd, 1H), 7.16 - 7.27 (m, 4H), 7.35 (dd, 1H), 7.56 (d, 1H), 8.32 (s, 1H).
LC/MS m/z = 380.

EXAMPLE 167



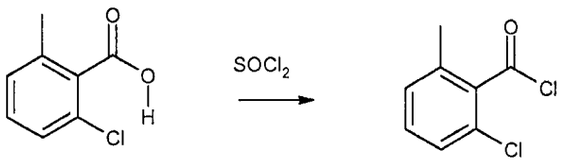
167

2-[(2,2-Dimethyl-2,3-dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid (167):

A 50mL round bottom flask containing the 2-[(2,2-dimethyl-2,3-dihydro-benzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.45g, 1.179mmol) is charged with MeOH (25mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (8mL) and the LiOH (108mg, 2.58mmol) are added. After 56h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 3 by slowly adding dilute aqueous HCl (3%, ~20mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (30mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 460mg of material. The sample is purified by column chromatography (silica, 2 % to 15 % CH_3OH in DCM) using an ISCO Companion and a 12g cartridge. Fraction 3 is collected and evaporated. After pumping to constant weight, 375mg (90 %) of a dry white powder is obtained.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.36 (s, 6 H) 2.99, (s, 2 H), 3.40 (dd, 4H), 6.88 (dd, 1H), 7.11 - 7.20 (m, 4H), 7.30 (dd, 1H), 7.57 (d, 1H), 8.34 (s, 1H).
LC/MS m/z = 352.

EXAMPLE 168

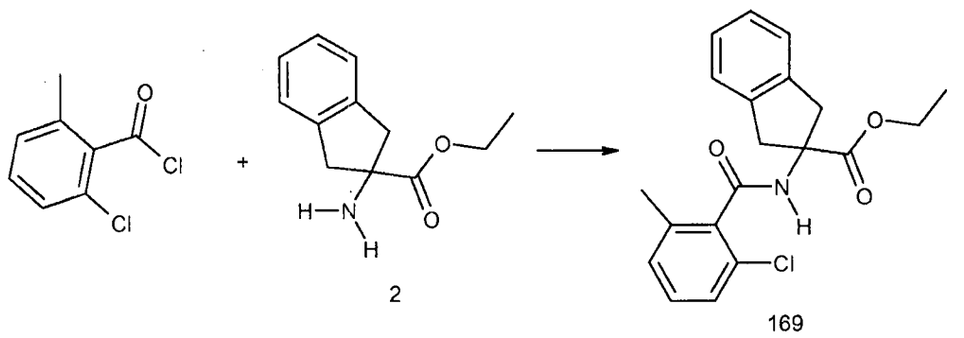


168

2-Chloro-6-methylbenzoyl chloride(168):

A round bottom flask containing the 2-chloro-6-methy-benzoic acid (1.5g, 8.79mmol) and a stirring bar is charged with dry DCM (10mL). Stirring is initiated. After several min, a solution of thionyl chloride (in DCM (2M), 6.6mL, 13.2mmol) is added via syringe. 2 drops of DMF are then added. The reaction immediately began to bubble gently. After 2h bubbling ceases. After 3h, the solvent is removed from the reaction mixture *in vacuo*. The oily residue is redissolved in DCM (6mL) and the solvent once again removed *in vacuo*. The residue is dissolved in dry DCM (6mL) and used without further purification in the next reaction sequence.

EXAMPLE 169



169

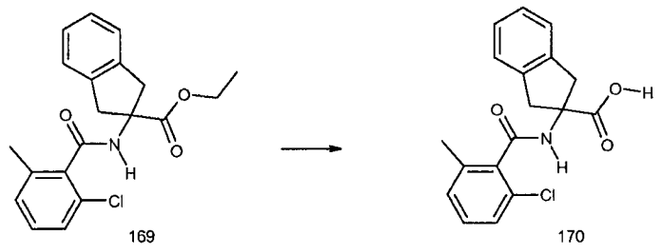
2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid ethyl ester (169):

A test tube (25 x 150 mm) containing a stirring bar and 2-amino-indan-2-carboxylic acid ethyl ester (0.53g, 2.58mmol) is charged with dry DCM (3mL). Stirring is initiated. After dissolution, the DIPEA (1.50mL, 8.6mmol) and 4-dimethylaminopyridine (2mg, 17μmol) are added. A solution of 2-chloro-6-methylbenzoyl chloride (5.8mmol) in dry DCM (4mL), as prepared above, is added to the reaction tube. After stirring for 18h, tlc analysis (silica, 10 % CH_3OH in DCM) indicates complete consumption of the amine. The reaction mixture is diluted with DCM (10mL) and washed with 5% aqueous HCl (2 x 5mL) and brine (5mL), dried over MgSO4 filtered and evaporated by pumping to constant weight gives 1.07g of light brown solid. This material is purified by chromatography (silica, 2 % to 20 % EtOAc in

DCM) on the ISCO Companion using a 40g cartridge. Fractions 6 - 10 are combined, evaporated and pumped to yield a constant weight 550mg of white amorphous solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.19 (t, 3 H) 3.33, (s, 3 H), 3.45 (dd, 4H), 4.13 (q, 2H), 6.88 (dd, 1H), 7.12 - 7.47 (m, 7H), 9.11 (s, 1H).
LC/MS m/z = 358.

EXAMPLE 170

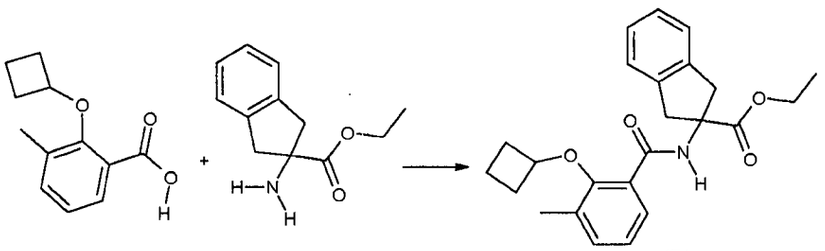


2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid (170):

A 100mL round bottom flask containing the 2-(2-chloro-6-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (0.255g, 0.712mmol) is charged with MeOH (15mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (5mL) is added and starting material begins to precipitate out. Tetrahydrofuran is added to re-solublize the starting material. LiOH (90mg, 2.14mmol) is added. After 16h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 3 by slowly adding dilute aqueous HCl (3%, ~20mL). The contents of the flask are poured into an addition funnel containing DCM (30mL). The layers are separated. The aqueous layer is extracted with DCM (20mL). The combined organic extracts are washed with water (30mL) and brine (20mL), dried over MgSO4, filtered and concentrated to yield 280mg of material. The material is purified by column chromatography (silica, 2% to 15 % CH_3OH in DCM) using an ISCO Companion and a 12g cartridge. Fraction 2 is collected and evaporated. After pumping to constant weight, 130mg of dry white powder is obtained.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.27, (s, 3 H), 3.45 (dd, 4H), 7.14 - 7.39 (m, 7H), 8.96 (s, 1H). LC/MS m/z = 330.

EXAMPLE 171

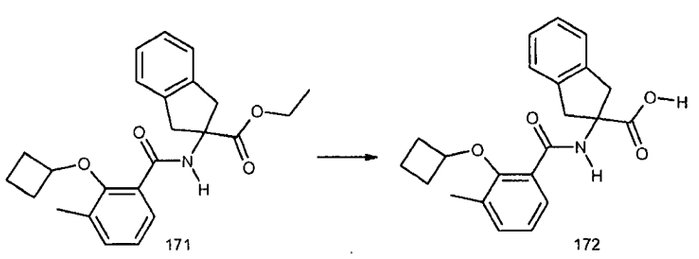


165 2 171

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (171):

A 25mL vial containing a stirring bar is charged with 2-cyclobutoxy-3-methyl-benzoic acid (1.01g, 4.87mmol) and dry DCM (14mL). Stirring is initiated. HBTU (1.84g, 4.86mmol) is added. After 5min, the 2-aminoindane-2-carboxylic acid ethyl ester (1g, 4.87mmol) is added followed by the DIPEA (1.9mL, 10.92mmol). The reaction is allowed to stir for 12 days. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (70mL) and transferred to a separartory funnel. This is washed consecutively with dilute aqueous HCl (3%, 35mL), saturated aqueous $NaHCO_3$ (35mL) and brine (35mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 2.56g of an off-white solid. This material is dissolved in 15mL of DCM. This is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10% EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 100 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 7 through 22 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 1.73g.

EXAMPLE 172



171 172

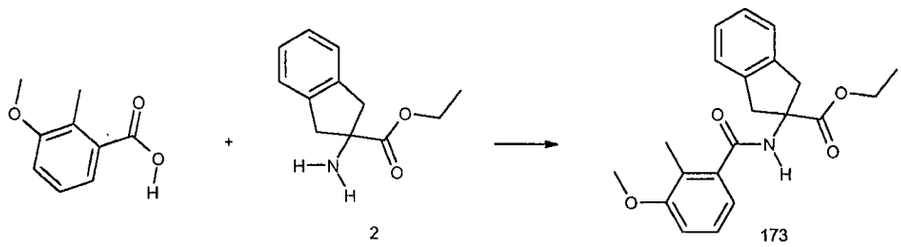
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (172):

A 50mL flask containing the 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid ethyl ester (1.72g, 4.37mmol) is charged with 1,4-dioxane (16mL) and MeOH (16mL). A stirring bar is added and stirring is initiated. After dissolution, water (8mL) is added followed

by the LiOH (458mg, 10.91mmol). After 20h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~25mL). The contents of the flask are poured into a separatory funnel containing EtOAc (60mL). The layers are separated. The aqueous layer is extracted with EtOAc (30mL). The combined organic extracts are washed with water (35mL) and brine (35mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 1.58g of a white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.16 – 1.27 (m, 1H), 1.38 – 1.53 (m, 1H), 1.78 – 2.03 (m, 4H), 2.23, (s, 3 H), 3.44 (dd, 4H), 4.34 (m, 1H), 7.03 (dd, 1H), 7.17 - 7.37 (m, 6H), 8.64 (s, 1H), 12.59 (bs, 1H).
LC/MS m/z = 364.

EXAMPLE 173



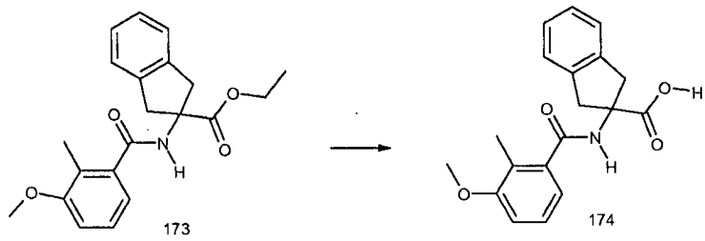
2-(3-Methoxy-2-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (173):

A 100mL round bottom flask is charged with 2-amino-indane-2-carboxylic acid ethyl ester (750mg, 3.65mmol) and dry DCM (10mL). A stirring bar is added and stirring is initiated. The HBTU (1.38g, 3.65mmol) is added. After 2min, the 2-methyl-3-methoxy-benzoic acid (0.61g, 3.65mmol) and DIPEA (1.5mL, 8.6mmol) are added. The reaction is allowed to stir for 36h. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 1.1g of thick brownish gum. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes over 2 column volumes followed by a step gradient to 30% EtOAc then 50% and then 70% EtOAc for 3 column volumes each with ramp of 1 column volume. 35mL fractions are collected.

Fractions 15 through 21 are combined and evaporated in vacuo. Pumping to a constant weight gives a white solid (1.15 g).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.19 (t, 3 H), 2.12 (s, 3 H), 3.54 (dd, 4H), 3.78 (s, 3 H), 4.12 (q, 2H), 6.79 (d, 1H), 6.99 (d, 1H), 7.14 - 7.24 (m, 6H), 8.97 (s, 1H).
LC/MS m/z = 354.

EXAMPLE 174

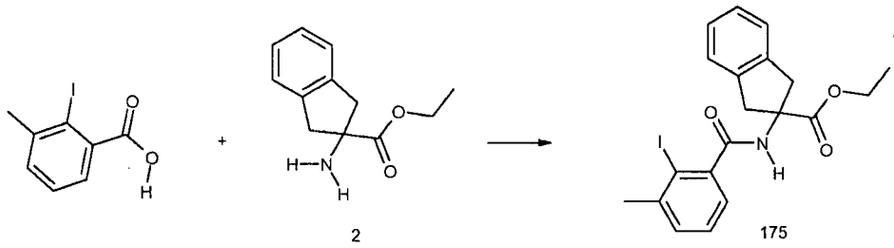


2-(3-Methoxy-2-methyl-benzoylamino)-indane-2-carboxylic acid (174):

A 40mL vial containing the 2-(3-methoxy-2-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (0.65g, 1.84mmol) is charged with THF (10mL) MeOH (10mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (5mL) is added followed by the LiOH (267mg, 6.36mmol). After 36h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into an addition funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over MgSO4, filtered and concentrated to yield 620mg of amorphous white solid. The sample is purified by column chromatography (silica, 2% to 15 % CH_3OH in DCM) using an ISCO Companion and a 40g cartridge. Fractions 14-16 are collected and evaporated by pumping to constant weight gives 380mg of dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.11, (s, 3 H), 3.44 (dd, 4H), 3.77, (s, 3 H), 6.79 (d, 1H), 6.97 (d, 1H), 7.13-7.23 (m, 5H), 8.82 (s, 1H), 12.49 (s, 1H).
LC/MS m/z = 326.

EXAMPLE 175



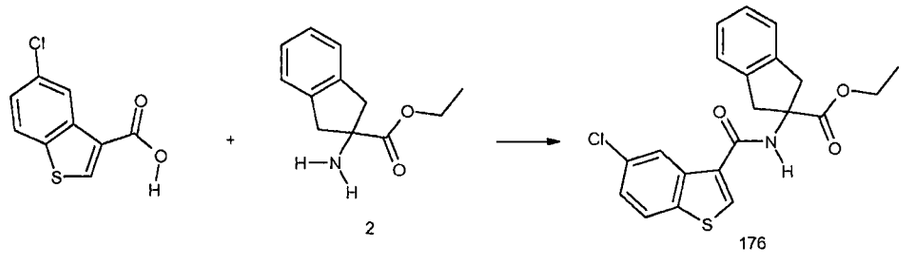
2-(2-Iodo-3-methyl-benzoylamino)-indane-2-carboxylic acid ethyl ester (175):

A 100mL round bottom flask is charged with 2-iodo-3-methylbenzoic acid (1.92g, 7.31mmol) and dry DCM (25mL). A stirring bar is added and stirring is initiated. After 5min, the HBTU (2.37g, 7.31mmol) is added. After 5min, the 2-amino-indane-2-carboxylic acid ethyl ester (1.5g, 7.31mmol) is added followed by N,N-diisopropylethyl-amine (3.2mL, 18.37mmol). The reaction is allowed to stir for 118h. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (70mL). This is washed dilute aqueous HCl (3%, 2 x 30mL), saturated aqueous $NaHCO_3$ (2 X 30mL) and brine (30mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 2.04g of a white solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 10 column volumes. 27mL fractions of UV active eluent are collected. Fractions 10 through 15 are combined and evaporated *in vacuo*. Pumping to constant weight gives 1.04g a white solid material.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.20 (t, 3 H), 2.39 (s, 3 H), 3.52 (dd, 4H), 4.15 (q, 2H), 6.79 (d, 1H), 6.97 (d, 1H), 7.16 - 7.24 (m, 4H), 7.28 - 7.38 (m, 2H), 9.15 (s, 1H).

LC/MS m/z = 450.

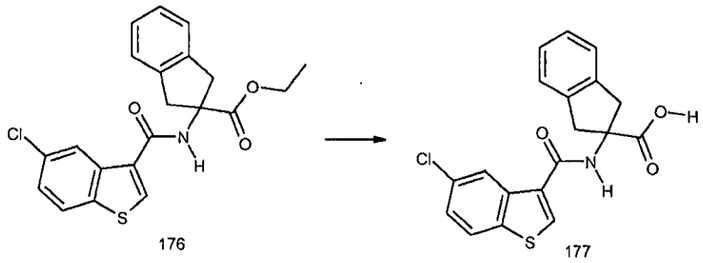
EXAMPLE 176



2-[(5-Chloro-benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (176):

To a 40mL vial containing a stirring bar, 5-chloro-benzo[b]thiophene-3-carboxylic acid (518g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and DIPEA (0.95mL, 8.0mmol) are added. Then 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 20h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.64g of off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 7 through 31 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.94g.

EXAMPLE 177



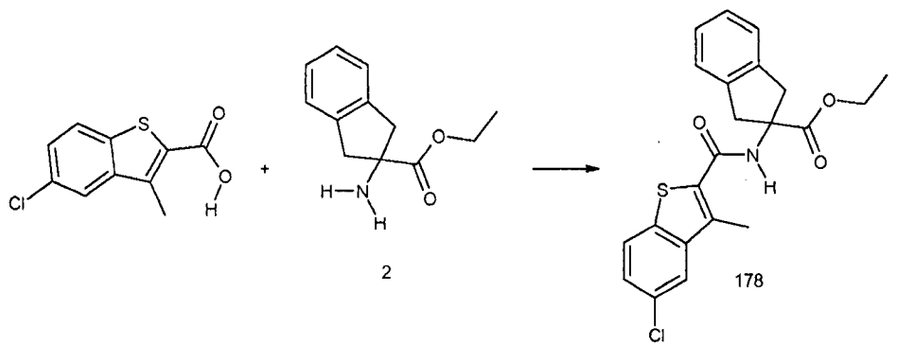
2-[(5-Chloro-benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid (177):

A 50mL flask containing the 2-[(5-chloro-3-benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (0.66g, 1.65mmol) is charged with 1,4-dioxane (10mL) and MeOH 10mL). A stirring bar is added and stirring is initiated. After dissolution, water (5mL) is added followed by the LiOH (173mg, 4.13mmol). After 15h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over MgSO4, filtered and concentrated. Pumping to constant weight gives 590mg of dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.52 (dd, 4H), 7.15 – 7.27 (m, 4H), 7.46 (dd, 1H), 8.09 (d, 1H), 8.44 (d, 1H), 8.52 (s, 1H), 8.99 (s, 1H), 12.55 (bs, 1H).

LC/MS m/z = 372.

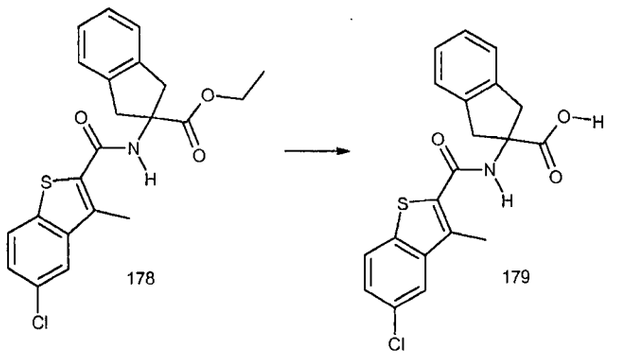
EXAMPLE 178



2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester(178):

To a 40mL vial containing a stirring bar, 5-chloro3-methyl-benzo[b]thiophene-2-carboxylic acid ([50451-84-8], 0.81g, 3.53mmol) is charged with dry DCM (10mL). Stirring is initiated. HBTU (1.34g, 3.54mmol) and the DIPEA (1.4mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (0.725g, 3.53mmol) is added. The reaction is allowed to stir for 240h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (80mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.26g of a off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a step gradient to 30% and then 50% and then 70 % EtOAc for 2 column volumes each with a ramp of 1 column volume. 25mL fractions are collected. Fractions 22 through 60 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.78g.

EXAMPLE 179

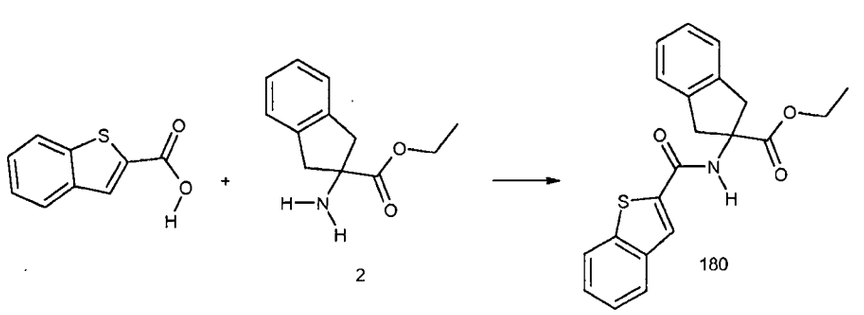


2-[(5-Chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid (179):

40mL vial containing the 2-[(5-chloro-3-methyl-benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (0.53g, 1.28mmol) is charged with MeOH (7.5mL) and a stirring bar is added. Stirring is initiated. After dissolution, water (3.8mL) is added followed by the LiOH (134mg, 3.20mmol). After 36h, tlc analysis (silica, 5% i-PrOH/ DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated to yield 360mg of amorphous white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.45 (s, 3H) 3.49 (dd, 4H), 7.15 – 7.29 (m, 4H), 7.48 (dd, 1H), 7.92 (d, 1H), 8.02 (d, 1H), 8.96 (s, 1H).
LC/MS m/z = 386.

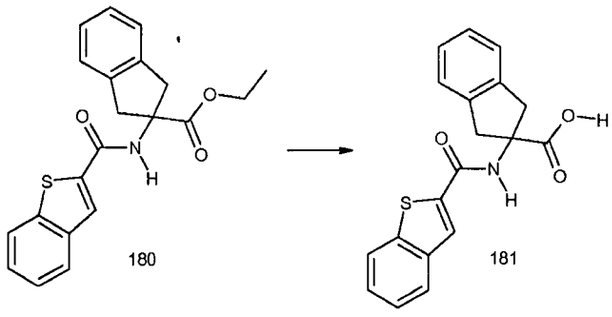
EXAMPLE 180



2-[(Benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (180):

To a 40mL vial containing a stirring bar, benzo[b]thiophene-2-carboxylic acid (518g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and the DIPEA (0.95mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 110h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/ DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over MgSO4, filtered and evaporated *in vacuo* to provide 1.54g of an off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 13 through 27 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.62g.

EXAMPLE 181

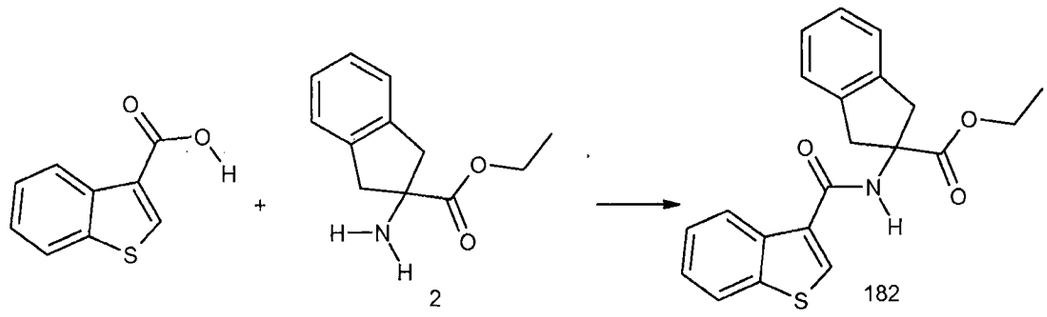


2-[(Benzo[b]thiophene-2-carbonyl)-amino]-indane-2-carboxylic acid (181):

A 50mL flask containing the 2-[(Benzo[b]thiophene-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.37g, 1.01mmol) is charged with 1,4-dioxane (6mL) and MeOH 6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3.0mL) is added followed by the LiOH (106mg, 2.53mmol). After 18h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 290mg (89 %) of dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.57 (dd, 4H), 7.15 – 7.32 (m, 4H), 7.45 – 7.48 (m, 2H) 7.91 (dd, 1H), 8.01 (dd, 1H), 8.18 (s, 1H), 9.11 (s, 1H), 12.58 (bs, 1H).
LC/MS m/z = 338.

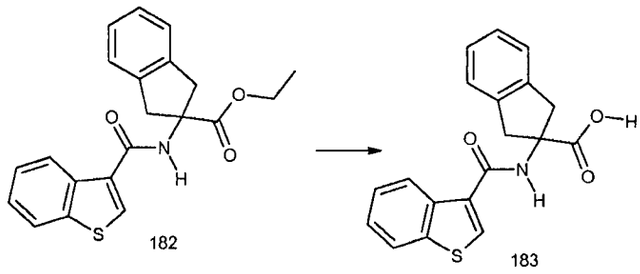
EXAMPLE 182



2-[(Benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (182):

To a 40mL vial containing a stirring bar, benzo[b]thiophene-3-carboxylic acid ([5381-25-9], 434g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and DIPEA (0.95mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 20h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 1.64g of off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 20 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 4 through 16 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.69g.

EXAMPLE 183

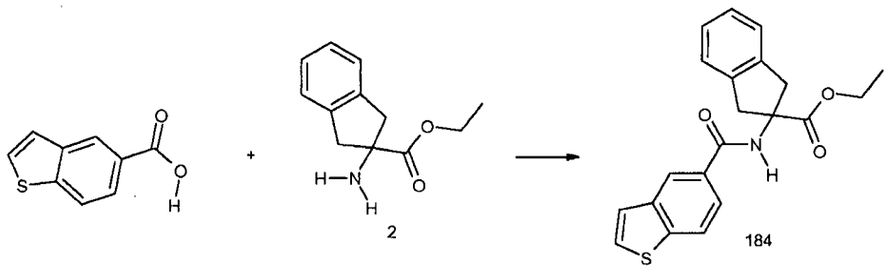


2-[(Benzo[b]thiophene-3-carbonyl)-amino]-indane-2-carboxylic acid (183):

A 50mL flask containing the 2-[(benzo[b]thiophene-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (182, 0.40g, 1.10mmol) is charged with 1,4-dioxane (10mL) and MeOH 10mL). A stirring bar is added and stirring is initiated. After dissolution, water (5.0mL) is added followed by the LiOH (115mg, 2.74mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Dilute aqueous HCl (3%, ~15mL) and EtOAc (25mL) are added to the reaction flask. After stirring for 10min, the contents of the flask are poured into a separatory funnel. The layers are separated. The aqueous layer is extracted with EtOAc (30mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 450mg of a dry white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.52 (dd, 4H), 7.18 – 7.28 (m, 4H), 7.38 – 7.43 (m, 2H) 8.03X (dd, 1H), 8.37 - 8.41 (m, 2H), 8.92 (s, 1H), 13.53 (bs, 1H).
LC/MS m/z = 338.

EXAMPLE 184

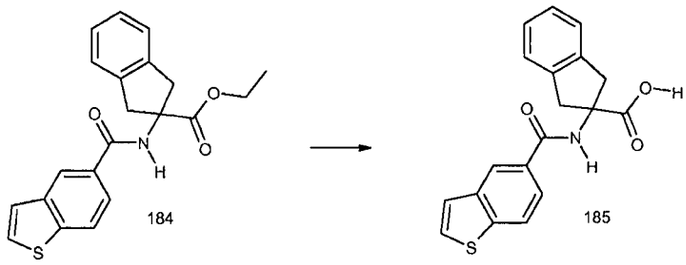


2-[(Benzo[b]thiophene-5-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester(184):

To a 40mL vial containing a stirring bar, benzo[b]thiophene-5-carboxylic acid (434g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and DIPEA (0.95mL, 8mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 64h. Analysis by tlc of the

reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over MgSO4, filtered and evaporated in vacuo to provide 1.4g of an off white solid. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 4 through 16 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.79g.

EXAMPLE 185

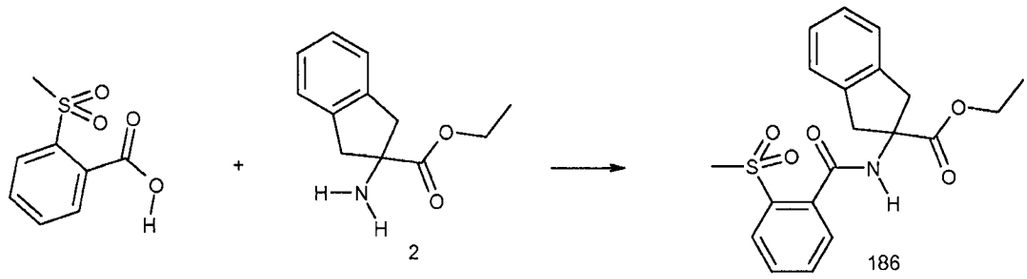


2-[(Benzo[b]thiophene-5-carbonyl)-amino]-indane-2-carboxylic acid (185):

A 50mL flask containing the 2-[(benzo[b]thiophene-5-carbonyl)-amino]-indane-2-carboxylic acid ethyl ester (184, 0.45g, 1.25mmol) is charged with 1,4-dioxane (8mL) and MeOH (8mL). A stirring bar is added and stirring is initiated. After dissolution, water (4.0mL) is added followed by the LiOH (131mg, 3.11mmol). After 114h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.42g of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.57 (dd, 4H), 7.18 - 7.28 (m, 5H), 7.59 (d, 1H), 7.78 - 7.93 (m, 2H), 8.08 (d, 1H), 8.41 (s, 1H), 8.91 (s, 1H).
LC/MS m/z = 338.

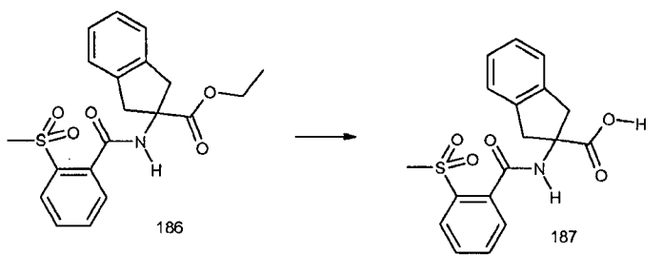
EXAMPLE 186



2-[(2-methylsulfonylbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (186):

To a 40mL vial containing a stirring bar, 2-(methylsulfonyl)benzoic acid (0.4g, 2.88mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol). The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added followed by the DIPEA (0.95mL, 8mmol). The reaction is allowed to stir for 36h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over MgSO4, filtered and evaporated in vacuo to provide 1.32g of white solid. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 5 through 8 are combined and evaporated in vacuo. Pumping to a constant weight gives amorphous white solid 0.71g.

EXAMPLE 187



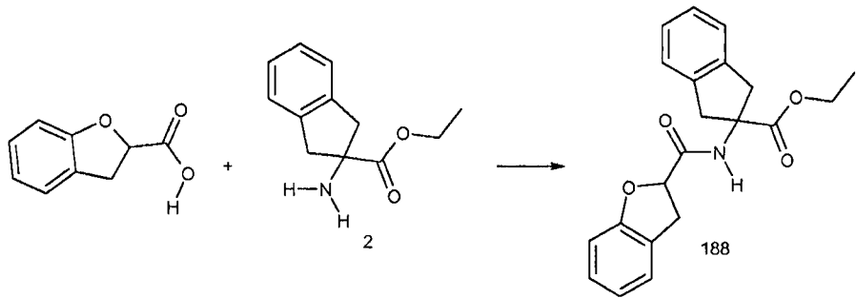
2-[(2-methylsulfonylbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid (187):

A 50mL flask containing 2-[(2-methylsulfonylbenzene-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (186, 0.50g, 1.27mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL)

is added followed by the LiOH (133mg, 3.17mmol). After 69h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.46g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.37 – 3.61 (m, 7 H), 7.16 – 7.23 (m, 4 H), 7.54 (d, 1H), 7.69 (dd, 1H), 7.79 (dd, 1H), 7.93 (d, 1H), 9.25 (s, 1H), 12.55 (s, 1H).
LC/MS m/z = 360.

EXAMPLE 188

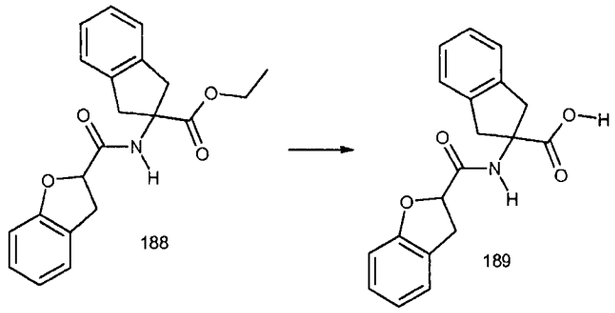


2-[(2,3-Dihydrobenzofuran-2-carbonyl)-amino]-indan-2-carboxylic acid acid ethyl ester(188):

To a 40mL vial containing a stirring bar, 2,3-dihydro-1-benzofuran-2-carboxylic acid (0.4g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) and the DIPEA (0.95mL, 8.0mmol) are added. The 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added. The reaction is allowed to stir for 16h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.47g of viscous yellow oil. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are

collected. Fractions 3 through 6 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.68g.

EXAMPLE 189



188 189

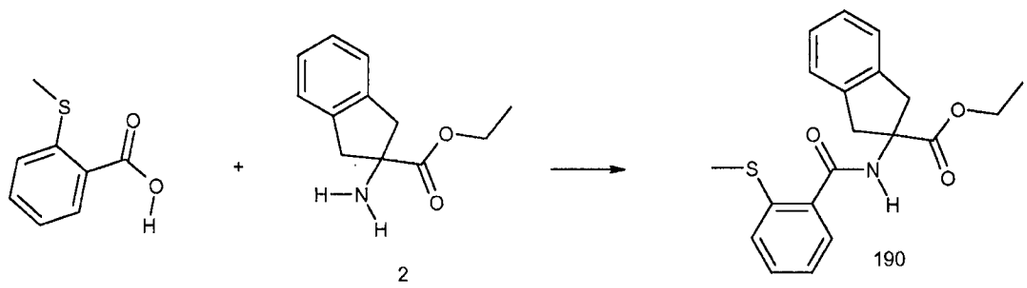
2-[(2,3-Dihydrobenzofuran-2-carbonyl)-amino]-indan-2-carboxylic acid (189):

A 50mL flask containing the 2-[(2,3-dihydrobenzofuran-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.447g, 1.39mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH hydrate (133mg, 3.17mmol). After 19h, tlc analysis (silica, 5% *i*-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.43g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.17 (dd, 1H), 3.21 – 3.58 (m, 5H), 5.13 (dd, 1H), 6.79 (dd, 1H), 6.84 (dd, 1H), 7.03 – 7.28 (m, 6H) 8.64 (s, 1H), 12.55 (bs, 1H).

LC/MS m/z = 324.

EXAMPLE 190

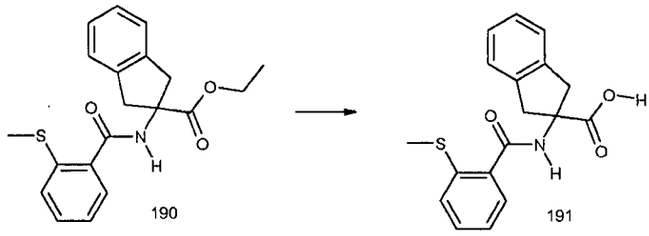


2 190

2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (190):

To a 40mL vial containing a stirring bar, 2-(methythiol)benzoic acid ([3724-10-5], 0.410g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) is added. After 2min, the 2-aminoindane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added followed by DIPEA (0.95mL, 8.0mmol). The reaction is allowed to stir for 38h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.49g of viscous yellow oil. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% over 8 column volumes and then 90 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 8 through 15 are combined and evaporated *in vacuo*. Pumping to a constant weight gives amorphous white solid 0.69g.

EXAMPLE 191



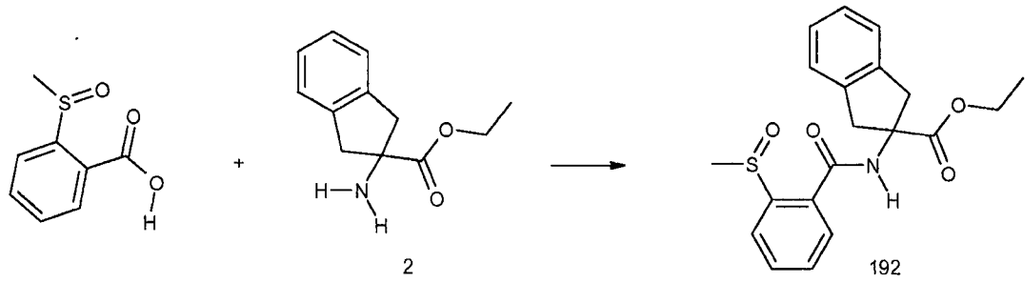
2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid (191):

A 50mL flask containing the 2-[(2-methylthiobenzene-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.510g, 1.44mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH hydrate (150mg, 3.58mmol). After 96h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over MgSO4, filtered and concentrated. Pumping to constant weight gives 0.34g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.37 (s, 3 H), 3.47 (dd, 4 H), 7.14– 7.21 (m, 5 H), 7.22–7.44 (m, 3 H), 8.88 (s, 1H), 12.46 (s, 1H).

LC/MS m/z = 328.

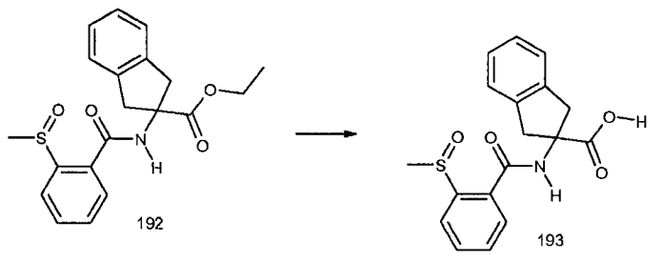
EXAMPLE 192



2-[(2-methylsulfinylbenzoyl)-amino]-indan-2-carboxylic acid ethyl ester (192):

To a 40mL vial containing a stirring bar, 2-(methylsulfinyl)benzoic acid (0.449g, 2.44mmol) is charged with dry DCM (7mL). Stirring is initiated. HBTU (922mg, 2.43mmol) is added. The 2-aminoindane-2-carboxylic acid ethyl ester ([500mg, 2.44mmol) is added followed by DIPEA (0.95mL, 8.0mmol). The reaction is allowed to stir for 94h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 1.2g of yellow foam. This material is dissolved in 10mL of DCM and purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 100% EtOAc over 8 column volumes and then hold for 5 column volumes. 25mL fractions are collected. Fractions 9 through 18 are combined and evaporated *in vacuo* to a constant weight to give 0.75g of amorphous off-white solid.

EXAMPLE 193

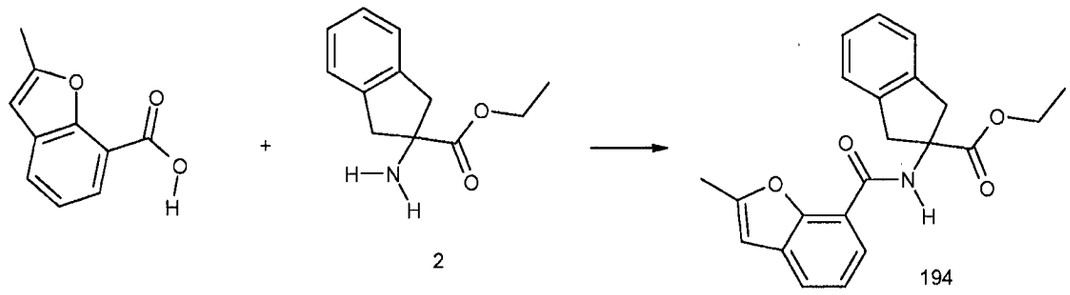


2-[(2-methylsulfinylbenzoyl)-amino]-indan-2-carboxylic acid (193):

A 50mL flask containing the 2-(2-methylsulfinylbenzoyl-amino)-indan-2-carboxylic acid ethyl ester (0.50g, 1.34mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH (141mg, 3.36mmol). After 39h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by vacuum to constant weight of 0.39g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 3.35 (s, 3 H), 3.48 (dd, 4 H), 7.16 – 7.27 (m, 4 H), 7.60 (dd, 1H), 7.67 – 7.84, (m, 2 H), 8.07 (d, 1H), 9.22 (s, 1H), 12.63 (bs, 1H).
LC/MS m/z = 344.

EXAMPLE 194

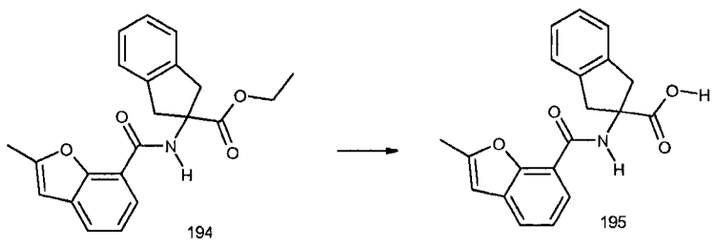


2-[(2-Methylbenzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (194):

To a 25mL vial containing a stirring bar, 2-methylbenzofuran-7-carboxylic acid (0.343g, 1.95mmol) is charged with dry DCM (6mL). Stirring is initiated. HBTU (738mg, 1.95mmol) is added. The 2-aminoindane-2-carboxylic acid ethyl ester (400mg, 1.95mmol) is added followed by DIPEA (0.75mL, 4.31mmol). The reaction is allowed to stir for 16h. Analysis by tlc of the reaction mixture (silica, 10% EtOH/dichloromethane) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.97g of yellow oil. This material is dissolved in 10mL of DCM. This is purified utilizing an ISCO Companion with a 40g

cartridge of silica. The gradient is 15 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 90% over 15 column volumes and then 100 % EtOAc for 2 column volumes with a ramp of 1 column volume. 25mL fractions are collected. Fractions 2 through 7 are combined and evaporated *in vacuo* to a constant weight to give 0.63g of amorphous white solid.

EXAMPLE 195

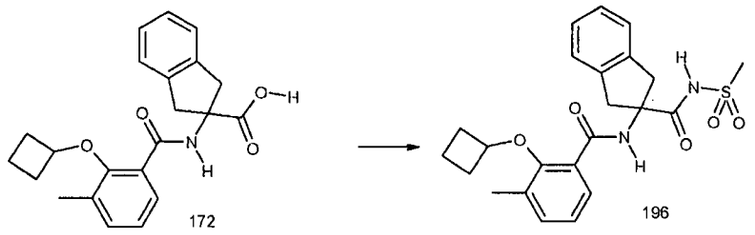


2-[(2-Methylbenzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid (195):

A 50mL flask containing the 2-[(2-methylbenzofuran-7-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (0.40g, 1.10mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (115mg, 2.75mmol). After 18h, tlc analysis (silica, 5% *i*-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by vacuum to constant weight to give 0.37g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.42, (s, 3 H), 3.47 (dd, 4H), 6.68, (s, 1 H), 7.17-7.27 (m, 5 H) 7.57 (dd, 1H), 7.67 (dd, 1H), 8.68 (s, 1H), 12.63 (s, 1H).
LC/MS m/z = 336.

EXAMPLE 196

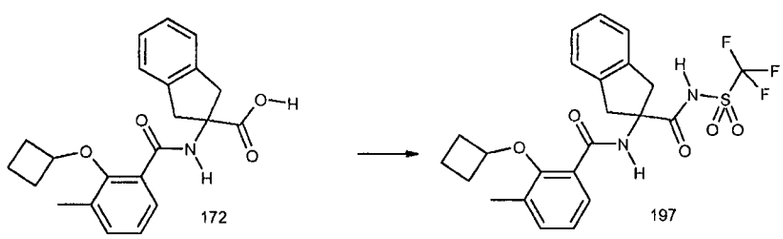


2-Cyclobutoxy-N-(2-methanesulfonylaminocarbonyl-indan-2-yl)-3-methyl-benzamide (196):

A 30mL vial is charged with 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid (245mg, 0.67mmol) and dry DCM (5.0mL). A stirring bar is added and stirring is initiated. The methanesufonamide (89mg, 0.936mmol) is added. To the resultant suspension, (N-(3-dimethylaminopropyl)-N'-ethylcarbodiiimide hydrochloride (120mg, 0.624mmol) and 4-dimethylaminopyridine (76mg, 0.62mmol) are added. After 6 days, tlc analysis (silca, 10% MeOH in DCM) indicates that the starting acid is consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to a separatory funnel and washed with dilute aqueous HCl (3 N, 3 x 20mL) and brine, dried over $MgSO_4$, filtered and evaporated by pumping to constant weight gives 0.26g of amorphous white foam. This material is dissolved in DCM (5mL) and applied to a 12g column (silica) on an ISCO Companion. The column is eluted with 1% iPrOH in DCM for 3 column volumes followed by a linear gradient to 30% iPrOH in DCM over 15 column volumes. 12mL fractions of UV active eluent are collected. Fractions 4 through 9 are combined and evaporated to a constant weight to give 0.2g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.01 – 1.31 (m, 2H), 1.45 – 1.68 (m, 2H), 1.72 – 1.83 (m, 2H), 2.21 (s, 3 H), 3.18 (s, 3 H), 3.42 (m, 4H), 4.18 (m, 1 H), 7.16 (t, 1 H), 7.19 – 7.22 (m, 2H), 7.27 – 7.36 (m, 2H), 7.38 (d, 1H), 7.62 (d, 1H), 8.43 (s, 1H), 11.59 (s, 1H).
LC/MS m-/z = 441.

EXAMPLE 197

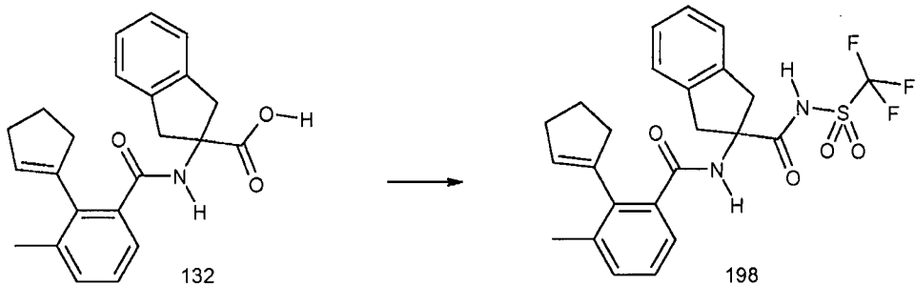


2-Cyclobutoxy-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide (197):

A 30mL vial is charged with 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid (323mg, 0.884mmol) and dry DCM (7.0mL). A stirring bar is added and stirring is initiated, and then trifluoromethanesulfonamide (198mg, 1.33mmol) is added. To the resultant suspension, N-(3-dimethylaminopropyl)-N'-ethylcarbodiiimide hydrochloride (170mg, 0.88mmol) and 4-dimethylaminopyridine (108mg, 0.88mmol) are added. After 8 days, tlc analysis (silca, 10% MeOH in DCM) indicates that the starting acid had been consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to a separatory funnel and washed with dilute aqueous HCl (3 N, 2 x 20mL) and brine, dried over $MgSO_4$, filtered and evaporated to constant weight to give 0.51g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.21 – 1.38 (m, 1H), 1.41 – 1.56 (m, 1H), 1.91 – 2.04 (m, 4H), 2.23 (s, 3 H), 3.42 (m, 4H), 4.37 (m, 1 H), 7.04 (t, 1 H), 7.14 – 7.21 (m, 4H), 7.31 (d, 1H), 7.51 (d, 1H), 8.66 (s, 1H), 8.95 (s, 1H).
LC/MS m/z = 497.

EXAMPLE 198



132 198

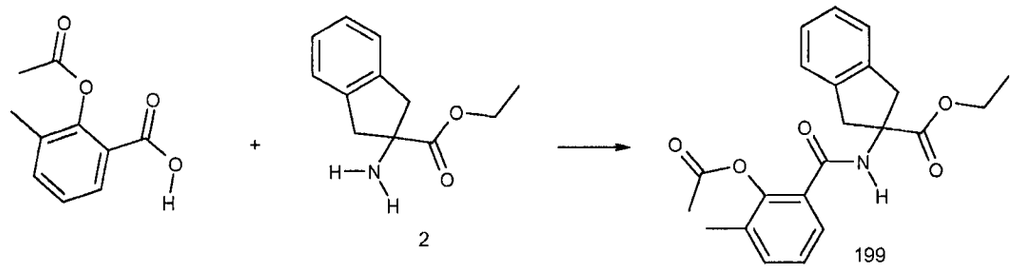
2-Cyclopent-1-enyl-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide (198):

A 50mL flask is charged with 2-(2-cyclopent-1-enyl-3-methyl-benzoyllamino)-indan-2-carboxylic acid (323mg, 0.884mmol) and dry DCM (7.0mL). A stirring bar is added and stirring is initiated. Trifluoromethanesulfonamide (198mg, 1.33mmol) is added. To the resultant suspension, N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride 170mg, 0.88mmol) and 4-dimethylaminopyridine ([MFCD00006418], 108mg, 0.88mmol) are added. After 80h, tlc analysis (silca, 10% MeOH in DCM) indicates that the starting acid had been consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to a separatory

funnel and washed with dilute aqueous HCl (3 N, 2 X 20mL) and brine, dried over $MgSO_4$, filtered and evaporated to constant weight to give 0.50g of white solid.

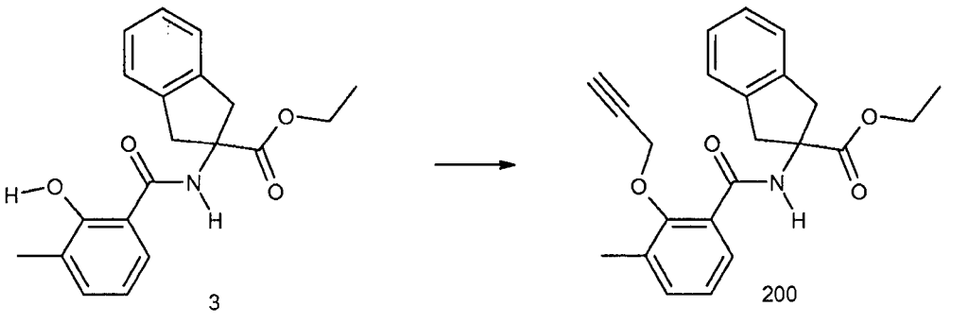
^{1}H NMR (300 MHz, DMSO-d6): δ 1.76 (m, 2H), 2.17 (s, 3 H), 2.22 – 2.42 (m, 4H), 3.38 (dd, 4H), 5.39, (s, 1 H), 7.04 – 7.29 (m, 7H), 8.02 (s, 1H), 8.94 (s, 1H).
LC/MS m/z = 493.

EXAMPLE 199



2-(2-Acetoxy-3-methyl-benzoyl-amino)-indane-2-carboxylic acid ethyl ester (199):
A 40mL vial containing a stirring bar is charged with 2-acetoxyl-3-methyl-benzoic acid (1g, 4.87mmol) and dry DCM (14mL), and stirring is initiated. After dissolution is complete, HBTU (1.85g, 4.87mmoles) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester (1g, 4.87mmol) is added followed by DIPEA (2.1mL, 12.18mmol). The reaction is allowed to stir for 110h. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (100mL). This is washed consecutively with dilute aqueous HCl (3%, 40mL), saturated aqueous $NaHCO_3$ (50mL) and brine (50mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3g of a light orange solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with an 80g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% EtOAc over 12 column volumes. Fractions 19 through 27 are combined and evaporated *in vacuo* to give 1.38g of white solid.

EXAMPLE 200

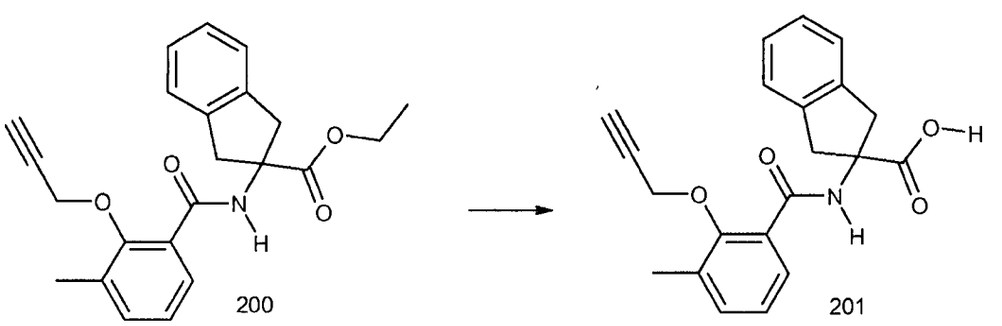


3 200

2-(3-Methyl-2-prop-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (200):

A 100mL round bottom flask containing the 2-(hydroxy-3-methyl-benzoyl)-indan-2-carboxylic acid ethyl ester (3) (0.29g 0.855mmol) is charged with DMF (4mL) and a stirring bar is added. After dissolution of the starting material, K_2SO_4 (0.3g, 2.17mmol) is added followed by a solution of propargyl bromide in toluene (11.59 M, 240μL, 2.78mmol). After stirring for 62h tlc analysis (silica, 1:1 EtOAc/heptanes) indicates that the starting material had been consumed. The material is cleanly converted to a UV positive spot with a slightly lower Rf. The reaction is diluted with EtOAc (80mL) and filtered through a pad of Celite. The filtrate is transferred to a separatory funnel. This is washed repeatedly with a saturated aqueous solution of $NaHCO_3$ (2 x 50mL) and brine (50mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to yield 2.09g of a light brown oil. This is purified (silica, 40g ISCO column 10% EtOAc in heptanes for 3 column volumes followed by a linear gradient to 50% EtOAc in heptanes for 10 column volumes). 17mL fractions of UV positive eluent are collected. Fractions 4 through 10 are combined, evaporated *in vacuo* and pumped to constant weight to give 0.21g of white solid.

EXAMPLE 201



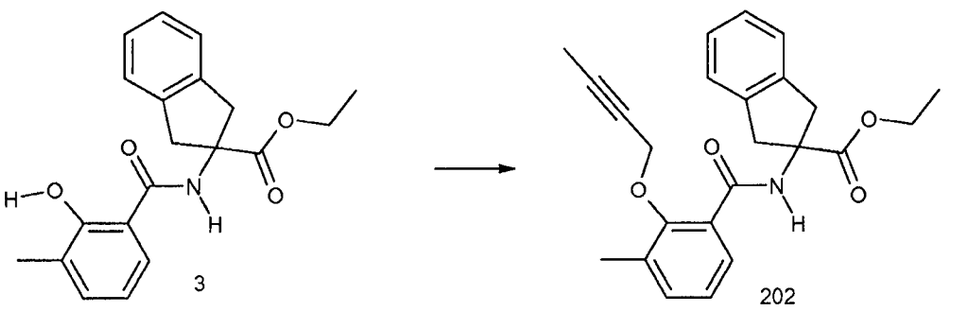
200 201

2-(3-Methyl-2-prop-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid (201):

A 50mL flask containing the 2-(3-methyl-2-prop-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (0.20g, 0.53mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (56mg, 1.35mmol). After 108h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated to constant weight to give 0.2g of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 2.26 (s, 3 H), 3.43 (dd, 4H), 4.52 (s, 2 H), 7.08 (dd, 1H), 7.12 – 7.38 (m, 6H), 8.79 (s, 1H), 12.53 (bs, 1H).
LC/MS m/z = 350.

EXAMPLE 202

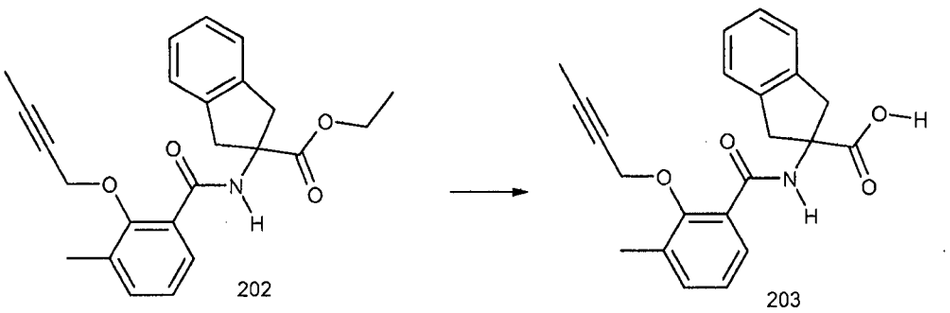


2-(3-Methyl-2-but-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid ethyl ester (202):

A 100mL round bottom flask containing the 2-(hydroxy-3-methyl-benzoyl)-indan-2-carboxylic acid ethyl ester (0.62g, 1.87mmol) is charged with DMF (3mL) and a stirring bar is added. After dissolution of the starting material, the K_2SO_4 (0.791g, 5.95mmol) is added followed by a solution of 1-bromo-2-butyne (537μL, 5.95mmol). After stirring for 110h tlc analysis (silica, 1:1 EtOAc/heptanes) indicates that the starting material is consumed. The material is cleanly converted to a UV positive spot with a slightly lower Rf. The reaction is diluted with EtOAc (80mL) and filtered through a pad of Celite. The filtrate is transferred to a separatory funnel. This is washed repeatedly with a saturated aqueous solution of $NaHCO_3$ (2 x 50mL) and brine (50mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to yield 0.75g of a light brown oil. This is purified (silica, 40g ISCO column 10% EtOAc in heptanes for 3

column volumes followed by a linear gradient to 50% EtOAc in heptanes for 10 column volumes). 17mL fractions of UV positive eluent are collected. Fractions 2 through 8 are combined, evaporated *in vacuo* and pumped dry to yield 0.79g of a white solid.

EXAMPLE 203

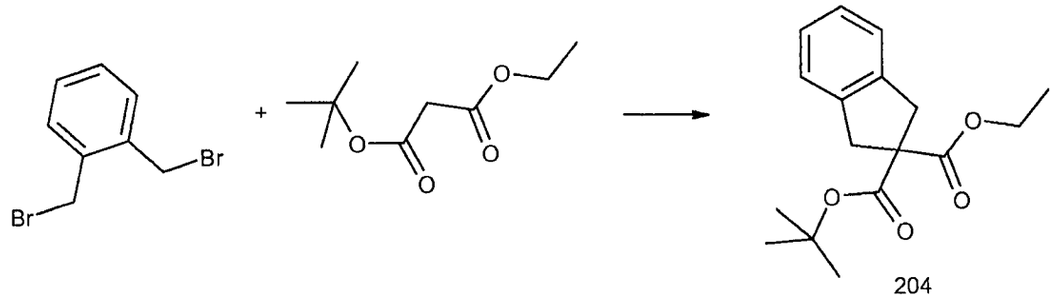


2-(3-Methyl-2-but-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid (203):

A 100mL flask containing 2-(3-methyl-2-but-2-ynyloxy-benzoylamino)-indan-2-carboxylic acid (0.30g, 0.77mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (81mg, 1.93mmol). After 14h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give 0.25g of off-white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.77 (s, 3 H), 2.24 (s, 3 H), 3.44 (dd, 4H), 4.42 (s, 2 H), 7.08 (dd, 1H), 7.14 – 7.23 (m, 4H), 7.31 (d, 2 H), 8.75 (s, 1H), 12.52 (bs, 1H).
LC/MS m/z = 364.

EXAMPLE 204

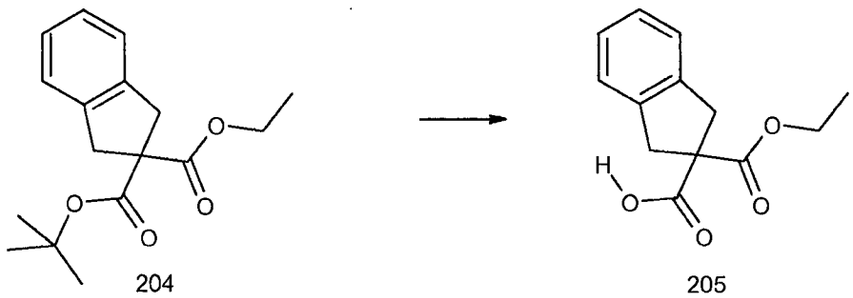


204

Indan-2,2-dicarboxylic acid *tert*-butyl ester ethyl ester (204):

A 3-neck flask containing a stirring bar is fitted with an addition funnel and flushed with nitrogen. The flask is charged with NaH (60% dispersion in oil, 3.38g, 84.48mmol) and dry THF (50mL), and then stirring is initiated. *t*-Butyl ethyl malonate (8mL, 42.24mmol) is added dropwise via syringe over a period of 5 minutes. After 1/2 hour the addition funnel is charged with a solution of o-xylenedibromide (11.15g, 42.24mmol) in dry tetrahydrofuran (THF, 50mL). The solution is added to the reaction mixture over a period of 30 minutes. At the end of this time the addition funnel is washed with dry THF (10mL). This is also added to the reaction mixture. The reaction mixture is allowed to stir for 6 days. The reaction mixture is then transferred to a round-bottom flask and the solvent removed under reduced pressure. The resultant white semi-solid is dissolved in a mixture of EtOAc (200mL) and water (150mL) this is transferred to a separatory funnel. The layers are separated. The aqueous phase is extracted with EtOAc (150mL). The organic extracts are combined, washed with brine (150mL), dried over $MgSO_4$, filtered and evaporated to constant weight to give 12.44g of viscous oil. This material is diluted with heptanes (30mL) and applied to a silica gel column (300g). The material is eluted with EtOAc/heptanes (5 % over 5 column volumes) with a gradient to 75 % EtOAc in heptanes over 7 column volumes. 43mL fractions of UV positive eluent are collected. Fractions 11- 20 are combined and evaporated by pumping to a constant weight to give 9.82g of clear viscous oil.

EXAMPLE 205

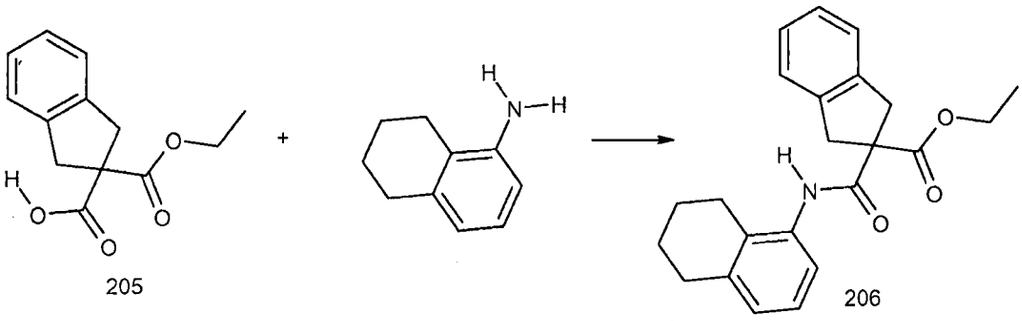


204 205

Indan-2,2-dicarboxylic acid ethyl ester (205):

A 200mL round bottom flask is charged with indan-2,2-dicarboxylic acid *tert*-butyl ester ethyl ester (8.69g, 29.93mmol). DCM (40mL) and a stirring bar are added. Stirring is initiated. Trifluoroacetic acid (20.0mL, 269mmol) is added. After 20h, tlc analysis (silica, 1:1 ethyl actetate:heptanes), indicates complete consumption of starting material. The reaction mixture is diluted with DCM (50mL) and evaporated under reduced pressure. The resultant oil is diluted with DCM (55mL) and evaporated under reduced pressure. The resultant oil is diluted with toluene (50mL) and evaporated under reduced pressure by pumping to constant weight to give 6.78g of white solid material.

EXAMPLE 206



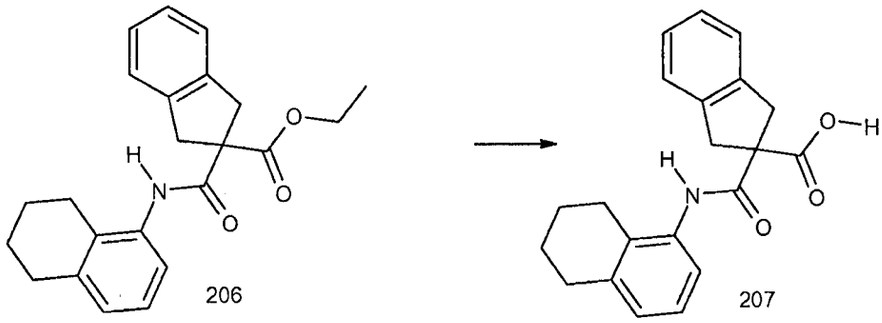
205 206

2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (206):

A 25mL reaction vial containing a stirring bar is charged with indane-2-carboxylic acid ethyl ester (0.48g, 1.79mmol) and dry DCM (7mL). Stirring is initiated. After dissolution is complete, HBTU (0.68g, 1.79mmol) is added. After 5min, the 5,6,7,8-tetrahydro1-naphthylamine (0.26mL, 1.79mmol is added followed by DIPEA (0.72mL, 4.12mmol). The reaction is allowed to stir for 68h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting acid. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (40mL). This is

washed consecutively with dilute aqueous HCl (3%, 20mL), saturated aqueous $NaHCO_3$ (20mL) and brine (20mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.50g of a light purple solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 12 column volumes. 17mL fractions of eluent are collected. Fractions 11 through 16 are combined and evaporated *in vacuo* by pumping to constant weight to give 0.41 of white solid material.

EXAMPLE 207



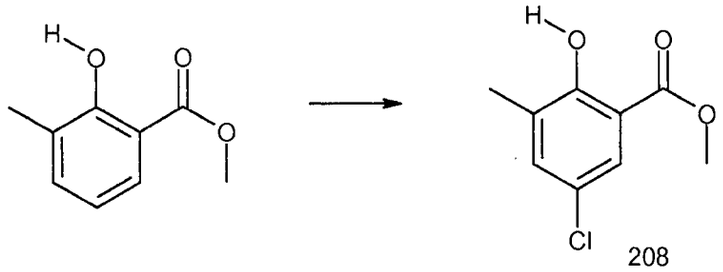
2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid (207):

A 100mL flask containing 2-(5,6,7,8-tetrahydro-napthalene-1-yl-carbamoyl)-indan-2-carboxylic acid ethyl ester (0.23g, 0.63mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (67mg, 1.58mmol). After 14h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give 0.18g of white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.58 - 1.78 (m, 4 H), 2.43 - 2.58 (m, 2 H), 2.63 - 2.78 (m, 2 H), 3.57 (dd, 4H), 6.96 (dd, 1H), 6.98 - 7.08 (m, 2H), 7.09 - 7.19 (m, 2H), 7.20 - 7.28 (m, 2 H), 9.15 (s, 1H), 12.82 (bs, 1H).

LC/MS m/z = 336.

EXAMPLE 208



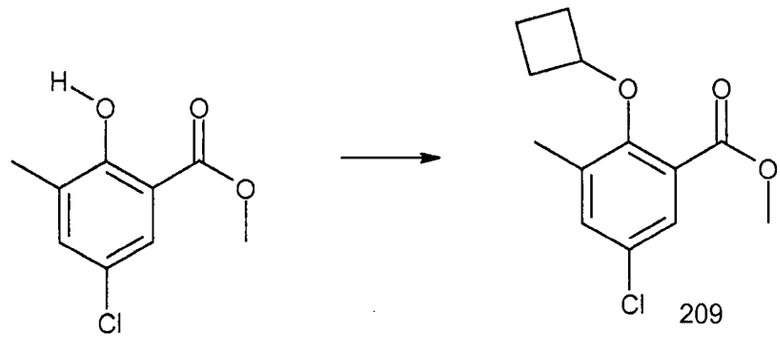
208

2-Hydroxy-3-methyl-5-chlorobenzoic acid methyl ester (208):

A 250mL 3-neck round bottom flask is charged with 2-hydroxy-3-methyl-5-benzoic acid methyl ester (5g, 30.1mmol) and dry DCM (50mL). A stirring bar is added and the flask is immersed in an ice/water bath. After 10 minutes, sulfuryl chloride (2.9mL, 36.1mmol) is added via syringe over a period of 5 minutes. After 0.5h, the ice-water bath is removed. After 2 additional h, tlc Analysis (silica, 40% EtOAc-heptanes) indicates no reaction.

After 27 days, tlc analysis (silica, 40% EtOAc-heptanes) still indicated no reaction. MeOH (50mL) is added to the reaction mixture. A white crystalline solid began to precipitate. The precipitate is collected by suction filtration to give 2.1g of white solid. A 2nd crop of 1.25g of additional white solid is collected from the filtrate.

EXAMPLE 209



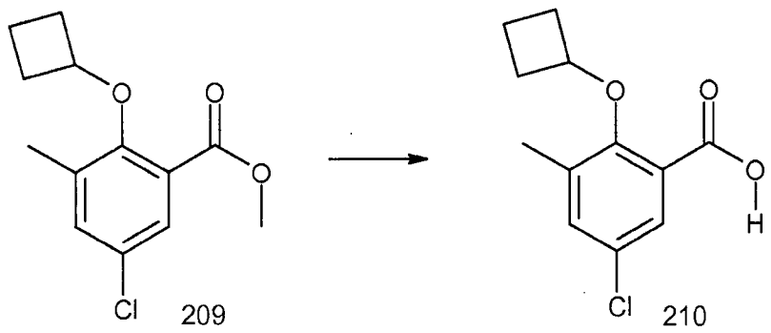
209

5-Chloro-2-cyclobutoxy-3-methyl-benzoic acid methyl ester (209):

A 100mL round bottom flask is charged with 5-chloro-2-hydroxy-3-methyl-benzoic acid methyl ester (0.92g, 4.59mmol). Dry N,N-dimethylformamide (DMF, 15mL) and a stirring bar are added. Stirring is initiated. After dissolution, K_2SO_4 (1.90g, 13.76mmol) and bromocyclobutane (0.65mL, 6.88mmol) are added. After 12 days, tlc analysis (silica, 25 %

EtOAc/heptanes) indicated a slight consumption of starting material and the appearance of a UV positive spot with a slightly higher R_f value. The reaction is fitted with a heating mantle and warmed to 37°C. After 3 more days, tlc analysis (silica, 25% EtOAc/heptanes) indicates a slight consumption of starting material and complete conversion to a UV positive spot with a slightly higher R_f value. The reaction mixture is filtered through a pad of Celite. The filtrate is diluted with EtOAc and (100mL) and transferred to a separatory funnel. The EtOAc solution is washed with saturated $NaHCO_3$ (2 x 25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight togive 0.79g of semi-solid material.

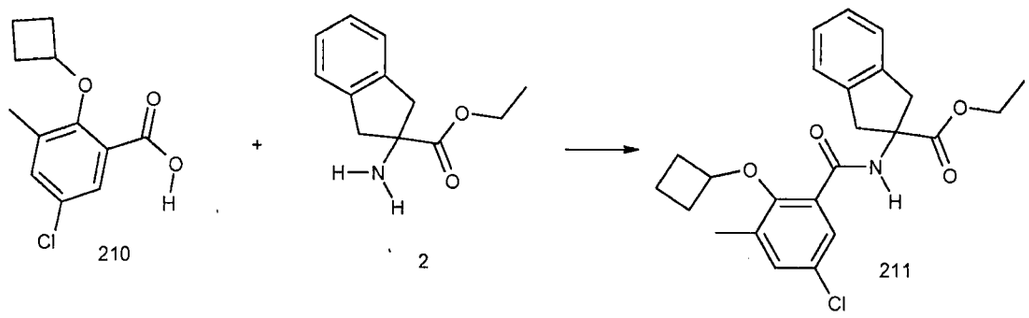
EXAMPLE 210



5-Chloro-2-cyclobutoxy-3-methyl-benzoic acid (210):

A 100mL flask containing 5-chloro-2-cyclobutoxy-3-methyl-benzoic acid methyl ester (0.57g, 2.23mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (237mg, 5.65mmol). After 39h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give 0.53g of white solid.

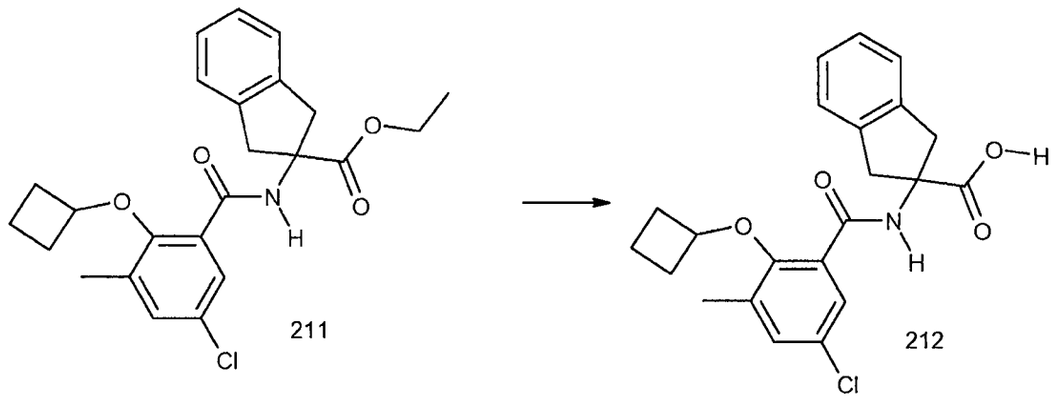
EXAMPLE 211



(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (211):

A 100mL round bottom flask containing a stirring bar is charged with 2-cyclobutoxyl-3-methyl-5-chloro-benzoic acid (0.36g, 1.5mmol) and dry DCM (7mL). Stirring is initiated. After dissolution is complete, HBTU (567mg, 1.5mmol) is added. After 5min, the 2-amino-indane-2-carboxylic acid ethyl ester (307mg, 1.50mmol) is added followed by DIPEA (0.74mL, 3.74mmol). The reaction is allowed to stir for 39h. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (100mL). This is washed consecutively with dilute aqueous HCl (3%, 40mL), saturated aqueous $NaHCO_3$ (50mL) and brine (50mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.8g of a light orange solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 70% EtOAc in heptanes over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 8 through 11 are combined and evaporated *in vacuo* by pumping to a constant weight to give 0.48g white solid.

EXAMPLE 212



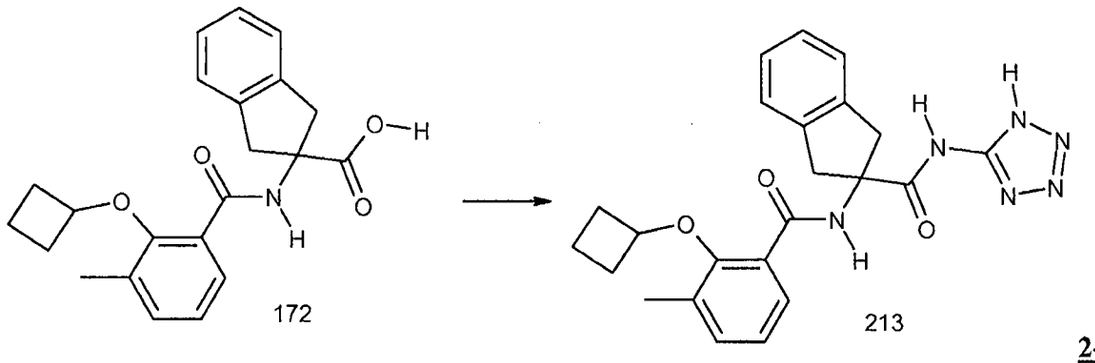
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (212):

A 100mL flask containing 2-(5-chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (0.3g, 0.7mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH (74mg, 1.77mmol). After 20h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives 0.21g of a white solid.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.17 – 1.28 (m, 1 H), 1.49 (m, 1 H), 1.78 – 1.95 (m, 2 H), 1.96 – 2.04 (m, 2 H), 3.46 (dd, 4H), 4.28 (m, 1H), 7.15 – 7.26 (m, 5H), 7.39 (d, 1H), 8.78 (s, 1H), 12.62 (bs, 1H).

LC/MS m/z = 400.

EXAMPLE 213



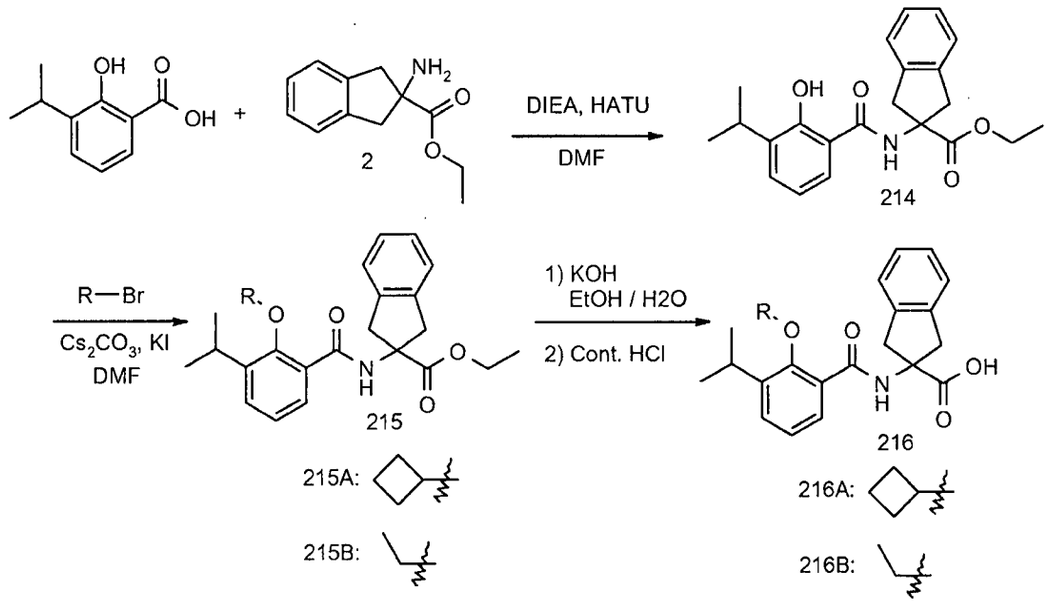
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (1H-tetrazol-5-yl)-amide (213):

A 40mL tube is charged with 2-[(2-cyclobutoxy-3-methyl-benzoyl)-amino]-indan-2-carboxylic acid (323mg, 0.884mmol) and dry DCM (7mL). A stirring bar is added and stirring is initiated. 5-Amino-1H-tetrazole (113mg, 1.33mmol) is added. To the resultant suspension, N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (170mg, 0.88mmol) and 4-dimethylaminopyridine (108mg, 0.88mmol) is added. After 11 1/2 days, tlc analysis (silca, 10% MeOH in DCM) indicates that the starting acid had been consumed. The reaction mixture is diluted with EtOAc (50mL), transferred to an Erlenmeyer flask containing saturated aqueous ammonium chloride (50mL). This mixture is allowed to stir. After 16h of stirring, this mixture contained a white solid that is collected by suction filtration and washed with water (2 x 25mL). Air drying gives 0.26g of white powder.

^{1}H NMR (300 MHz, DMSO-d6): δ 1.01 – 1.31 (m, 2 H), 1.62 (m, 2 H), 1.73 – 1.93 (m, 2 H), 2.22 (s, 3 H), 3.39 (dd, 4H), 4.19 (m, 1H), 7.08 (t, 1H), 7.19 – 7.51 (m, 5H), 7.57 (dd, 1H), 8.61 (s, 1H), 12.01 (bs, 1H).

LC/MS m/z = 433.

EXAMPLE 214



2-(2-Hydroxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (214):

To a solution of 2-hydroxy-3-isopropyl-benzoic acid (539mg, 2.99mmol), 2-amino-indan-2-carboxylic acid ethyl ester (737mg, 3.59mmol), HATU (1.36g, 3.59mmol) in anhydrous DMF (30mL) is added DIPEA (0.59mL, 3.59mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (222) as white solid (920mg, 84%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 1.21(d, 6H), 1.24(t, 3H), 3.32-3.44(m, 1H), 3.41(d, 2H), 3.74(d, 2H), 4.25(q, 2H), 6.74-6.81(m, 2H), 7.16(d, 1H), 7.18-7.25(m, 3H), 7.32(d, 1H), 12.26(s, 1H)
LC/MS (ES+) m/z = 368.17

EXAMPLES 215A and 215B

2-(2-Cyclobutoxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (215A) and 2-(2-Ethoxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (215B):

To a suspension of 2-(2-hydroxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (214) (1eq., 0.82mmol), anhydrous Cs_2CO_3 (2eq., 1.64mmol), and KI (0.2eq., 0.16mmol) in DMF (15mL) is added RBr (4eq., 3.28mmol). The resulting reaction suspension is heated in a microwave vessel (215A: 130°C, 2hr; 215B: 50°C, 30min). After the removal of DMF *in*

vacuo, the residue is dissolved in EtOAc (30mL) and washed with water (1 x 5mL) and brine (2 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (120g silica gel, gradient elution: 10-50% EtOAc in heptane) to give a pure product (215) as white solid (215A: 340mg, 98%; 215B: 300mg, 93%).

215A: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.19(d, 6H), 1.26(t, 3H), 1.16-1.57(m, 2H), 1.87-2.07(m, 4H), 3.24-3.38(m, 1H), 3.36(d, 2H), 3.78(d, 2H), 4.26(q, 2H), 4.15-4.30(m, 1H), 7.12-7.26(m, 5H), 7.35(dd, 1H), 7.83(dd, 1H), 8.20(s, 1H).
LC/MS (ES+) m/z = 422.24

215B: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.13(t, 3H), 1.20(d, 6H), 1.26(t, 3H), 3.24(m, 1H), 3.35(d, 2H), 3.72(q, 2H), 3.78(d, 2H), 4.26(q, 2H), 7.14-7.26(m, 5H), 7.36(dd, 1H), 7.82(dd, 1H), 8.36(s, 1H)
LC/MS (ES+) m/z = 396.22

EXAMPLES 216A and 216B

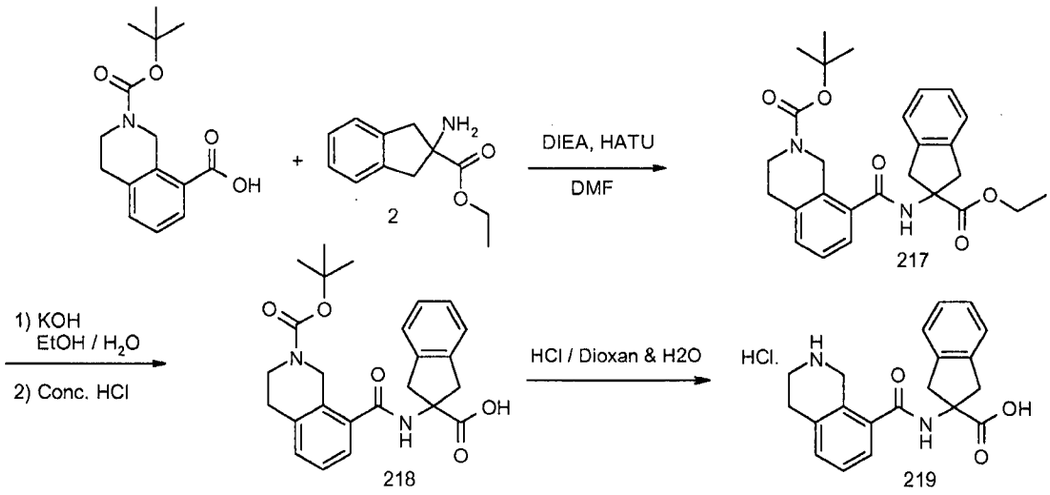
2-(2-Cyclobutoxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid (216A) and 2-(2-Ethoxy-3-isopropyl-benzoylamino)-indan-2-carboxylic acid (216B):

The mixture of (215) (1eq., 0.69mmol) and KOH (13eq., 8.9mmol) is dissolved in EtOH (10mL) and water (0.5mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (216) as white solid (216A: 190mg, 70%; 216B: 220mg, 91%).

216A: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.17(d, 6H), 1.13-1.30(m, 1H), 1.41(m, 1H), 1.78-2.02(m, 4H), 3.27(m, 1H), 3.38(d, 2H), 3.81(d, 2H), 4.13(m, 1H), 7.09(t, 1H), 7.13-7.23(m, 4H), 7.34(dd, 1H), 7.81(dd,1H), 8.37(s, 1H).
LC/MS (ES+) m/z = 394.19

216B: ^{1}HNMR ($CDCl_3$, 300MHz): δ 1.08(t, 3H), 1.19(d, 6H), 3.20(m, 1H), 3.46(d, 2H), 3.55(q, 2H), 3.88(d, 2H), 7.18-7.27(m, 5H), 7.42(dd, 1H), 7.89(dd, 1H), 8.63(s, 1H) LC/MS (ES+) m/z = 368.19

Example 217



8-(2-Ethoxycarbonyl-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (217):

To a solution of 3,4-dihydro-1H-isoquinoline-2,8-dicarboxylic acid 2-tert-butyl ester (2.0g, 7.2mmol), 2-amino-indan-2-carboxylic acid ethyl ester (1.5g, 7.2mmol), HATU (3.3g, 8.6mmol) in anhydrous DMF (70mL) is added DIPEA (1.4mL, 8.6mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel, gradient elution: 5-50% EtOAc in heptane) to give a pure product (217) as white solid (3.3g, 99%).

Example 218

8-(2-Carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (218):

The product (217) (2.46g, 5.3mmol) and KOH (2.5g, 45mmol) is dissolved in EtOH (20mL) and water (1mL) under a water bath. The water bath is removed when the KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (50mL) and acidified with conc. HCl until no more white precipitate came out of the water. The precipitate is filtered to give a pure product (218) as white solid (1.4g, 61%).

^{1}HNMR (DMSO-d6, 300MHz): δ 1.40(s, 9H), 2.79(t, 2H), 3.34(d, 2H), 3.52(t, 2H), 3.57(d, 2H), 4.59(s, 2H), 7.10-7.31(m, 7H), 8.88(s,1H), 11.56-12.92(br s, 1H)
LC/MS (ES+) m/z = 437.26

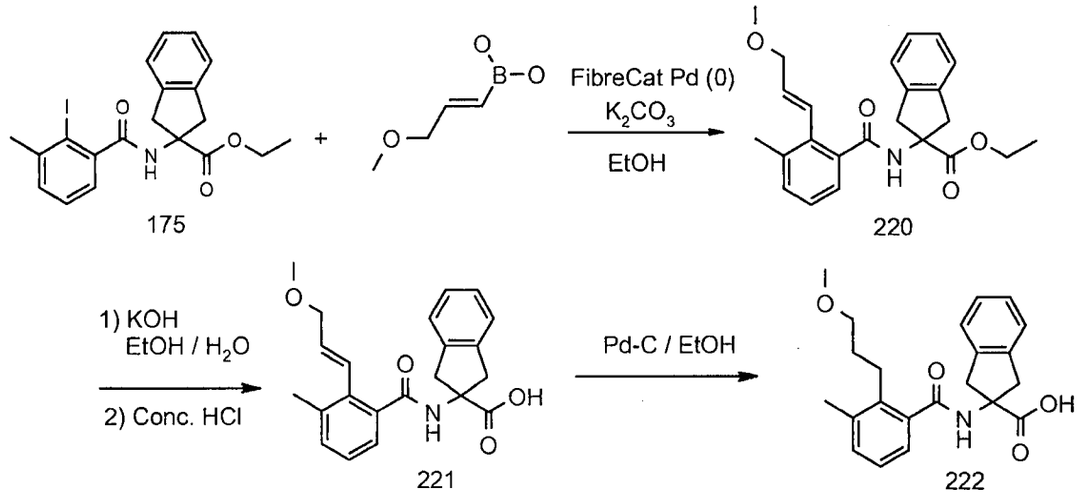
Example 219

2-[(1,2,3,4-Tetrahydro-isoquinoline-8-carbonyl)-amino]-indan-2-carboxylic acid (219):

To a solution of 8-(2-carboxy-indan-2-ylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (226) (128mg, 0.29mmol) in 6ml dioxane is added dropwise 4N solution of HCl in dioxane/water (0.72mL) and the resulting solution is stirred at RT for 4h. The concentration gave an HCl salt of (219) as white solid (246mg, 100%).

^{1}HNMR (DMSO-d6, 300MHz): δ 3.04(t, 3H), 3.28-3.41(m, 4H), 3.58(d, 2H), 4.31(s, 2H), 7.13-7.27(m, 4H), 7.32(s, 3H), 9.05(s, 1H), 9.30-9.57(br s, 1H), 12.46-12.77(br s, 1H)
LC/MS (ES+) m/z = 337.18

Example 220



175 220 221 222

2-[2-(3-Methoxy-propenyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (220):

To a solution of 2-(2-Iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (400mg, 0.89mmol) and 3-methoxy-1-propenylboronic acid (206mg, 1.78mmol) in 10mL EtOH/10mL dioxane is added palladium anchored homogeneous catalyst, FibreCatPd(0), (4.84%Pd, 195mg, 0.089mmol) and 2M aqueous solution of K_2SO_4 (1.78mL, 3.56mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 4h. After concentration *in vacuo*, the residue is purified by HPLC to give the product (220) as pale yellow oil.

Example 221

2-[2-(3-Methoxy-propenyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (221):

The product (220) and KOH (1.0g, 18mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 3h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the obtained brown solid is purified by HPLC to give pure product (221) as white solid (200mg, 62%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 2.28(s, 3H), 3.31(s, 1H), 3.37(s, 4H), 3.78(d, 2H), 3.93(dd, 2H), 5.83(dt, 1H), 6.44(s, 1H), 6.64(d, 1H), 7.10-7.35(m, 7H)

LC/MS (ES+) m/z = 366.15

Example 222

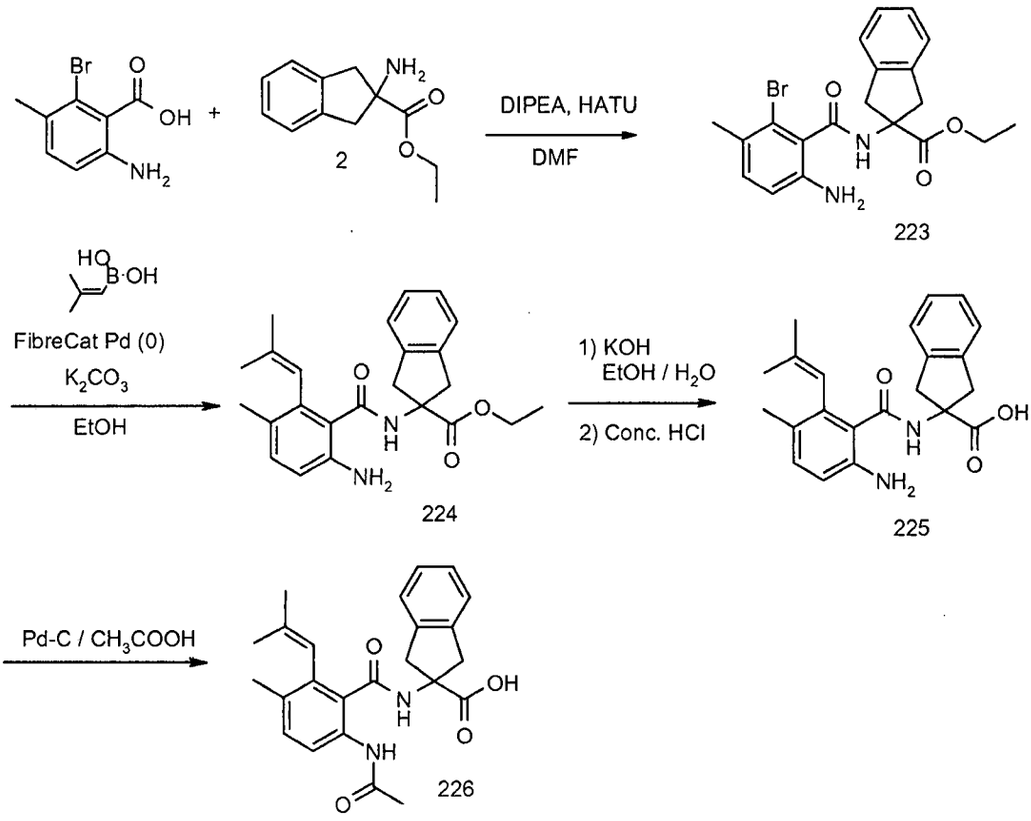
2-[2-(3-Methoxy-propyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (222):

To a solution of 2-[2-(3-methoxy-propenyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid (229) (120mg, 0.34mmol) in absolute EtOH (15mL) is added the catalyst, Pd-C (5wt.%Pd, 93mg, 4.4%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 50°C, overnight. The catalyst is removed by the filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (222) as white solid (80mg, 49%).

^{1}HNMR (DMSO-d6, 300MHz): δ 1.64(m, 2H), 2.27(s, 3H), 2.59-2.69(m, 2H), 3.16-3.40(m, 7H), 3.56(d, 2H), 6.97-7.24(m, 7H), 8.84(s, 1H), 12.48(s, 1H)

LC/MS (ES+) m/z = 368.18

Example 223



2-[6-Acetylamino-3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (223):

To a solution of 6-amino-2-bromo-3-methyl-benzoic acid (688mg, 2.99mmol), 2-amino-indan-2-carboxylic acid ethyl ester (737mg, 3.59mmol), HATU (1.36g, 3.59mmol) in anhydrous DMF (30mL) is added DIPEA (0.59mL, 3.59mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (150mL) and washed with water (1 x 10mL) and brine (2 x 10mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give 278mg brown oil (223).

EXAMPLE 224

2-[6-Amino-3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (224)

To a solution of (223) (278mg, 0.67mmol) and 2,2-dimethylethyleneboronic acid (134mg, 1.34mmol) in 10ml EtOH is added palladium anchored homogeneous catalyst, FibreCatPd(0), (4.84%Pd, 195mg, 0.089mmol) and 2M aqueous solution of K_2SO_4 (1.78mL, 3.56mmol). The resulting reaction mixture is covered with argon and run in a microwave reaction: 110°C, 5h. After concentration *in vacuo*, the residue is purified by HPLC to give 380mg brown semi-solid (224).

EXAMPLE 225

2-[6-Amino-3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (225)

The mixture (224) and KOH (500mg, 8.9mmol) is dissolved in EtOH (8mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 4h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more white precipitate formed. After the filtration, the crude solid is purified by HPLC to give 48mg brown solid (225).

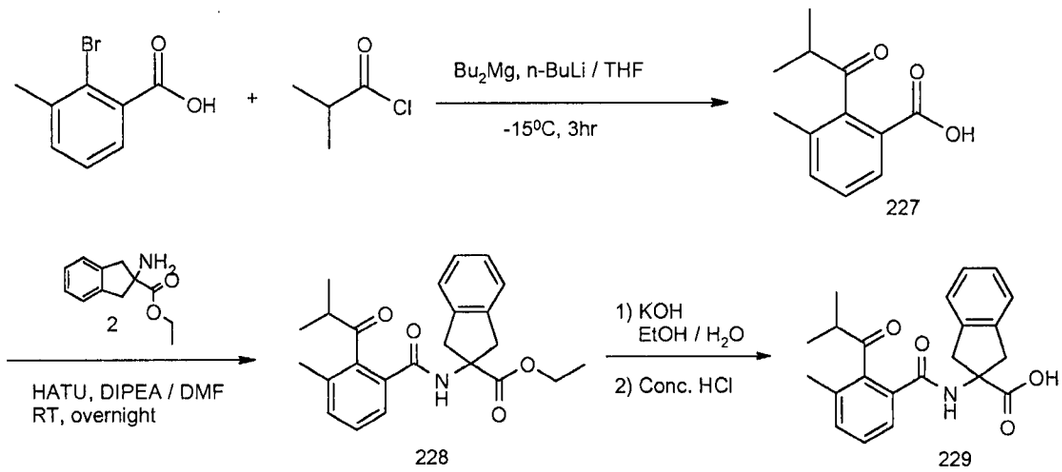
EXAMPLE 226

2-[6-Acetylamino-3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (226)

To a solution of (225) (48mg, 0.1mmol) in acetic acid (10mL) is added the catalyst, Pd-C (5wt.%Pd, 21mg, 1%mmol) under argon. The resulting reaction mixture is moved to the Paar apparatus to run hydrogenation: 55psi, 90°C, overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (226) as white solid (35mg, 86%).

^{1}HNMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 1.17(s, 3H), 1.70(s, 3H), 2.08(d, 3H), 2.16(d, 3H), 3.26(d, 2H), 3.72(d, 2H), 5.89(s, 1H), 7.12-7.25(m, 5H), 7.48(s, 1H), 7.74(d, 1H)
LC/MS (ES+) m/z = 407.18

Example 227



2-Isobutyryl-3-methyl-benzoic acid (227):

The solution of 2-bromo-3-methyl-benzoic acid (1.5g, 6.98mmol) in 10mL THF is treated with 1M Bu_2Mg/heptane at -15°C under argon. After stirring for 30min, 1.6M n-BuLi/hexane is added dropwise at -15°C and the mixture is left for 1hr. Then isobutyryl chloride (2.95ml, 27.9mmol) is added dropwise. After another 30min stirring, the reaction is quenched with 2N HCl aqueous solution (2ml). After concentration, the residue is purified by HPLC to give a pure product (227) as white solid (840mg, 58%).

^{1}HNMR ($CDCl_3$ + drops of CD_3OD, 300MHz): δ 0.62(d, 3H), 1.31(d, 3H), 2.51(s, 3H), 2.61(s, 1H), 7.42-7.50(m, 2H), 7.68(m, 1H)
LC/MS (ES-) m/z = 205.06

Example 228

2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (228):

To a solution of 2-isobutyryl-3-methyl-benzoic acid (227) (200mg, 0.97mmol), 2-amino-indan-2-carboxylic acid ethyl ester (220mg, 1.07mmol), HATU (441mg, 1.16mmol) in anhydrous DMF (10mL) is added DIPEA (192μL, 1.16mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in DCM (50mL) and washed with water (1 x 5mL) and brine (1 x 5mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by HPLC to give a pure product (228) as a pale yellow solid (340mg, 89%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 1.06(d, 6H), 1.25(t, 3H), 2.24(s, 3H), 2.86(m, 1H), 3.30(d, 2H), 3.72(d, 2H), 4.23(q, 2H), 6.47(s, 1H), 7.14-7.43(m, 7H)
LC/MS (ES+) m/z = 394.23

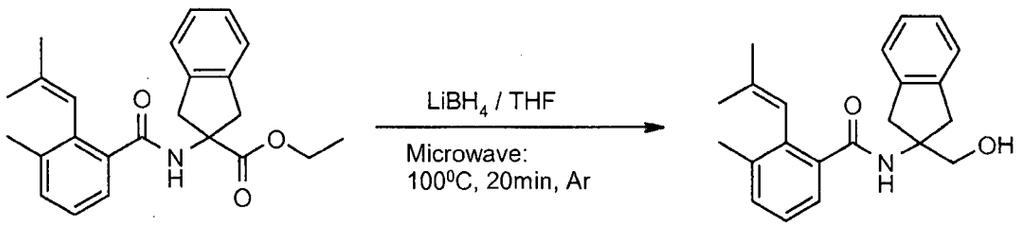
Example 229

2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid (229):

The mixture of 2-(2-isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (228) (170mg, 0.43mmol) and KOH (500mg, 8.9mmol) is dissolved in EtOH (20mL) and water (1mL) under a water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl until no more precipitate came out of the water. The precipitate is filtered to give a pure product (229) as white solid (140mg, 89%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 1.07(d, 6H), 2.25(s, 3H), 2.87(m, 1H), 3.35(d, 2H), 3.74(d, 2H), 7.16-7.42(m, 7H)
LC/MS (ES+) m/z = 366.16

Example 230



134 230

N-(2-Hydroxymethyl-indan-2-yl)-3-methyl-2-(2-methyl-propenyl)-benzamide (230):

To a solution of 2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (80mg, 0.21mmol) in anhydrous THF (1mL) is added dropwise 2M $LiBH_4$/THF (0.84mL, 1.68mmol) at RT under argon. The resulting solution is heated for 20min at 100°C on microwave. After cooling to room temperature, the reaction solution is poured into ice-water and aq. NH_4Cl saturated solution to reach pH 7. The solution is extracted with EtOAc (50mL x 3). The combined EtOAc phase is washed with brine (10ml x 2), dried over Na_2SO_4 and concentrated. The residue is purified by HPLC to give a pure product (230) as white solid (58mg, 82%).

^{1}HNMR ($CDCl_3$, 300MHz): δ 1.38(s, 3H), 1.80(s, 1H), 2.16(s, 1H), 3.11(d, 2H), 3.33(d, 2H), 3.88(s, 2H), 6.11(s, 1H), 6.71(br s, 1H), 7.13-7.33(m, 6H), 7.60(d, 1H)
LC/MS (ES+) m/z = 336.21

EXAMPLES 231 AND 232

Chiral Separation of Example 150 into Examples 231 and 232

1. Experimental conditions:

	Instrument: Americhrom Global Technologies VERSAPrep 100 (Detector module, Fraction Collection and Recycle and Injection Valves Module, Pump Module, Sample Injection Pump Module)
Software:	Chiralpak AD, 20 mmID x 250mm, 10micron
Eluent:	EtOH / Heptane (20/80) with 0.1 TFA (Pre-mixed)
Flow rate:	15mL/min

Detection:	UV214nm
Column temperature:	RT
Injection volume:	1mL
Concentration:	~ 10mg/mL

2. Results:

Sample	Enantiomer 1	Enantiomer 2
	RT (min)	RT (min)
	iMax Time 6.78	iMax Time 10.02
	47.7mg, white solid	45.1mg, white solid

Fraction 1(-) (231):

^{1}HNMR (DMSO-d6, 300MHz): δ 0.76(d, 6H), 1.74(m, 1H), 2.27(s, 3H), 2.62(d, 2H), 3.24-3.38(m, 2H), 3.43-3.62(m, 2H), 6.90-7.28(m, 6H), 8.83(s, 1H), 12.51(s, 1H)

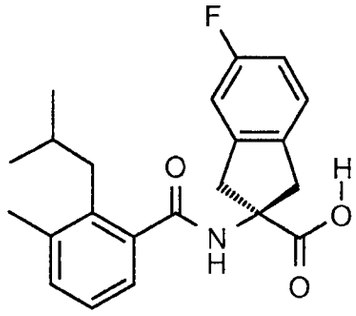
LC/MS (ES+) m/z = 370.18

Fraction 2(+) (232):

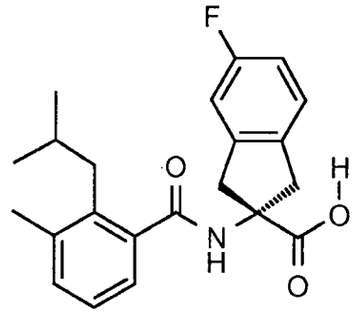
^{1}HNMR (DMSO-d6, 300MHz): δ 0.76(d, 6H), 1.74(m, 1H), 2.27(s, 3H), 2.62(d, 2H), 3.24-3.38(m, 2H), 3.43-3.62(m, 2H), 6.90-7.28(m, 6H), 8.83(s, 1H), 12.51(s, 1H)

LC/MS (ES+) m/z = 370.18

The structures for the enantiomers are as follows:

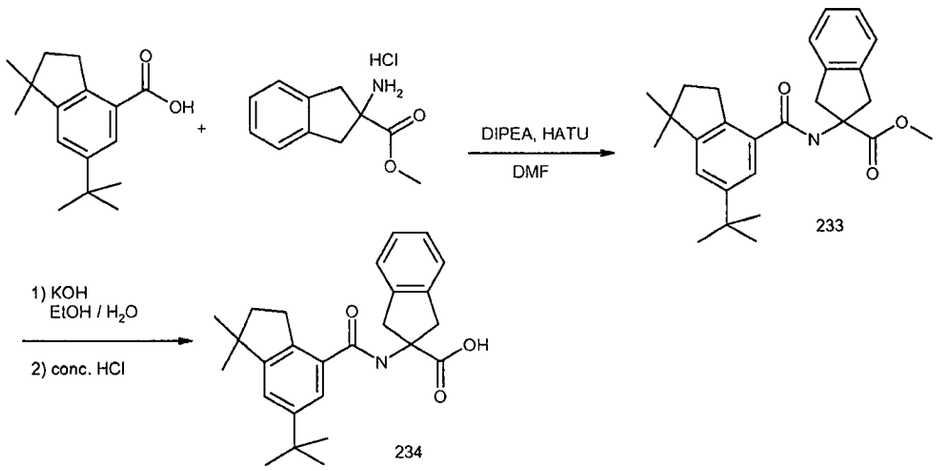


and



. However, the structures are not assigned to either of the particular eluting fraction.

EXAMPLE 233



2-[(6-tert-Butyl-1,1-dimethyl-indane-4-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (233):

To a solution of 6-*tert*-butyl-1,1-dimethyl-indan-4-carboxylic acid (1g, 4.1mmol), HCl salt of 2-amino-indan-2-carboxylic acid methyl ester (924mg, 4.1mmol), HATU (1.85g, 4.9mmol) in anhydrous DMF (15mL) is added DIPEA (2.5mL, 14.4mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with water (1 x 100mL), 1N HCl (1 x 100mL) and brine (1 x 100mL). The organic layer is dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash column chromatography (60g silica gel, gradient elution: 10-60% EtOAc in heptane) to give pure product as white solid (660mg, 39%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.20(s, 6H), 1.27(s, 9H), 1.80(t, 2H), 2.87(t, 2H), 3.37(s, 2H), 3.57(s, 2H), 3.63(s, 1H), 3.64(s, 3H), 7.15-7.29(m, 6H), 8.78(s, 1H)
LC/MS (ES+) m/z = 420.24

EXAMPLE 234

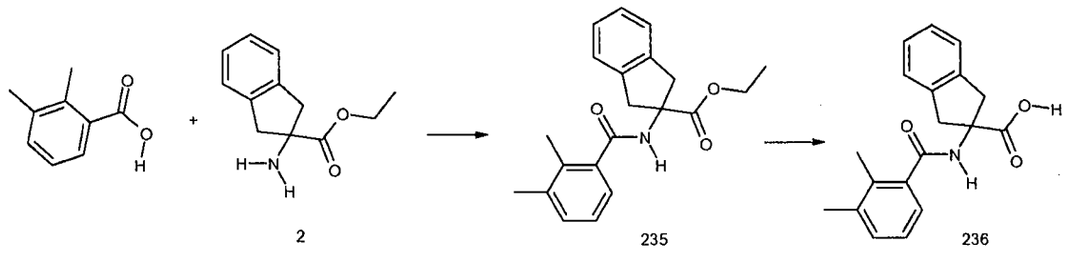
2-[(6-tert-Butyl-1,1-dimethyl-indane-4-carbonyl)-amino]-indan-2-carboxylic acid (234):

A mixture of 2-[(6-tert-butyl-1,1-dimethyl-indane-4-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (600mg, 1.4mmol) and KOH (1.8g, 30.8mmol) is dissolved in EtOH (25mL) and water (2mL) under water bath. The water bath is removed when KOH is completely dissolved and the resulting reaction solution is stirred at RT for 8h. After concentration *in vacuo*, the residue is neutralized with 1N HCl and extracted with EtOAc (3 x 150mL), the

organic washes are combined and concentrated *in vacuo*. The residue is purified by preparative HPLC (C18 column 10 micron, gradient elution: 20-100% ACN 0.1% TFA in H_2O 0.1% TFA). Product crystallizes out of the collected fractions on standing. Filtration and drying gave pure product as white solid (454mg, 78%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.20(s, 6H), 1.27(s, 9H), 1.79(t, 2H), 2.87(t, 2H), 3.37(s, 2H), 3.55(s, 2H), 3.61(s, 1H), 7.12-7.29(m, 6H), 8.62(s, 1H)
LC/MS (ES+) m/z = 406.22

Example 235



2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (235) :

2-Amino-indane-2-carboxylic acid ethyl ester (250mg, 1.2 mmol), 2,3-dimethyl-benzoic acid (183mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After a few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel column using 20-50% EtOAc in heptane as a gradient to afford 2-(2,3-dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (350mg, 87%).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.3 (t, 3 H), 2.26 (s, 3 H), 2.29 (s, 3 H), 3.55 (dd, 4H), 4.28 (q, 2H), 6.19 (s, 1H), 7.04 - 7.22 (m, 7H).
LC/MS m/z = 338.17.

EXAMPLE 236

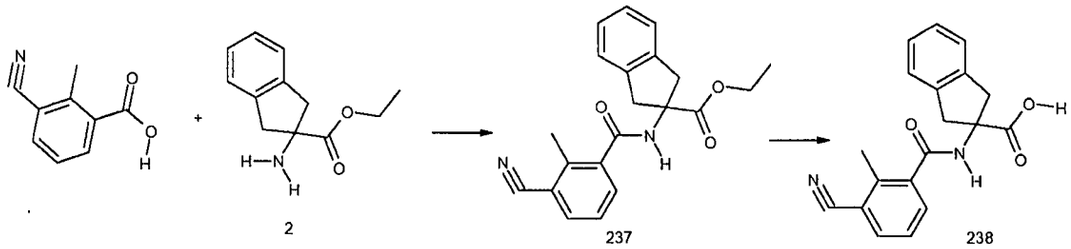
2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid (236) :

The mixture of 2-(2,3-dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (235) (290mg, 0.86 mmol), KOH (50% aqueous solution, 1.92g, 17.2mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (5mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration gives 2-(2,3-dimethyl-benzoylamino)-indan-2-carboxylic acid (236) as white solid (240mg, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.22 (s, 3H), 2.25 (s, 3H), 3.61 (dd, 4H), 6.24 (s, 1H), 7.06 (m, 2H), 7.18 - 7.23 (m, 5H).

LC/MS m/z = 310.13.

EXAMPLE 237



2-(3-Cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (237) :

2-Amino-indane-2-carboxylic acid ethyl ester (250mg, 1.2 mmol), 3-cyano-2-methyl-benzoic acid (196mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After a few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel column using 20-50% EtOAc in heptane as a gradient to afford 2-(3-cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (373mg, 89%).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.3 (t, 3 H), 2. 6 (s, 3 H), 3.57 (dd, 4H), 4.29 (q, 2H), 6.23 (s, 1H), 7.23 - 7.30 (m, 5H), 7.51 (d, 1 H), 7.64 (d, 1 H).

LC/MS m/z = 349.16.

EXAMPLE 238

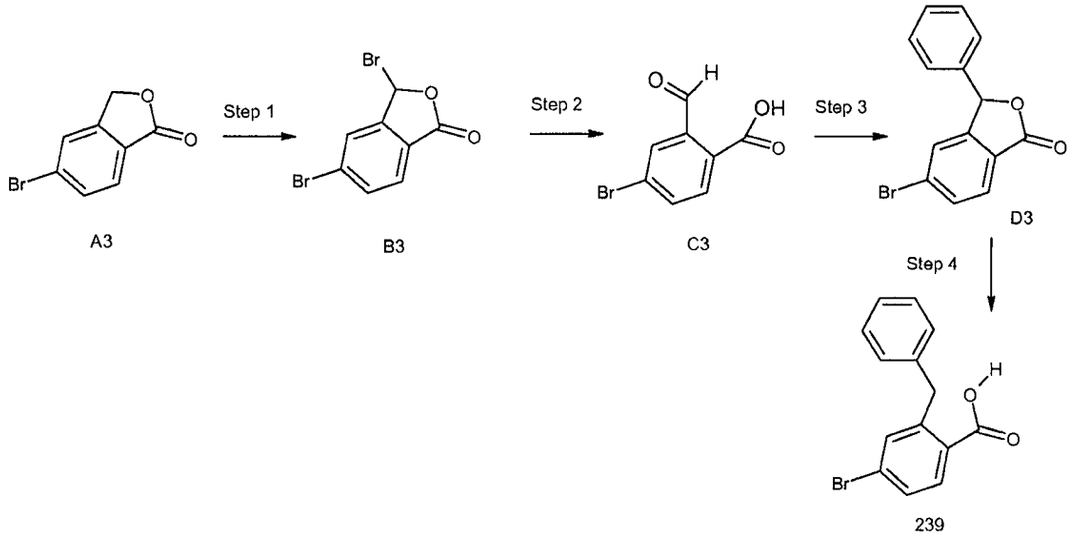
2-(3-Cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid (238) :

The mixture of 2-(3-cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3) (310mg, 0.89 mmol), KOH (50% aqueous solution, 2g, 17.8 mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (5mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration affords 2-(3-cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid (238) as white solid (270mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.56 (s, 3H), 3.62 (dd, 4H), 6.30 (s, 1H), 7.22 - 7.31 (m, 5H), 7.51 (d, 1 H), 7.65 (d, 1 H).
LC/MS m/z = 321.12.

EXAMPLE 239

2-Benzyl-4-bromo-benzoic acid (239):



Ste

p 1

3,5-Dibromo-3H-isobenzofuran-1-one (B3): The mixture of 5-bromo-3H-isobenzofuran-1-one (A3) (51.5g, 242 mmol) in bromobenzene (100mL) is heated to 158°C. Bromine (18.8mL, 363 mmol) is added dropwise to the mixture over 2h. The mixture is stirred for another 30 min. at 158°C. The bromobenzene is removed by distillation under vacuum. The residue is vacuum dried 1 hour at 120°C to yield a black crystalline residue. Recrystallization: The residue is

dissolved in hot isopropyl ether (300mL). Activated charcoal (1 g) is added, stirred and filtered while hot. The filtrate is cooled in ice-water bath (0°C) over night. The solid is filtered and is rinsed with cold isopropyl ether (2 x 10mL) and vacuum dry over KOH (KOH) to yield 3,5-dibromo-3H-isobenzofuran-1-one (B3) (38g, 54%, mp: 100°C).

Step 2

4-Bromo-2-formyl-benzoic acid (C3): The mixture of 3,5-dibromo-3H-isobenzofuran-1-one (B3) (38g, 130 mmol) in a solution of 10N NaOH (28.6mL, 286 mmol) and water (240mL) is heated for 2h at 80°C. Activated charcoal (2g) is added and the mixture is refluxed for another 1 hour. Mixture is hot filtered and acidified with 2N methanesulfonic acid (100mL). The resulting mixture is cooled in an ice-water bath for 1h. The solid is filtered and washed with water (4 x 25mL) and vacuum dried under KOH to yield 4-bromo-2-formyl-benzoic acid (C3) (26.5g, 89%, mp: 202°C). Recrystallization: Dissolved 4-bromo-2-formyl-benzoic acid (C3) in hot EtOH (220mL) and cooled the mixture in an ice-water bath for 4h. The solid is filtered and rinsed with cold EtOH (3 x 20mL). The solid is then vacuum dried over KOH to yield 4-bromo-2-formyl-benzoic acid (16.8g, 63%, mp: 204-205°C).

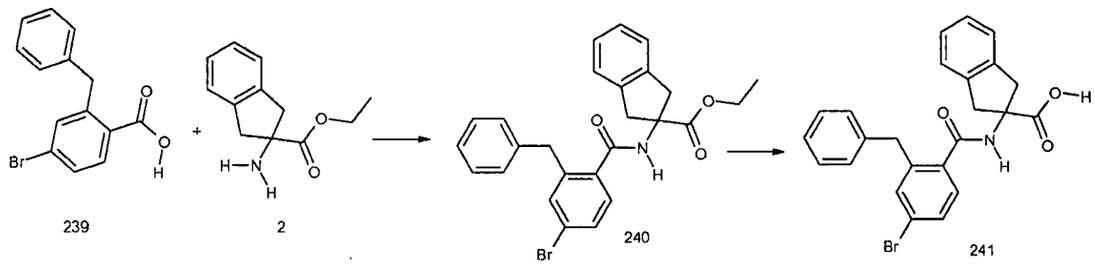
Step 3

5-Bromo-3-phenyl-3H-isobenzofuran-1-one (D3): A tricol of 1L with a condenser and an addition funnel is purged with N_2 and magnesium turnings (5g, 206 mmol) in tetrahydrofuran (80mL) are added. Bromobenzene (32g, 206 mmol) in tetrahydrofuran (80mL) is added dropwise over 1¼ hour by maintaining the mixture temperature at 30°C. The resulting mixture is stirred for 45 min. at 30°C. 4-Bromo-2-formyl-benzoic acid (C3) (18.9g, 83 mmol) in anhydrous tetrahydrofuran (200mL) is added dropwise over 45 min. The mixture is stirred for 2h at 30°C. The mixture is cooled in an ice-water bath and water (120mL) and 5N HCl solution (80mL) are added. The mixture is stirred overnight. THF is removed *in vacuo* and extracted with DCM (3 x 100mL). The combined organics are washed with water (2 x 100mL), dried over Na_2SO_4, filtered and the solvent is removed *in vacuo* to yield 5-bromo-3-phenyl-3H-isobenzofuran-1-one (22.5g, 94%). Recrystallization: 5-bromo-3-phenyl-3H-isobenzofuran-1-one is dissolved in hot acetone (250mL) and the mixture cooled in an ice-water bath over night. The resultant solid is filtered, rinsed with cold ACN (2 x 15mL), and then vacuum dried over KOH to yield 5-bromo-3-phenyl-3H-isobenzofuran-1-one (D3) (14.4g, 61%, mp: 189°C).

Step 4

2-Benzyl-4-bromo-benzoic acid (239): The mixture of 5-bromo-3-phenyl-3H-isobenzofuran-1-one (D3) (14.4g, 50 mmol), iodine (9g, 70 mmol), amorphous red phosphorous (7.8g, 250 mmol), acetic acid (125mL) and distilled water (15mL) are taken in this order in a 3-neck flask with a mechanical stirrer and condenser. After stirring overnight at 50°C (90% product and 10% starting material), the reaction is quenched by adding into water (500mL), added ether (200mL) and filtered off phosphorous. The aqueous layer is extracted with ether (3 x 100mL) and the combined organic layers are washed with sodium bisulfite solution (100mL) and water (2 x 100mL). The organic phase is extracted using 1N NaOH aqueous solution (4 X 100mL), washed again with water (4 x 100mL), dried over Na_2SO_4 and evaporated to get the neutral fraction (2g, mp 180°C). The basic phase is acidified with 5N HCl (150mL) and extracted with DCM (4 x 100mL). The combined extracts are washed with water (3 x 100mL), dried over Na_2SO_4 and evaporated to get product (12g, mp 137°C). This is further recrystallized from boiling ACN (50mL) to afford 2-benzyl-4-bromo-benzoic acid (239) (10g, 83%, mp 145°C).

EXAMPLE 240



2-(2-Benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid ethyl ester (240) : 2-Amino-indane-2-carboxylic acid ethyl ester (2) (250mg, 1.2 mmol), 2-benzyl-4-bromo-benzoic acid (239) (354mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/ heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel column using 20-50% EtOAc in heptane as a gradient to afford 2-(2-benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid ethyl ester (495mg, 86%).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.26 (t, 3 H), 3.35 (dd, 4H), 4.14 (s, 3 H), 4.24 (q, 2H), 6.12 (s, 1H), 7.05 - 7.39 (m, 12H).
LC/MS m/z = 478.13.

EXAMPLE 241

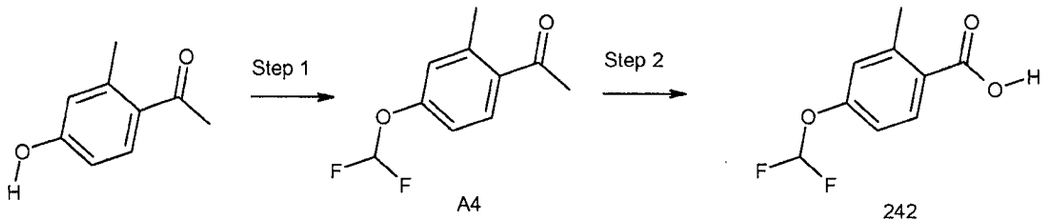
2-(2-Benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid (241) :

The mixture of 2-(2-benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid ethyl ester (240) (339mg, 0.71 mmol), KOH (50% aqueous solution, 1.58g, 14.14 mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (5mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration affords 2-(2-benzyl-4-bromo-benzoylamino)-indan-2-carboxylic acid (241) as white solid (310mg, 97%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.37 (dd, 4H), 4.10 (s, 2H), 6.23 (s, 1H), 7.01 - 7.38 (m, 12H).
LC/MS m/z = 450.06.

EXAMPLE 242

4-Difluoromethoxy-2-methyl-benzoicacid (242):



Step 1

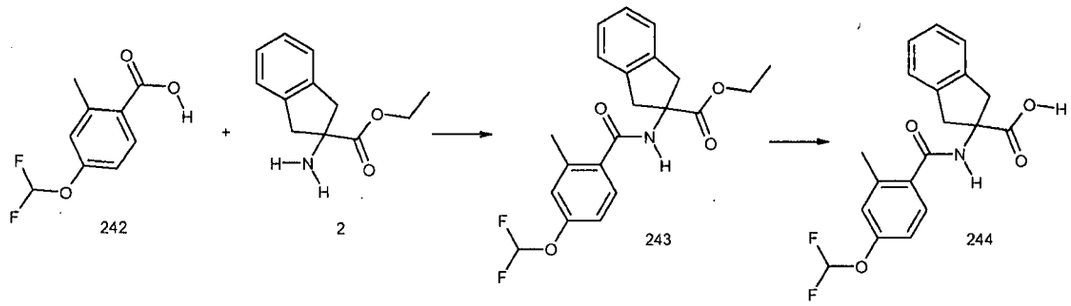
1-(4-Difluoromethoxy-2-methyl-phenyl)-ethanone (A4): To a stirred suspension of 1-(4-hydroxy-2-methyl-phenyl)-ethanone (15g, 100 mmol) in dioxane (30mL) is added water (25mL) followed by the addition of NaOH (20g, 500 mmol). Reaction is heated to 65°C and passed gaseous chlorodifluoromethane (30g, 150 mmol) using a glass tube dipped below the solution level for 75 minutes. Stirred for 30min longer and left at RT over the weekend. Water (100mL) and ether (40mL) are added after transferring to a separatory funnel. A semi-

gelatinous material settled at the bottom of the aqueous layer after some time. The bottom aqueous layer is drained off and extracted with ether (2 x 40mL). The combined ether layers are washed with water (5 x 25mL), dried over solid K_2SO_4, evaporated and distilled (0.04 mm Hg, 61-64°C) to afford 1-(4-difluoromethoxy-2-methyl-phenyl)-ethanone (A4) (16.2g, 81%). Rf in tlc 0.60 with ether.

Step 2

4-Difluoromethoxy-2-methyl-benzoic acid (242): A stirred solution of sodium hypochlorite (5.25% Aqueous, 204mL, 143 mmol) and 2N aqueous KOH (22mL, 44 mmol) are heated to 50°C and 1-(4-difluoromethoxy-2-methyl-phenyl)-ethanone (A4) (5.8g, 29 mmol) is added. After maintaining the temperature at 50-70°C for 3h and keeping at RT overnight, the reaction is reheated to 50°C and sodium metabisulfite (4.5g) is added in 3 portions. The reaction is then acidified with 12N HCl and stirred well. The precipitated white solid is filtered off, rinsed with a little water and air dried to afford 4-difluoromethoxy-2-methyl-benzoic acid (242) (5.4g, 92%). The product is recrystallized from 1:1 mixture of ACN and water. mp: 117-119°C. Elemental Analysis: Actual C (53.23),H (3.88), F (18.66) Theoretical C (53.47),H (3.99), F (18.80).

EXAMPLE 243



2-(4-Difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (243) : 2-Amino-indane-2-carboxylic acid ethyl ester (2) (250mg, 1.2 mmol), 4-difluoromethoxy-2-methyl-benzoic acid (242) (246mg, 1.2 mmol) and HATU (555mg, 1.46 mmol) are taken in a vial, evacuated and refilled with nitrogen. Anhydrous DMF (2mL) is added and stirring is initiated. After few min, DIPEA (0.302mL, 1.82 mmol) is added and stirred at RT overnight. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. Water (10mL) is added, extracted with EtOAc (3 x 5mL), dried over Na_2SO_4, concentrated and the crude product is chromatographed on a 25g silica gel

column using 20-50% EtOAc in heptane as a gradient to afford 2-(4-difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (415mg, 89%).

^{1}H NMR ($CDCl_3$, 300 MHz,): δ 1.29 (t, 3 H), 2.42 (s, 3 H), 3.56 (dd, 4H), 4.27 (q, 2H), 6.21 (s, 1H), 6.91 (m, 2H), 7.22 (m, 4H), 7.33 (d, 1H).
LC/MS m/z = 390.16.

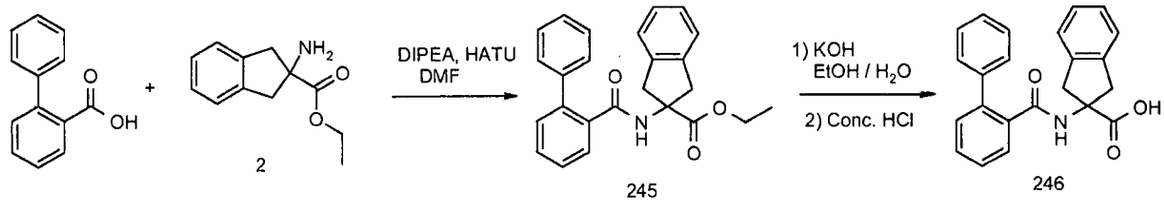
EXAMPLE 244

2-(4-Difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid (244) :

The mixture of 2-(4-difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (243) (301mg, 0.77 mmol), KOH (50% aqueous solution, 1.73g, 15.5 mmol), EtOH (10mL) and water (1mL) are stirred in a 20mL vial at 50°C for 30 min. After concentration *in vacuo*, the residue is dissolved in water (10mL) and acidified with conc. HCl until no more white precipitate came out of the water. The filtration affords 2-(4-difluoromethoxy-2-methyl-benzoylamino)-indan-2-carboxylic acid (244) as white solid (245mg, 88%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.37 (s, 3H), 3.62 (dd, 4H), 6.23 (s, 1H), 6.92 (m, 2H), 7.24 (m, 5H).
LC/MS m/z = 362.10.

EXAMPLE 245



2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (245):

To a solution of biphenyl-2-carboxylic acid (289mg, 1.46mmol), 2-amino-indan-2-carboxylic acid ethyl ester (300mg, 1.46mmol), HATU (666mg, 1.75mmol) in anhydrous DMF (1.8mL) is added DIPEA (381μL, 2.19mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3 x 5mL). The combined organic layers are concentrated *in vacuo* and the residue purified by flash column chromatography (12g silica

gel, gradient elution: 0-30% EtOAc in heptane) to give product (245) as off-white solid (525mg, 93%).

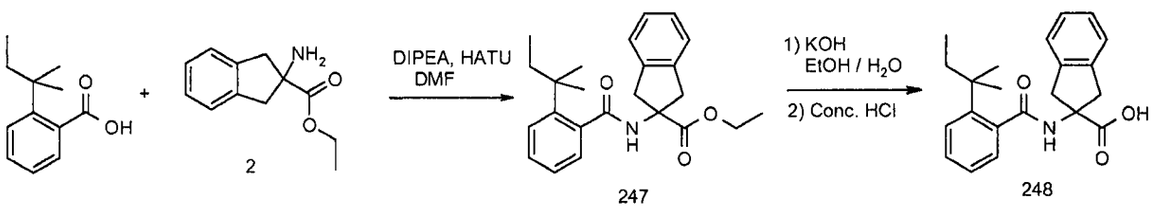
EXAMPLE 246

2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid (246):

2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (525mg, 1.36mmol) is dissolved in EtOH (15mL), and solid KOH (1.42g, 24.7mmol) and water (1.5mL) are added. The mixture is stirred at RT for 30 minutes then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (246) as white solid (453mg, 93%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 2.92(d, 2H), 3.63(d, 2H), 5.84(s, 1H), 7.08-7.12(m, 2H), 7.15-7.19(m, 2H), 7.24(s, 4H), 7.30(dd, 2H), 7.40-7.54 (m, 2H), 7.85 (dd, 1H)
LC/MS (ES+) m/z = 358.14

EXAMPLE 247



2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (247):

To a solution of 2-(1,1-dimethyl-propyl)-benzoic acid (140mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190μL, 1.1mmol). The resulting solution is stirred at RT overnight. Water (10mL) is then poured into the reaction mixture, and then the reaction mixture is extracted with EtOAc (3 x 5mL). The combined organic layers are concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (247) as yellow oil (220mg, 89%).

EXAMPLE 248

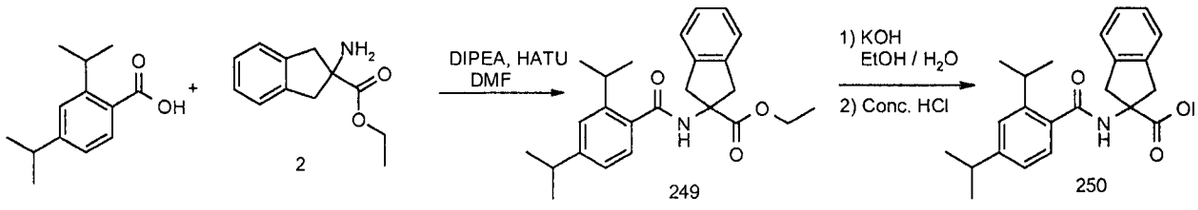
2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid (248):

2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (220mg, 0.58mmol) is dissolved in EtOH (8mL), and solid KOH (600mg, 10mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30 minutes then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (248) as white solid (158mg, 78%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 0.53(t, 3H), 1.29(s, 6H), 1.66-1.73(q, 2H), 3.44(d, 2H), 3.80(d, 2H), 6.14(s, 1H), 7.13-7.14(m, 1H), 7.15(d, 1H), 7.22(d, 4H), 7.32(d, 1H), 7.34 (t, 1H), 7.37 (dd, 1H)

LC/MS (ES+) m/z = 352.17

EXAMPLE 249



2-(2,4-Diisopropyl-benzoylamino)-indan-2-carboxylic acid ether ester (249):

To a solution of 2,4-diisopropyl-benzoic acid (150mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190μL, 1.10mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3 x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (249) as off-white solid (211mg, 73%).

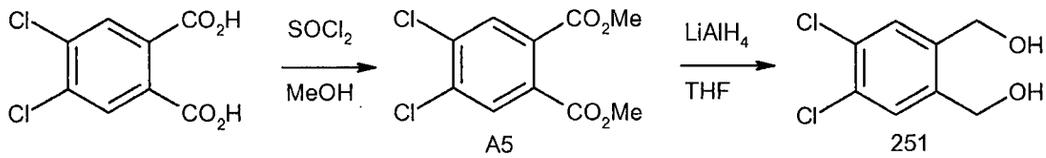
EXAMPLE 250

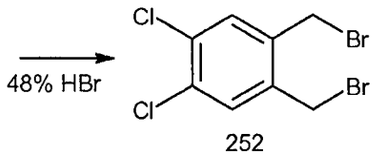
2-(2,4-Diisopropyl-benzoylamino)-indan-2-carboxylic acid (250):

2-(2,4-diisopropyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (211mg, 0.54mmol) is dissolved in EtOH (8mL), and solid KOH (823mg, 14mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (250) as white solid (188mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.12(d, 6H), 1.21(d, 6H), 2.83-2.92(m, 1H), 3.10-3.19(m, 1H), 3.41(d, 2H), 3.82(d, 2H), 6.18(s, 1H), 7.00-7.10(m, 2H), 7.16(s, 1H), 7.22-7.31(m, 4H)
LC/MS (ES+) m/z = 366.20

EXAMPLE 251





Dimethyl 4,5-Dichlorophthalate (A5):

Thionyl chloride (150mL, 2.05 mol) is added dropwise over 2h to a magnetically stirred solution of 4,5-dichlorophthalic acid (110.43g, 469.8 mmol) in MeOH (1L) at RT. After stirring overnight, the MeOH is removed *in vacuo* on a rotary evaporator. The residue is dissolved in EtOAc (750mL) and extracted with water (1 x 500mL) and saturated aqueous $NaHCO_3$ (1 x 500mL). The organic layer is separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to afford A5 (122.8g) as a pale yellow liquid. [A. Rosowsky, C. M. Vaidya,h. Bader, J. E. Wright, B. A. Teicher, *J. Med. Chem.* 40, 286-299 (1997); E. J. Hennessy, S. L. Buchwald, *J. Org. Chem.*, 70, 7371-7375 (2005)]

^{1}H NMR ($CDCl_3$, 300MHz): δ 3.92 (s, 3H), 7.82 (s, 1H)

4,5-Dichloro-1,2-bis(hydroxymethyl)benzene (251):

A solution of dimethyl 4,5-dichlorophthalate A5 (98.86g, 375.78 mmol) in tetrahydrofuran (150mL) is added dropwise over 1h to a mechanically stirred suspension of LAH (20.8g,

548.1 mmol) in tetrahydrofuran (1.5L). During the addition, the reaction is cooled in an ice-water bath. When the addition is completed, the reaction is stirred overnight at RT. The excess LAH is decomposed by cautious addition of water (20mL), 10% aqueous NaOH (40mL) and water (20mL). The solids are removed by filtration through a celite pad and washed with tetrahydrofuran. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to afford crude 251 as white solid that is purified by crystallization from acetone (150mL)-heptane (150mL). The crystals are collected by filtration, washed with heptane and dried to give 4,5-dichloro-1,2-bis(hydroxymethyl)benzene (37.2g). The combined filtrate and wash afforded a second crop of 251 (18.8g, 24.1%). [L. A. Levy, *Synth. Commun.*, 13, 639-648 (1983); O. Farooq, *Synthesis*, 1035-1036 (1994)]

^{1}H NMR (DMSO-d6, 300MHz): δ 4.49 (d, 2H), 5.32 (t, 1H), 7.57 (s, 1H)
EI-MS m/z 209,207
Anal. Calcd. for $C_8H_8Cl_2O_2$: C, 46.41;H, 3.89. Found: C, 46.50;H, 3.83

EXAMPLE 252

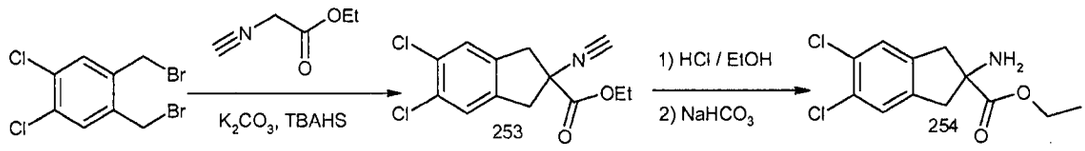
1,2-Bis-(bromomethyl)-4,5-dichlorobenzene (252):

A mixture of 4,5-dichloro-1,2-bis(hydroxymethyl)benzene (251, 32.87g, 158.75 mmol) and 48% aqueous hydrobromic acid (160mL) is heated at reflux temperature for 6h. The reaction is cooled and extracted with diethyl ether (1 x 450mL + 2 x 200mL). The combined organic extracts are backwashed with water (1 x 200mL) and with brine (1 x 200mL). The organic layer is separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to afford a light yellow solid that is dissolved in heptane-0.5% EtOAc by heating and placed atop a column of silica gel (7.2cm x 23cm) prepared in heptane-0.5% EtOAc and flash chromatographed taking 500mL fractions and eluting with heptane-0.5% EtOAc (1.6L), and heptane-1% EtOAc (4L). The product containing fractions (5-14) are combined and concentrated *in vacuo* on a rotary evaporator to give 1,2-bis-(bromomethyl)-4,5-dichlorobenzene (252, 50.01g) as a colorless liquid. [L. A. Levy, *Synth. Commun.*, 13, 639-648 (1983)]

^{1}H NMR ($CDCl_3$, 300MHz): δ 4.55 (s, 2H), 7.46 (s, 1H)
EI-MS m/z 330,332,334,336

Anal. Calcd. for $C_8H_6Br_2Cl_2$: C, 28.87;H, 1.82. Found: C, 28.84;H, 1.68

EXAMPLE 253



4,

5-Dichloro-isocyano-indan-2-carboxylic acid ethyl ester (253) :

To a solution of ethyl isocyanoacetate (3.85mL, 35mmol) in anhydrous ACN (300mL) is added finely ground anhydrous K_2CO_3 (29g, 210mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.34g, 7mmol), and 1,2-bis-(bromomethyl)-4,5-dichlorobenzene (11.6g, 35mmol). The resulting heterogeneous mixture is stirred at 80°C overnight. The reaction mixture is cooled down to RT and filtered to remove the unwanted salts. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel; gradient elution: 0-25% EtOAc in heptane) to give a pure product as white powder (6.63g, 66%).

^1H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.46 (s, 2H)

LC/MS (ES+) m/z = 286.14

EXAMPLE 254

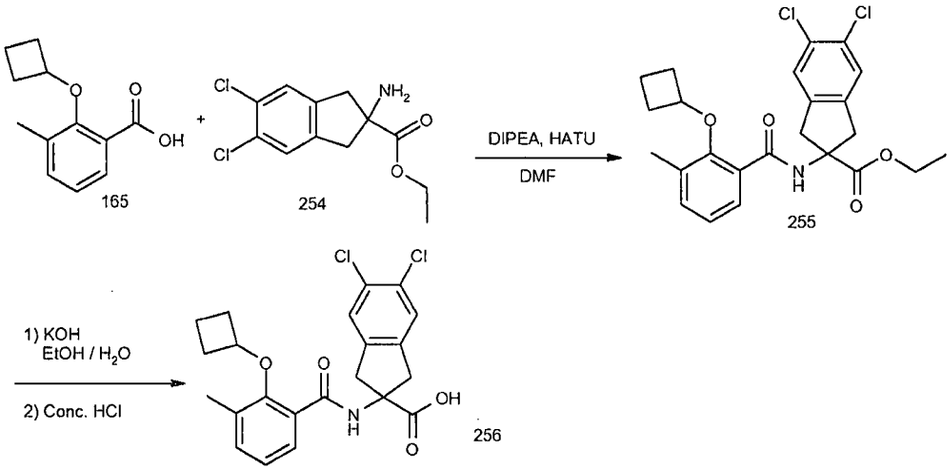
2-Amino-4,5-dichloro-indan-2-carboxylic acid ethyl ester (254):

To a solution of 4,5-dichloro-isocyano-indan-2-carboxylic acid ethyl ester (253) (6.63g, 23.2mmol) in absolute EtOH (200mL) is added concentrated HCl (10mL) dropwise. The resulting solution is stirred at RT for 24h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride salt is dissolved in water (100mL) and extracted with ethyl ether (3 x 50mL) to remove unwanted organic impurities. The aqueous layer is brought to pH 9 by addition of saturated $NaHCO_3$ solution and then extracted with EtOAc (3 x 100mL). The combined EtOAc layer is washed with brine (100mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (5.2g, 82%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.46 (s, 2H)

LC/MS (EZ+) m/z = 275.18

EXAMPLE 255



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid ethyl ester (255):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (225mg, 1.1mmol), 2-amino-4,5-dichloro-indan-2-carboxylic acid ethyl ester (254) (360mg, 1.31mmol), HATU 622mg, 1.64mmol) in anhydrous DMF (10mL) is added DIPEA (360μL, 2.20mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is suspended in H_2O (50mL) and washed with EtOAc (3 x 50mL). Organics are combined and washed successively with $NaHCO_3$ and brine, and then the organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (255) as white powder (460mg, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21- 4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.19(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)

LC/MS (ES+) m/z = 428.93

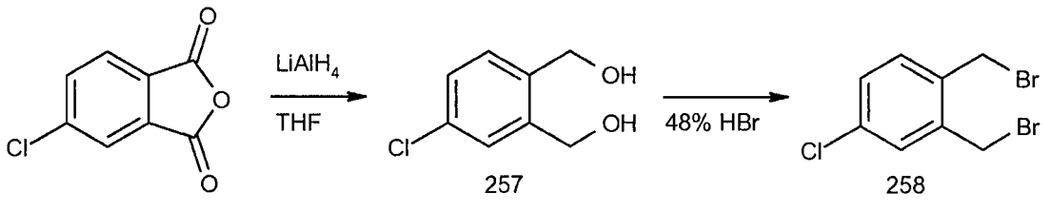
EXAMPLE 256

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid (256):

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid ethyl ester (255) (460mg, 0.99mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with concentrated HCl to pH 2. The resultant mixture is washed with EtOAc (3 x 100ml). Organics are combined and washed with brine, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product (256) is obtained as white solid (405mg, 94%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)
LC/MS (ES+) m/z = 434.32

EXAMPLE 257



257 258

4-Chloro-1,2-bis(hydroxymethyl)benzene (257):

A solution of 4-chlorophthalic anhydride (24.83g, 136.01 mmol) in tetrahydrofuran (100mL) is added dropwise to a mechanically stirred suspension of LAH (8.72g, 229.78 mmol) in tetrahydrofuran (500mL). After stirring overnight at room temperature, the excess LAH is decomposed by cautious addition of water (8.5mL), 10% aqueous NaOH (17mL) and water (8.5mL). The reaction is diluted with tetrahydrofuran (300mL) and the solids are removed by filtration through a celite pad and washed with tetrahydrofuran. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to afford diol 257 as a colorless liquid (22.16g) that crystallized on standing. Crystallization is effected in benzene. [O. Farooq, *Synthesis*, 1035-1036 (1994); R. F. Bird, E. E. Turner, *J. Chem. Soc.* 5050-5051 (1952); J. Tirouflet, *Compt. rend.*, 238, 2246-2247 (1954)]

^{1}H NMR (DMSO-d6, 300MHz): δ 4.48 (t, 2H), 4.52 (t, 2H), 5.15 (t, 1H), 5.24 (t, 1H), 7.27 (dd, 1H), 7.38 (s, 1H), 7.41 (t, 1H)

EXAMPLE 258

1,2-Bis(bromomethyl)-4-chlorobenzene (258):

A mixture of 4-chloro-1,2-bis(hydroxymethyl)benzene (257, 20.57g, 119.17 mmol) and 48% aqueous hydrobromic acid (140mL) is heated at 137°C for 4.5h. The reaction is cooled to RT then diluted with cold water (250mL) and extracted with diethyl ether (1 x 400mL + 2 x 200mL). The combined organic extracts are washed with water (1 x 200mL), with brine (1 x 200mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator to afford crude dibromide 258 as a yellow liquid. This material is dissolved in heptane-0.5% EtOAc, placed atop a column of silica gel (7.2cm x 22cm) and flash chromatographed taking 400mL fractions eluting with heptane-0.5% EtOAc (1.6L) and heptane-1% EtOAc (3L). Product containing fractions (5-9) are combined and concentrated *in vacuo* on a rotary evaporator to afford dibromide 258 as a colorless liquid (34.46g). [D. R. Lyon, F.G. Mann, G. H.. Cookson, *J. Chem. Soc.*, 662-670 (1947)]

^{1}H NMR ($CDCl_3$, 300MHz): δ 4.58 + 4.61 (s + s, 4H), 7.28-7.32 (m, 2H), 7.36 (d, 1H)

EI-MS 298,300

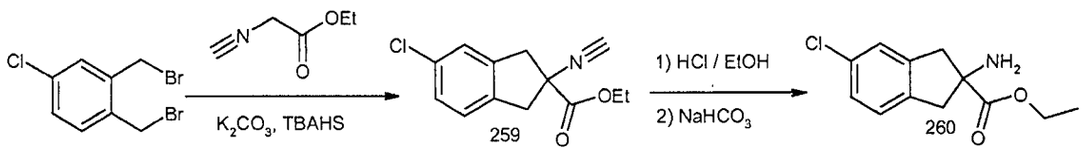
Anal. Calcd. For $C_8H_7Br_2Cl$: C, 32.20;H, 2.36. Found: C, 32.30;H, 2.22

Alternate Route:

A magnetically stirred mixture of 4-chloro-*ortho*-xylene (5g, 35.56 mmol), *N*-bromosuccinimide (12.65g, 71.07 mmol), AIBN (0.55g) and CCl_4 (150mL) is heated at reflux temperature for 3.5h, and then cooled to RT. The solids are removed by filtration and washed with CCl_4. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to give crude dibromide 10 as a colorless liquid that is dissolved in heptane-1% EtOAc, placed atop a column of silica gel (7.2cm x 18cm) prepared in heptane-1% EtOAc and flash chromatographed taking 200mL fractions eluting with heptane-1% EtOAc. Product containing fractions (7-11) are combined and concentrated *in vacuo* on a rotary evaporator to afford impure 258 as colorless liquid.

^{1}H NMR ($CDCl_3$, 300MHz): δ 4.46 (s, 0.3H), 4.51 (s, 0.6H), 4.58 + 4.61 (pr s, 4H), 7.26-7.29 (m, 2.5H), 7.36 (d, 1.2H).

EXAMPLE 259



4-Chloro-isocyano-indan-2-carboxylic acid ethyl ester (259) :

To a solution of ethyl isocyanoacetate (3.85mL, 35.0mmol) in anhydrous ACN (300mL) is added finely ground anhydrous K_2CO_3 (29g, 210mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.34g, 7mmol), and 1,2-bis(bromomethyl)-4-chlorobenzene (10.4g, 35mmol). The resulting heterogeneous mixture is stirred at 80°C overnight. The reaction mixture is cooled to RT and filtered to remove the unwanted salts. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel; gradient elution: 0-25% EtOAc in heptane) to give a pure product as a colorless oil (5.06g, 58%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.28-7.32 (m, 2H), 7.36 (d, 1H)

LC/MS (ES+) m/z = 250.56

EXAMPLE 260

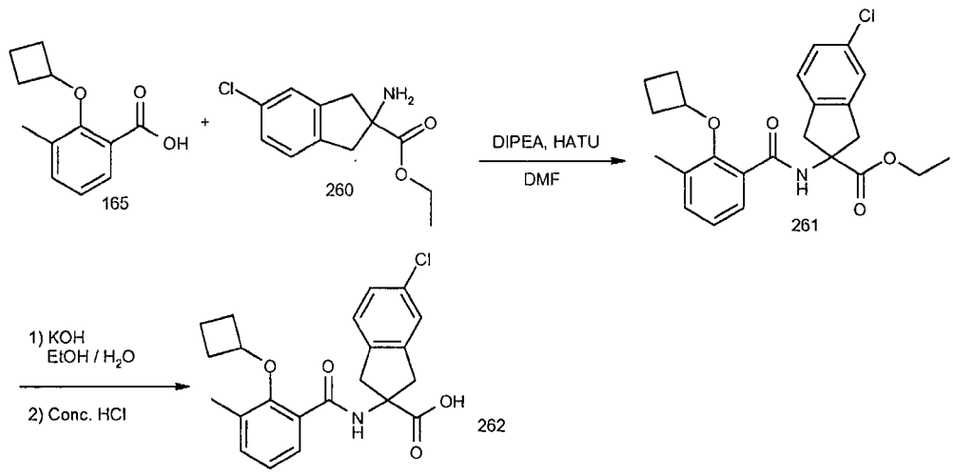
2-Amino-4-chloro-indan-2-carboxylic acid ethyl ester (260):

To a solution of 4-chloro-isocyano-indan-2-carboxylic acid ethyl ester (259) (5.06g, 20.2mmol) in absolute EtOH (200mL) is added concentrated HCl (10mL) dropwise. The resulting solution is stirred at RT for 24h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride salt is dissolved in water (100mL) and extracted with of ethyl ether (3 x 50mL) to remove unwanted organic impurities. The aqueous layer is brought to pH 9 by addition of saturated $NaHCO_3$ solution and then extracted with EtOAc (3 x 100mL). The combined EtOAc layer is washed with brine (100mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (4.2g, 87%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.28-7.32 (m, 2H), 7.36 (d, 1H)

LC/MS (EZ+) m/z = 239.58

EXAMPLE 261



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid ethyl ester (261):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (213mg, 1.04mmol), 2-amino-4-chloro-indan-2-carboxylic acid ethyl ester (260) (298mg, 1.24mmol), HATU (591mg, 1.55mmol) in anhydrous DMF (10mL) is added DIPEA (345μL, 2.07mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is suspended in H_2O (50mL) and washed with EtOAc (3 x 50mL). Organics are combined and washed successively with $NaHCO_3$ and brine, and then the organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (261) as white powder (370mg, 83%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21- 4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.19(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)

LC/MS (ES+) m/z = 428.93

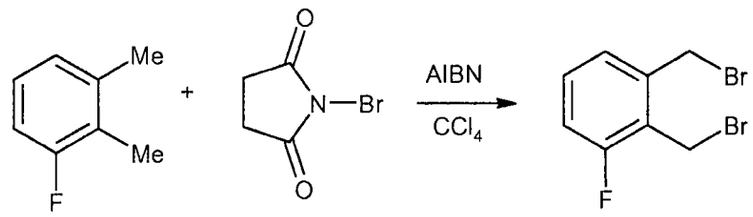
EXAMPLE 262

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid (262):

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid ethyl ester (261) (370mg, 0.86mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with conc. HCl to pH 2. The resultant mixture is washed with EtOAc (3 x 100ml). Organics are combined and washed with brine, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product (262) is obtained as white solid (320mg, 93%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)
LC/MS (ES+) m/z = 399.93

EXAMPLE 263



263

1,2-Bis(bromomethyl)- 3-fluorobenzene (263):

A magnetically stirred mixture of 3-fluoro-*ortho*-xylene (5.05g, 40.67 mmol), *N*-bromosuccinimide (15.23g, 85.56 mmol), AIBN (78mg) and CCl_4 (75mL) is heated at reflux temperature for 1.75h, then cooled to RT. The solids are removed by filtration and washed with CCl_4. The combined filtrate and wash is concentrated *in vacuo* on a rotary evaporator to give crude dibromide 263 as a yellow liquid that is dissolved in heptane-0.5% EtOAc, placed atop a column of silica gel (7.2cm x 18cm) prepared in heptane-0.5% EtOAc and flash chromatographed taking 200mL fractions eluting with heptane-0.5% EtOAc. Product containing fractions are combined and concentrated *in vacuo* on a rotary evaporator to afford a colorless liquid. On standing crystals form in the liquid. The liquid is separated using a pipette. The process is repeated once more. The resulting liquid is pure 1,2 bis(bromomethyl)-3-fluorobenzene. [J. E. Rice, A. Czech, N, Hussain, E. J. La Voie, *J. Org. Chem.*, 53, 1775-1779 (1988) ; R. A. Aitken, P. K.g. Hodgson, M. J. Morrison, A. O. Oyewale, *J. Chem. Soc. (Perkin 1)*, 402-415 (2002)]

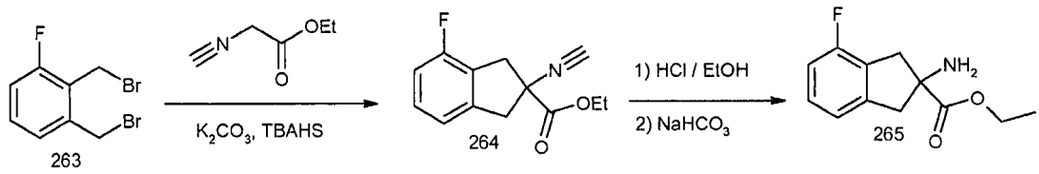
^{1}H NMR ($CDCl_3$, 300MHz): δ 4.63 (s, 3H), 4.70 (s, 3H), 7.05 (ddd, 1H), 7.17 (d, 1H), 7.29 (ddd, 1H)

F NMR ($CDCl_3$, 300MHz): δ 115.26 (d)

LC-MS 3.23 (no parent ion)

Anal. Calcd. for $C_8H_7Br_2F$: C, 34.08;H, 2.50; F, 6.74. Found: C, 34.11;H, 2.28; F, 6.88

EXAMPLE 264



3-Fluoro-isocyano-indan-2-carboxylic acid ethyl ester (264) :

To a solution of ethyl isocyanoacetate (3.85mL, 35.0mmol) in anhydrous ACN (300mL) is added finely ground anhydrous K_2CO_3 (K_2SO_4, 29.0g, 210mmol), TBAHS (tetrabutyl ammonium hydrogen sulfate, 2.34g, 7.0mmol), and 1,2-bis(bromomethyl)-3-fluorobenzene (9.87g, 35mmol). The resulting heterogeneous mixture is stirred at 80°C overnight. The reaction mixture is cooled down to RT and filtered to remove the unwanted salts. The filtrate is concentrated *in vacuo*. The residue is purified by flash column chromatography (200g silica gel; gradient elution: 0-25% EtOAc in heptane) to give a pure product as colorless oil (4.5g, 55%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.35 (t, 3H), 3.47 (d, 2H), 3.71 (d, 2H), 4.32 (q, 2H), 7.05 (ddd, 1H), 7.17 (d, 1H), 7.29 (ddd, 1H)

LC/MS (ES+) m/z = 234.26

EXAMPLE 265

2-Amino-3-fluoro-indan-2-carboxylic acid ethyl ester (265):

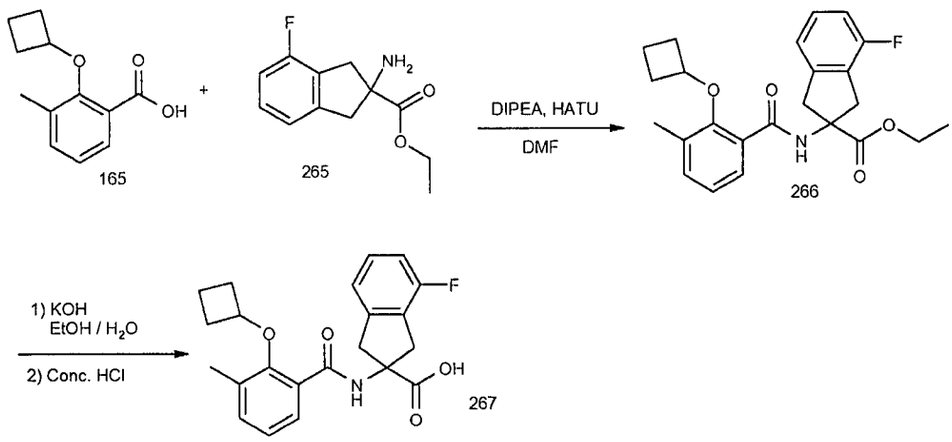
To a solution of 2-isocyano-indan-2-carboxylic acid ethyl ester (264) (4.5g, 19.3mmol) in absolute EtOH (200mL) is added concentrated HCl (10mL) dropwise. The resulting solution is stirred at RT for 24h. After the removal of the EtOH *in vacuo*, the remaining hydrochloride

salt is dissolved in water (100mL) and extracted with of ethyl ether (3 x 50mL) to remove unwanted organic impurities. The aqueous layer is brought to pH 9 by addition of saturated $NaHCO_3$ solution and then extracted with EtOAc 3 x 100mL). The combined EtOAc layer is washed with brine (100mL). The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to give a pure product as white solid (2.3g, 53%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.29 (t, 3H), 2.88 (d, 2H), 3.57 (d, 2H), 4.23 (q, 2H), 7.05 (ddd, 1H), 7.17 (d, 1H), 7.29 (ddd, 1H)

LC/MS (EZ+) m/z = 223.08

EXAMPLE 266



2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid ethyl ester (266):

To a solution of 2-cyclobutoxy-3-methyl-benzoic acid (127mg, 0.61mmol), 2-Amino-3-fluoro-indan-2-carboxylic acid ethyl ester (265) (165mg, 0.74mmol), HATU 352mg, 0.93mmol) in anhydrous DMF (10mL) is added DIPEA (204μL, 1.23mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is suspended in H_2O (50mL) and washed with EtOAc (3 x 50mL). Organics are combined and washed successively with $NaHCO_3$ and brine, and then the organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (266) as a colorless oil (210mg, 84%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.21-1.36(m, 4H), 1.50-1.56(m, 1H), 1.96-2.09(m, 4H), 2.27(s, 3H), 3.44(t, 2H), 3.73(dd, 2H), 4.21- 4.33(m, 3H), 6.85-6.94(m, 2H), 7.08(t, 1H), 7.14-7.19(m, 1H), 7.27(d, 1H), 7.85(dd, 1H), 8.37(s, 1H)

LC/MS (ES+) m/z = 412.19

EXAMPLE 267

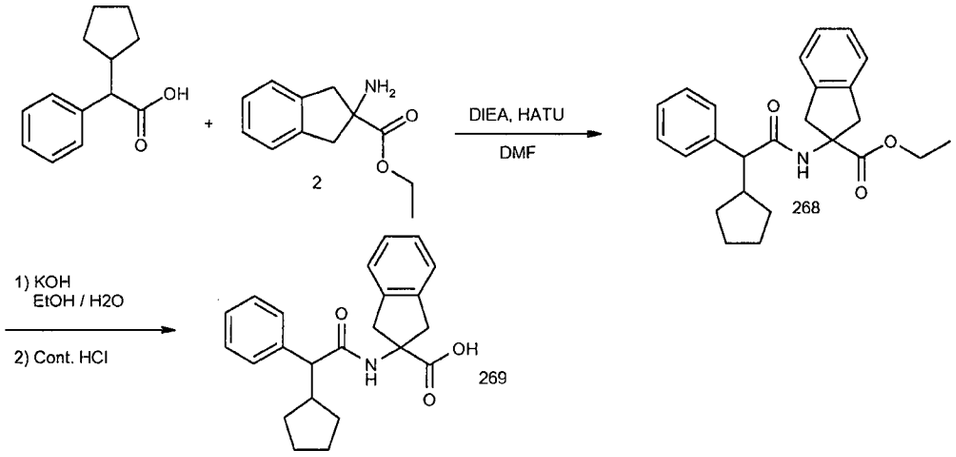
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid (267):

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid ethyl ester (7) (210mg, 0.51mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and acidified with concentrated HCl to pH 2. The resultant mixture is washed with EtOAc (3 x 100ml). Organics are combined and washed with brine, then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired product (267) is obtained as white solid (168mg, 86%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 1.21-1.36(m, 1H), 1.50 (m, 1H), 1.92-2.14(m, 4H), 2.26(s, 3H), 3.38(t, 2H), 3.73(dd, 2H), 4.29(m, 1H), 6.86-6.95(m, 2H), 7.11(t, 1H), 7.15-7.20(m, 1H), 7.29(d, 1H), 7.83(dd, 1H), 8.51(s, 1H)

LC/MS (ES+) m/z = 384.15

EXAMPLE 268



2-(2-Cyclopentyl-2-phenyl-acetylamino)-indan-2-carboxylic acid ethyl ester (268):

To a solution of α-phenylcyclopenteacetic acid (2.04g, 10mmol), 2-Amino-indan-2-carboxylic acid ethyl ester (2.05g, 10mmol), HATU (7.60g, 20mmol) in anhydrous DMF (50mL) is

added DIPEA (3.30mL, 20mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (100mL) and washed with saturated $NaHCO_3$ (1 x 100mL), water (1 x 100mL) and brine (1 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-20% EtOAc in heptane) to give a pure product (268) as a solid (3.16g, 82%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 0.91(m, 1H), 1.23(m, 2H), 1.29 (t, 3H), 1.35-1.64(m, 4H), 1.65-1.81(m, 1H), 2.34-2.49(m, 1H), 2.78(d, 2H), 2.89-3.03(d, 1H), 3.13-3.23(m, 2H), 3.42-3.52(m, 2H), 7.1-7.35(m, 9H)
LC/MS (ES+) m/z = 392.19

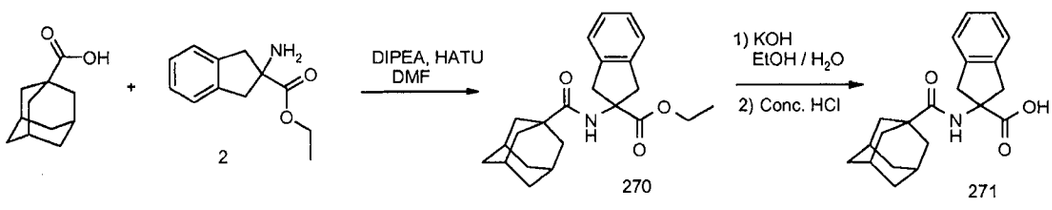
EXAMPLE 269

2-(2-Cyclopentyl-2-phenyl-acetylamino)-indan-2-carboxylic acid (269):

2-(2-Cyclopentyl-2-phenyl-acetylamino)-indan-2-carboxylic acid ethyl ester (268) (1g, 2.56mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (3ml). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue is dissolved in water (20mL) and washed with EtOAc (20ml). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The solid precipitate is collected via filtration and dried under vacuum. The desired product (269) is obtained as white solid (710mg, 71%).

^{1}H NMR (d-DMSO-d6, 300MHz): δ 0.91(m, 1H), 1.23(m, 2H), 1.35-1.64(m, 4H), 1.65-1.81(m, 1H), 2.34-2.49(m, 1H), 2.89-3.03(d, 1H), 3.13-3.23(m, 2H), 3.42-3.52(m, 2H), 7.1-7.35(m, 9H), 8.57(s, 1H)
LC/MS (ES+) m/z = 364.46

EXAMPLE 270



2-[(Adamantane-1-carbonyl)-amino]-indan-2-carboxylic acid ether ester (270):

To a solution of adamantane-1-carboxylic acid (131mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190µL, 1.1mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3 x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (270) as white solid (261mg, 97%).

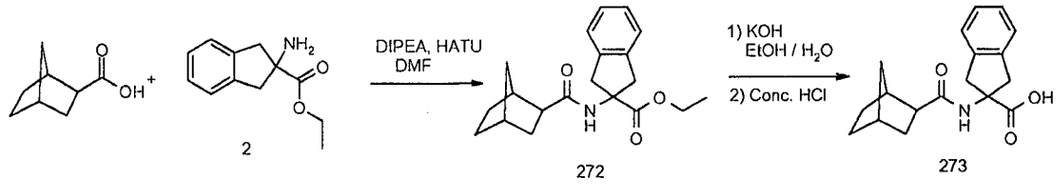
2-[(Adamantane-1-carbonyl)-amino]-indan-2-carboxylic acid (271):

2-[(Adamantane-1-carbonyl)-amino]-indan-2-carboxylic acid ether ester (261mg, 0.71mmol) is dissolved in EtOH (8mL), and solid KOH (823mg, 14mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30 minutes then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (271) as white solid (159mg, 66%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.62-1.76 (q, 6H), 1.76 (d, 6H), 2.02 (s, 3H), 3.25(d, 2H), 3.79(d, 2H), 6.04(s, 1H), 7.15(d, 1H), 7.21 (s, 4H)

LC/MS (ES+) m/z = 340.18

EXAMPLE 272



2 272 273

2-[(Bicyclo[2.2.1]heptane-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (272):

To a solution of bicyclo[2.2.1]heptane-2-carboxylic acid (102mg, 0.73mmol), 2-amino-indan-2-carboxylic acid ethyl ester (150mg, 0.73mmol), HATU (333mg, 0.87mmol) in anhydrous DMF (1mL) is added DIPEA (190µL, 1.10mmol). The resulting solution is stirred at RT overnight. Water (10mL) is poured into the reaction mixture and then extracted with EtOAc (3x 5mL). The combined organic layers are concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (272) as yellow oil (148mg, 62%).

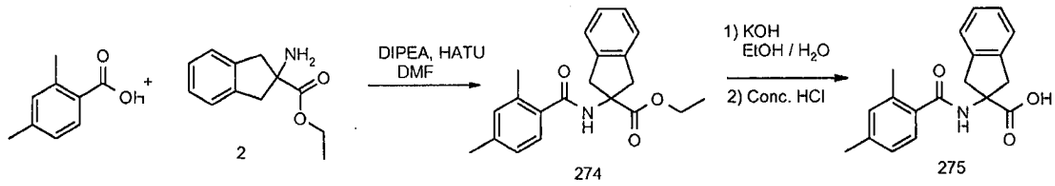
EXAMPLE 273

2-[(Bicyclo[2.2.1]heptane-2-carbonyl)-amino]-indan-2-carboxylic acid (273):

2-[(Bicyclo[2.2.1]heptane-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (148mg, 0.45mmol) is dissolved in EtOH (8mL), and solid KOH (600mg, 10mmol) and water (0.8mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (273) as white solid (105mg, 77%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.14 (d, 1H), 1.26-1.40 (m, 4H), 1.44-1.54(q, 2H), 1.57-1.67 (m, 1H), 2.27(d, 2H), 2.58-2.64(m, 1H) 3.27(t, 2H), 3.75(d, 2H), 5.97(s, 1H), 7.20 (s, 4H)
LC/MS (ES+) m/z = 300.13

EXAMPLE 274



2-(2,4-Dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (274):

To a solution of 2,4-dimethyl-benzoic acid (219mg, 1.46mmol), 2-amino-indan-2-carboxylic acid ethyl ester (300mg, 1.46mmol), HATU (666mg, 1.75mmol) in anhydrous DMF (1.8mL) is added DIPEA (381μL, 2.19mmol). The resulting solution is stirred at RT overnight. Water (10mL) is poured into the reaction mixture, and then extracted with EtOAc (3x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (274) as white solid (414mg, 84%).

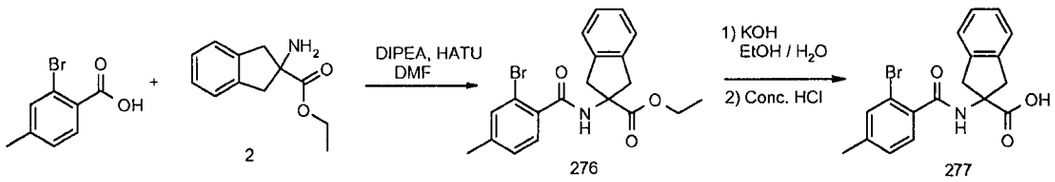
EXAMPLE 275

2-(2,4-Dimethyl-benzoylamino)-indan-2-carboxylic acid (275):

2-(2,4-Dimethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (414mg, 1.23mmol) is dissolved in EtOH (15mL), and solid KOH (1.42g, 24.7mmol) and water (1.5mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with concentrated HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (275) as white solid (350mg, 92%).

^{1}H NMR ($CDCl_3$, 300MHz): 2.30(s, 6H), 3.41(d, 2H), 3.84(d, 2H), 6.20(s, 1H), 6.96(d, 1H), 7.00(s, 1H), 7.13(d, 1H), 7.24(d, 4H)
LC/MS (ES+) m/z = 310.14

EXAMPLE 276



2-(2-Bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (276):

To a solution of 2-bromo-4-methyl-benzoic acid (314mg, 1.46mmol), 2-amino-indan-2-carboxylic acid ethyl ester (300mg, 1.46mmol), HATU (666mg, 1.75mmol) in anhydrous DMF (1.8mL) is added DIPEA (381μL, 2.19mmol). The resulting solution is stirred at RT overnight. Poured reaction into water (10mL) and extracted with EtOAc (3x 5mL). The combined organic layers and concentrated *in vacuo*. The residue is purified by flash column chromatography (12g silica gel, gradient elution: 0-30% EtOAc in heptane) to give product (276) as off-white solid (445mg, 76%).

EXAMPLE 277

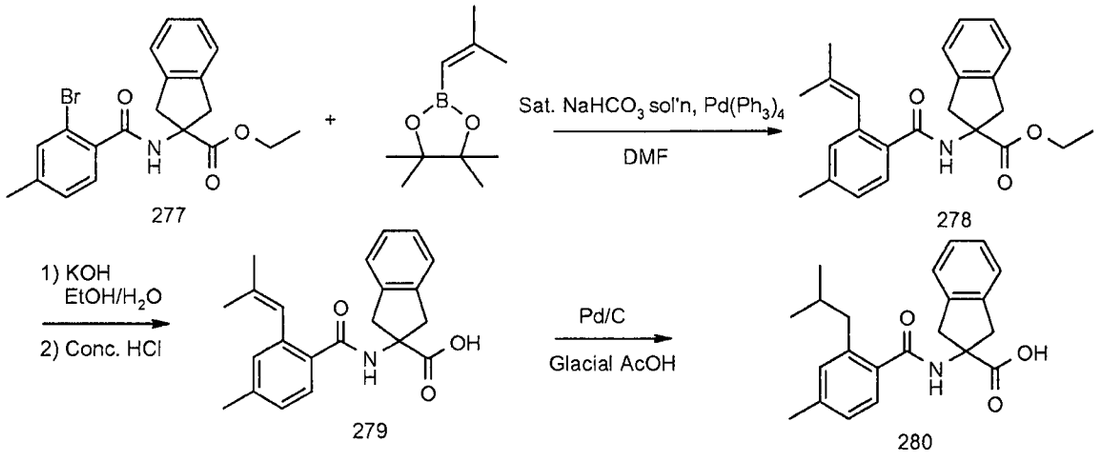
2-(2-Bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid (277):

2-(2-bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (445mg, 1.11mmol) is dissolved in EtOH (15mL), and solid KOH (1.42g, 24.7mmol) and water (1.5mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with conc. HCl until no more white solid precipitated. The solid is collected by vacuum filtration to give product (277) as white solid (415mg, 100%).

^{1}H NMR ($CDCl_3$, 300MHz): 2.33 (s, 3H), 3.45(d, 2H), 3.83(d, 2H), 6.70(s, 1H), 7.15(d, 1H), 7.19-7.25 (m, 4H), 7.35(s, 1H), 7.51 (d, 1H)

LC/MS (ES+) m/z = 374.04, 376.04

EXAMPLE 278



2-[4-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (278):

A mixture of 2-(2-bromo-4-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (880mg, 2.2mmol), 4,4,5,5-tetramethyl-2-(2-methyl-propenyl)-[1,3,2]dioxaborolane (903µL, 4.4mmol) and saturated $NaHCO_3$ solution (4.4mL) in anhydrous DMF (20mL) is degassed with N_2. While under N_2 atmosphere, tetrakis(triphenylphosphine)palladium (196mg, 10mol%) is added and the reaction is heated in a 110°C oil bath for 2h. The reaction is cooled to room temperature, poured into water (40mL) and extracted with EtOAc (2 x 30mL). The combined organic layers are washed with water (15mL) and brine (20mL) then concentrated *in vacuo*. The residue is purified by flash column chromatography (24g silica gel, gradient elution: 0-50% EtOAc in heptane) to give product (278) as a reddish-brown viscous oil (764mg, 92%).

EXAMPLE 279

2-[4-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (279):

2-[4-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (764mg, 2.02mmol) is dissolved in EtOH (25mL), and solid KOH (2.32g, 40mmol) and water (2.5mL) are added. The mixture is stirred at RT for 30min then concentrated *in vacuo*. The residue is dissolved in a mixture of water (40mL) and EtOAc (20mL) and the organic layer is

separated. The aqueous layer is adjusted to approximately pH 7 with conc. HCl then extracted with EtOAc (2 x 15mL). The combined organic layers are concentrated *in vacuo* to yield product (279) as off-white solid (544mg, 78%).

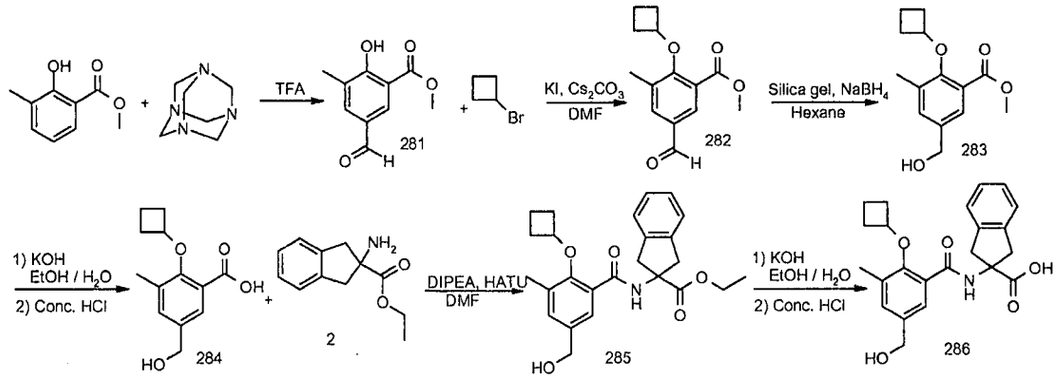
^{1}H NMR ($CDCl_3$, 300MHz): 1.49 (s, 3H). 1.70 (s, 3H), 2.34 (s, 3H), 3.34(d, 2H), 3.82(d, 2H), 6.01 (s, 1H), 6.87 (s, 1H), 7.14(d, 1H), 7.22 (s, 4H), 7.31(d, 1H), 7.91 (d, 1H)
LC/MS (ES+) m/z = 350.17

2-(2-Isobutyl-4-methyl-benzoylamino)-indan-2-carboxylic acid (280):

To a solution of 2-[4-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (510mg, 1.45mmol) in glacial acetic acid (65mL) under N_2 is added Pd/C (10% Pd, 138mg, 10mol%). The reaction is hydrogenated at 60psi H_2 and 90°C overnight. The reaction is cooled to RT and filtered through Celite, washing the filter cake with water (2 x 15mL) and MeOH (2 x 15mL); the filtrate is concentrated *in vacuo*. The residue is dissolved in water (75mL) and extracted with EtOAc (2 x 30mL). The combined organic layers are washed with a 5% $NaHCO_3$ solution (3 x 20mL), water (20mL) and brine (20mL) then dried over anhydrous Na_2SO_4. The organic layer is concentrated *in vacuo* to give product (280) as white solid (350mg, 69%).

^{1}H NMR ($CDCl_3$, 300MHz): 0.78 (d, 6H), 1.72-1.81 (m, 1H), 2.30(s, 3H), 2.55 (d, 2H), 3.38 (d, 2H), 3.77(d, 2H), 6.30 (s, 1H), 6.94 (d, 1H), 6.95 (s, 1H), 7.16(d, 1H), 7.20 (s, 4H)
LC/MS (ES+) m/z = 352.22

EXAMPLE 281



5-Formyl-2-hydroxy-3-methyl-benzoic acid methyl ester (281):

To a solution of HMTA (1,3,5,7-Tetraaza-tricyclo[3.3.1.1^{3,7}]decane, 8.43g, 60.2mmol) in TFA (100mL) is added 2-hydroxy-3-methyl-benzoic acid methyl ester (5g, 30.1mmol) and the reaction is refluxed (78°C) overnight. The reaction is cooled to 50°C and water (400mL) is added with stirring. The mixture is stirred at 50°C for 2h then cooled to RT and extracted with EtOAc (2 x 200mL). The combined organic layers are washed with brine (75mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash column chromatography (120 silica gel, gradient elution: 0-50% EtOAc in heptane) to give product (281) as off-white solid (5.05g, 86%).

EXAMPLE 282

2-Cyclobutoxy-5-formyl-3-methyl-benzoic acid methyl ester (282):

To a mixture of bromocyclobutane (1.39g, 10.3mmol), potassium iodide (43mg, 5mol%), and $CsCO_3$ (3.84g, 11.84mmol) in DMF (18mL) is added 5-formyl-2-hydroxy-3-methyl-benzoic acid methyl ester (1.0g, 5.15mmol). The reaction is placed in the microwave reactor and heated at 110°C for 6h. Water (50mL) is added to the reaction and the solution is extracted with EtOAc (3x 40mL). The combined organic layers are dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give product (282) as orange-yellow oil (1.20g, 94%).

EXAMPLE 283

2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid methyl ester (283):

A mixture of 2-cyclobutoxy-5-formyl-3-methyl-benzoic acid methyl ester (676mg, 2.7mmol), silica gel (5.15g) and $NaBH_4$ (103mg, 2.7mmol) in hexane (30mL) is heated at 40°C overnight. The mixture is cooled to RT and filtered, washing the solids with EtOAc (15mL) and diethyl ether (15mL). The filtrate is concentrated *in vacuo* to give product (283) as viscous yellow oil (566mg, 84%).

EXAMPLE 284

2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid (284):

2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid methyl ester (410mg, 1.64mmol) is dissolved in EtOH (15mL), and solid KOH (1.90g, 32.8mmol) and water (1.5mL) are added. The mixture is stirred at RT for 1h then concentrated *in vacuo*. The residue is dissolved in water (10mL) and acidified with conc. HCl then extracted with EtOAc (3 x 10mL). The combined organic layers are dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give product (284) as viscous yellow oil (387mg, 100%).

EXAMPLE 285

2-(2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (285):

To a solution of 2-cyclobutoxy-5-hydroxymethyl-3-methyl-benzoic acid (410mg, 1.7mmol), 2-amino-indan-2-carboxylic acid ethyl ester (425mg, 1.7mmol), HATU (760mg, 2mmol) in anhydrous DMF (5mL) is added DIPEA (435µL, 2.5mmol). The resulting solution is stirred at RT overnight. Water (10mL) is poured into the reaction mixture, and then extracted with EtOAc (3 x 7mL). The combined organic layers are concentrated *in vacuo*. The residue is purified by reverse phase chromatography (gradient elution: 20-100% ACN in water) to give product (285) as colorless oil (70mg, 10%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.14-1.24 (m, 1H), 1.34-1.44 (q, 1H), 1.80-1.86 (m, 2H), 1.90-1.99 (m, 2H), 2.20(s, 3H), 3.37 (d, 2H), 3.81(d, 2H), 4.13-4.24 (m, 1H), 4.55 (s, 2H) 7.17-7.24 (m, 4H), 7.26 (d, 1H), 7.78 (d, 1H), 8.45 (s, 1H)
LC/MS (ES+) m/z = 396.16

EXAMPLE 286

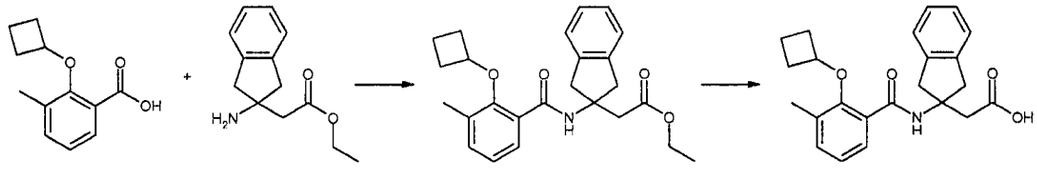
2-(2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (286):

2-(2-Cyclobutoxy-5-hydroxymethyl-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (70mg, 0.16mmol) is dissolved in ethanol (1.5mL), and solid KOH (191mg, 3.3mmol) and water (150µL) are added. The mixture is stirred at room temperature for 30min then concentrated *in vacuo*. The residue is dissolved in water (1.5mL) and acidified with conc. HCl until no more white solid precipitated. The mixture is extracted with ethyl acetate (2 x

8mL) and the combined organic layers are concentrated *in vacuo* to give product (286) as white solid (60mg, 95%).

^{1}H NMR ($CDCl_3$, 300MHz): δ 1.14-1.24 (m, 1H), 1.34-1.44 (q, 1H), 1.80-1.86 (m, 2H), 1.90-1.99 (m, 2H), 2.20(s, 3H), 3.37 (d, 2H), 3.81(d, 2H), 4.13-4.24 (m, 1H), 4.55 (s, 2H) 7.17-7.24 (m, 4H), 7.26 (d, 1H), 7.78 (d, 1H), 8.45 (s, 1H)
LC/MS (ES+) m/z = 396.16

EXAMPLE 287



165 A6 287 288

2-aminoindan-2-acetic acid ethyl ester (A6)

This compound is prepared according to the US Patent WDF2006/134111.

2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid ethyl ester (287)

To a solution of 2-cyclobutyloxy-3-methylbenzoic acid (210mg-1.02mmol), 2-aminoindan-2-acetic acid ethyl ester (A6)(260mg-1.02mmol) and HATU (470mg-1.224mmol-1.2eq) in dry DMF (10mL) is added diisopropylethylamine (0.36mL-2.24mmol-2.2eq) and the resulting solution is stirred at RT overnight. After the removal of the DMF in vacuo, the residue is dissolved in EtOAc (60mL) and washed with water (2 x 20mL) and brine (2 x 20mL). The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography (120g silica gel, 15% EtOAc in heptane) to give the pure product as colorless oil (400mg, 96%).

LC/MS(ES+) m/z 408

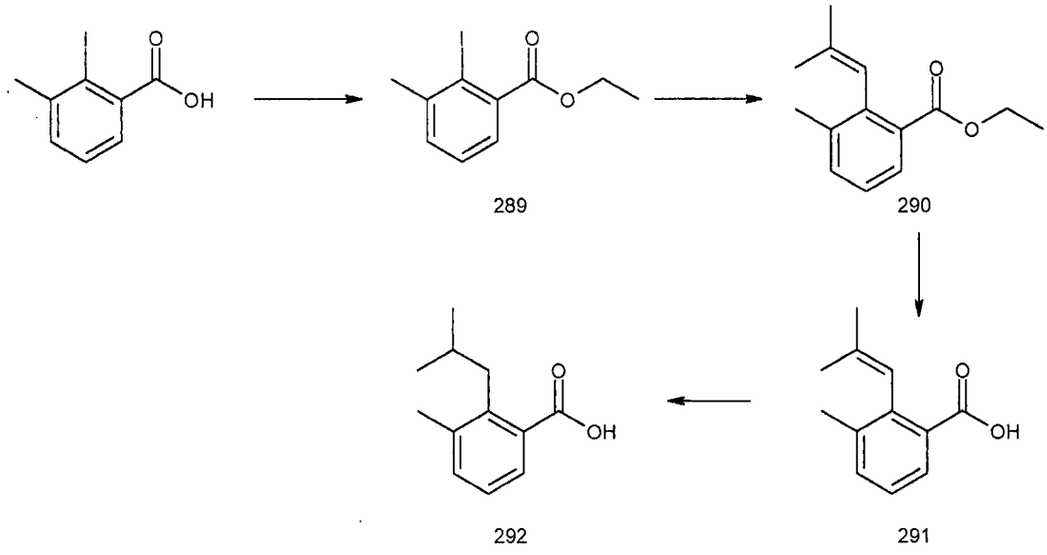
EXAMPLE 288

2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid (288)

A solution of the 2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid ethyl ester (288) (400mg-1mmol) in EtOH(15mL)/ water (1mL) is treated with NaOH pellets (800mg-20mmol) and stirred at RT for 24h. After concentration *in vacuo*, the residue is dissolved in water (30mL) and acidified with HCl to pH 2-3. The product is extracted into EtOAc (3 x 20mL) and the combined extracts washed with water (2 x 10mL) and brine (2 x 15mL). The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. The residue is triturated with heptane and the pure product isolated by filtration to give white solid (350mg, 92%).

LC/MS(ES+) m/z 380

Example 289



289 290 291 292

2-iodo-3-methylbenzoic acid ethyl ester (289)

A solution of the 2-iodo-3-methylbenzoic acid (6g-0.023mol) in EtOH (150mL) is treated with concentrated HCl (20mL) and refluxed for 48h. After removal of the EtOH *in vacuo*, the residue is diluted with water (125mL) and cooled to 0°C in an ice bath. The pH is adjusted to 10 with solid NaOH pellets and extracted with EtOAc (3 x 75mL). The organic extracts are washed with water (2 x 50mL) and brine (2 x 50mL) and dried over $MgSO_4$. Concentrated *in vacuo* to give the product as a pale yellow oil. (6g, 90%).

LC/MS(ES+) m/z 291

Example 290

3-methyl-2-(2-methyl-1-propenyl)benzoic acid ethyl ester (290)

A suspension of the 2-iodo-3-methylbenzoic acid ethyl ester (289) (2.9g-0.01mol) and 2-methyl-1-propenylboronic acid pinacol ester (3.64g-0.02mol-2eq) in dry DMF(50mL) and saturated $NaHCO_3$ (10mL) is degassed for 10 minutes and then treated with tetrakis(triphenylphosphine)palladium(0) (400mg). The mixture is stirred at 110°C overnight. The reaction is cooled and the DMF removed *in vacuo* and the residue diluted with water (120mL). The aqueous is filtered through hyflo and extracted with EtOAc (3 x 75mL). The organic extracts are washed with water (2 x 50mL) and brine (2 x 50mL), and dried over $MgSO_4$. The organic extracts are concentrated *in vacuo* and purified by flash chromatography (400g silica gel, 5% EtOAc in heptane) to give the product as pale yellow oil (1.85g, 85%).

LC/MS (ES+) m/z 218

Example 291

3-methyl-2-(2-methy-1-propenyl)benzoic acid (291)

A solution of the 3-methyl-2-(2-methy-1-propenyl)benzoic acid ethyl ester (290)(3g-0.014mol) in MeOH (50mL) is treated with 2N NaOH(10mL) and refluxed for 6h. The solvent is removed *in vacuo* and the residue diluted with water (75mL). The aqueous phase is extracted with EtOAc (30mL) and then separated and acidified to pH 2-3 with concentrated HCl. The solid precipitated is extracted into EtOAc (3 x 50mL). The extracts are washed with water (2 x 30mL) and brine (2 x 30mL), and dried over $MgSO_4$ and concentrated *in vacuo* to give the product as white solid (2.0g, 75%).

^1H NMR ($CDCl_3$, 300MHz): 1.43 (s, 3H), 1.91 (s, 3H), 2.24 (s, 3H), 6.35 (s, 1H), 7.2-7.27 (t, 1H), 7.37-7.44 (m, 1H), 7.79-7.81 (d, 1H).
LC/MS (ES+) m/z 191

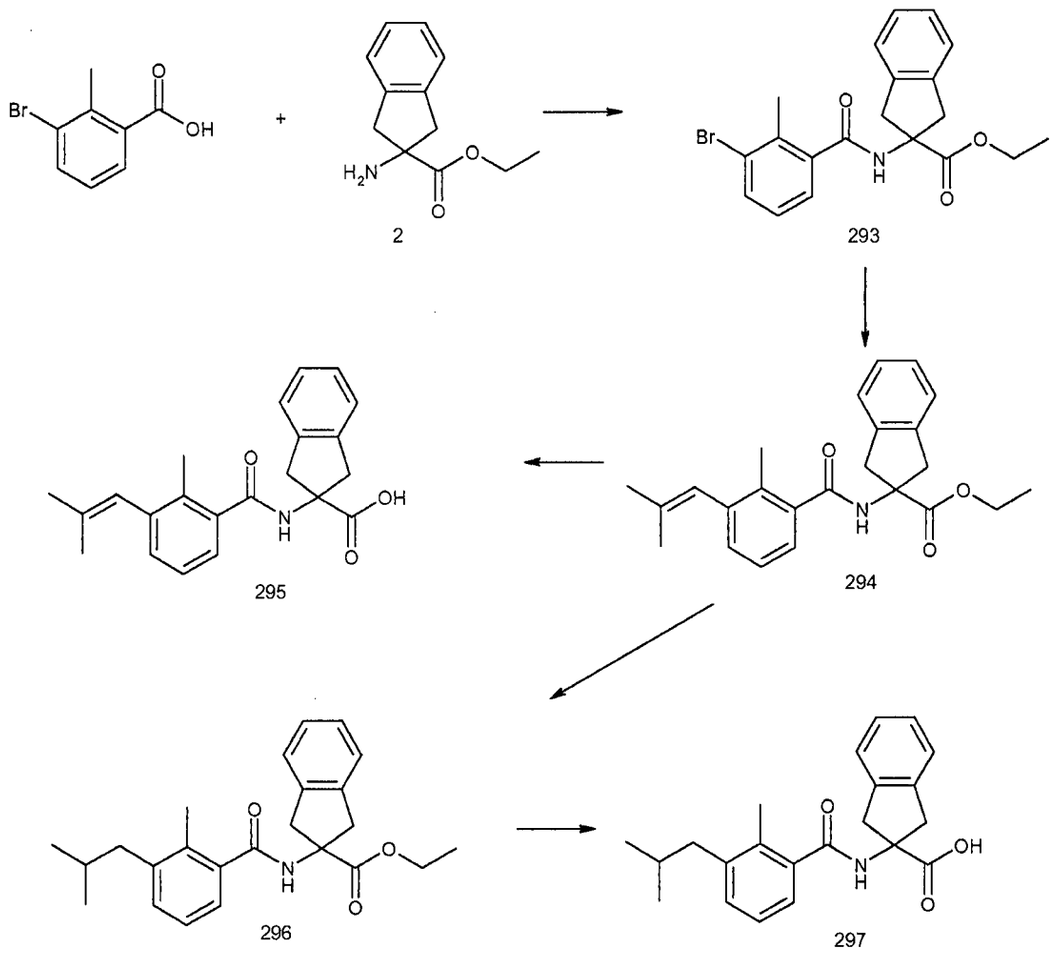
Example 292

2-isobutyl-3-methylbenzoic acid (292)

A solution of the 3-methyl-2-(2-methy-1-propenyl)benzoic acid (291)(2g, 10.5mmol) in MeOH (40mL) is hydrogenated using 10% palladium/carbon catalyst at 40 bar/30°C using the Thales nanotechnology H-cube for 48h. The MeOH is concentrated *in vacuo* to give the product as colorless oil (1.85g, 90%).

^{1}H NMR ($CDCl_3$, 300MHz): 0.92 (d, 6H), 1.78-1.90 (m, 1H), 2.38 (s, 3H), 7.1-7.2 (t, 1H), 7.35-7.38 (d, 1H), 7.75-7.80 (d, 1H).
LC/MS (E/S+) m/z 193

Example 293



2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid ethyl ester (293)

This compound is prepared in a similar manner to example 287. The crude product obtained is purified by flash chromatography (120g silica gel, 20% EtOAc in heptane) to give the pure product as white solid (1.9g, 91%).

^{1}H NMR ($CDCl_3$, 300MHz): 1.20-1.25 (t, 3H), 3.30-3.40 (d, 2H), 3.40 (s, 3H), 3.70-3.80 (d,2H), 4.25-4.40 (m, 2H), 6.30-6.40 (s, 1H), 6.95-7.05 (t,1H), 7.20-7.30 (m,2H), 7.55-7.60 (d, 1H).
LC/MS(ES+) m/z 403

Example 294

2-[2-methyl-3-(2-methyl-1-propenyl)benzoylamino]indan-2-carboxylic acid ethyl ester (294)

A suspension of 2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid ethyl ester (293) (402mg-1mmol) and 2-methyl-1-propenylboronic acid (200mg, 2mmol, 2eq) in dry DMF (20mL) and saturated $NaHCO_3$ (5mL) is degassed for 10min and then treated with tetrakis(triphenylphosphine)palladium(0) (400mg). The mixture is stirred at 110°C for 5h. The reaction is cooled and the DMF removed *in vacuo* and the residue diluted with water (80mL). The aqueous is filtered through celite and extracted with EtOAc (3 x 50mL). The organic extracts are washed with water (2 x 30mL) and brine (2 x 30mL), and dried over $MgSO_4$. The organic phase is then concentrated *in vacuo* and purified by flash chromatography (120g silica gel, 30% EtOAc in heptane) to give pale yellow oil (350mg, 92%).

LC/MS (E/S+) m/z 378

Example 295

2-[2-methyl-3-(2-methyl-1-propenyl)benzoylamino]indan-2-carboxylic acid (295)

This compound is prepared in a similar manner to example 288. Purification by flash chromatography (120g silica gel, 20% EtOAc in heptane) gives white solid. (20mg, 6%)

LC/MS (E/S+) m/z 350

Example 296

2-(2-methyl-3-isobutylylbenzoylamino)indan-2-carboxylic acid ethyl ester (296)

A solution of 2-[2-methyl-3-(2-methyl-1-propenyl)benzoylamino]indan-2-carboxylic acid ethyl ester (294) (700mg, 1.86mmol) in glacial AcOH (125mL) is treated with the catalyst, Pd-C (10wt.%Pd, 360mg) under nitrogen. The resulting reaction mixture is then hydrogenated in a Paar apparatus at 55psi 75°C overnight. The catalyst is removed by filtration through a pre-column (10g silica gel) and washed with EtOH. The combined organic solution is concentrated *in vacuo*. The residue is dissolved in EtOAc (75mL) and washed with water (30mL) and brine (30mL), and dried over $MgSO_4$ and concentrated *in vacuo* to leave the product as white solid (660mg, 94%).

LC/MS (E/S+) m/z 380

Example 297

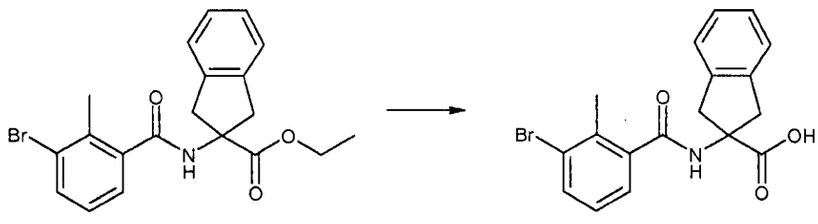
2-(2-methyl-3-isobutylylbenzoylamino)indan-2-carboxylic acid (297)

This compound is prepared in a similar manner to example 288. Purification by flash chromatography (120g silica gel, 50% EtOAc in heptane) gives the product as white solid. (130mg, 21%)

^{1}H NMR (DMSO-d6, 300MHz): 0.87-0.89 (d, 6H), 1.73-1.82 (m, 1H), 2.21 (s, 3H), 2.40-2.45 (m, 2H), 3.32-3,36 (d, 2H), 3.53-3.59 (d, 2H), 7.00-7.23 (m, 7H), 8.83 (s, 1H), 11.0 (s, 1H).

LC/MS (E/S+) m/z 353

Example 298



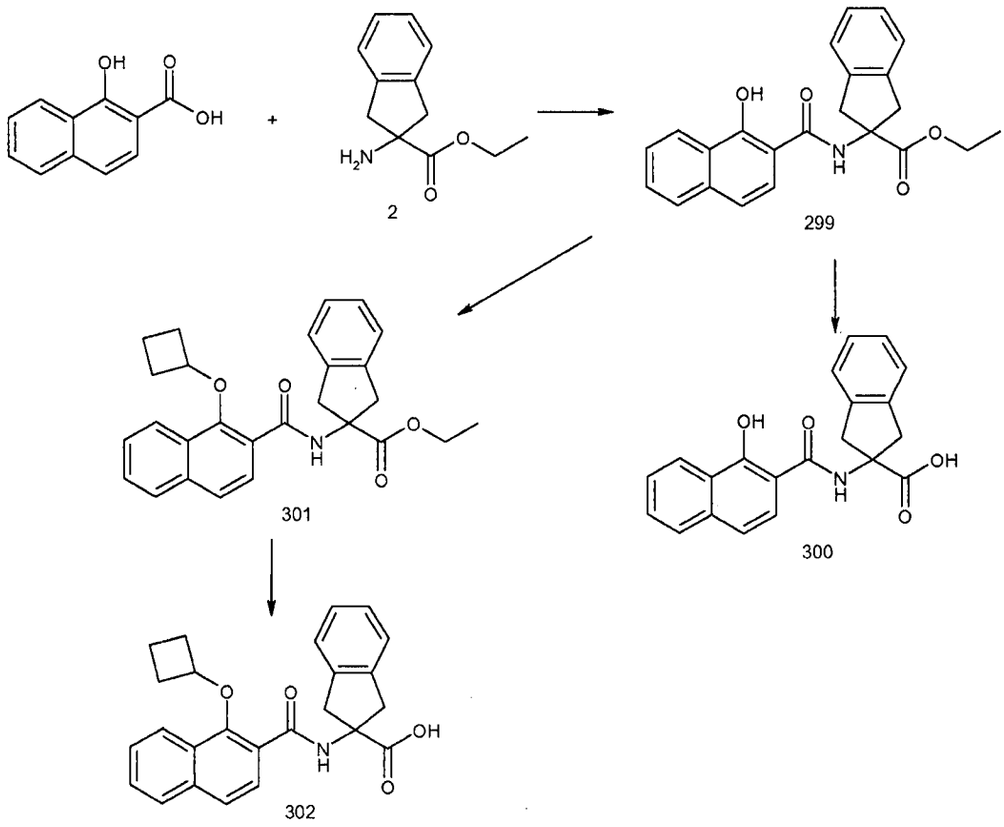
293 298

2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid (298)

This compound is prepared in a similar manner to example 288. The organic extract is evaporated in vacuo to give the product as white solid (270mg, 96%)

^{1}H NMR (DMSO-d6, 300MHz): 2.33 (s, 3H), 2.29-3.35 (d, 2H), 3.54-3.60 (d, 2H), 7.13-7.24 (m, 6H), 7.63-7.66 (d, 1H), 8.99 (s, 1H), 12.55-12.60 (s, 1H).

LC/MS (E/S+) m/z 376



Example 299

2-[(1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (299)

This compound is prepared in a similar manner to example 287. Purification by flash chromatography (400g silica gel, 30% EtOAc in heptane) gives orange oil. (1.75g, 93%)

LC/MS (E/S+) m/z 376

Example 300

2-[(1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (300)

This compound is prepared in a similar manner to example 288. The organic extract is evaporated in vacuo to give white solid. (280mg, 99%)

^{1}H NMR (DMSO-d6, 300MHz): 3.48-3.53 (d, 2H), 3.63-3.69 (d, 2H), 7.17-7.28 (m, 5H), 7.34-7.37 (d, 1H), 7.53-7.66 (m, 2H), 7.85-7.88 (d, 1H), 7.96-7.99 (d, 1h), 8.26-8.28 (d, 1H), 9.22 (s, 1H).

LC/MS (E/S+) m/z 376

Example 301

2-[(1-cyclobutyloxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (301)

A solution of 2-[(1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (289) (560mg, 1.5mmol) in dry DMF is treated with NaH oil dispersion (60%, 100mg, 2.25mmol, 1.5eq) and stirred for 10 min. The cyclobutyl bromide (405mg, 3mmol, 2eq) is added and the reaction heated and stirred in the microwave at 150°C for 3hours. After the removal of DMF *in vacuo*, the residue is dissolved in EtOAc (75mL) and washed with water (2x30mL) and brine (30mL). The organic layer is dried over $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography (200g silica gel, 10% EtOAc in heptane) to give white solid. (290mg, 45%)

LC/MS (E/S+) m/z 430

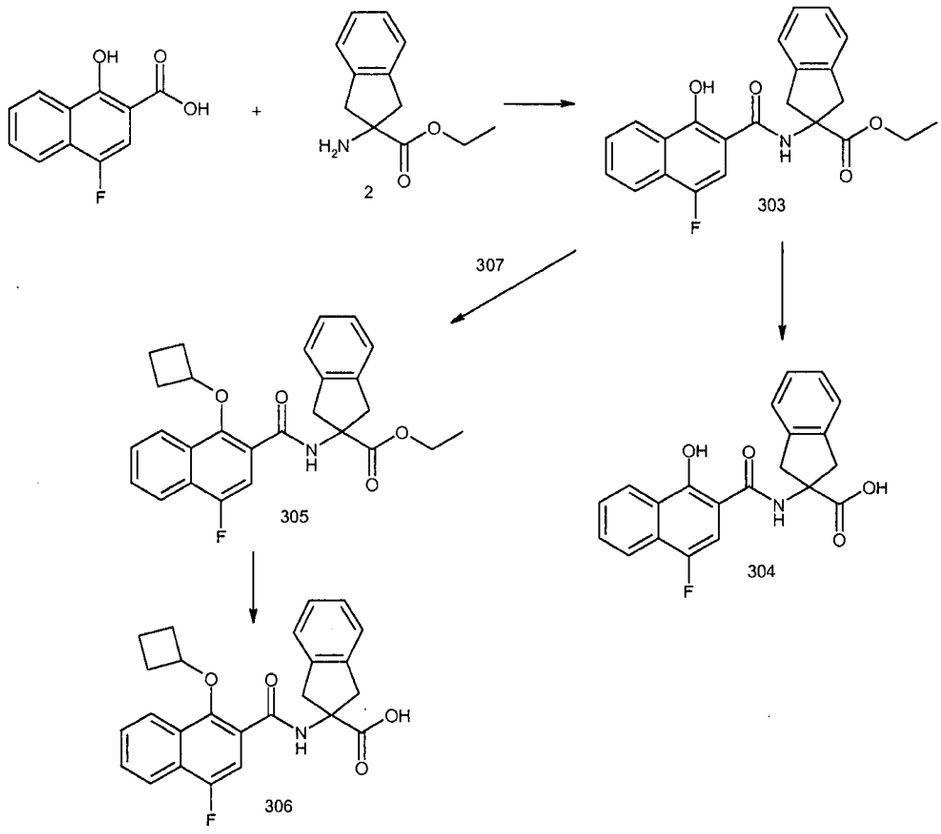
Example 302

2-[(1-cyclobutyloxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (302)

This compound is prepared in a similar manner to example 288. Purification by flash chromatography (400g silica gel, gradient elution: 25-60% EtOAc in heptane) gives the product as white solid. (20mg, 9%)

LC/MS (E/S+) m/z 402

Example 303



2-[(4-fluoro-1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (303)

This compound is prepared in a similar manner to example 287. Purification by flash chromatography (400g silica gel, 30% EtOAc in heptane) gives orange oil. (1.67g, 85%)

^{1}H NMR (DMSO-d6, 300MHz): 1.13-1.16 (t,3H), 3.46-3.52 (d,2H), 3.64-3.69 (d, 2H), 4.11-4.18 (q, 2H), 7.19-7.29 (m, 4H), 7.69-7.72 (t, 1H), 7.76-7.81 (t, 1H), 7.93-8.01 (m,2H), 8.31-8.34 (d, 1H), 9.26 (s,1H), 13.90 (s, 1H).

LC/MS (E/S+) m/z 394

Example 304

2-[(4-fluoro-1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (304) This compound is prepared in a similar manner to example 288. The organic extract is evaporated *in vacuo* to give the product as white solid. (270mg, 97%)

^{1}H NMR (DMSO-d6, 300MHz): 3.47-3.58 (d, 2H), 3.64-3.75 (d, 2H), 7.18-7.29 (m, 5H), 7.66-7.75 (m,1H), 7.77-7.85 (m, 1H), 7.95-8.8.01 (m, 1H), 8.31-8.34 (d,1H), 9.16 (s, 1H),12.75 (s, 1H).
LC/MS (E/S-) m/z 364

Example 305

2-[(1-cyclobutyloxy-4-fluoronaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (305)

A solution of 2-[(4-fluoro-1-hydroxynaphthalene-2-carbonyl)amino]indan-2-carboxylic acid ethyl ester (303) (197mg, 0.5mmol) and 3,3-dimethyl-1,2,5-thiadiazolidine-5 triphenylphosphine-1,1-dioxide (example 307, 245mg, 0.6mmol, 1.2eq) in DCM (6mL) is treated with cyclobutanol (44mg, 0.6mmol, 1.2eq) and stirred at RT for 6 days. The crude reaction mixture is purified by flash chromatography (100g silica gel, 100% DCM) to give colorless oil. (120mg, 54%)

LC/MS (E/S+) m/z 448

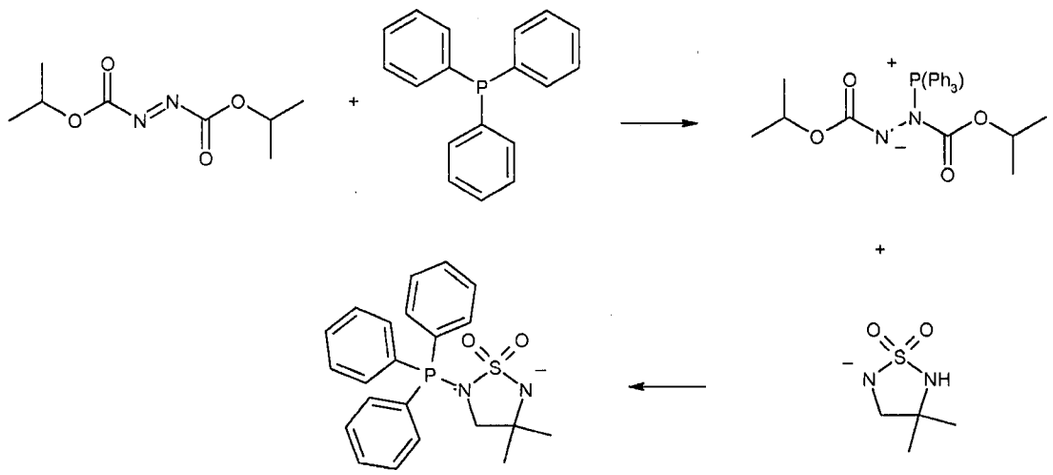
Example 306

2-[(1-cyclobutyloxy-4-fluoronaphthalene-2-carbonyl)amino]indan-2-carboxylic acid (306)

This compound is prepared in a similar manner to example 288. The organic extract is evaporated in vacuo to give white solid. (95mg, 84%)

^{1}H NMR (DMSO-d6, 300MHz): 1.20-1.33 (m, 1H), 1.44-1.54 (m, 1H), 3.42-3.47 (d, 2H), 3.58-3.63 (d, 2H), 4.49-4.57 (m, 1H), 7.17-7.36 (m, 6H), 7.69-7.75 (m, 2H), 8.03-8.06 (m, 1H), 8.17-8.19 (m, 1H), 8.88 (s, 1H), 12.70 (s,1H).
LC/MS (E/S+) m/z 420

Example 307

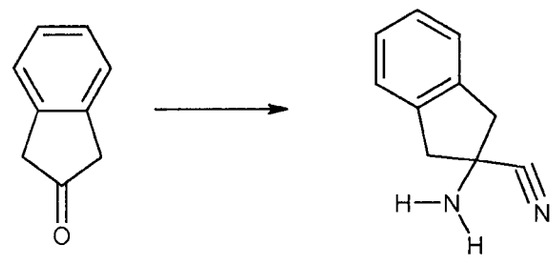


307

3,3-dimethyl-1,2,5-thiadiazolidine-5 triphenylphosphine-1,1-dioxide (307)

A solution of triphenylphosphine (4.4g, 0.016mol) and 3,3-dimethyl-1,2,5-thiadiazoli-dine-1,1-dioxide (2.5g, 0.016mol) in dry THF (50mL) is treated dropwise with diisopropyldiazodicarboxylate (3.3g, 0.016mol). The white solid precipitated is stirred at RT for a further 4h. The product is then collected by filtration and washed with diethyl ether (5.7g, 86%).

Example 308



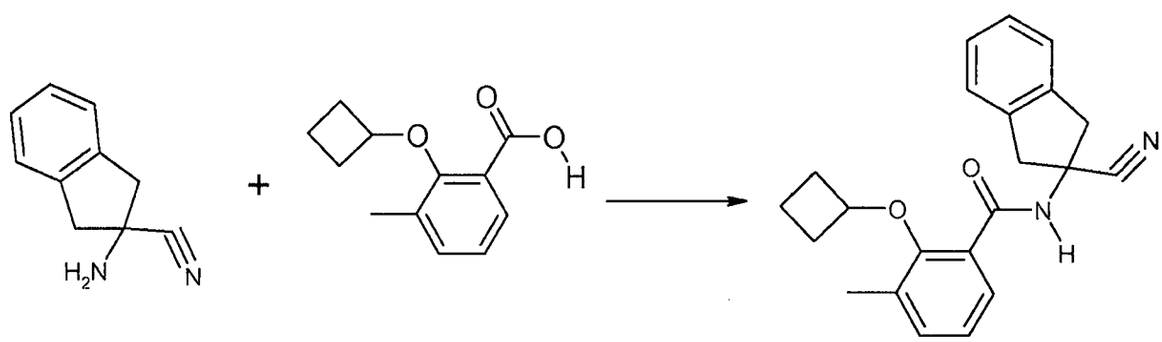
(308)

2-Amino-indan-2-carbonitrile (308)

A 250mL round bottom flask is charged with 2-indanone (2.64g, 19.98mmol) and iPrOH (40mL). A stirring bar is added and stirring is initiated. After dissolution, an aqueous solution of ammonium hydroxide (29 %, 8.3 M 16mL, 132.3mmol) is added. Ammonium chloride

(2.14g, 39.96mmol) and NaCN (1.96g, 39.96mmol) are added. After 11 days, tlc analysis (silica, 2:1, heptanes:EtOAc) indicates that the starting indone is consumed. The organic solvent is removed *in vacuo*. The resultant material is transferred to a separatory funnel and partitioned between DCM (200mL) and water (100mL). The phases are separated. The aqueous phase is extracted with DCM (100mL). The organic extracts are combined and washed with brine (100mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight yields 2.6g of dark brown solid. This material is dissolved in DCM (15mL). This solution is applied to a column (Silica, 40 g) which is fitted to an ISCO Companion. The gradient is 1% iPrOH in DCM for 4 column volumes followed by a linear gradient to 20 % iPrOH in DCM over 10 column volumes. The eluent is collected in 17mL fractions. Fractions 15 to 32 are combined and evaporated by pumping to constant weight to give light beige solid (0.82g, 26 %).

Example 309



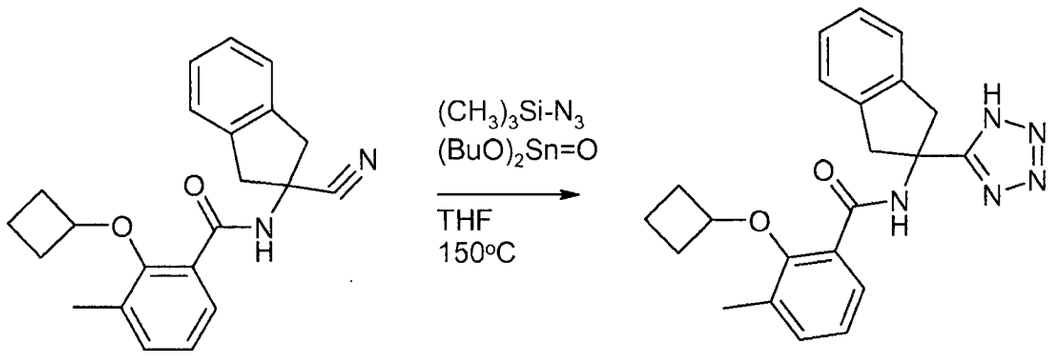
308 309

N-(2-Cyano-indan-2-yl)-2-cyclobutoxy-3-methyl-benzamide (309)

A 30mL vial is charged with 2-cyclobutoxy-3-methyl-benzoic acid (734mg, 3.56mmol) and dry DCM (10mL). A stirring bar is added and stirring is initiated. After 5min, HTBU (1.35g, 3.56mmol) is added. After 5min, 2-amino-indane-2-carbonitrile. (308, 563mg, 3.56mmol) is added followed by DIPEA (1.5mL, 8.95mmol). The reaction is allowed to stir for 38h. Analysis of the reaction mixture by tlc (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed saturated aqueous $NaHCO_3$ (2 X 20mL) and brine (20mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide

1.2g of thick black oil. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 8 column volumes and then 90% EtOAc in heptanes for 2 column volumes. 17mL fractions of UV active eluent are collected. Fractions 27 through 30 are combined and evaporated *in vacuo* to give white solid (0.51g, 41%).

Example 310



309 310

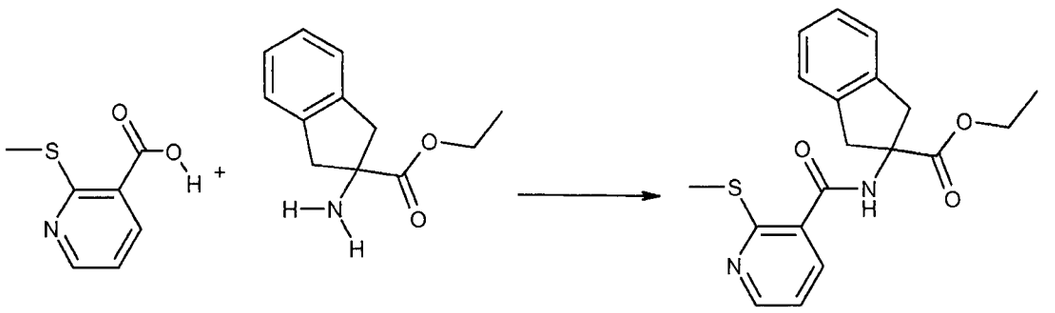
2-Cyclobutoxy-3-methyl-N-[2-(1H-tetrazol-5-yl)-indan-2-yl]-benzamide (310)

A 10mL microwave reaction vial is charged with N-2-(cyano-indan-2-yl)-2-cylcobutoxy-3-methyl-benzamide (309, 300mg, 0.87mmol) and dry tetrahydrofuran (THF, 4mL). A stirring bar is added and stirring is initiated. After 1 minute, trimethylsislyazide (228 μL, 1.73mmol) and di-n-butyltinoxide (22mg, 0.087mmol) are added to the reaction vial. The reaction vial is capped and inserted into an Emyrs Optimizer microwave apparatus. The reaction vial is prestirred for 10sec. The temperature is set to hold at 150°C for 10min. At the end of this process, additional aliquots of trimethylsislyazide (228 μL, 1.73mmol) and di-n-butyl tin oxide (22mg, 0.087mmol) are added to the reaction vial. The reaction vial is capped and inserted into a Emyrs Optimizer microwave apparatus. The reaction vial is pre-stirred for 10sec. The temperature is set to hold at 150°C for 10min. tlc analysis (silica, 10 % MeOH in DCM) indicates that the starting material is completely consumed. The contents of the reaction vial are reconstituted in DCM (8mL) and iPrOH (4mL). This solution is stirred for 10min and filtered through a pad of Celite. The filtrate is evaporated under reduced pressure

by pumping to constant weight to give 0.4g of light yellow foam. The foam is dissolved in DCM (10mL) and applied to an ISCO Companion (silca, 40 g) Column. The following gradient is applied: 1% iPrOH in DCM for 4 column volumes, followed by a linear gradient to 50 % iso-propanol in DCM over 10 Column Volumes. 14mL fractions of UV-active eluent are collected. Fractions 2 to 6 are combined and evaporated by pumping to constant weight to give white solid (0.31g, 92%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.08-1.25(m, 2H), 1.38-1.51(m, 1H), 1.71-1.96 (m, 4H), 2.22 (s, 3 H) 3.79-3.93 (m, 4H), 4.35 (m, 1H), 7.03 (dd, 1H), 7.1-7.37(m, 6H), 8.98(s, 1H). LC/MS (ES+) m/z = 390.16.

Example 311



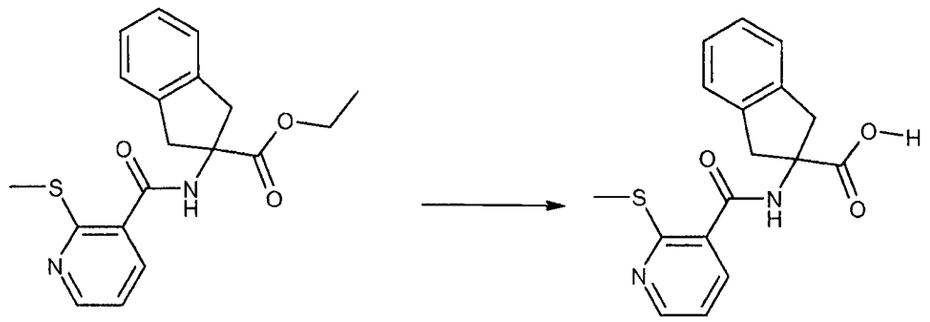
311

2-[(2-Methylsufamyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid Ethyl Ester (311)

40mL vial is charged with 2-(methylthio)-nicotnic acid (0.37g, 2.19mmol) and dry DCM (8mL). A stirring bar is added and stirring is initiated. After dissolution 5min, HTBU (831mg, 2.19mmol) is added. After 5min, the 2-amino)-indane-2-carboxylic acid ethyl ester. (450mg, 2.19mmol) is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir for 14 days. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). The organic phase is washed with brine (20mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.23g of light yellow foam. The foam is dissolved in 10mL of DCM. This solution is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over

3 column volumes followed by a linear gradient to 50% EtOAc in heptanes over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 8 through 12 are combined and evaporated *in vacuo* by pumping to constant weight under reduced pressure gives solid white (0.47g, 60%).

Example 312



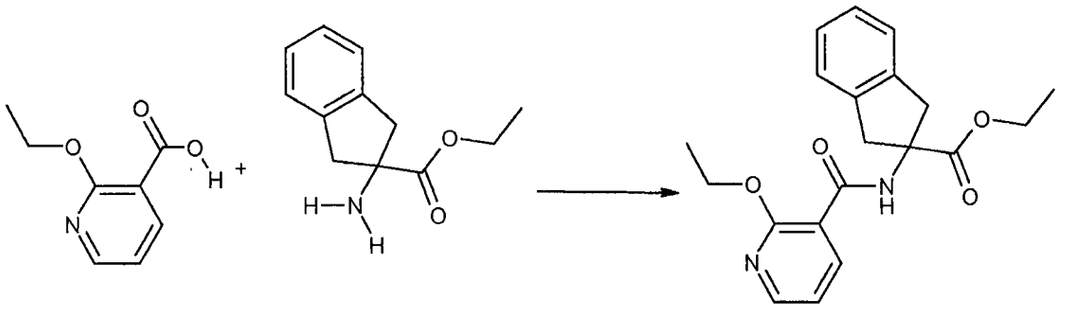
311 312

2-[(2-Methylsufamyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid (312)

To a 100mL flask containing 2-[(2-methylsufamyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (311, 490mg, 1.38mmol) is added 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH (146mg, 3.5mmol). After 40h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The contents of the flask are diluted with iPrOH (30mL). Dowex Highly Acidic Ion Exchange Resin (10 g) is added. The reaction flask is capped and allowed to stir at ambient temperature. After 7 days, additional iPrOH (35mL) is added to the reaction flask. The contents of the reaction flask are filtered through a pad of Celite and concentrated under reduced pressure by pumping to constant weight to give white solid (0.44g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 2.41 (s, 3 H), 3.26-3.48 (m, 4H), 7.16-7.25 (m, 5H), 7.71 (dd, 1H), 8.51 (dd, 1 H), 9.01(s, 1H).
LC/MS (ES+) m/z = 329.14.

Example 313

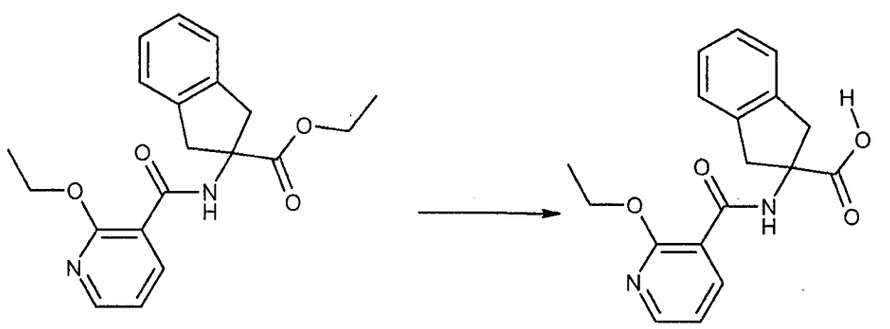


313

2-[(2-Ethoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid Ethyl Ester (313)

A 40mL vial is charged with 2-ethoxynicotnic acid (366mg, 2.19mmol) and dry DCM (7mL). A stirring bar is added and stirring is initiated. After dissolution 5min, HTBU (831mg, 2.19mmol) is added. After 5min, the 2-amino-indane-2-carboxylic acid ethyl ester. (450mg, 2.19mmol) is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir for 17 days. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). The organic phase is washed with brine (20mL), dried over $MgSO_4$, filtered and evaporated in vacuo to provide 2.38g of light yellow syrup. The syrup is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 1 % iPrOH/DCM over 4 column volumes followed by a linear gradient to 30% iPrOH/DCM over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 5 through 10 are combined and evaporated *in vacuo* by pumping to constant weight to yield white solid (0.34g, 44%).

Example 314



313 314

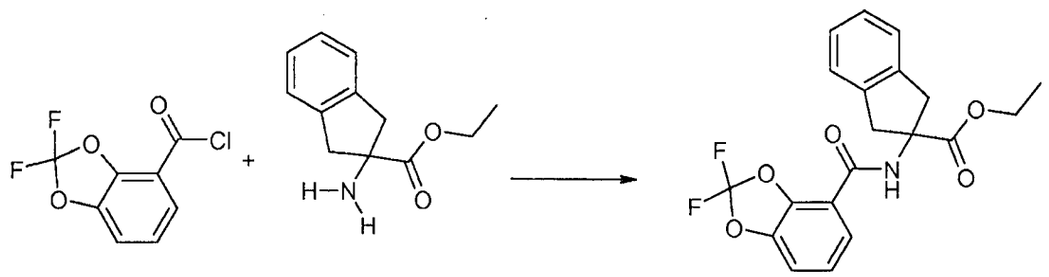
2-[(2-Ethoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid (314)

A 100mL flask containing 2-[(2-ethoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester ([313], 340mg, 0.96mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH monohydrate (102mg, 2.42mmol). After 13 days, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The contents of the flask are diluted wth iPrOH (30mL). Dowex Highly Acidic Ion Exchange Resin (2g) is added. The reaction flask is capped and allowed to stir at ambient temperature. After 18h, additional iPrOH (35mL) is added to the reaction flask. The contents of the reaction flask are filtered through a pad of Celite and concentrated under reduced pressure by pumping to constant weight to yield 0.44g of white solid. This material is dissolved in a mixture of DCM (10mL) and iPrOH (3mL). Celite (15 g) is added to the flask. The solvent is removed under reduced pressure. The remaining material is transferred to a 40mL plastic syringe that is fitted with a fritted disk. The syringe is fitted onto an ISCO Companion which had a 40g column (silica). The following gradient is applied. 1 % IPrOH/DCM for 4 column volumes. Then a linear gradient to 50 % iPrOH/DCM over 10 column volumes. Hold at 50 % iPrOH/DCM for 2 Column Volumes. 14mL fractions are collected. Fractions 39 - 41 are combined and evaporated by pumping to constant weight to yield white solid (0.28g, 89%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.22 (t, 3H), 3.26-3.63 (m, 4H), 4.36 (q, 2H), 7.14-7.25 (m, 5H), 8.13 (dd, 1H), 8.28 (dd, 1 H), 8.76 (s, 1H).

LC/MS (ES+) m/z = 327.11.

Example 315

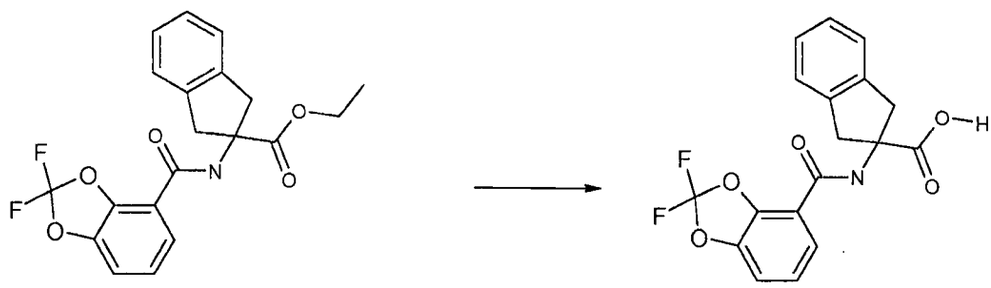


315

2-[(2,2-Difluoro-benzo[1,3]dioxole-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (315)

A 100mL round bottom flask is charged with 2-aminoindan-2-carboxylic acid (340mg, 1.66mmol) and dry DCM (6mL). A stirring bar is added and stirring is initiated. DIPEA (0.46mL, 2.65mmol) is added. 2-[(2,2-difluoro-benzo[1,3]dioxole-4-carbonyl chloride (438mg, 1.99mmol) is added. 4-Dimethylaminopyridine ([MFCD0006418], 2mg, cat.) is added. The reaction is capped. After 18 days, tlc analysis (silica, 5% iPrOH/DCM) indicates that the starting is completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed with dilute aqueous HCl (2x 25mL), saturated aqueous $NaHCO_3$ (2x 25mL), and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight to yield 0.73g of dark brown foam. This is diluted with DCM and applied to a silica column (40 g) on an ISCO Companion. The column is eluted with 3 column volumes of 10 % EtOAc-heptanes followed by a linear gradient to 50 % EtOAc/heptanes over 10 Column Volumes. And then 90 % EtOAc/heptanes for 2 Column Volumes. 17mL fractions of UV positive eluent are collected. Fraction 8-10 are combined and evaporated by pumping to constant weight to give light orange solid (0.57g, 88 %).

Example 316



315 316

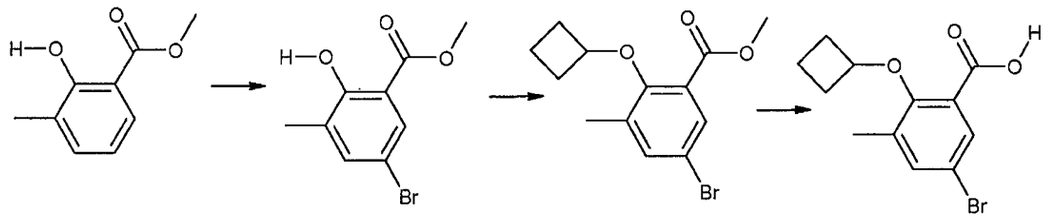
2-[(2,2-Difluoro-benzo[1,3]dioxole-4-carbonyl)-amino]-indan-2-carboxylic acid (316)

A 100mL flask containing 2-[(2,2-diflouro-1,3-benzodioxole-4-carbonyl)-aminol-indan-2-carboxylic acid ethyl ester (0.38g, 0.98mmol) is charged with 1,4-dioxane (6mL) and MeOH (6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3mL) is added followed by the LiOH monohydrate (103mg, 2.46mmol). After 70h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%,

~6mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give off white solid (0.33g, 94%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.26-3.63 (m, 4H), 7.13-7.32 (m, 5H), 7.48 (dd, 1H), 7.55 (dd, 1 H), 8.97 (s, 1H), 12.63 (bs, 1H).
LC/MS (ES+) m/z = 362.05.

Example 317



317

5-Bromo-2-cyclobutoxy-3-methyl-benzoic acid (317)

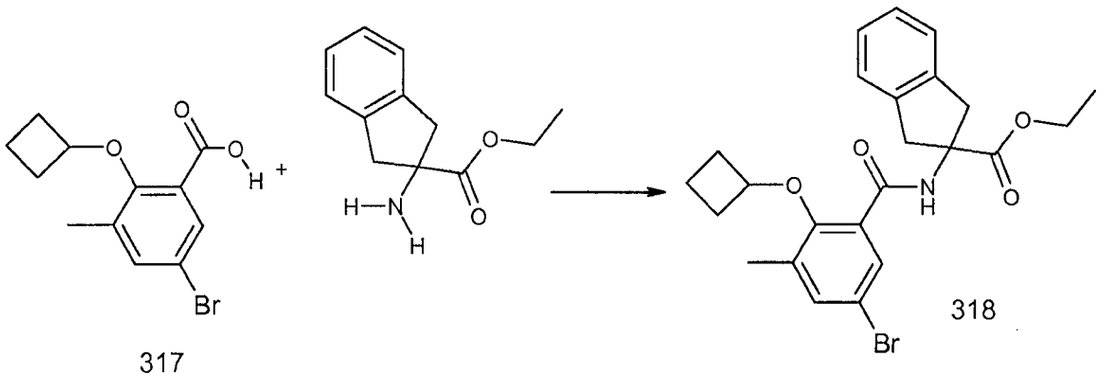
A 250mL 3-necked round bottom flask which is fitted with an addition funnel, a N_2 inlet and a stopper. The flask is charged with bromine (3.6mL 70.11mmol) and DCM (40mL). A stirring bar is added and stirring is initiated. The reaction flask is immersed in an ice-water bath. After stirring for 15min, the addition funnel is charged with a solution of methyl 2-hydroxy-3-methylbenzoate (10g, 60.18mmol) in 1,4-dioxane (40mL). This solution is added to the stirred reaction mixture dropwise over 30min. The addition funnel is then washed with 1,4-dioxane (10mL). This too is added to the reaction mixture. The reaction mixture is then allowed to slowly warm to ambient temperature. After 18 days, the contents of the reaction flask are transferred to a round bottom flask. The solvent is removed under reduced pressure by pumping to constant weight to give 17.66g of light yellow solid. This solid is triturated with ice-cold MeOH (75mL). The resultant crystals are collected by suction filtration. Air-drying provides white solid (14.26g, 97%).

A 100mL round bottom flask is charged with 5-bromo-2-hydroxy-3-methyl-benzoic acid methyl ester 4.05g, 16.53mmol) as prepared above. Dry DMF (20mL) and a stirring bar are added. Stirring is initiated. After dissolution, K_2SO_4 (6.85g, 49.59mmol) and bromocyclobutane (2.35mL, 24.8mmol) are added. The reaction flask is fitted with a heating mantle. The temperature of the mantle is set to 35 degrees C. After 8 days, tlc analysis (silica, 25 % EtOAc/heptanes) indicates a slight consumption of starting material and the appearance of a UV positive spot with a slightly higher R_f value. The reaction is fitted with a heating mantle and warmed to 37°C. After 3 more days, tlc analysis (silica, 25 % EtOAc/heptanes) indicates consumption of starting material and complete conversion to a UV positive spot with a slightly higher R_f value. The reaction mixture is filtered through a pad of Celite. The filtrate is diluted with EtOAc and (100mL) and transferred to a separatory funnel. The EtOAc solution is washed with saturated $NaHCO_3$ (2 x 25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight to give semi-solid material (2.09g, 42 %). This material is utilized in the subsequent step.

A 100mL flask containing 5-bromo-2-cyclobutoxy-3-methyl-benzoic acid methyl ester (2.07g, 7.25mmol) as prepared above is charged with 1,4-dioxane (12mL) and MeOH (12mL). A stirring bar is added and stirring is initiated. After dissolution, water (6mL) is added followed by the LiOH (768mg, 18.31mmol). After18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~11mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (50mL). The layers are separated. The aqueous layer is extracted with EtOAc (40mL). The combined organic phases are washed with water (40mL) and brine (40mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give a white solid (1.82g, 88%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.16-1.25 (m, 2H), 1.38-1.51 (m, 1H), 1.71-2.12 (m, 3H), 2.23 (s, 3H), 4.37 (m, 1H), 7.53-7.62 (m, 2H).
LC/MS (ES+) m/z = 390.16.

Example 318

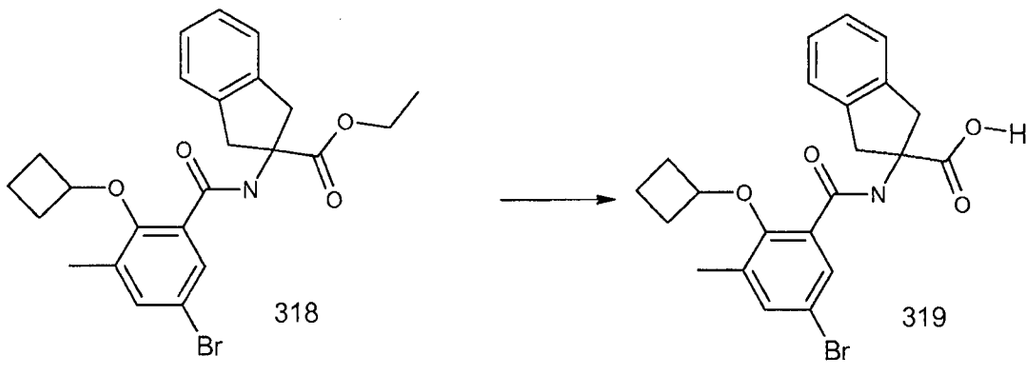


317 318

2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (318)

A 100mL round bottom flask which contains a stirring bar is charged with 2-cyclobutoxyl-3-methyl-5-bromo-benzoic acid 317 (695mg, 2.44mmol) and dry DCM (8mL). Stirring is initiated. After dissolution is complete, HTBU (924mg, 2.44mmol) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester (500mg, 2.44mmol) is added followed by DIPEA (1.1mL, 6.1mmol). The reaction is allowed to stir for 15 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). The organic phase is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated in vacuo to give 1.42g of light orange solid. This solid is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 17mL fractions of UV active eluent are collected. Fractions 4 through 9 are combined and evaporated in vacuo. This yields white solid material (0.8g, 70%).

Example 319



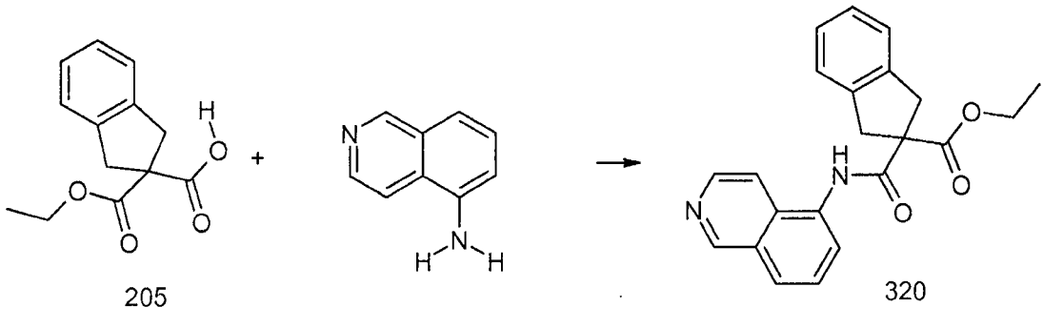
2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (319)

A 30mL reaction vial is charged with 2-(5-bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (0.29g, 0.61mmoles) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH monohydrate (65mg, 1.55mmol). After 38h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~6mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give off white solid (0.26g, 95%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.11-1.27(m, 2H), 1.43-1.57(m, 1H), 1.79-1.99 (m, 4H), 2.21 (s, 3 H) 3.55-3.84 (m, 4H), 4.37 (m, 1H), 7.18-7.33 (m, 4H), 7.35 (d, 1H), 7.51 (d, 1H), 8.78 (s, 1H) 12.62 (s, 1H).

LC/MS (ES+) m/z = 446.11.

Example 320

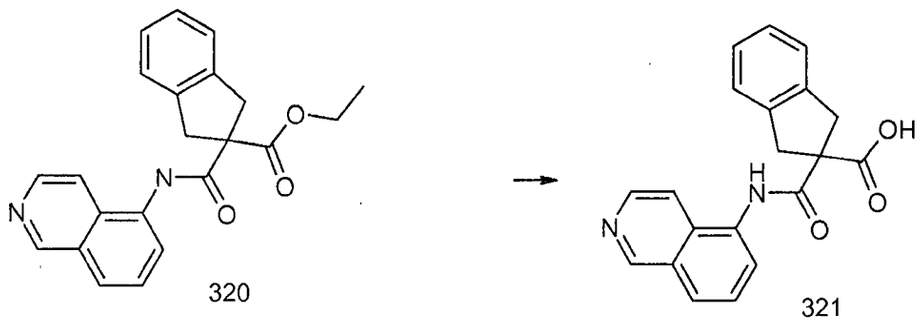


205 320

2-(Isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic Acid Ethyl Ester (320)

A 25mL reaction vial which contains a stirring bar is charged with indane-2-carboxylic acid ethyl ester (205, 1.0g, 4.27mmol) and dry DCM (15mL). Stirring is initiated. After dissolution is complete, the HTBU (1.62g, 4.27mmol) is added. After 5min, the 5,-aminoisoquinoline. (616mg, 4.27mmol) is added followed by DIPEA (1.72mL, 9.8mmol). The reaction is allowed to stir for 63h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting acid. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (40mL). The organic phase is washed consecutively with dilute aqueous HCl (3%, 20mL), saturated aqueous $NaHCO_3$ (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3.13g of light orange solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10% EtOAC in heptanes over 4 column volumes followed by a linear gradient to 90% EtOAc over 12 column volumes. 17mL fractions of eluent are collected. Fractions 17 through 31 are combined and evaporated *in vacuo*. This gives white solid (1.39g, 90%).

Example 321



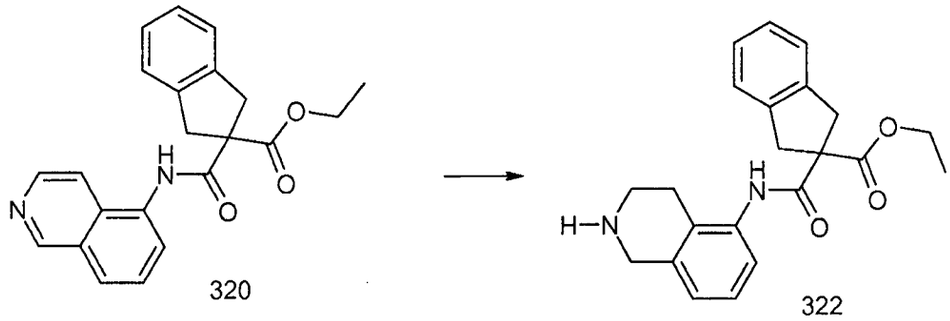
320 321

2-(Isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic Acid (321)

A 30mL reaction vial is charged with 2-(isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (320, 354mg, 0.98mmol) is charged with 1,4-dioxane (6mL) and MeOH (6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3mL) is added followed by the LiOH monohydrate (104mg, 252mmol). After 20h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (1g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 64h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate by pumping to constant weight to give 0.29g of off white solid. This material is triturated with DCM (15mL). The solids are collected by suction filtration and washed with DCM (20mL). Suction drying provides off white solid (280mg, 86%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.55-3.76 (m, 4H), 4.37 (m, 1H), 7.02-7.19 (m, 4H), 7.61 (dd, 1H), 7.78 (d, 1H), 8.06 (d, 1H), 8.46 (d, 1H), 8.57 (d, 1H), 9.30 (s, 1H) 13.77 (s, 1H). LC/MS (ES+) m/z = 333.11.

Example 322

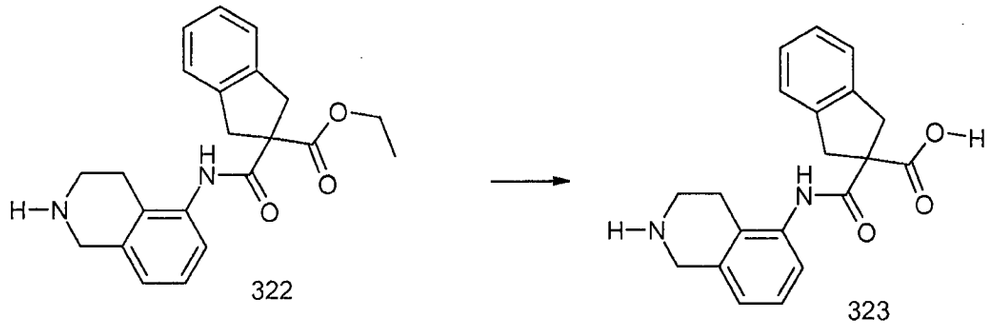


2-(1,2,3,4-Tetrahydro-isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (322)

A 100mL Parr reaction vessel is charged with 2-(Isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (320, 500mg, 1.39mmol) and EtOH (10mL). The reaction vessel is agitated by swirling until dissolution°Ccurred. Acetic acid (10mL) and platinum (IV) oxide

(117mg, 0.52mmol) are added. The vessel is fitted on a Parr hydrogenation apparatus, flushed with N_2 and then evacuated. The vessel is charged with hydrogen to 50 psi. The apparatus is set to agitate. After 4h, agitation is ceased. The reaction vessel is evacuated and flushed with nitrogen. This process is repeated. The contents of the reaction vessel are diluted with iPrOH (50mL) and filtered through a pad of celite. Solvent is removed from the filtrate under reduced pressure. The resulting residue is reconstituted in iPrOH (15mL) and toluene (15mL). The solvent is removed under reduced pressure. This process is repeated. Pumping to constant weight yields light beige solid (0.5g, 99%).

Example 323



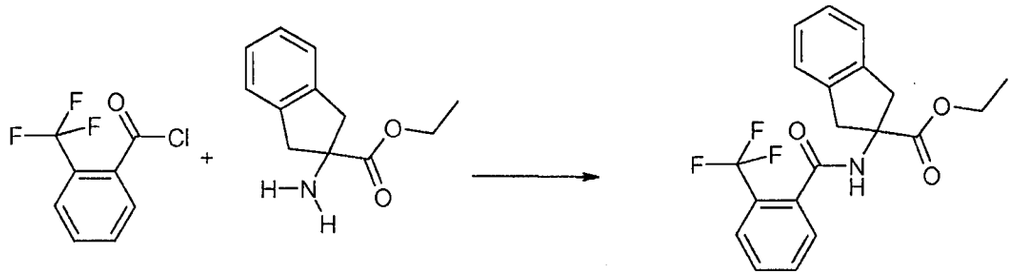
2-(1,2,3,4-Tetrahydro-isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic Acid (323)

A 250mL round bottom flask containing 2-(1,2,3,4-tetrahydro-isoquinolin-5-ylcarbamoyl)-indan-2-carboxylic acid ethyl ester (322, 440mg, 1.21mmoles) is charged with 1,4-dioxane (7mL) and MeOH (7mL). A stirring bar is added and stirring is initiated. After dissolution, water (3.5mL) is added followed by the LiOH monohydrate (128mg, 3.05mmol). After 18h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (1g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 24h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The resultant residue is reconstituted with iPrOH/ toluene (1:1, 25mL). The solvent is removed *in vacuo*. This process is repeated twice. Pumping to constant weight provides an off-white solid (400mg, 99%).

^{1}H NMR (DMSO-d6, 300MHz): δ 2.58 (m, 1H), 2.99 (m, 1H), 3.43-3.71 (m, 4H), 3.81 (m, 1H), 6.72 (d, 1H), 7.01 (dd, 1H), 7.04-7.18 (m, 4H), 7.84 (d, 1H), 11.82 (s, 1H).

LC/MS (ES+) m/z = 337.15.

Example 324

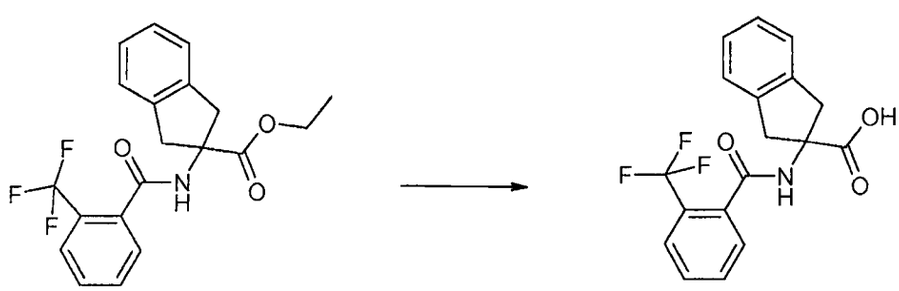


324

2-(2-Trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (324)

A 30mL vial is charged with 2-aminoindan-2-carboxylic acid (450mg, 2.19mmol) and dry DCM (5mL). A stirring bar is added and stirring is initiated. DIPEA (0.61mL, 3.51mmol) is added. 2-(trifluoromethyl)-benzoyl chloride (388 μL, 2.63mmol) and DMAP (3mg, cat.) are added. The reaction is capped. After 38 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting is completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). The organic phase is washed with dilute aqueous HCl (2x 25mL), saturated aqueous $NaHCO_3$ (2 x 25mL), and brine (25mL), dried over $MgSO_4$, filtered and evaporated by pumping to constant weight yields 0.84g of light orange solid. This is diluted with DCM and applied to a silica column ((24 g) on an ISCO Companion. 14mL fractions of UV positive eluent are collected. Fraction 4 -10 are combined and evaporated by pumping to constant weight to give light yellow solid (0.76g, 92%).

Example 325



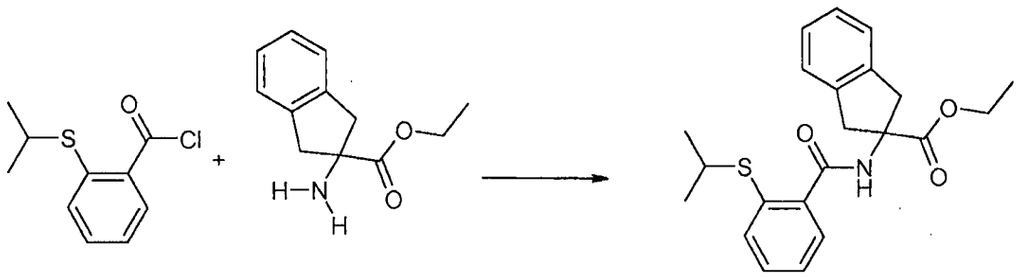
324 325

2 2-(2-Trifluoromethyl-benzoylamino)-indan-2-carboxylic acid (325)

A 100mL flask containing 2-(2-trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (324, 0.57g, 1.51mmol) is charged with 1,4-dioxane (9mL) and MeOH (9mL). A stirring bar is added and stirring is initiated. After dissolution, water (4.5mL) is added followed by the LiOH monohydrate (160mg, 3.81mmol). After 110h, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~9mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (40mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), and then dried over MgSO4, filtered and concentrated by pumping to constant weight yields off white solid (0.51g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.23-3.63 (m, 4H), 7.11-7.23 (m, 4H), 7.47 (d, 1H), 7.60-7.76 (m, 3H), 9.12 (s, 1H), 12.55 (s, 1H).
LC/MS (ES+) m/z = 350.11.

Example 326



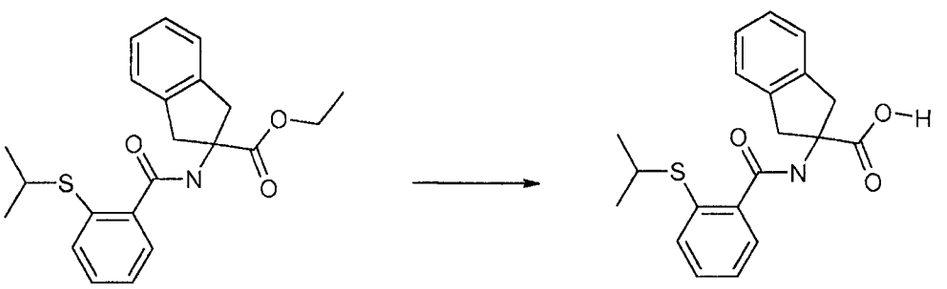
326

2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (326)

A 30mL reaction vial is charged with 2-isopropylsulfanylbenzoic acid (430mg, 2.19mmol) and dry DCM (7mL). A stirring bar is added. Stirring is initiated. After dissolution is complete, the HTBU (831mg, 2.19mmol) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester. (450mg, 2.19mmol) is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir for 3 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM)

indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 0.87g of light yellow solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% EtOAc in heptanes over 10 column volumes. 17mL fractions of eluent are collected. Fractions 32 through 40 are combined and evaporated *in vacuo*. This provides white solid material (0.69g, 82 %).

Example 327



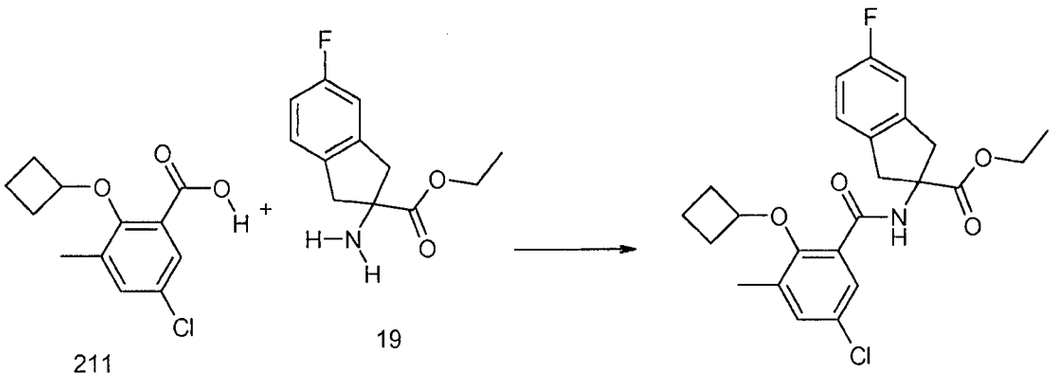
326 327

2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid (327)

A 100mL flask containing 2-(2-isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (326, 0.52g, 1.45mmol) is charged with 1,4-dioxane (8mL) and MeOH (8mL). A stirring bar is added and stirring is initiated. After dissolution, water (4mL) is added followed by the LiOH monohydrate (145mg, 3.46mmol). After 20 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~9mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (40mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give off white solid (0.45g, 93%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.14 (d, 6H), 3.24-3.623 (m, 5H), 7.12-7.44 (m, 8H), 8.85 (s, 1H), 12.92 (s, 1H).
LC/MS (ES+) m/z = 356.15.

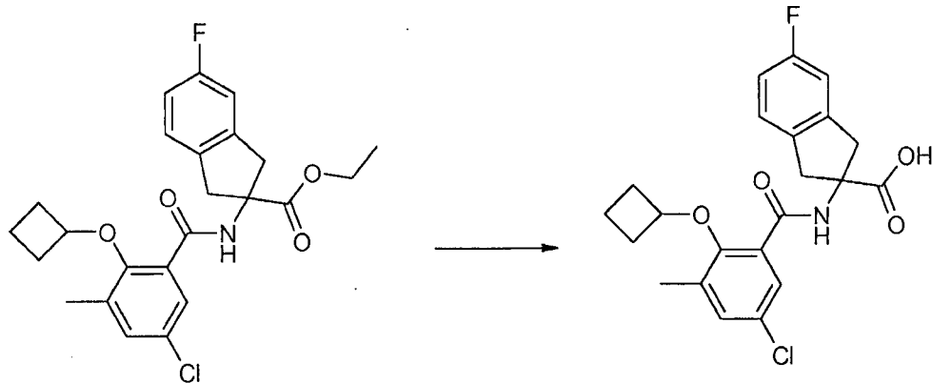
Example 328



2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (328)

A 40mL reaction vial is charged with 2-cyclobutoxyl-3-methyl-5-chloro-benzoic acid (221, 0.40g, 1.62mmol) and dry DCM (5mL). A stirring bar is added. Stirring is initiated. After dissolution is complete, the HBTU (630mg, 1.66mmol) is added. After 5min, the 2-amino-5-fluoro-indane-2-carboxylic acid ethyl ester. (19, 371mg, 1.66mmol is added followed by DIPEA (0.74mL, 4.16mmol). The reaction is allowed to stir for 5 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with dilute aqueous HCl (3%, 20mL), saturated aqueous $NaHCO_3$ (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1g of light yellow oil. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 24g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 70% EtOAc in heptanes over 10 column volumes. 17mL fractions are collected. Fractions 22 through 28 are combined and evaporated *in vacuo* by pumping to a constant weight to give white solid (0.65g, 88%).

Example 329



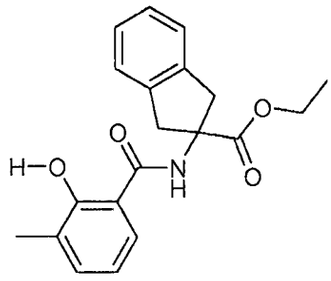
328 329

2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid (329)

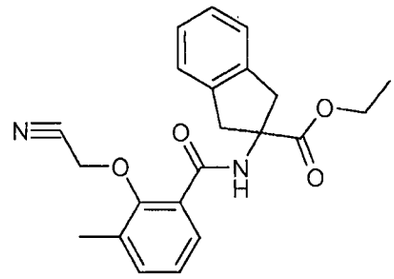
A 100mL flask containing 2-(5-chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid ethyl ester (328, 0.49g, 1.09mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (117mg, 2.78mmol). After 1 day, tlc analysis (silica, 10% MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~8mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (25mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic phases are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give white solid (0.45g, 98%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.22-1.37(m, 1H), 1.43-1.57(m, 1H), 1.78-1.95 (m, 4H), 2.03 (s, 3 H) 3.285-3.63 (m, 5H), 4.37 (m, 1H), 6.98 (m, 1H), 7.06-7.11 (m, 1H), 7.20-7.27 (m, 2H), 7.385 (d, 1H), 8.82 (s, 1H) 12.67 (s, 1H).
LC/MS (ES+) m/z = 418.18

Example 330



3

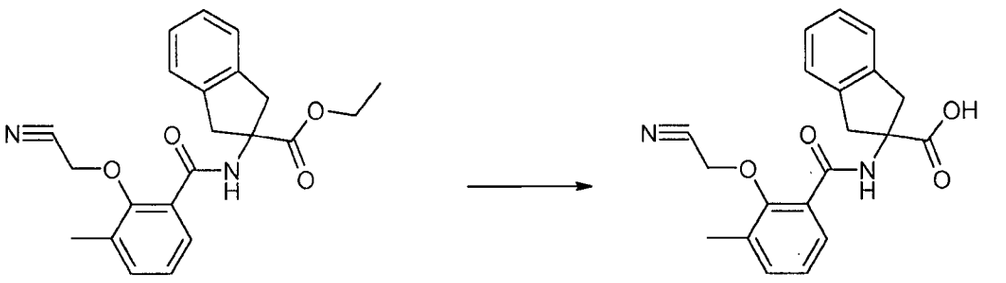


330

2-(2-Cyanomethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (330)

A 30mL reaction vial is charged with 2-(2-hydroxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (3, 400mg, 1.18mmol) and dry DMF (5mL). A stirring bar is added and stirring is initiated. After dissolution, K_2SO_4 (326mg, 2.36mmol) and bromoacetonitrile (164 μL, 2.36mmol) are added in turn. The reaction vial is capped and placed in a heating block which is set atop of an orbital shaker. The heating block is set at 55°C. After 16h, tlc analysis (silica, 1:1 EtOAc in heptanes) indicates that the starting material is completely consumed. Heating is terminated. After sitting at ambient temperature for 1 day, the contents of the flask are filtered through a pad of Celite. The filtrate is transferred to a separatory funnel which contains EtOAc (40mL). The layers are separated. The organic phase is washed with water (20mL), saturated aqueous $NaHCO_3$ and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give dark brown solid (0.42g). This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 25g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 50% EtOAc in heptanes over 10 column volumes. 17mL fractions of eluent are collected. Fractions 4 through 6 are combined and evaporated *in vacuo*. This provides white solid (0.26g, 58 %).

Example 331



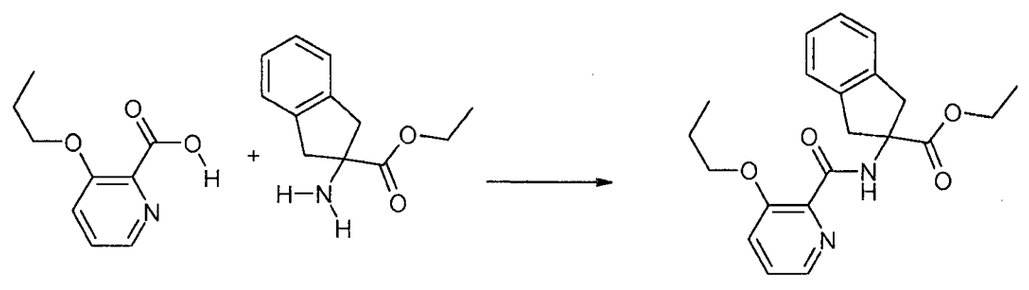
330 331

2-(2-Cyanomethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid (331)

A 100mL flask containing 2-(2-cyanomethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (330, 0.25g, 0.66mmol) is charged with 1,4-dioxane (2mL) and MeOH (2mL). A stirring bar is added and stirring is initiated. After dissolution, water (1mL) is added followed by the LiOH monohydrate (71mg, 1.67mmol). After 18h, tlc analysis (silica, 5 % MeOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~8mL). The contents of the flask are poured into a separatory funnel which contains EtOAc (25mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated by pumping to constant weight to give white solid (0.23g, 99%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.26-3.63 (m, 4H), 3.43 (s, 3H), 4.56 (s, 2H), 7.07 (dd, 1H), 7.14-7.23 (m, 5H), 7.29 (dd, 1H), 8.81 (s, 1H), 12.55 (bs, 1H).
LC/MS (ES+) m/z = 351.14.

Example 332

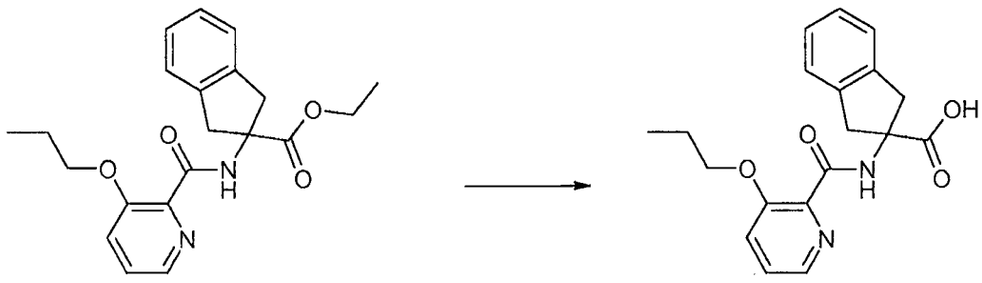


332

2-[(3-Propoxy-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester(332)

A 40mL reaction vial which contains a stirring bar is charged with 3-*n*-propoxypicolinic acid (397mg, 2.19mmol) and dry DCM (6mL). Stirring is initiated. After 2min, the HTBU (831mg, 2.195mmol) is added. After 5min, the 2-amino)-indane-2-carboxylic acid ethyl ester (450mg, 2.19mmol is added followed by DIPEA (0.96mL, 5.48mmol). The reaction is allowed to stir at ambient temperature. After 20 days, analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with dilute aqueous HCl (3%, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and dried over $MgSO_4$, filtered and evaporated *in vacuo* to give 1.23g of light orange solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAc in heptanes over 3 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 17mL fractions eluent are collected. Fractions 57 through 67 are combined and evaporated *in vacuo* by pumping to constant weight to give white solid (0.8g, 99%).

Example 333



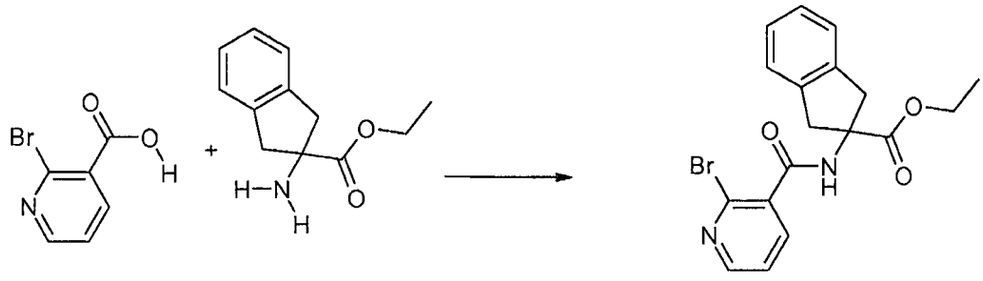
2-[(3-Propoxy-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid (333)

A 100mL round bottom flask which contains 2-[(3-propoxy-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (332, 620mg, 1.68mmol) is charged with 1,4-dioxane (6mL) and MeOH (6mL). A stirring bar is added and stirring is initiated. After dissolution, water (3mL) is added followed by the LiOH monohydrate (178mg, 4.25mmol). After 22h, tlc

analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 125h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 10mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides 0.58g of white solid.

^{1}H NMR (DMSO-d6, 300MHz): δ 0.76 (t,3H), 1.71 (dt, 2H), 3.17-3.53 (m, 4H), 3.98 (t, 2H), 7.03-7.12 (m, 4H), 7.43 (dd, 1H), 7.55 (dd, 1H), 7.43 (dd, 1H), 8.12 (dd, 1H), 8.86 (s, 1H).
LC/MS (ES+) m/z = 341.14

Example 334



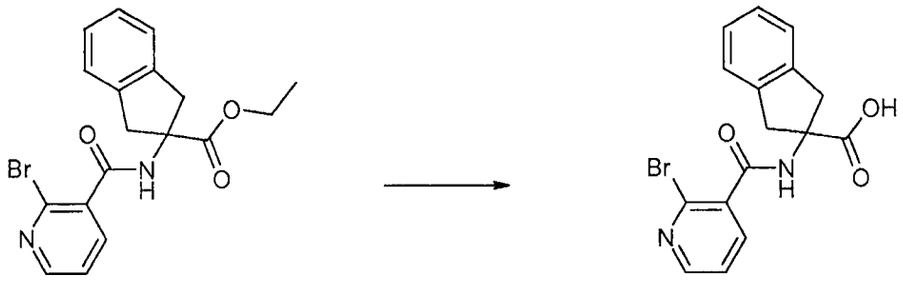
334

2-[(2-Bromo-pyridinyl-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester(334)

A 40mL reaction vial which contains a stirring bar is charged with 2-bromonicotinic acid (1.18g, 5.85mmol) and dry DCM (15mL). Stirring is initiated. After 2min, the HTBU (2.22g, 5.85mmol) is added. After 5min, 2-Amino-indan-2-carboxylic acid ethyl ester (1.2g, 5.25mmol is added followed by DIPEA (2.55mL, 14.62mmol). The reaction is allowed to stir for 32 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with water (3%, 25mL), saturated aqueous $NaHCO_3$ (2 x 25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3.1g of light orange solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 5 % EtOAc in heptanes for 4 column volumes

followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 17mL fractions of eluent are collected. Fractions 30 through 43 are combined and evaporated *in vacuo* to yield white solid, (1.62g, 72%).

Example 335



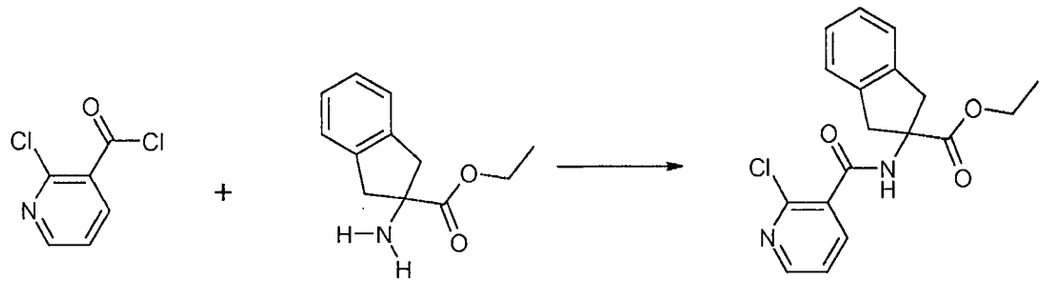
334 335

2-[(2-Bromo-pyridinyl-3-carbonyl)-amino]-indan-2-carboxylic acid (335)

A 50mL round bottom flask which contains 2-[(2-bromo-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (335, 356mg, 0.92mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (97mg, 2.31mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 6h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.32g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 3.23-3.53 (m, 4H), 7.03-7.18 (m, 4H), 7.49 (dd, 1H), 7.86 (dd, 1H), 8.40-8.51 (m, 2H).
LC/MS (ES+) m/z = 361.02.

Example 336

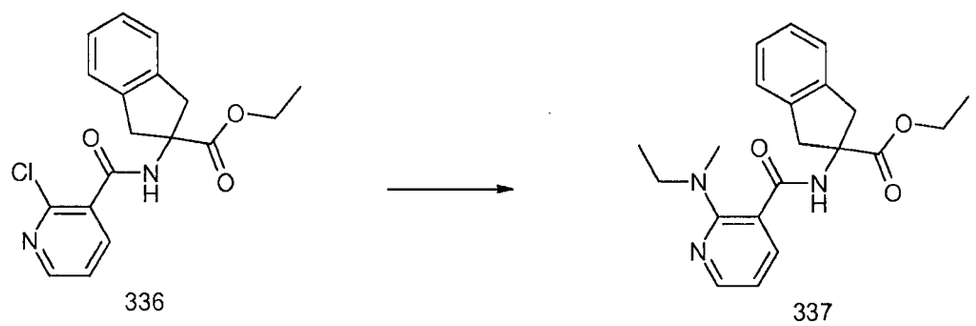


336

2-[(2-Chloro-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (336)

A 100mL round bottom flask is charged with 2-amino-indan-2-carboxylic acid (1.5g, 7.31mmol) and dry DCM (15mL). A stirring bar is added and stirring is initiated. DIPEA (2mL, 11.69mmol) is added. 2-[chloronicotinoyl chloride (1.54g, 8.77mmol) and DMAP (8mg, cat.) are added. The reaction is capped. After 2 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting is completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed with water (2 x 25mL), saturated aqueous $NaHCO_3$ (2x 25mL), and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated by pumping to constant weight to give 2.15g of off-white solid. This is dissolved with DCM (20mL) and applied to a silica column ((80 g) on an ISCO Companion. The column is eluted with 10 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 75% EtOAc in heptanes over 12 column volumes. 17mL fractions of UV positive eluent are collected. Fractions 14 - 20 are combined and evaporated by pumping to constant weight to give light yellow solid (2g, 79%).

Example 337

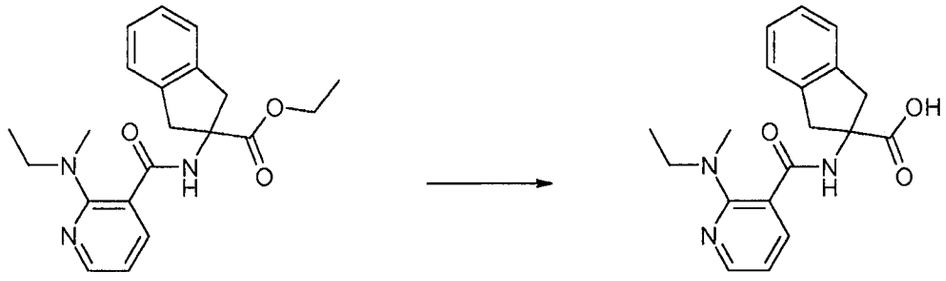


336 337

2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (337)

A 25mL microwave reaction vessel is charged with 2-[2-(chloro-pyridine-3-carbonyl]-amino]-indan-2-carboxylic acid ethyl ester (336, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30 seconds DIPEA (2.1mL, 11.6mmol) and N-methylisopropylamine (1.2mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 6 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight to give 0.78g of viscous yellow oil. The material is dissolved in DCM (10mL) and applied to an ISCO chromatography column (silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 13 are combined and evaporated by pumping to constant weight to give off-white solid (0.41g, 93%).

Example 338



337 338

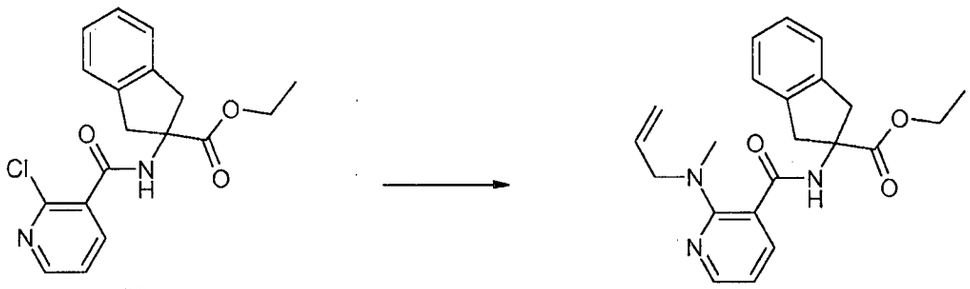
2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (338)

A 100mL round bottom flask which contains 2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (337, 650mg, 1.77mmol) is charged with 1,4-dioxane (10mL) and MeOH (10mL). A stirring bar is added and stirring is initiated. After dissolution, water (5mL) is added followed by the LiOH monohydrate (187mg, 4.46mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (1g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 18h, the contents of the flask are filtered through a pad of celite. The solvent is removed from the

filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed under reduced pressure. This process is repeated 1 time. Pumping to constant weight gives beige solid (0.58g, 97%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.07 (t,3H), 3.18-3.48 (m,4H), 3.37 (q, 2H), 6.75 (dd, 1H), 7.03-7.13 (m, 4H), 7.63 (dd, 1H), 8.15 (dd, 1H), 8.77 (s, 1H).
LC/MS (ES+) m/z = 340.17.

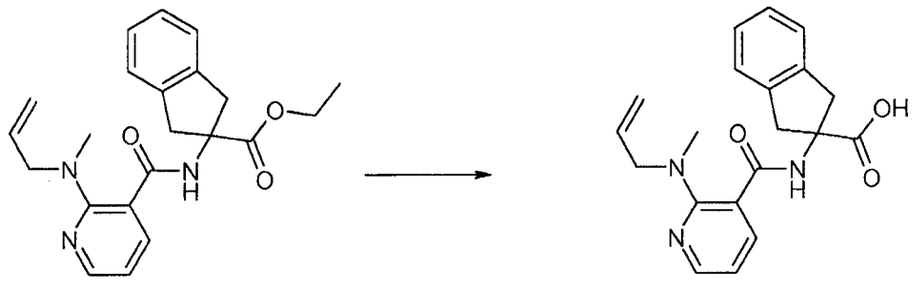
Example 339



2-{[2-(Allylmethyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (339)

A 25mL microwave reaction vessel is charged with 2-[2-(chloro-pyridine-3-carbonyl]-amino]-indan-2-carboxylic acid ethyl ester (336, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30 seconds DIPEA (2.1mL, 11.6mmol) and N-allylmethylamine (1.1mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 21 days, tlc analysis silica, (2:1 EtOAc:heptanes) indicates that the starting material is consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight to give 0.85mg of dark brown material. The material is dissolved in DCM and applied to an ISCO chromatography column (Silica, 25 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 2 to 8 are combined and evaporated by pumping to constant weight give off-white solid (0.43g, 98).

Example 340



339 340

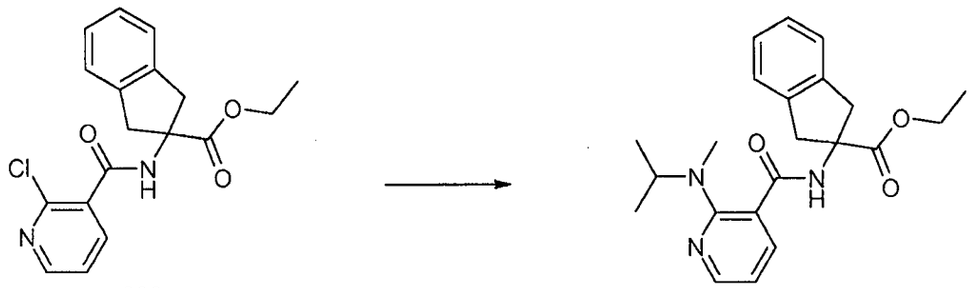
2-{[2-(Allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (340)

A 100mL round bottom flask which contains 2-{[2-(allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (339, 280mg, 0.74mmol) is charged with 1,4-dioxane (2mL) and MeOH (2mL). A stirring bar is added and stirring is initiated. After dissolution, water (1mL) is added followed by the LiOH monohydrate (78mg, 1.86mmol). After 38h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 15 days, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.26g, 100%).

^{1}H NMR (DMSO-d6, 300MHz): δ 2.82 (s,3H) 3.18-3.48 (m,4H), 3.92 (dd,2H), 5.04-5.22 (m, 2H), 5.86-6.02 (m, 1H), 6.79 (dd, 1H), 7.04-7.11 (m, 4H), 7.67 (dd, 1H), 8.16 (dd, 1H), 8.77 (s, 1H).

LC/MS (ES+) m/z = 352.20.

Example 341

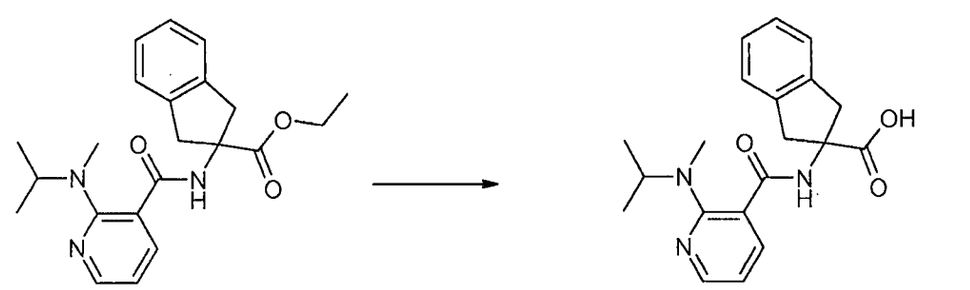


336 341

2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (341)

A 25mL microwave reaction vessel is charged with 2-[2-(chloro-pyridine-3-carbonyl]-amino]-indan-2-carboxylic acid ethyl ester (341, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30sec DIPEA (2.1mL, 11.6mmol) and N-methylethylamine (1.2mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in a oil bath which is heated to 80°C. After 6 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 0.78g of viscous yellow oil. The material is dissolved in DCM and applied to an ISCO chromatography column (Silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 13 are combined and evaporated by pumping to constant weight yield 0.41g of off-white solid.

Example 342



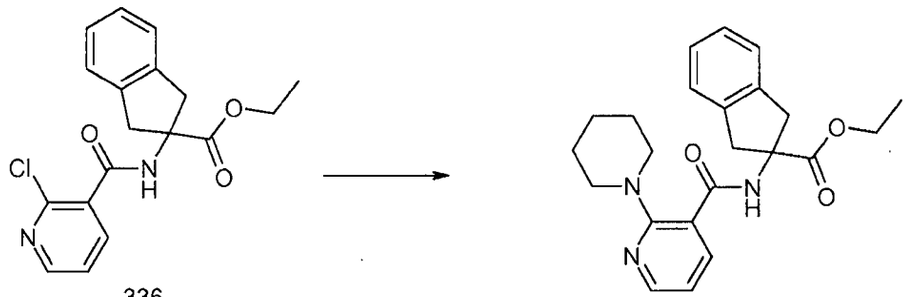
341 342

2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (342)

A 100mL round bottom flask which contains 2-{[2-(isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (341, 220mg, 0.58mmol) is charged with 1,4-dioxane (2mL) and MeOH (2mL). A stirring bar is added and stirring is initiated. After dissolution, water (1mL) is added followed by the LiOH monohydrate (61mg, 1.46mmol). After 16h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 4 days, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.2g, 98%).

^{1}H NMR (DMSO-d6, 300 MHz): δ 1.15 (d,6H), 2.48 (s,3H), 3.18-3.42 (m,4H), 4.18 (septet, 1H), 6.78 (dd, 1H), 7.05-7.12 (m, 4H), 7.67 (dd, 1H), 8.16 (dd, 1H), 8.81 (s, 1H).
LC/MS (ES+) m/z = 354.17

Example 343



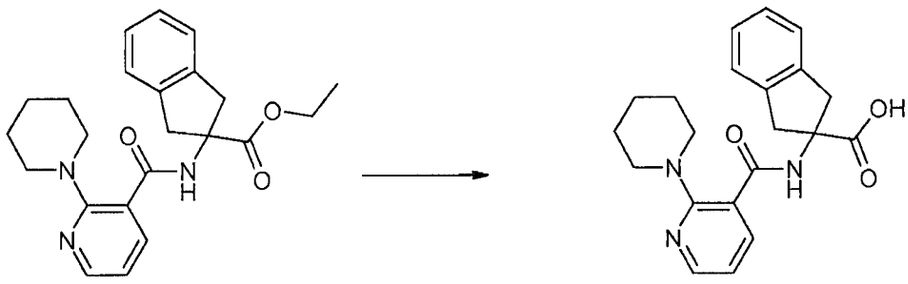
336 343

2-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (343)

25mL microwave reaction vessel is charged with 2-[2-(chloro-pyridine-3-carbonyl)-amino]-indan-2-carboxylic Acid Ethyl Ester (336, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A

stirring bar is added and stirring is initiated. After 30 seconds DIPEA (2.1mL, 11.6mmol) and N-methylisopropylamine (1.2mL, 11.6, mmole) are added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 6 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material is consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 0.78g of viscous yellow oil. The material is dissolved in DCM and applied to an ISCO chromatography column (Silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 13 are combined and evaporated by pumping to constant weight give off-white solid (0.41g, 90%).

Example 344



343 344

2-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3'-carbonyl)-amino]-indan-2-carboxylic acid (344)

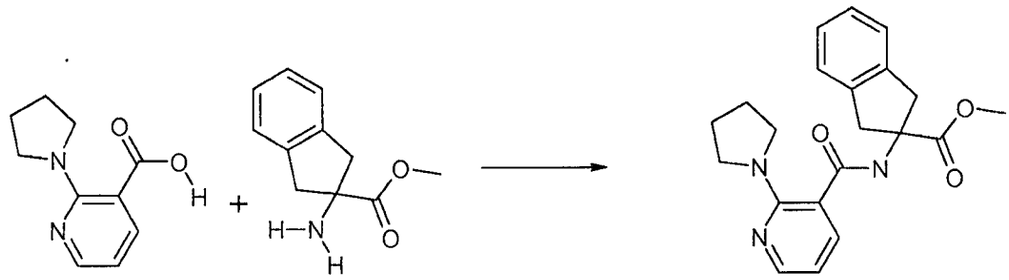
A 100mL round bottom flask which contains 2-[(3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-3'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (343, 330mg, 0.84mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (89mg, 2.12mmol). After 62h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 38h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is

removed. This process is repeated 1 time. Pumping to constant weight provides 0.3g of a white solid.

^{1}H NMR (DMSO-d6, 300MHz): δ 1.52 (m,2H), 1.76 (m, 4H), 3.13 (m, 4H), 3.18-3.43 (m, 4H), 3.92 (dd, 2H), 6.94 (dd, 1H), 7.05-7.12 (m, 4H), 7.81 (dd, 1H), 8.24 (dd, 1H), 9.35 (s, 1H).

LC/MS (ES+) m/z = 366.17.

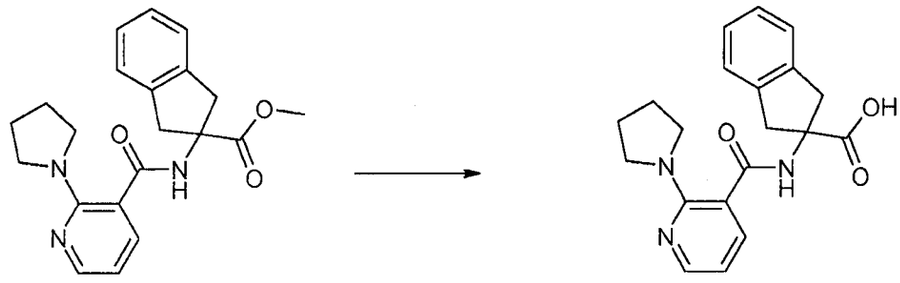
Example 345



2-[(2-Pyrrolidin-1-yl-3-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (345)

A 40mL reaction vial which contains a stirring bar is charged with 2-(1-pyrrolidinyl)-nicotinic acid (422mg, 2.2mmol) and dry DCM (6mL). Stirring is initiated. After 2min, the HTBU (833mg, 2.2mmol) is added. After 5min, 2-amino-indan-2-carboxylic acid methyl ester HCl salt. (0.5g, 2.2mmol) is added followed by DIPEA (1.17mL, 6.7mmol). The reaction vial is capped and allowed to stir at ambient temperature. After 18h, analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with water (3%, 25mL), saturated aqueous $NaHCO_3$ (2 X 25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.05g of light yellow solid. This material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 24g cartridge of silica. The gradient is 5 % EtOAc in heptanes for 4 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 14mL fractions of UV active eluant are collected. Fractions 6 through 12 are combined and evaporated *in vacuo* to give white solid (0.73g, 91%).

Example 346



345 346

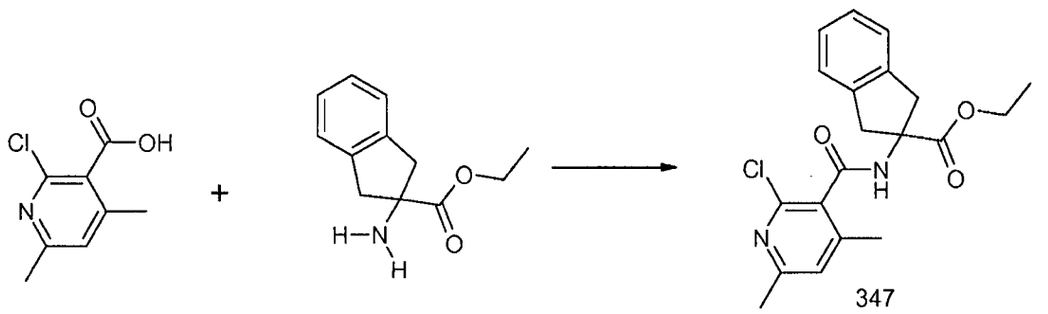
2-[(2-Pyrrolidin-1-yl-3-carbonyl)-amino]-indan-2-carboxylic acid (346)

A 100mL round bottom flask which contains 2-[(2-pyrrolidin-1-yl-3-carbonyl)-amino]-indan-2-carboxylic acid methyl ester (345, 440mg, 1.20mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (128mg, 3.05mmol). After 30h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction flask. The reaction is capped and allowed to stir at ambient temperature. After 18h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides 0.38g of white solid.

^{1}H NMR (DMSO-d6, 300MHz): δ 1.82 (m, 4H), 3.21-3.48 (m, 8H), 3.92 (dd, 2H), 6.59 (dd, 1H), 7.04-7.11 (m, 4H), 7.46 (dd, 1H), 8.08 (dd, 1H), 8.22 (bs, 1H).

LC/MS (ES+) m/z = 352.14.

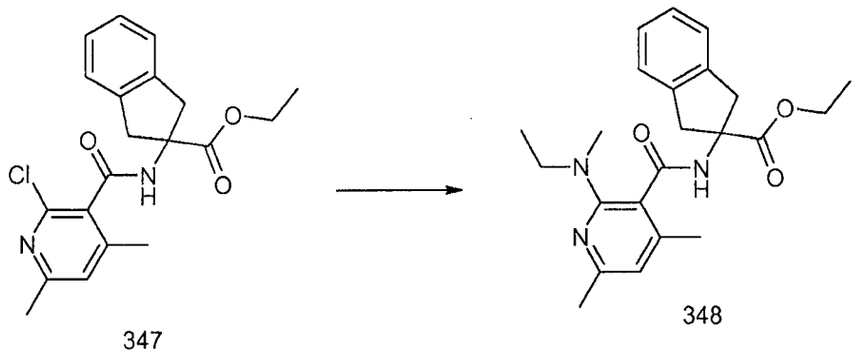
Example 347



2-[(2-Chloro-4,6-dimethyl-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (347)

A 40mL vial is charged with 2-chloro-4,6-dimethylnictotinic acid (497mg, 2.68mmol) and dry DCM (9mL). A stirring bar is added and stirring is initiated. After 2min, the HTBU (1.02g, 2.68mmol) is added. After 5min, 2-amino)-indane-2-carboxylic acid ethyl ester. (550mg, 2.68mmol) is added followed by DIPEA (1.2mL, 6.74mmol). The reaction is allowed to stir for 14 days. Analysis by tlc of the reaction mixture (silica, 15% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (70mL). This is washed dilute aqueous HCl (3%, 2 x 30mL), saturated aqueous $NaHCO_3$ (2 x 30mL) and brine (30mL), and then dried over $MgSO_4$, filtered and evaporated in vacuo to provide1.6g of yellow foam. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 4 column volumes followed by a linear gradient to 50% EtOAc over 10 column volumes. 27mL fractions of UV active elutant are collected. Fractions 32 through 40 are combined and evaporated in vacuo to give yellow semi-solid material. (0.67g, 67%).

Example 348

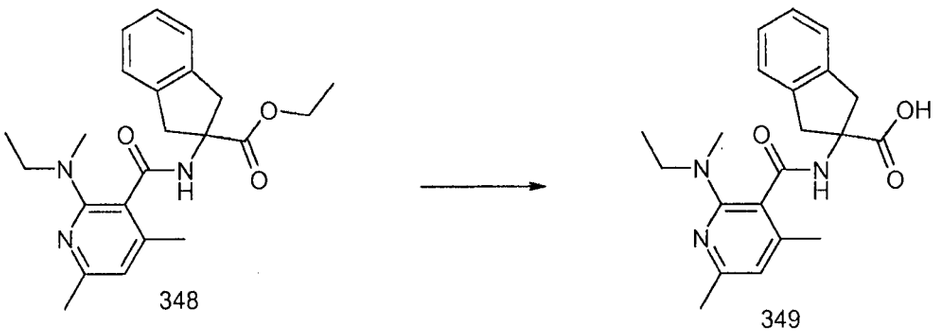


347 348

2-{[2-(Ethyl-methyl-amino)-4,6-dimethyl-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (348)

A 25mL microwave reaction vessel is charged with 2-[2-(chloro-4,6-dimethyl-pyridine-3-carbonyl]-amino]-indan-2-carboxylic acid ethyl ester (347, 480mg, 1.29mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30 seconds, N-ethylmethylamine (2mL, 23.28 mmole) is added. The reaction vessel is sealed with a crimped cap. The reaction vessel is placed in a Smith Optimizer microwave apparatus. The pre-stir is set at 20sec followed by heating to 100°C. Hold time is set to 18min. TLC analysis silica, 2:1 EtOAc:heptanes) indicates that a new Spot appears with a higher R_f value as visualized by UV. Starting material is still present. N-Ethylmethylamine (506 μL, 5.89, mmole) is added. The reaction vessel is sealed with a crimped cap. The reaction vial is immersed in an oil bath that is heated at 80°C. After 5 days, tlc analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been converted to a higher moving spot as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 1.3g of viscous yellow oil. The material is dissolved in DCM (10mL) and applied to an ISCO Chromatography Column (Silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 Column Volumes. 14mL fractions of UV active eluent are collected. Fractions 4 to 9 are combined and evaporated by pumping to constant weight to give white solid (0.41g, 83%).

Example 349



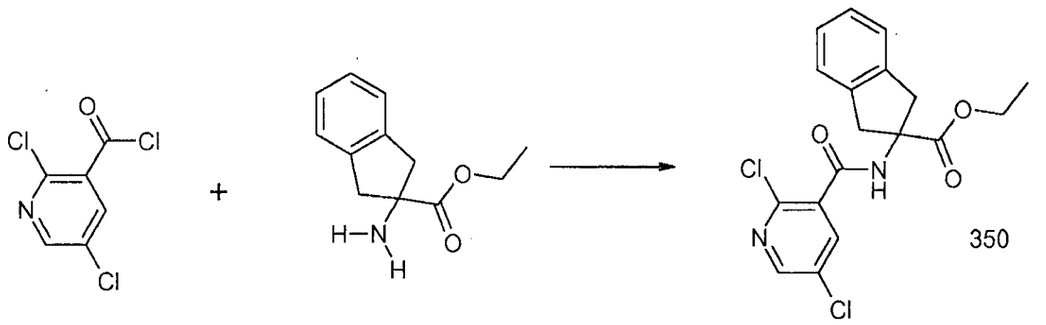
2-{[2-(Ethyl-methyl-amino)-4,6-dimethyl-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid (349)

A 100mL round bottom flask which contains 2-{[2-(ethyl-methyl-amino)-4,6-dimethyl-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (348, 260mg, 0.66mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (70mg, 1.66mmol). After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 38h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.18g, 75%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.03 (t, 3H), 3.17-3.53 (m, 6H), 6.41 (s, 1H), 7.05-7.12 (m, 4H), 8.05 (s, 1H).

LC/MS (ES+) m/z = 368.25.

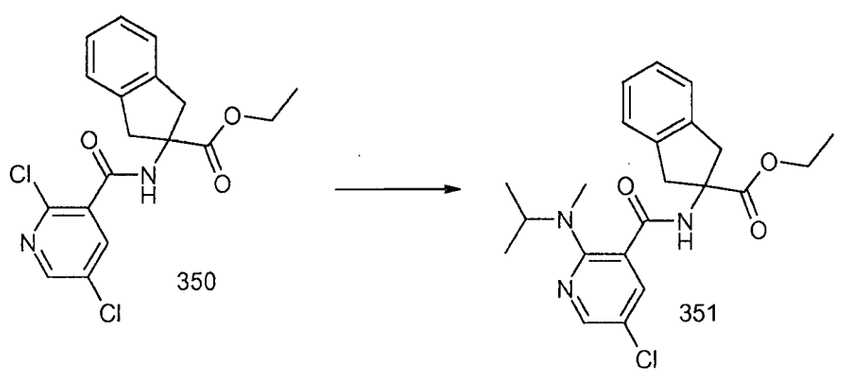
Example 350



2-[(2,5-Dichloro-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (350)

A 30mL reaction vial is charged with 2-aminoindan-2-carboxylic acid ethyl ester (1g, 4.87mmol) and dry DCM (5mL). A stirring bar is added and stirring is initiated. DIPEA (1.35mL, 7.8mmol) is added. 2,5-dichloro-pyridine3-carbonyl chloride (1.23g, 5.85mmol) and DMAP (8mg, cat.) are added. The reaction is capped. After 57 days, tlc analysis (silica, 10% iPrOH/DCM) indicates that the starting has been completely consumed. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (60mL). This is washed with water (2x 25mL), saturated aqueous $NaHCO_3$ (2x 25mL), and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated by pumping to constant weight yields 1.99g of off-white solid.. This is diluted with DCM (20mL) and applied to a silica column ((80 g) on an ISCO Companion. The column is eluted with 5 % EtOAc in heptanes for 3 column volumes followed by a linear gradient to 75% EtOAc in heptanes over 12 column volumes. 17mL fractions of UV positive eluent are collected. Fraction 12 - 16 are combined and evaporated by pumping to constant weight to give light yellow solid (1.39g, 75%).

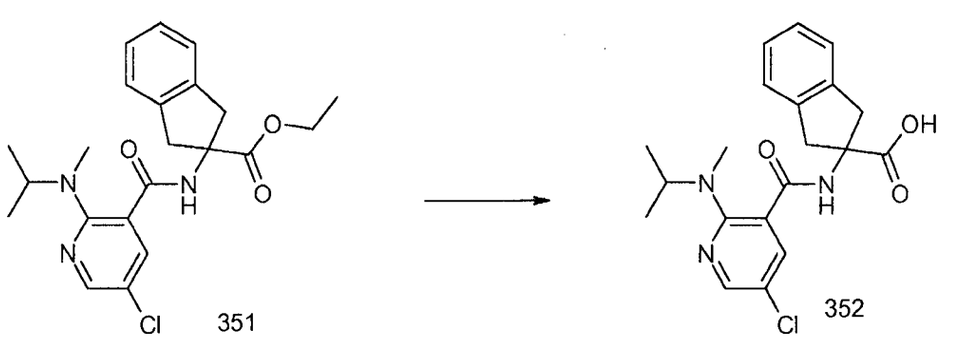
Example 351



2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (351)

A 40mL reaction vial is charged with 2-[2-(chloro-pyridine-3-carbonyl]-amino]-indan-2-carboxylic acid ethyl ester 350, 400mg, 1.16mmol) and dry 1,4-dioxane (4mL). A stirring bar is added and stirring is initiated. After 30sec DIPEA (2.1mL, 11.6mmol) and N-methylisopropylamine (1.2mL, 11.6, mmole) are added. The reaction vial is tightly sealed with Teflon coated cap. The reaction vessel is placed in an oil bath that is heated to 80°C. After 7 days, TLC analysis silica, 2:1 EtOAc:heptanes) indicates that the starting material had been consumed as visualized by UV. The contents of the reaction flask are transferred to a round bottom flask and the solvent removed *in vacuo* by pumping to constant weight provides 0.84g of viscous yellow oil. The material is dissolved in DCM and applied to an ISCO chromatography column (silica, 40 g). A gradient of 5% EtOAc in heptanes is applied for 3 column volumes followed by a linear ramp to 60 % EtOAc in heptanes over 12 column volumes. 14mL fractions of UV active eluent are collected. Fractions 2 to 5 are combined and evaporated by pumping to constant weight to give a light yellow solid (0.42g, 85%).

Example 352



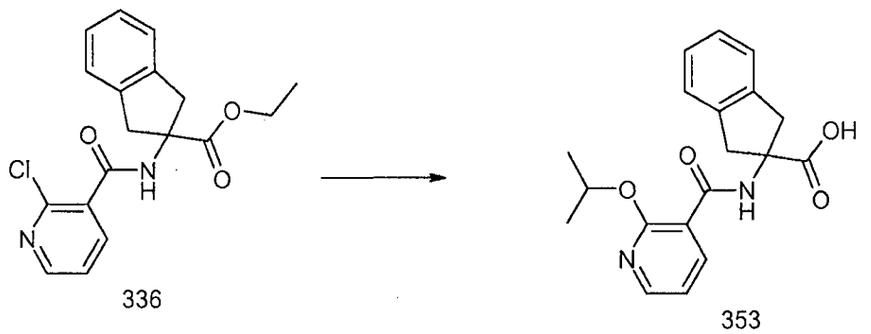
2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid (352)

A 100mL round bottom flask which contains 2-{[5-chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (351, 270mg, 0.58mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH (62mg, 1.48mmol).

After 18h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 20h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.21g, 94%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.09 (t, 3H), 2.71 (s,3H), 3.22-3.48 (m, 4H), 4.18 (septet, 1H), 7.04-7.11 (m, 4H), 7.65 (s, 1H), 8.17 (s, 1H), 8.48 (s, 1H), 8.72 (bs, 1H).
LC/MS (ES+) m/z = 390.10.

Example 353



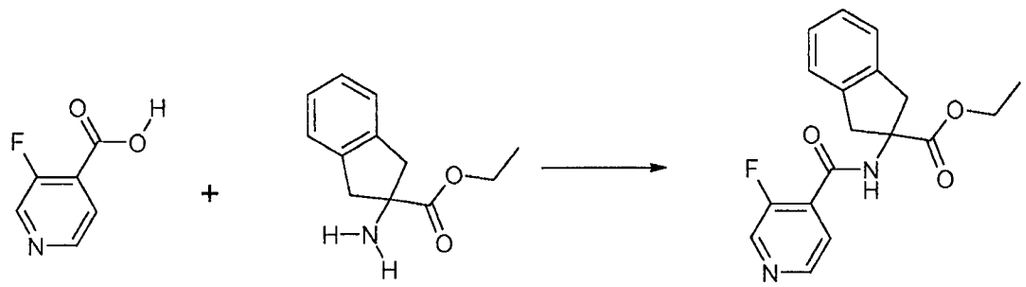
2- [2-(Isopropoxy-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid (353)

A 10mL microwave reaction vial is charged with iPrOH (4mL, 51.9mmol). A stirring bar is added and stirring is initiated. A suspension of NaH in oil (104mg, 2.61mmol) is added. After 2min, 2-[(2-Chloro-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (336, 450mg, 1.31mmol) is added. The reaction flask is loosely capped and allowed to stir at ambient temperature. After 7 days, tlc analysis (slica, 2:1, EtOAc/heptanes) indicates that the starting material is consumed. Dowex Highly Acidic Ion Exchange Resin (0.5g) is added to the reaction flask. The flask is allowed to stir at ambient temperature. After 1 week, the reaction mixture is diluted with iPrOH (20mL) and filtered through a pad of Celite. The filtrate is transferred to a round bottom flask and evaporated under reduced pressure. The residue is reconstituted with iPrOH (10mL) and toluene (10mL). The solvent is removed under reduced pressure. The reconstitution and evaporation steps are repeated. Pumping to

constant weight yields amorphous white solid (0.40 g). This material is dissolved in DCM (5mL). This solution is applied to an ISCO Companion that is fitted with a 12g column (silica). The column is eluted with 5% ACN/DCM for 5 column volumes followed by a linear gradient to 90 % ACN/DCM over 10 Column Volumes. 14mL fractions of UV active eluent are collected. Fractions 6-9 are combined and evaporated by pumping to constant weight give white solid (0.1g, 12%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.21 (d, 6H), 3.23-3.58 (m, 4H), 5.33 (septet, 1H), 7.13 (dd, 1H), 7.20-7.26 (m, 4H), 8.17 (dd, 1H), 8.29 (dd, 1H), 8.77 (s, 1H) 13.77 (bs, 1H).
LC/MS (ES+) m/z = 341.10.

Example 354



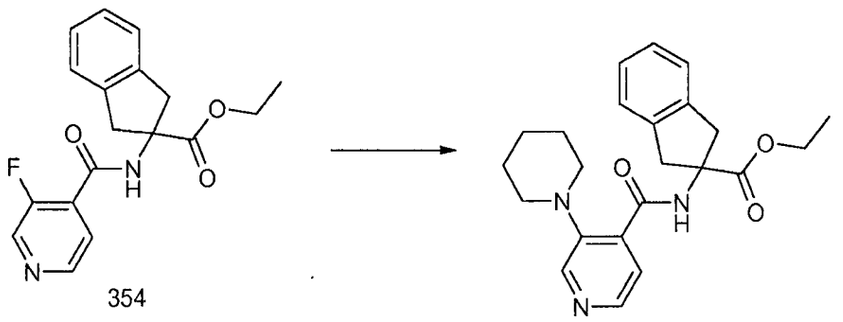
354

2-[(2-Fluoro-pyridine-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (354)

A 40mL reaction vial which contains a stirring bar is charged with 3-fluoroisinicotinic acid (825mg, 5.85mmol) and dry DCM (15mL). Stirring is initiated. After 2min, the HTBU (2.22g, 5.85mmol) is added. After 5min, 2-amino-indane-2-carboxylic acid ethyl ester (1.2g, 5.25mmol) is added followed by DIPEA (2.55mL, 14.62mmol). The reaction is allowed to stir for 7 days. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (75mL). This is washed consecutively with brine (25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 3.93g of light yellow solid. This material is dissolved in 15mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 5 % EtOAc in heptanes over 4 column volumes followed by a linear gradient to 65% EtOAc in heptanes over 10 column volumes. 14mL fractions of UV

active eluent are collected. Fractions 4 through 9 are combined and evaporated in vacuo. This yields white solid (1.5g, 94%).

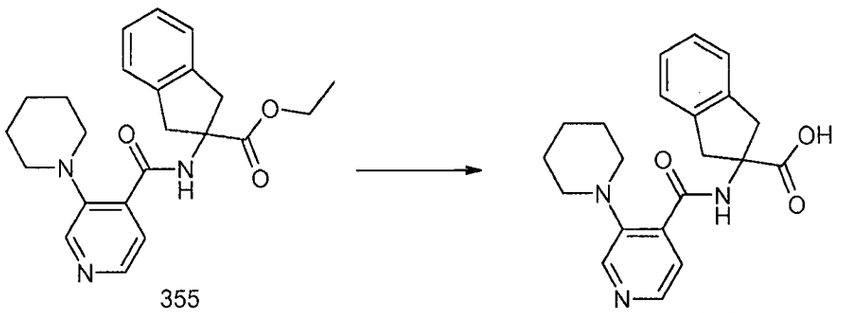
Example 355



2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (355)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridiine-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (354, 500mg, 1.52mmol), 1,4-dioxane (1.5mL) and piperidine (1.51mL, 15.23mmol). A stirring bar is added. The reaction vial is crimped sealed. The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 150°C with a fixed hold time of 10min. Pre-stir time is set for 20sec. The reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constant weight gives 1.2g of yellow semi-solid. The residue is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions are collected. Fractions 42-50 are combined and evaporated by pumping to constant weight to give white solid (0.56g, 93%).

Example 356



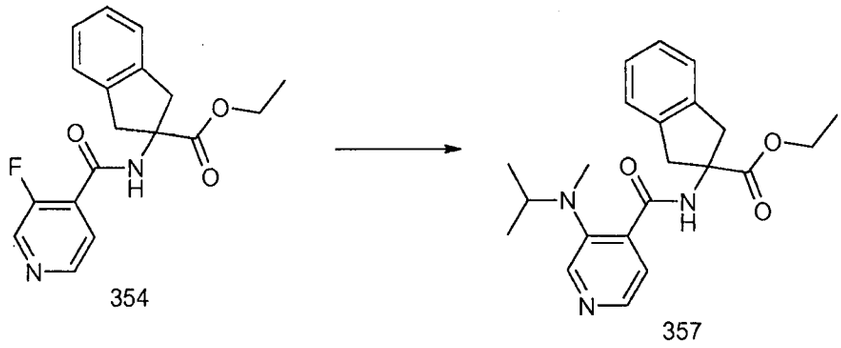
355 356

2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-4'-carbonyl)-amino]-indan-2-carboxylic acid (356)

A 100mL round bottom flask which contains 2-[(3,4,5,6-tetrahydro-2H-[1,3']bipyridinyl-4'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (355, 370mg, 0.94mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by the LiOH monohydrate (100mg, 2.38mmol). After 68h, tlc analysis (silica, 50% EtOAc/Heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 20h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.35g, 96%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.43 (m, 2H), 1.78 (m, 4H) 2.96 (m, 4H), 3.22-3.46 (m, 4H), 7.05-7.12 (m, 4H), 7.46 (d, 1H), 8.28 (d, 1H), 8.40 (s, 1H), 9.83 (bs, 1H).
LC/MS (ES+) m/z = 366.16.

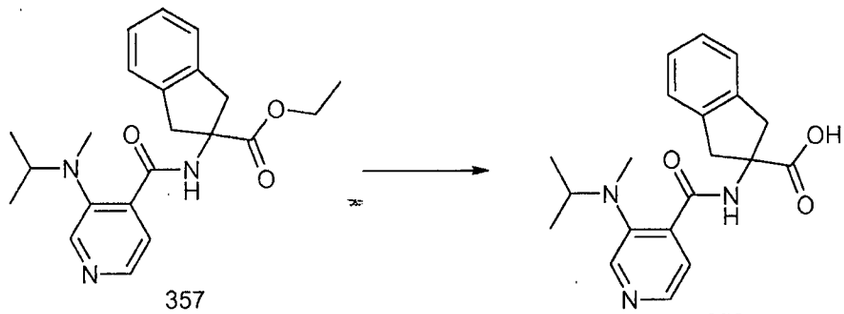
Example 357



2-{[3-(Isopropyl-methyl-amino)- pyridine-4-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (357)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridiine-4-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (354, 500mg, 1.52mmol), 1,4-dioxane (2mL) and piperidine 2mL, 29.5mmol). A stirring bar is added. The reaction vial is crimped sealed. The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 150°C with a fixed hold time of 10min. Pre-stir time is set for 20sec. After this sequence is completed, the reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constant weight gives 0.71g of brown syrup. This is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions of UV active eluent are collected. Fractions 5-11 are combined and evaporated by pumping to constant weight to give 0.29g of an amorphous white solid (0.29g, 51%).

Example 358



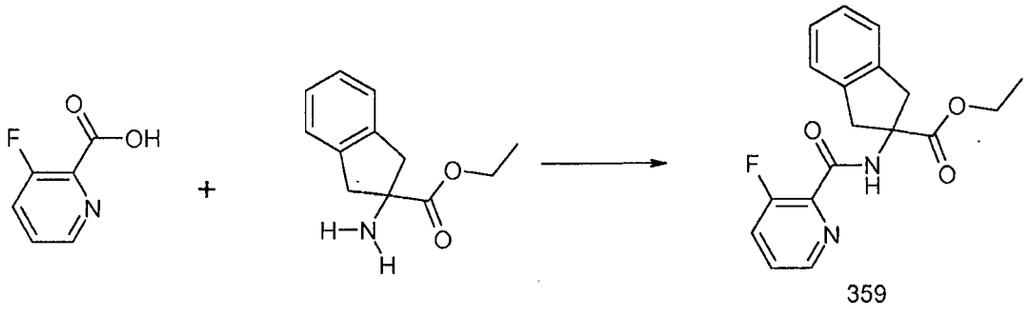
357 358

2-{[3-(Isopropyl-methyl-amino)- pyridine-4-carbonyl]-amino}-indan-2-carboxylic acid (358)

2-{[3-(Isopropyl-methyl-amino)-pyridine-4'-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester 357, 270mg, 0.71mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (75mg, 1.94mmol). After 4 days, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 3h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.22g, 88%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.03 (d, 6H), 2.69 (s, 3H), 3.77 (septet, 1H), 7.05-7.12 (m, 4H), 7.43 (d, 1H), 8.21 (d, 1H), 8.39 (s, 1H).
LC/MS (ES+) m/z = 354.19.

Example 359

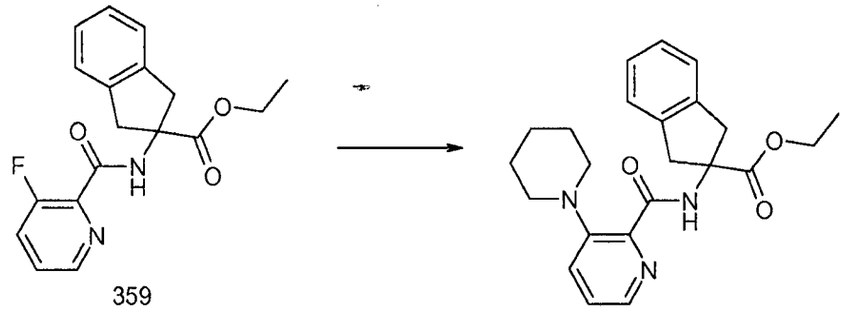


359

2-[(3-Fluoro-pyridine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (359)

A 40mL reaction vial which contains a stirring bar is charged with 3-Fluooropyridine-2-carboxylic acid (997mg, 7.07mmol) and dry DCM (15mL). Stirring is initiated. After 2min, the HTBU (2.7g, 7.07mmol) is added. After 5min, 2-Amino-indan-2-carboxylic acid ethyl ester (1.45g, 7.07mmol) is added followed by DIPEA (2.50mL, 14.5mmol). The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 5% iPrOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are transferred to a separatory funnel and diluted with EtOAc (50mL). This is washed consecutively with water (3%, 25mL), saturated aqueous NaHCO3 (2 X 25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated in vacuo to provide 4.15g of light orange solid. This material is dissolved in 20mL of DCM. This material is purified utilizing an ISCO Companion with an 80g cartridge of silica. The gradient is 5 % EtOAc in heptanes for 4 column volumes followed by a linear gradient to 60% EtOAc in heptanes over 10 column volumes. 14mL fractions of UV active elutant are collected. Fractions 6 through 14 are combined and evaporated *in vacuo*. This yields 2.04g white solid (2.04g, 88%).

Example 360

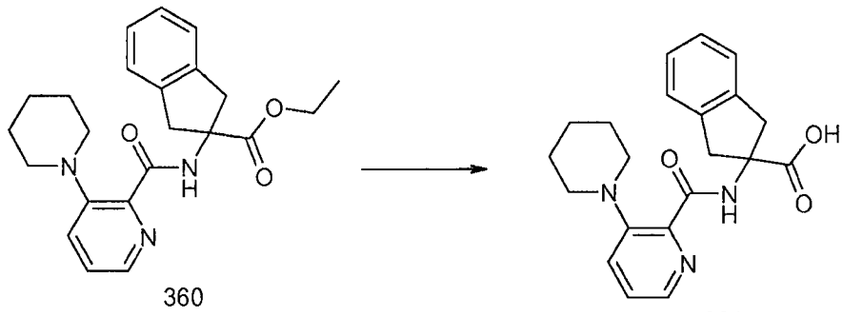


2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-2'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (360)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridiine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (359, 488mg, 1.49mmol), 1,4-dioxane (1.5mL) and piperidine (1.51mL, 15.23mmol). A stirring bar is added. The reaction vial is crimped sealed.

The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 150°C with a fixed hold time of 10min. Pre-stir time is set for 20sec. The reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constant weight gives 1.02g of off white solid. This is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions of UV Active eluent are collected. Fractions 2-10 are combined and evaporated by pumping to constant weight to give white solid (0.5g, 86%).

Example 361



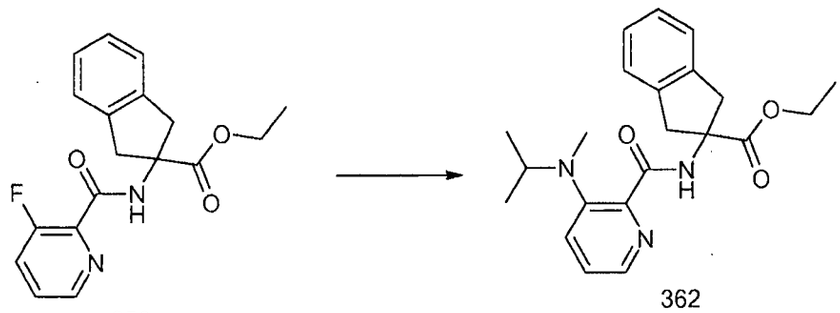
360 361

2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-2'-carbonyl)-amino]-indan-2-carboxylic acid (361)

A 100mL round bottom flask which contains 2-[(3,4,5,6-Tetrahydro-2H-[1,3']bipyridinyl-2'-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (360, 370mg, 0.94mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by LiOH monohydrate (100mg, 2.38mmol). After 38h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material has been completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 4h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides white solid (0.29, 84%).

^{1}H NMR 300MHz): δ 1.43 (m, 2HH), 1.78 (m, 4H), 2.96 (m, 4H), 3.22-3.46 (m, 4H), 7.05-7.12 (m, 4H), 7.46 (d, 1H), 8.28 (d, 1H), 8.40 (s, 1H), 9.83 (bs, 1H).
LC/MS (ES+) m/z = 366.16.

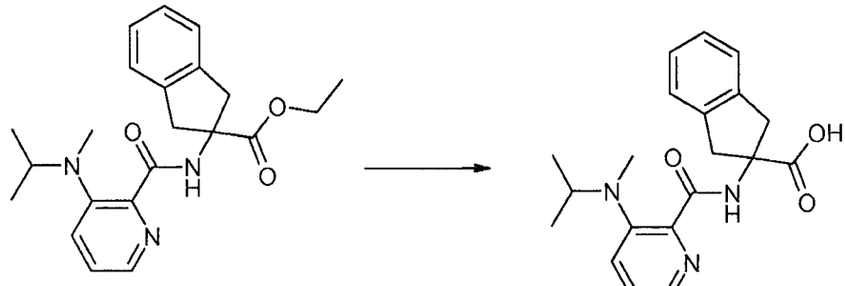
Example 362



2-{[[3-Isopropylmethyl-amino)-pyridine-2-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (362)

A 10mL microwave reaction vessel is charged with 2-[(3-fluoro-pyridiine-2-carbonyl)-amino]-indan-2-carboxylic acid ethyl ester (359, 492mg, 1.5mmol), 1,4-dioxane (1.5mL) and N-methylisopopyl amine (2mL, 19.25mmol).and DIPEA (2mL, 11.48mmol) are added. A stirring bar is added. The reaction vial is crimped sealed. The reaction vial is placed in a Smith Microwave reaction apparatus. The temperature is set for 155°C with a fixed hold time of 90min. Pre-stir time is set for 20sec. The reaction vial is removed from the apparatus. The stirring bar is extracted. The contents of the flask are transferred to a round bottom flask and the solvent removed under reduced pressure. Pumping to a constat weight gives 0.75g of brown syrup. This is dissolved in DCM (10mL) and applied to an ISCO Companion which had been fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 65 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 14mL fractions of UV Active eluent are collected. Fractions 7-15 are combined and evaporated by pumping to constant weight to give amorphous white solid (0.38g, 67%).

Example 363



362 363

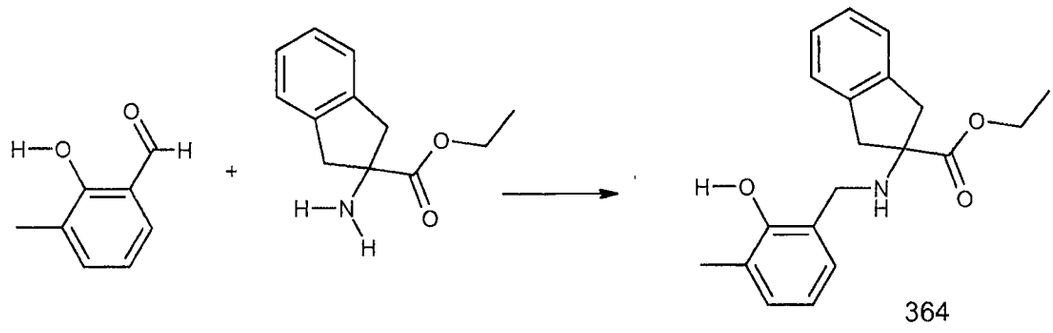
2-{[3-Isopropylmethyl-amino)-pyridine-2-carbonyl]-amino}-indan-2-carboxylic acid (363)

A 100mL round bottom flask which contains 2-{[[3-isopropylmethyl-amino)-pyridine-2-carbonyl]-amino}-indan-2-carboxylic acid ethyl ester (362, 370mg, 0.97mmol) is charged with 1,4-dioxane (4mL) and MeOH (4mL). A stirring bar is added and stirring is initiated. After dissolution, water (2mL) is added followed by LiOH monohydrate (103mg, 2.46mmol). After 62h, tlc analysis (silica, 50% EtOAc/heptanes) indicates that the starting material has been completely consumed. Amberlyst highly acidic exchange resin (0.7 g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 4h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provides a white solid (0.33, 96%).

^{1}H NMR 300MHz): δ 1.04 (d, 6H), 2.39 (s, 3H), 3.18-3.53 (m, 4H), 3.64 (septet, 1H), 7.02-7.12 (m, 4H), 7.28 (dd, 1H), 7.36 (dd, 1H), 7.98 (dd, 1H), 8.84 (s, 1H).

LC/MS (ES+) m/z = 354.17.

Example 364

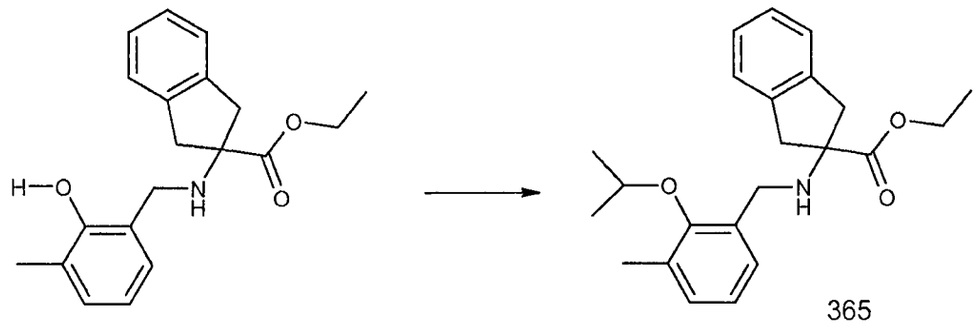


364

2-(2-Hydroxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (364)

A 10mL microwave reaction vessel is charged with 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.44mmol) and dry tetrahydrofuran (THF, 5mL). A stirring bar is added and stirring is initiated. After dissolution, 2-hydroxy-3-methyl-benzaldehyde (0.3mL, 2.43mmol) is added. Stirring is continued. Phenylsilane (0.61mL, 4.87mmol) and dibutyltin dichloride (53 μL, 244 μM) are added. The reaction vial is crimped sealed and placed in a Smith Microwave Apparatus. The pre-stir time is set to 10sec. Heating is set at 100°C for 10min. The contents of the reaction vial are transferred to a round bottom flask and evaporated by pumping to a constant weight yields 1.67g of light yellow solid. This material is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g Cartridge (silica). The column is eluted with 5 % EtOAc/heptanes for 3 column volumes followed by a linear gradient to 50 % EtOAc/heptanes over 10 column volumes and then 90 % EtOAc/heptanes for 2 column volumes. 14mL fractions of UV active eluent are collected. Fractions 5 to 8 are combined and evaporated by pumping to constant weight to give 0.59g of white solid material (0.59g, 74%).

Example 365



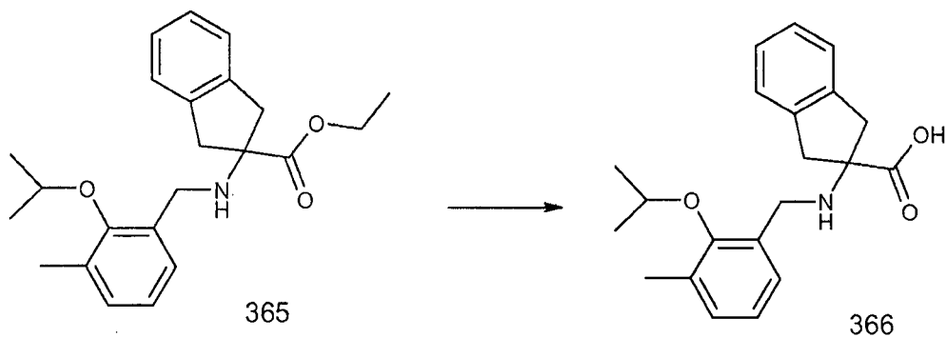
364 365

2-(2-Isopropoxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (365)

A 100mL round bottom flask containing the 2-(2-hydroxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (364, 1.01g, 3.10mmol) is charged with dry tetrahydrofuran (THF, 10mL). A stirring bar is added and stirring is initiated. After dissolution, iPrOH ([67-63-0], 0.47mL, 6.21mmol) and triphenylphosphine ([603-35-0], 1.63g, 6.21mmol) are added in turn. After dissolution of the triphenylphosphine, diisopropylazodicarboxylate (1.20mL, 6.21mmol) is added. The reaction flask is capped and allowed to stir at ambient temperature overnight. After 24h, tlc analysis (silica, 1:2 EtOAc/Heptanes) indicates that the starting material is completely consumed and converted to a higher moving spot as visualized by UV. The stirring bar is removed from the reaction flask and the solvent removed under reduced pressure. Pumping to constant weight gives 2.06g of viscous yellow oil. This is dissolved in DCM (10mL) and applied to an ISCO Companion which had been fitted with a 40g column (silica). The column is eluted with EtOAc/heptanes (5%) for 4 column volumes followed by a linear gradient to 60 % EtOAc/heptanes over 10 column volumes and then 90% EtOAc/heptanes for 2 column volumes. 17mL fractions of UV Active eluent are collected. Fractions 5-14 are combined and evaporated by pumping to constant weight to give viscous residue (0.42g, 37%).

^{1}H NMR 300MHz): δ 1.18 (d, 6H), 1.22 (t, 3H), 2.18 (s, 3H), 2.98-3.41 (m, 4H), 3.61 (d, 2H), 4.16 (q, 1H), 6.90 (dd, 1H), 7.04 (dd, 1H), 7.11-7.20 (m, 4H)
LC/MS (ES+) m/z = 368.24.

Example 366



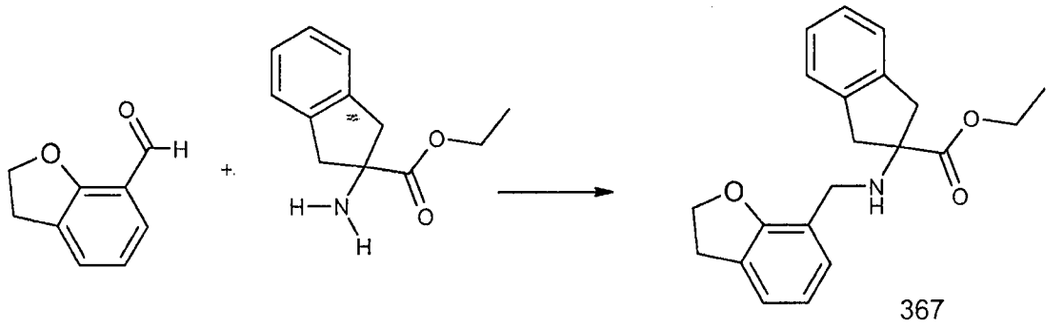
2-(2-Isopropoxy-3-methyl-benzylamino)-indan-2-carboxylic acid (366)

A 100mL round bottom flask containing 2-(2-isopropoxy-3-methyl-benzylamino)-indan-2-carboxylic acid ethyl ester (365, 360mg, 0.98mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (104mg, 2.47mmol). After 39h, tlc analysis (silica, 50% EtOAc/Heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 15 days, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provided white solid (0.24g, 72%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.12 (d, 6H), 2.17 (s, 3H), 2.77-3.68 (m, 6H), 4.16 (septet, 1H), 6.84 (dd, 1H), 6.97-7.22 (m, 6H).

LC/MS (ES+) m/z = 340.20.

Example 367



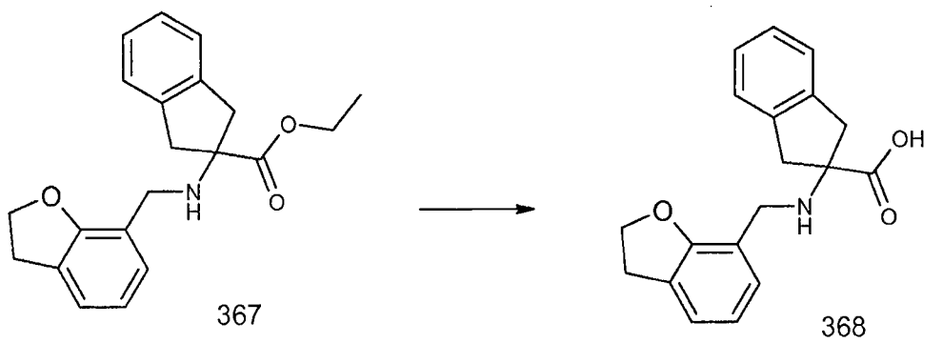
367

2-[(2,3-Dihydro-benzofuran-7-ylmethyl)-amino]-indan-2-carboxylic acid ethyl ester (367)

A 10mL microwave reaction vessel is charged with 2-amino-indan-2-carboxylic acid ethyl ester (500mg, 2.44mmol) and dry tetrahydrofuran (THF, 5mL). A stirring bar is added and stirring is initiated. After dissolution, 2,3-dihydro-1-benzofuran-7carbaldehyde (361mg, 2.43mmol) is added. Stirring is continued. Phenylsilane ([694-18-1], 0.61mL, 4.87mmol) and dibutyltin dichloride (53 μL, 244 μM) are added. The reaction vial is crimped sealed and placed in a Smith Microwave Apparatus. The pre-stir time is set to 10sec. Heating is set at

100°C for 10min. The contents of the reaction vial are transferred to a round bottom flask and evaporated by pumping to a constant weight yields 1.56g of light yellow oil. This material is dissolved in DCM (10mL) and applied to an ISCO Companion that is fitted with a 40g Cartridge (silica). The column is eluted with 5 % EtOAc/heptanes for 3 column volumes followed by a linear gradient to 50 % EtOAc/heptanes over 10 column volumes and then 90 % EtOAc/heptanes for 2 column volumes. 14mL fractions of UV active eluent are collected. Fractions 7 to 11 are combined and evaporated by pumping to constant weight yields 0.59g of white solid material (0.52g, 63%).

Example 368



2-[(2,3-Dihydro-benzofuran-7-ylmethyl)-amino]-indan-2-carboxylic acid (368)

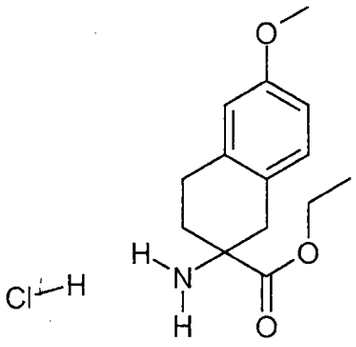
A 100mL round bottom flask containing 2-[(2,3-Dihydro-benzofuran-7-ylmethyl)-amino]-indan-2-carboxylic acid ethyl ester (367, 350mg, 1.037mmol) is charged with 1,4-dioxane (3mL) and MeOH (3mL). A stirring bar is added and stirring is initiated. After dissolution, water (1.5mL) is added followed by the LiOH monohydrate (110mg, 2.52mmol). After 16h, tlc analysis (silica, 50% EtOAc/Heptanes) indicates that the starting material is completely consumed. Amberlyst highly acidic exchange resin (0.5g) is added to the reaction vial. The reaction is capped and allowed to stir at ambient temperature. After 6h, the contents of the flask are filtered through a pad of Celite. The solvent is removed from the filtrate. The residue is reconstituted with iPrOH/toluene (20 + 20mL) and the solvent is removed. This process is repeated 1 time. Pumping to constant weight provided white solid (0.31g, 99%).

^{1}H NMR (DMSO-d6, 300MHz): δ2.77-3.58 (m, 6H), 3.11 (t, 2H), 4.45 (t, 2H), 6.70 (dd, 1H), 7.02-7.11 (m, 6H).

LC/MS (ES+) m/z = 310.14.

2-Amino-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl esters 369, 370, 371, 372 and 373 are synthesized according to the method of Michael Cox in Eur. Pat. Appl. EP 82-304382.

Example 369

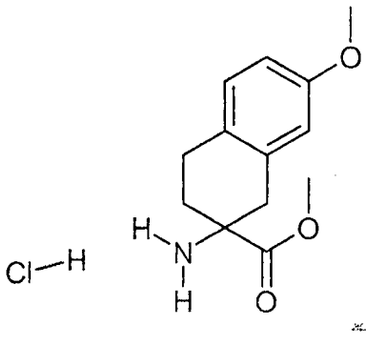


369

2-Amino-6-methoxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl ester hydrochloride salt (369)

LC/MS (ES+) m/z = 250.18.

Example 370



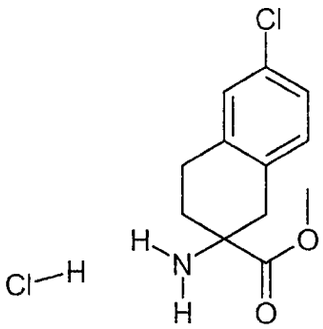
370

Example 370

2-Amino-7-methoxy-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester; hydrochloride (370)

LC/MS (ES+) m/z = 336.16.

Example 371

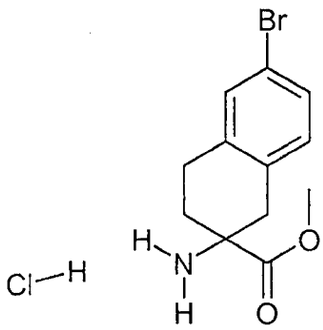


371

2-Amino-6-chloro-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester hydrochloride salt (371)

LC/MS (ES+) m/z = 340.11.

Example 372

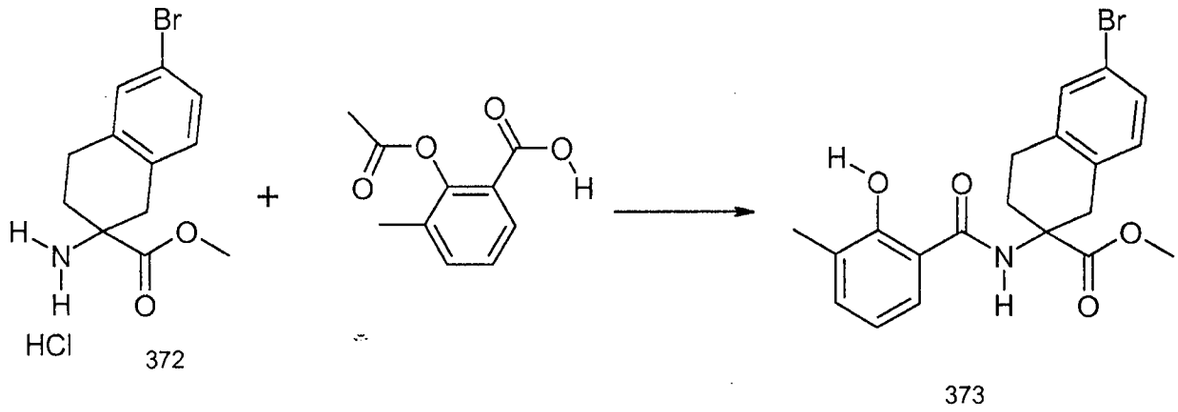


372

2-Amino-6-bromo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester hydrochloride salt (372)

LC/MS (ES+) m/z = 340.11.

Example 373

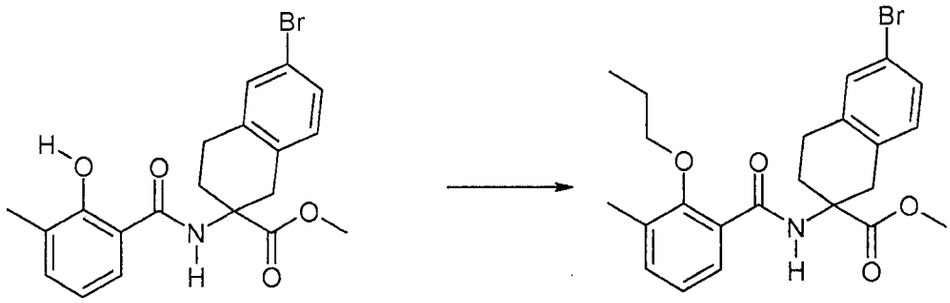


372 373

2-(2-Hydroxy-3-methyl-benzoyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (373)

A 40mL vial which contains a stirring bar is charged with 2-acetoxyl-3-methyl-benzoic acid ([2386-93-4], 1.69g, 8.7mmol) and dry DCM (10mL). Stirring is initiated. After dissolution is complete, The HTBU (3.29g, 8.7mmol) is added. After 5min, the 2-amino-6-bromo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic Acid hydrochloride Salt (372, 1.25g, 3.9mmol is added followed by DIPEA (3.4mL, 19.5mmol). An additional alliquot of dry DCM (4mL) is added. The reaction is allowed to stir for 36h. Analysis by tlc of the reaction mixture (silica, 50% EtOAc/heptanes) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (100mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous $NaHCO_3$ (50mL) and brine (50mL), dried over Na_2SO_4, filtered and evaporated *in vacuo* to provide 5.2g of thick brownish gum. This material is purified utilizing an ISCO Companion with a 120g cartridge of silica. The gradient is 2 % EtOAc in heptanes for 4 column volumes followed by a linear gradient to 30% EtOAc over 10 column volumes then to 100% EtOAc over 12 column volumes. 170mL fractions of UV active eluent are collected. Fractions 13 through 23 are combined and evaporated *in vacuo*. This yields a foamy material (0.42g, 26%).

Example 374

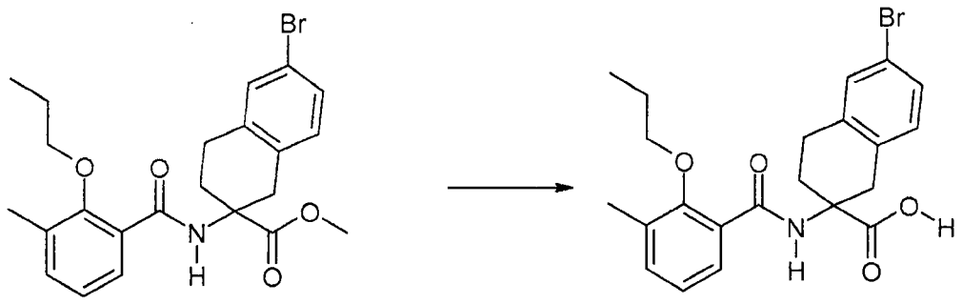


373 374

2-(2-Propoxy-3-methyl-benzoyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl ester (374)

A 100mL round botton flask which contains 6-bromo-(2-hydroxoxy-3-methyl-benzoylamino)-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid methyl ester (373, 0.39g, 0.932mmol) and a stirring bar is charged with dry DMF (10mL). Stirring is initiated. K_2SO_4 (0.258g, 1.86mmol), KI (1mg, 6 μM), and 1-bromopropane (0.2mL, 2.24mmol) are added in turn. The reaction flask is immersed in an oil bath and fitted with a reflux condenser. The oil bath is heated to 79°C. The reaction is stirred for 2h at this temperature then the oil bath is turned off. After 16h at ambient temperature, heating is reinitiated at 53°C for an additional hour. Analysis by ttlc (silica, 1:1 EtOAc:Heptanes), indicates consumption of starting material and appearance of a spot with a slightly lower R_f. The reaction is again allowed to cool to ambient temperature and filtered through a bed of Celite. The resulting solution is diluted with EtOAc (60mL) and washed repeatedly with brine (4 x 40mL), and then dried over $MgSO_4$, filtered and evaporated by pumping to a constant weight yields light yellow oil (0.42g, 98%).

Example 375



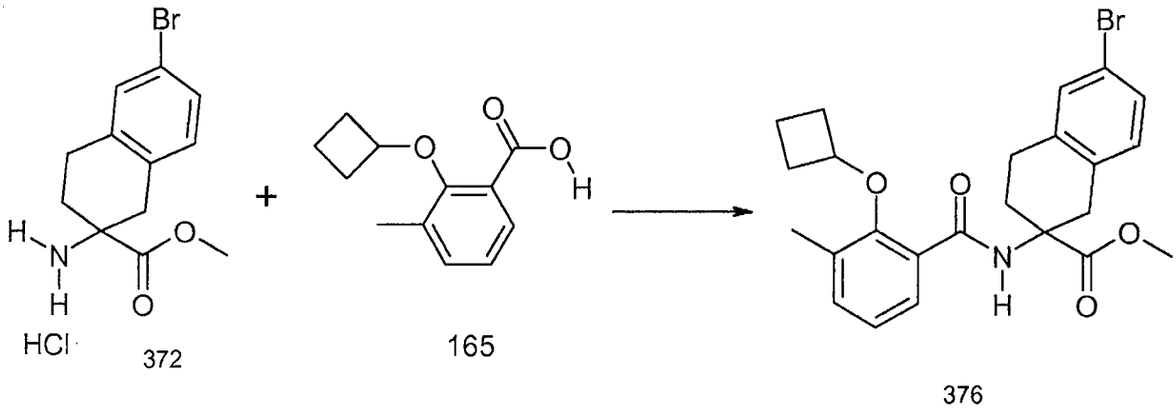
374 375

2-(2-Propoxy-3-methyl-benzoyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (375)

50mL flask containing the 6-bromo-2-(2-propoxy-3-methyl-benzoylamino)-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl ester (374, 0.34g, 0.74mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (77mg, 1.44mmol). After 16hours, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~12mL). The contents of the flask are poured into a separatory funnel that contains EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.30g, 91%).

^{1}H NMR (300 MHz, DMSO-d6): δ 0.82 (t, 3H), 1.43 (m, 1H), 1.96-2.08 (m, 1 H), 2.19 (s, 3 H), 2.38-2.91 (m, 1 H), 2.73-2.91 (m, 2 H), 3.02-3.38 (m, 5 H), 3.58-3.64 (m, 3 H), 7.03 – 7.09 (m, 2 H), 7.27 – 7.36 (m, 3 H), 8.36 (s, 1H), 12.56 (bs, 1H).
LC/MS m/z = 448.10.

Example 376

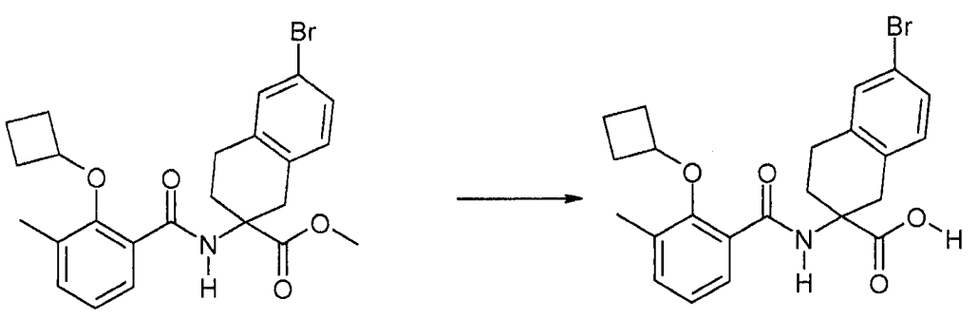


2-(2-cylobutoxy-3-methyl-benzoylamino)-6-bromo-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (376)

A 40mL vial containing a stirring bar and the 2-cyclobutoxy-3-methylbenzoiic acid (165, 447mg, 2.17mmol) is charged with dry DCM (6.5mL). Stirring is initiated. HTBU (824mg,

2.17mmol) is added. 2-Amino-6-bromo-1,2,3,4-tertrahydonaphtahalene-2-carboxylic acid methyl ester; hydrochloride salt (372, 590mg, 2.17mmol) followed by the DIPEA (1.1mL, 6.35mmol) are added. The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (1N, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.18g of off-white solid. The material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with ramp of 1 column volume. 25mL fractions are collected. Fractions 9 through 15 are combined and evaporated *in vacuo* by pumping to a constant weight to give amorphous white solid (0.81g, 79%).

Example 377



376 377

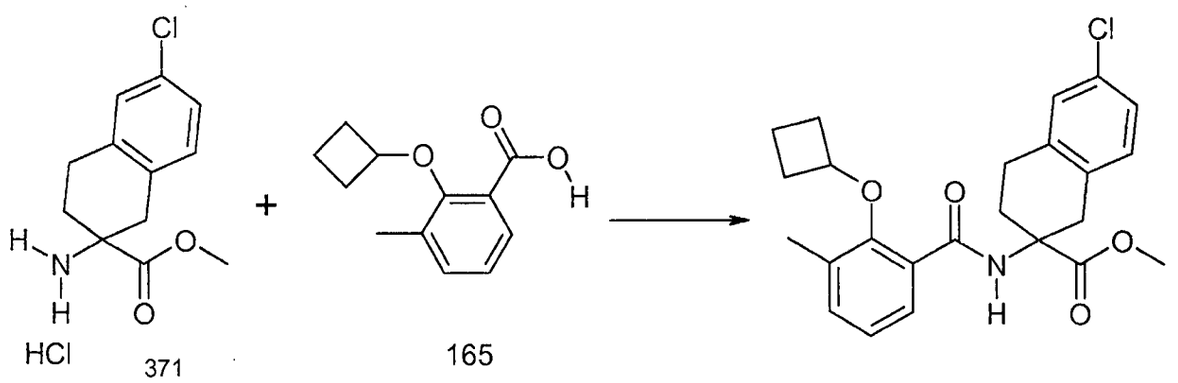
2-(2-cylobutoxy-3-methyl-benzoylamino)-6-bromo-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (377)

A 50mL flask containing the 2-(2-cylobutoxy-3-methyl-benzoylamino)-6-bromo-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (376, 0.44g, 0.93mmol) is charged with 1,4-dioxane (9mL) and MeOH (9mL). A stirring bar is added and stirring is initiated. After dissolution, water (4.5mL) is added followed by the LiOH monohydrate (173mg, 4.12mmol). After 64h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material is completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The

aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.40g, 98 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.17-1.34 (m, 1H), 1.39-1.57 (m, 1H), 1.78-2.16 (m, 4 H), 2.21 (s, 3 H), 2.37-2.42- (m, 1 H), 2.74-2.98 (m, 2 H), 3.15-3.27 (m, 3 H), 4.34 (m, 1 H), 7.01 – 7.11 (m, 2 H), 7.25 – 7.35 (m, 3 H), 8.34 (s, 1H), 12.53 (bs, 1H).
LC/MS m/z = 460.05

Example 378

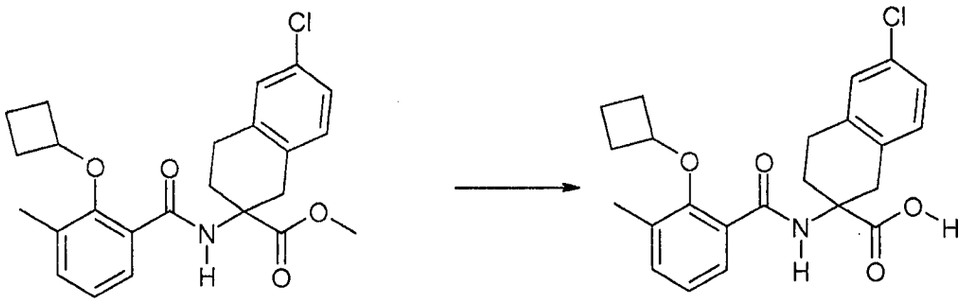


2-(2-cylobutoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (375)

A 40mL vial containing a stirring bar and the 2-cyclobutoxy-3-methylbenzoiic acid (165, 447mg, 2.17mmol) is charged with dry DCM (6.5mL). Stirring is initiated. HTBU (824mg, 2.17mmol) is added. 2-Amino-6-chloro-1,2,3,4-tertrahydonaphtahalene-2-carboxylic acid methyl ester; hydrochloride salt (371, 590mg, 2.17mmol) followed by the DIPEA (1.1mL, 6.35mmol) are added. The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (1 N, 25mL), saturated auqueous $NaHCO_3$ (25mL) and brine (25mL), and then dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide 1.18g of off-white solid. The material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 3 column volumes followed by a linear gradient

to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with ramp of 1 column volume. 25mL fractions of UV active eluent are collected. Fractions 2 through 11 are combined and evaporated *in vacuo* by pumping to a constant weight to give amorphous white solid (0.65g, 70%).

Example 379



378 379

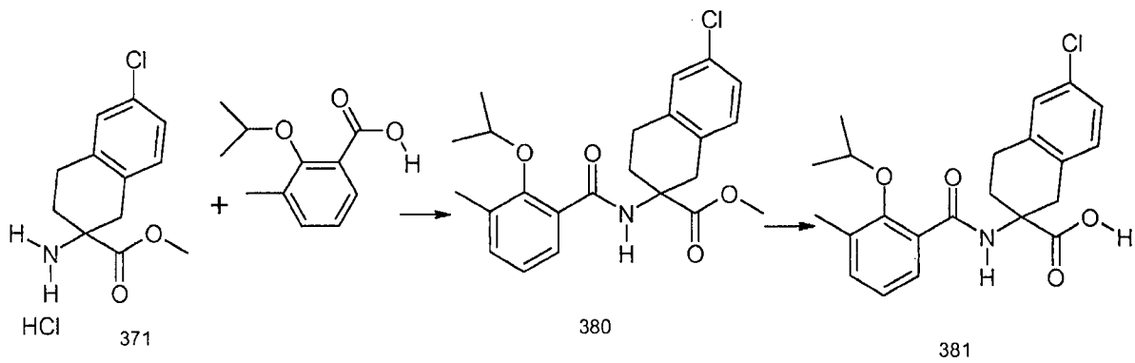
2-(2-cylobutoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (379)

A 50mL flask containing the 2-(2-cylobutoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (378, 0.42g, 0.98mmolg) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (103mg, 2.45mmol). After 260h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material has been completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.38g, 93 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.08-1.17 (m, 1H), 1.21-1.36 (m, 1H), 1.78-2.13 (m, 4 H), 2.21 (s, 3 H), 2.37-2.43- (m, 1 H), 2.77-2.98 (m, 2 H), 3.17-3.37 (m, 3 H), 4.34 (m, 1 H), 7.02 (dd, 1H), 7.10 – 7.35 (m, 5 H), 8.35 (s, 1H), 12.57 (bs, 1H).

LC/MS m/z = 414.15

Examples 380 and 381



2-(2-Isopropoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (380)

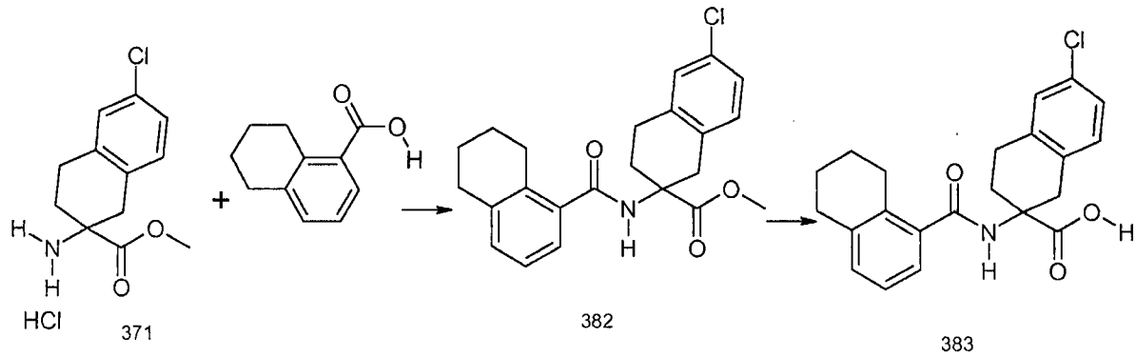
2-(2-Isopropoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (381)

2-(2-Isopropoxy-3-methyl-benzoylamino)-6-chloro-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (381) is synthesized according to the procedure for product 379 above excepting that 2-isopropoxy-3-methylbenzoiic acid 2-cyclobutoxy-3-methylbenzoic acid is substituted for 2-cyclobutoxy-3-methylbenzoiic acid in the amide bond formation step. Yield = 94% for step one. Step 2 yields white solid material (0.43g, 81 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 0.98 (d, 3H), 1.03 (d, 3H), 1.97-2.07 (m, 1 H), 2.21 (s, 3 H), 2.38-2.42- (m, 1 H), 2.76-2.93 (m, 2 H), 3.08-3.41 (m, 3 H), 4.19 (m, 1 H), 7.03 (dd, 1H), 7.11 – 7.20 (m, 3 H), 7.27 – 7.35 (m, 2 H), 8.35 (s, 1H), 12.52 (bs, 1H).

LC/MS m/z = 414.15

Examples 382 and 383

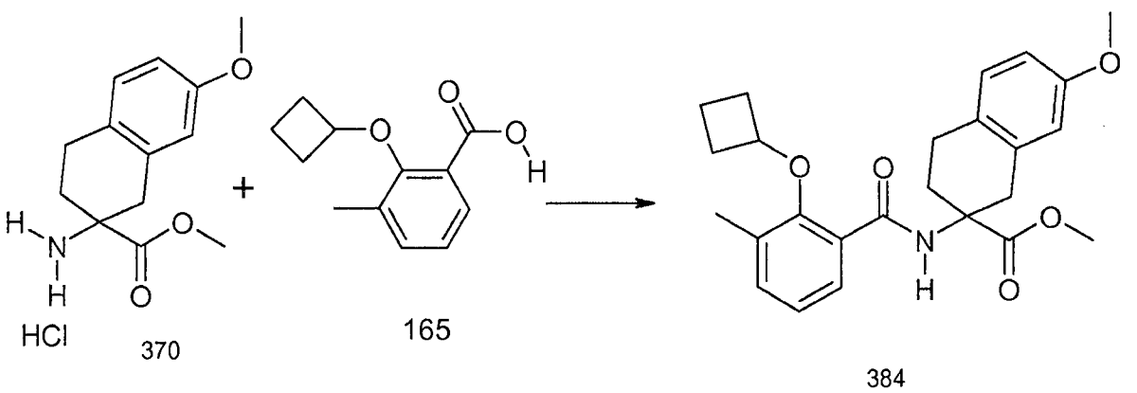


6-Chloro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-1,2,3,4-tetrahydro-naphthalene-2-carboylic acid (383)

6-Chloro-2-[(5,6,7,8-tetrahydronaphthalene-1-carbonyl)-amino]-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (383) is synthesized according to the procedure for product 379 above excepting that 5,6,7,8-tertrahydro-1-naphthalene carboxylic acid is substituted for 2-cyclobutoxy-3-methylbenzoic acid in the amide bond formation step. Yield = 83 % for step one. Step 2 yields a white solid material (0.42g, 99 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.56-1.78 (m, 4 H), 1.88-2.08 (m, 1 H), 2.33-2.41- (m, 1 H), 2.48-3.07 (m, 8 H), 6.92 (dd, 1H), 7.03 – 7.18 (m, 5 H), 8.72 (s, 1H), 12.49 (bs, 1H). LC/MS m/z = 384.11

Example 384

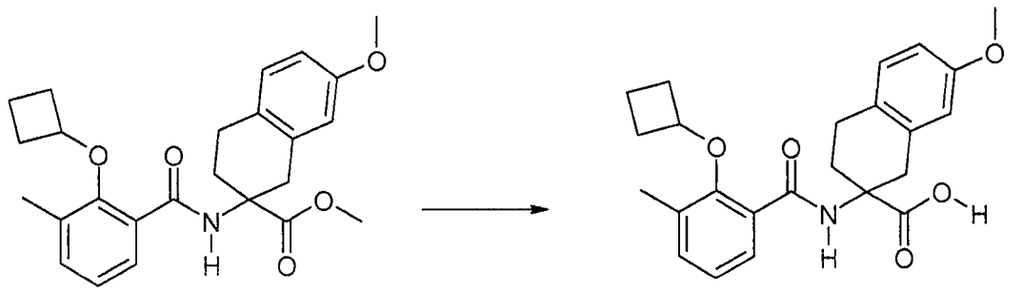


6-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid methyl ester (384)

A 40mL vial containing a stirring bar and the 2-cyclobutoxy-3-methylbenzoic acid (165, 447mg, 2.17mmol) is charged with dry DCM (6.5mL). Stirring is initiated. HTBU (824mg, 2.17mmol) is added. 2-Amino-7-methoxy-1,2,3,4-tertrahydonaphtahalene-2-carboxylic acid methyl ester hydrochloride salt (370, 590mg, 2.17mmol) followed by the DIPEA (1.1mL, 6.35mmol) are added. The reaction is allowed to stir for 18h. Analysis by tlc of the reaction mixture (silica, 10% MeOH/DCM) indicates complete consumption of the starting amine. The contents of the reaction flask are diluted with EtOAc (50mL) and transferred to a separatory funnel. This is washed consecutively with dilute aqueous HCl (1N, 25mL), saturated aqueous $NaHCO_3$ (25mL) and brine (25mL), dried over $MgSO_4$, filtered and evaporated *in vacuo* to

provide 1.2g of off-white solid. The material is dissolved in 10mL of DCM. This material is purified utilizing an ISCO Companion with a 40g cartridge of silica. The gradient is 10 % EtOAC in heptanes over 3 column volumes followed by a linear gradient to 50% over 10 column volumes and then 90 % EtOAc for 2 column volumes with ramp of 1 column volume. 25mL fractions of UV active eluent are collected. Fractions 9 through 15 are combined and evaporated *in vacuo* by pumping to a constant weight to give amorphous white solid (0.86g, 83%).

Example 385



384 385

2-(2-cylobutoxy-3-methyl-benzoylamino)-6-methoxy-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid (385)

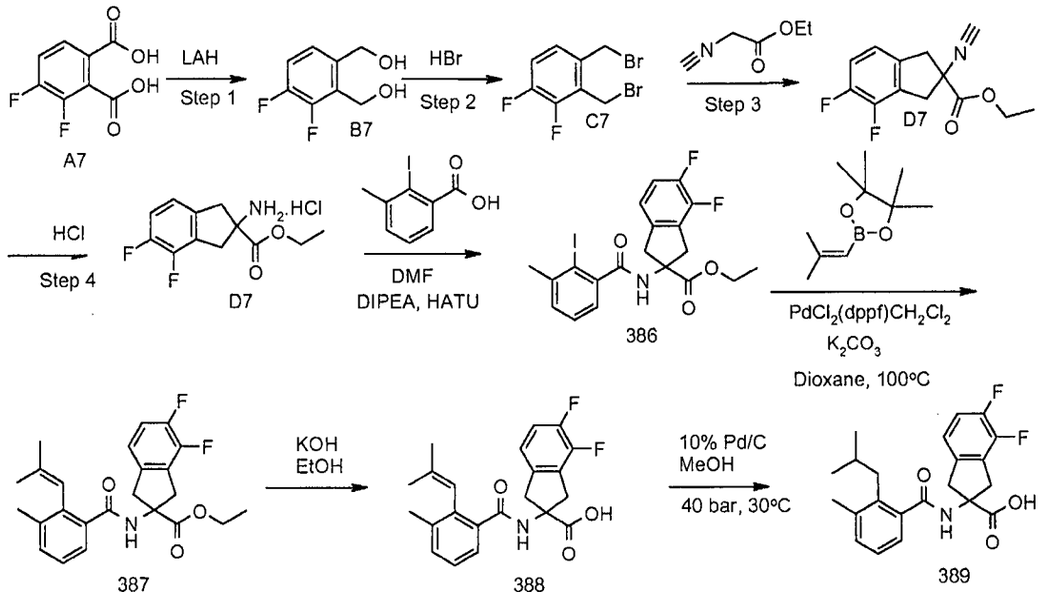
A 50mL flask containing the 2-(2-cylobutoxy-3-methyl-benzoylamino)-6-methoxy-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-2-carboxylic acid methyl ester (384, 0.45g, 1.06mmol) is charged with 1,4-dioxane (5mL) and MeOH (5mL). A stirring bar is added and stirring is initiated. After dissolution, water (2.5mL) is added followed by the LiOH monohydrate (111mg, 2.65mmol). After 37h, tlc analysis (silica, 5% i-PrOH/DCM) indicates that the starting material has been completely consumed. The pH of the reaction mixture is carefully adjusted to pH 2 by slowly adding dilute aqueous HCl (3%, ~10mL). The contents of the flask are poured into a separatory funnel containing EtOAc (30mL). The layers are separated. The aqueous layer is extracted with EtOAc (20mL). The combined organic extracts are washed with water (20mL) and brine (20mL), and then dried over $MgSO_4$, filtered and concentrated. Pumping to constant weight gives off-white solid (0.43g, 99 %).

^{1}H NMR (300 MHz, DMSO-d6): δ 1.18-1.33 (m, 1H), 1.41-1.57 (m, 1H), 1.79-2.11 (m, 4 H), 2.21 (s, 3 H), 2.37-2.43- (m, 1 H), 2.63-2.91 (m, 2 H), 3.07-3.37 (m, 3 H), 3.41 (s, 3H), 4.37

(m, 1 H), 6.69-6.72 (m, 2H), 7.00-7.05 (m, 2H), 7.26 – 7.35 (m, 2H), 8.31 (s, 1H), 12.49 (bs, 1H).

LC/MS m/z = 410.15

Examples 386 - 389



(2,3-Difluoro-6-hydroxymethyl-phenyl)-methanol (A7)

To a suspension of LAH (6.2g, 0.163mol) in dry THF (100 ml) is added a solution of compound 3,4-difluoro-phthalic acid (15g, 0.074mol) in THF (75mL), drop wise at 0^0C. The resulting mixture is refluxed for 3h. After 3h the reaction mixture is cooled and quenched with saturated Na_2SO_4 solution. Then the reaction mass is filtered through a pad of celite and the bed is washed thoroughly with MeOH. The combined filtrate is concentrated to yield a crude product that is purified by column chromatography (silica, 5% MeOH in DCM). Combination of appropriate fractions followed by removal of the solvent yields white solid (7g, 54.2%).

1,2-Bis-bromomethyl-3,4-difluoro-benzene (B7)

A suspension of (2,3-difluoro-6-hydroxymethyl-phenyl)-methanol (8g, 0.046mol) in 80mL aq. HBr (47%) is stirred at 80^0C for 3h. After complete consumption of starting material, the reaction mixture is cooled to RT and extracted with EtOAc. The combined organic layer is washed with brine, dried and concentrated to give brown solid (13g, 94.2%) that is used without further purification.

4,5-Difluoro-2-isocyano-indan-2-carboxylic acid ethyl ester: (C7)

A mixture of compound 1,2-bis-bromomethyl-3,4-difluoro-benzene (8g, 0.027mol), ethyl isocyanoacetate (3.01g, 0.0266mol), K_2CO_3 (22.07g, 0.159mol) and tetrabutylammonium hydrogen sulphate (5.45g, 0.016mol) in ACN (200 ml) is refluxed for overnight. After complete consumption of starting material the reaction mixture is cooled to RT and ACN is removed under reduced pressure. Water (300 mL) is added to the crude mass and then extracted with EtOAc (3x250 mL). The combined organic extracts are washed with water, dried and concentrated to give a crude product. The crude product is purified by column chromatography (silica, 3% EtOAc in hexane) and the the solvent removed to give a viscous liquid (1.6 g, 23.7%).

4,5-Difluoro-2-amin-indan-2-carboxylic acid ethyl ester hydrochloride salt (D7)

A stirred solution of 4,5-difluoro-2-isocyano-indan-2-carboxylic acid ethyl ester (6g, 0.0237mol) in EtOH (100mL) is immersed in an ice water bath and allowed to cool. After cooling, concentrated HCl (5 ml) is added. The reaction mixture is removed from the ice-water bath, allowed to come to ambient temperature and stirred at for 3h. Then the reaction mixture is concentrated, diluted with water and extracted with ether (2x50 mL). The organic layer is discarded and the aqueous layer is cooled and pH is adjusted to 9-10 using aq. ammonia solution. The resulting solution is extracted with EtOAc (3x100 mL). The combined extracts are washed with water, dried and concentrated to give a viscous mass (4.5 g, 78%). This crude mass is immediately cooled to 5^0C and acidified with methanolic HCl and concentrated to give 4,5-difluoro-2-amin-indan-2-carboxylic acid ethyl ester hydrochloride salt.

4,5-Difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (386):

To a solution of 2-iodo-3-methyl-benzoic acid (1.31g, 5mmol), 2-amino-4,5-difluoro-indan-2-carboxylic acid ethyl ester HCl salt (D7, 1.38g, 5mmol), HATU [O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF6, 3.8g, 10mmol) in anhydrous DMF (20mL) is added DIPEA (N, N-diisopropylethylamine, 3.3mL, 15mmol). The resulting solution is stirred at room temperature for two days. After the removal of DMF *in vacuo*, the residue obtained is dissolved in ethyl acetate (200mL) and washed with saturated $NaHCO_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

The obtained residue is purified by flash column chromatography (24g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (386) as white solid (1.93g, 79%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.15 (t, 3H), 1.20(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 7.13-7.30(m, 3H), 7.52(m, 2H)
LC/MS (ES+) m/z = 486.1

4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (387):

To a solution of 6-(4,5-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (386) (2.55g, 5.25mmol) and and 2-methyl-1-propenyl boronic acid pinacol ester (364mg, 10.5mmol) in dioxane (100mL) is added dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct (350mg, 8.2%mmol) and 2M aqueous solution of K_2CO_3 (7.87mL, 15.75mmol). The resulting reaction mixture is filled in with N_2, heated to 100°C and stirred continuously for 6h. Reaction mixture is filtered and concentrated *in vacuo*, and the resulting residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (387) as light brown solid (1.24g, 57%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.10 (t, 3H), 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), 7.13-7.30(m, 3H), 7.52(m, 2H)
LC/MS (ES+) m/z = 414.47

4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (388):

4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (387) (650mg, 1.57mmol) is dissolved in EtOH (50mL) and set to stir at RT. To this solution is added 5M KOH (4mL). The reaction mixture is stirred at RT overnight. After concentration *in vacuo*, the residue obtained is dissolved in water (20mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The solid precipitate is collected via filtration, dried under vacuum, and then purified on an HPLC. The desired product (388) is obtained as white solid (440.0mg, 73%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.08-7.36(m, 5H)

LC/MS (ES+) m/z = 386.3

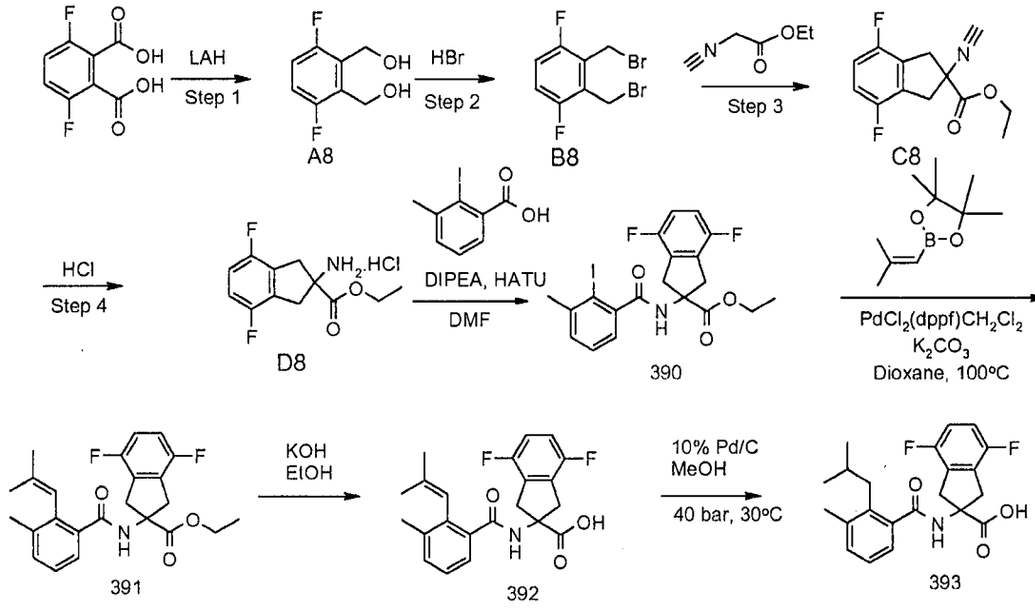
4,5-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (389)

A solution of 4,5-difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (388) (220mg, 0.57mmol) in methanol (40mL) is hydrogenated using 10% palladium/carbon catalyst at 40 bar and 30°C using the Thales nanotechnology H-Cube for 24 hours. The methanol is concentrated to dryness *in vacuo* to give the product (389) as white solid powder.

^{1}H NMR (DMSO-d6, 300MHz): δ 0.77(d, 6H), 1.74(m, 1H), 2.27(s, 3H), 2.62(d, 2H), 3.31(d, 2H), 3.48(d, 2H), 7.00-7.39(m, 5H)

LC/MS (ES+) m/z = 388.3

EXAMPLES 390-393



2-Amino-4,7-difluoro-indan-2-carboxylic acid ethyl ester HCl salt was prepared from

3,6-difluoro-phthalic acid as indicated by the scheme above regarding A7-D7 utilizing the same procedures as for the synthesis of 2-amino-4,5-difluoro-indan-2-carboxylic acid ethyl ester HCl salt.

4,7-Difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (390):

To a solution of 2-iodo-3-methyl-benzoic acid (1.31g, 5mmol), 2-amino-4,7-difluoro-indan-2-carboxylic acid ethyl ester HCl salt (1.38g, 5mmol), HATU [O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF6, 3.80g, 10mmol) in anhydrous DMF (20mL) is added DIPEA (N, N-diisopropylethylamine, 3.3mL, 15mmol). The resulting solution is stirred at RT for two days. After the removal of DMF *in vacuo*, the residue obtained is dissolved in EtOAc (200mL) and washed with saturated $NaHCO_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The obtained residue is purified by flash column chromatography (40g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (390) as white solid (1.83g, 75%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.15 (t, 3H), 1.20(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 7.13-7.30(m, 5H)
LC/MS (ES+) m/z = 486.1

4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (391):

To a solution of 4,7-difluoro-2-(2-iodo-3-methyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (390) (451mg, 1mmol) and 2-methyl-1-propenyl boronic acid pinacol ester (364mg, 2mmol) in dioxane (20mL) was added dichloro[1,1'-bis(diphenylphosphino)-ferrocene]palladium (II) dichloromethane adduct (65mg, 8.2%mmol) and 2M aqueous solution of K_2CO_3 (1.5mL, 3mmol). The resulting reaction mixture is filled in with N_2, heated to 100°C and stirred continuously for 4h. The reaction mixture is filtered and concentrated *in vacuo*, and the resulting residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (391) as light brown oil (150mg, 36%).

^{1}H NMR (DMSO-d6, 300MHz): δ 1.10 (t, 3H), 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), 7.13-7.30(m, 5H)

LC/MS (ES+) m/z = 414.47

4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (392):

4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (391) (133mg, 0.32mmol) is dissolved in EtOH (20mL) and set to stir at RT. To this solution was added 5M KOH (2ml). The reaction mixture was stirred at RT. After concentration *in vacuo*, the residue obtained is dissolved in water (20mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The aqueous phase is washed with 100mL EtOAc. The organic phases were collected, concentrated to dryness, and then the resulting residue is purified on an HPLC. The desired product (392) is obtained as white solid (38mg, 28%).

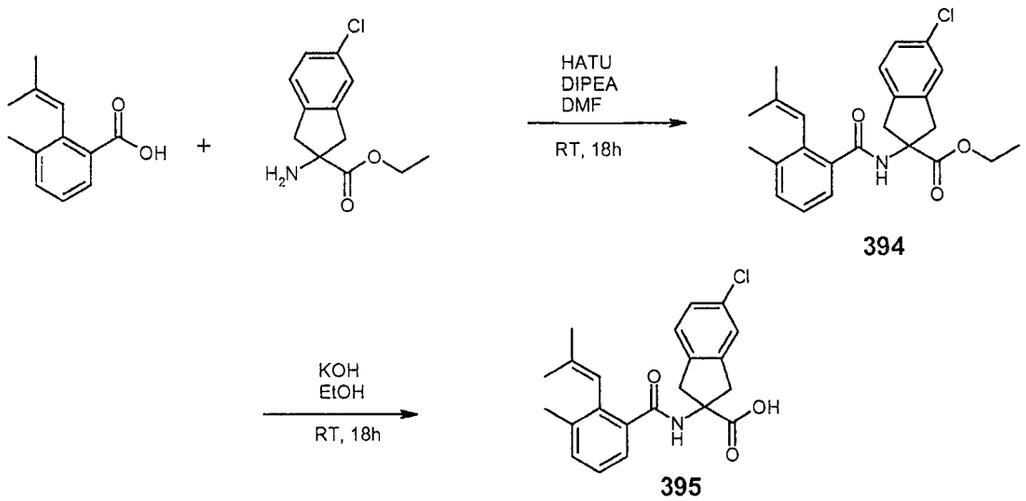
^{1}H NMR (DMSO-d6, 300MHz): δ 1.21(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.08-7.36(m, 5H)
LC/MS (ES+) m/z = 386.3

4,7-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid (393)

A solution of 4,7-difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (392) (82mg, 0.21mmol) in MeOH (40mL) is hydrogenated using 10% palladium/carbon catalyst at 40 bar and 30°C using the Thales nanotechnology H-Cube for 5h. The MeOH is concentrated to dryness *in vacuo* to give the product (393) as white solid powder.

^{1}H NMR (DMSO-d6, 300MHz): δ 0.76(d, 6H), 1.72(m, 1H), 2.28(s, 3H), 2.61(d, 2H), 3.42(d, 2H), 3.51(d, 2H), 6.93-7.30(m, 5H)
LC/MS (ES+) m/z = 388.3

EXAMPLES 394-395



5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (394):

To a solution of 3-methyl-2-(2-methyl-propenyl)-benzoic acid (95mg, 0.50mmol), 5-chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (120mg, 0.5mmol), HATU [O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium PF6, 380mg, 1mmol) in anhydrous DMF (10mL) is added DIPEA (N, N-diisopropylethylamine, 0.25mL, 1.5mmol). The resulting solution is stirred at RT for 18h. After the removal of DMF *in vacuo*, the resulting residue is dissolved in EtOAc (200mL) and washed with saturatedNaHCO$_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue is purified by flash column chromatography (40g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (394) as white solid (120mg, 58%).

^{1}H NMR (d-DMSO, 300MHz): δ 1.10 (t, 3H), 1.16(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), 7.13-7.30(m, 6H)
LC/MS (ES+) m/z = 411.93

5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid (395):

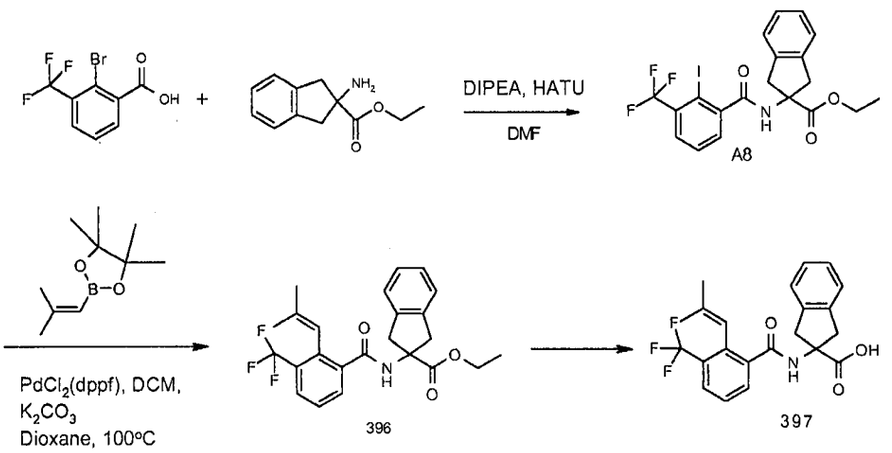
5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid ethyl ester (394) (120mg, 0.3mmol) is dissolved in EtOH (20mL) and set to stir at RT. To this solution is added 5M KOH (2mL). The reaction mixture is stirred at RT overnight. After

concentration *in vacuo*, the resulting residue is dissolved in water (20mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The aqueous phase is washed with 100mL EtOAc. The organic phases are collected, concentrated to dryness, and then the resulting residue is purified on an HPLC. The desired product (395) is obtained as white solid (73mg, 63%).

^{1}H NMR (d-DMSO, 300MHz): δ 1.21(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.08-7.36(m, 6H)

LC/MS (ES+) m/z = 383.88

EXAMPLES 394-395



2-(2-Iodo-3-trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (A8):

To a solution of 2-bromo-3-(trifluoromethyl) benzoic acid (5g, 18.59mmol), 2-amino-indan-2-carboxylic acid ethyl ester (3.82g, 18.59mmol), HATU (14.14g, 37.19mmol) in anhydrous DMF (75mL) is added DIPEA (6.15mL, 37.19mmol). The resulting solution is stirred at RT overnight. After the removal of DMF *in vacuo*, the resulting residue is dissolved in EtOAc (100mL) and washed with saturated $NaHCO_3$ (1x 100mL) and brine (2 x 100mL). The organic layer is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The obtained residue is purified by flash column chromatography (115g silica gel, gradient elution: 0%-50% ethyl acetate in heptane) to give a pure product (A8) as a light brown solid (4.9g, 58%).

^{1}H NMR (d-DMSO, 300MHz): 1.15 (t, 3H), 1.20(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), .12-7.28(m, 4H), 7.55(m, 2H), 7.75 (d, 1H)

LC/MS (ES+) m/z = 455.1

2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (396)

To a solution of 42-(2-Iodo-3-trifluoromethyl-benzoylamino)-indan-2-carboxylic acid ethyl ester (A8) (500mg, 1.10mmol) and 2-methyl-1-propenyl boronic acid pinacol ester (400mg, 2.20mmol) in dioxane (20mL) is added dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium (II) DCM adduct (71.8mg, 8.2%mmol) and 2M aqueous solution of K_2CO_3 (1.65mL, 3.30mmol). The resulting reaction mixture is filled in with N_2, heated to 100°C and stirred continuously overnight. Reaction mixture is filtered and concentrated *in vacuo*, and the resulting residue is purified by flash column chromatography (12g silica gel, gradient elution: 0%-50% EtOAc in heptane) to give a pure product (396) as light brown oil (100mg, 21%).

^{1}H NMR (d-DMSO, 300MHz): 1.10 (t, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 4.25 (m, 2H), 6.06 (s, 1H), .12-7.28(m, 4H), 7.55(m, 2H), 7.75 (d, 1H)
LC/MS (ES+) m/z = 431.27

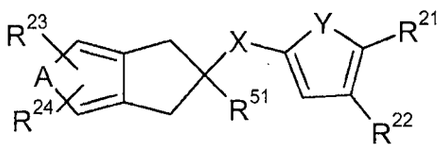
2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid (397):

2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid ethyl ester (2) (100mg, 0.32mmol) is dissolved in EtOH (20mL) and set to stir at RT. To this solution is added 5M KOH (2mL). The reaction mixture is heated to reflux and stirred for 1h. After concentration *in vacuo*, the resulting residue is dissolved in water (10mL) and washed with EtOAc (20mL). The phases are separated and the aqueous phase is acidified with concentrated HCl to pH 2. The aqueous phase is washed with 50mL ether (3X). Organic phases are collected, concentrated to dryness, then the resulting residue is purified on an HPLC. The desired product (397) is obtained as white solid (40.0mg, 43%).

^{1}H NMR (d-DMSO, 300MHz): 1.21(s, 3H), 1.66(s, 3H), 2.12(s, 3H), 3.24(d, 2H), 3.48(d, 2H), 6.06 (s, 1H), 7.12-7.28(m, 4H), 7.55(m, 2H), 7.75 (d, 1H)
LC/MS (ES+) m/z = 403.13

What is claimed is:

1. A compound of the formula Ia



wherein:

A is CH=CH or S;

R^{23} is hydrogen, halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S-, or nitro;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-S-, or nitro when A is S;

X is N(H)C=O, N(H)S(O)$_2$, C=ON(H), or S(O)$_2$N(H);

Y is N(R^{11}), S, O, C(R^{12})=C(R^{13}), N=C(R^{14}), or C(R^{15})=N, or fused optionally substituted 5-7 membered carbocyclyl;

R^{11} is hydrogen, (C_1-C_{10})-alkyl, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_1-C_{10})-alkyl-S(O)$_m$-, (C_1-C_{10})-alkylcarbonyl-, phenyl, amino, (C_1-C_{10})-alkylamino, or di((C_1-C_{10})-alkyl)amino;

R^{12} is hydrogen, halogen, (C_1-C_{10})-alkyl, (C_2-C_{10})-alkenyl, (C_3-C_6)-cycloalkyloxy, (C_3-C_{10})-cycloalkenyloxy, (C_3-C_6)-cycloalkyl, (C_3-C_{10})-cycloalkenyl, (C_3-C_6)-cycloalkyl[(C_1-C_4)-alkyl or (C_2-C_4)-alkenyl], (C_3-C_6)-cycloalkyl(C_1-C_4)-alkyloxy, hydroxy-(C_1-C_{10})-alkyl-, (C_1-C_{10})-alkyloxy, (C_2-C_{10})-alkenyloxy, (C_1-C_{10})-alkyl-S-, cyano, (C_1-C_{10})-alkylcarbonyl-, phenyl, or nitro;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

R^{14} is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro, provided that the total number of C, N, O and S atoms which is present in R^{14} does not exceed 4;

$R^{15}$is hydrogen, halogen, (C_1-C_{10})-alkyl, (C_2-C_{10})- alkenyl, (C_3-C_6)-cycloalkyl, (C_3-C_6)-cycloalkenyl, (C_3-C_6)-cycloalkyl[(C_1-C_4)-alkyl or (C_2-C_4)-alkenyl], hydroxy-(C_1-C_{10})-alkyl-, cyano, (C_1-C_{10})-alkylcarbonyl-, phenyl, amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]amino, [(C_1-C_{10})-alkyl or (C_2-C_{10})-alkenyl]((C_1-C_{10})-alkyl)amino or nitro;

R^{21} is hydrogen when Y is $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, and is hydrogen, halogen, (C_1-C_4)-alkyl, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{21} does not exceed 4;

R^{22} is hydrogen, halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$, $N=C(R^{14})$, or $C(R^{15})=N$, or is hydrogen, hydroxy-(C_1-C_3)-alkyl-, (C_1-C_3)-alkyloxy, (C_1-C_3)-alkyl-$S(O)_m$-, cyano, (C_1-C_2)-alkylcarbonyl-, amino, (C_1-C_3)-alkylamino, di((C_1-C_3)-alkyl)amino or nitro when Y is $N(R^{11})$, S, or O, provided that the total number of C, N, O and S atoms which is present in R^{22} does not exceed 4;

R^{51} is COOH or $CONH(R^{53})$;

R^{53} is R^{55}-SO_2- or tetrazolyl;

R^{55} is (C_1-C_4)-alkyl or phenyl optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_1-C_4)-alkyl, (C_1-C_4)-alkyloxy, (C_1-C_4)-alkyl-sulfonyl and cyano; and

m is 0, 1, or 2;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

2. The compound according to claim 1 wherein

R^{23} is hydrogen, halogen, (C_1-C_4)-alkyl, or (C_1-C_4)-alkyloxy;

R^{24} is hydrogen or halogen when A is CH=CH, or is hydrogen, halogen, or (C_1-C_4)-alkyl when A is S;

X is N(H)C=O, N(H)S(O)$_2$, or C=ON(H);

Y is C(R^{12})=C(R^{13}), or C(R^{15})=N, or fused optionally substituted 5-6 membered carbocyclyl;

R^{12} is (C_1-C_6)-alkyl, (C_3-C_6)-alkenyl, (C_4-C_6)-cycloalkyloxy, (C_5-C_6)-cycloalkyl, (C_5-C_6)-cycloalkenyl, (C_3)-cycloalkyl[(C_2)-alkyl or (C_2)-alkenyl], (C_3)-cycloalkyl(C_1)-alkyloxy, (C_3-C_4)-alkyloxy, (C_3)-alkenyloxy, (C_1-C_3)-alkyl-S-, or (C_3)-alkylcarbonyl-, phenyl;

R^{13} is hydrogen, halogen, or (C_1)-alkyl;

$R^{15}$is (C_1-C_6)-alkyl, (C_2-C_6)- alkenyl, or [(C_2-C_3)-alkyl or (C_3)-alkenyl]((C_1)-alkyl)amino;

R^{21} is hydrogen when Y is C(R^{12})=C(R^{13}), or C(R^{15})=N;

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$, or $C(R^{15})=N$;

R^{51} is COOH;

wherein all phenyl groups herein can independently of each other be optionally substituted by one or more identical or different substituents chosen from the group consisting of halogen, (C_{1-4})-alkyl, (C_{1-4})-alkyloxy, (C_{1-4})-alkylsulfonyl and cyano;

wherein all alkyl groups herein can independently of each other be optionally substituted by one or more fluorine atoms; or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

3. The compound according to claim 1 wherein

A is CH=CH.

4. The compound according to claim 1 wherein

R^{23} is hydrogen or halogen.

5. The compound according to claim 1 wherein

R^{24} is hydrogen or halogen when A is CH=CH;

6. The compound according to claim 1 wherein

X is N(H)C=O.

7. Thc compound according to claim 1 wherein

Y is $C(R^{12})=C(R^{13})$.

8. The compound according to claim 1 wherein

Y is $C(R^{15})=N$.

9. The compound according to claim 1 wherein

Y is fused optionally substituted 5-6 membered carbocyclyl.

10. The compound according to claim 1 wherein

R^{12} is (C_4-C_6)-alkyl.

11. The compound according to claim 1 wherein

R^{12} is (C_4)-alkenyl.

12. The compound according to claim 1 wherein

R^{12} is (C_4)-cycloalkyloxy.

13. The compound according to claim 1 wherein

R^{12} is (C_5-C_6)-cycloalkyl.

14. The compound according to claim 1 wherein

R^{12} is (C_5-C_6)-cycloalkenyl.

15. The compound according to claim 1 wherein

R^{12} is (C_3)-cycloalkyl[(C_2)-alkyl or (C_2)-alkenyl].

16. The compound according to claim 1 wherein

R^{12} is (C_3)-cycloalkyl(C_1)-alkyloxy.

17. The compound according to claim 1 wherein

R^{12} is $(C_3$-$C_4)$-alkyloxy.

18. The compound according to claim 1 wherein

R^{12} is (C_3)-alkenyloxy.

19. The compound according to claim 1 wherein

R^{12} is phenyl.

20. The compound according to claim 1 wherein

R^{13} is halogen, or (C_1)-alkyl.

21. The compound according to claim 1 wherein

R^{13} is (C_1)-alkyl wherein the alkyl is optionally substituted by 1-3 fluorine atoms.

.

22. The compound according to claim 1 wherein

R^{13} is (C_1)-alkyl.

.

23. The compound according to claim 1 wherein

R^{13} is (C_1)-alkyl that is substituted by 2-3 fluorine atoms.

24. The compound according to claim 1 wherein

R^{13} is halogen.

25. The compound according to claim 1 wherein

$R^{15}$is [(C_2-C_3)-alkyl or (C_3)-alkenyl]((C_1-C_{10})-alkyl)amino.

26. The compound according to claim 1 wherein

R^{15} is (C_2-C_3)-alkyl(C_1)-alkyl)amino.

27. The compound according to claim 1 wherein

R^{21} is hydrogen.

28. The compound according to claim 1 wherein

R^{22} is hydrogen or halogen, (C_1)-alkyl when Y is $C(R^{12})=C(R^{13})$.

29. The compound according to claim 1 wherein

R^{51} is COOH.

30. The compound according to claim 1 selected from:

2-(2-Allyloxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-Cyclopropylmethoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(2-sec-Butoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,

2-(3-Chloro-2-isopropoxy-benzoylamino)-indan-2-carboxylic acid

2-(2-Allyloxy-3-chloro-benzoylamino)-indan-2-carboxylic acid,

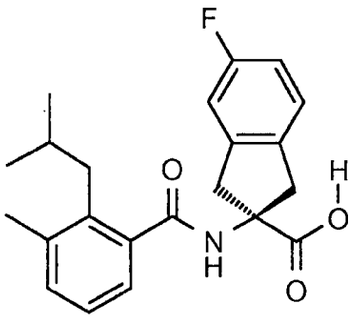
2-(3,5-Dichloro-2-cyclobutoxy-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-(3,5-Dichloro-2-isopropoxy-benzenesulfonylamino)-indan-2-carboxylic acid,
2-(2-Allyloxy-3,5-dichloro-benzenesulfonylamino)-indan-2-carboxylic acid,
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
1,3-Dimethyl-5-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,
5-Methoxy-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
2-[(5,6,7,8-Tetrahydro-naphthalene-1-carbonyl)-amino]-5-trifluoromethyl-indan-2-carboxylic acid
5-Fluoro-2-[(5,6,7,8-tetrahydro-naphthalene-1-carbonyl)-amino]-indan-2-carboxylic acid,
5-(2-Isopropoxy-3-methyl-benzoylamino)-1,3-dimethyl-5,6-dihydro-4H-cyclopenta[c]thiophene-5-carboxylic acid,
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-methoxy-indan-2-carboxylic acid,
2-(2-Isopropoxy-3-methyl-benzoylamino)-5-trifluoromethyl-indan-2-carboxylic acid,
5-Fluoro-2-(2-isopropoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-trifluoro-indan-2-carboxylic acid,
5-Bromo-2-(2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5,6-difluoro-indan-2-carboxylic acid,
2-[3-Methyl-2-((Z)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,
2-(3-Methyl-2-pentyl-benzoylamino)-indan-2-carboxylic acid,
2-[2-(-1-Ethyl-but-1-enyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-[2-(1-Ethyl-butyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopentyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[3-Methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
2-(2-Isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[2-(-2-Cyclopropyl-vinyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-[2-(2-Cyclopropyl-ethyl)-3-methyl-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclohex-1-enyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[3-Methyl-2-(1-propenyl)-benzoylamino]-indan-2-carboxylic acid,
2-(3-Methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,
2-[3-Methyl-2-((E)-pent-1-enyl)-benzoylamino]-indan-2-carboxylic acid,

5-Fluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Cyclopent-1-enyl-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
5-Fluoro-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,
5-Fluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5,6-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
5,6-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5,6-Difluoro-2-(3-methyl-2-propenyl-benzoylamino)-indan-2-carboxylic acid,
5,6-Difluoro-2-(3-methyl-2-propyl-benzoylamino)-indan-2-carboxylic acid,
5-Bromo-2-[3-methyl-2-((E)-propenyl)-benzoylamino]-indan-2-carboxylic acid,
2-[(2-Chloro-6-methyl-benzoyl)-amino]-indane-2-carboxylic acid,
2-[(2-methylthiolbenzen-1-carbonyl)-amino]-indan-2-carboxylic acid,
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Isobutyryl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2,3-Dimethyl-benzoylamino)-indan-2-carboxylic acid,
2-(3-Cyano-2-methyl-benzoylamino)-indan-2-carboxylic acid,
2-[(Biphenyl-2-carbonyl)-amino]-indan-2-carboxylic acid,
2-[2-(1,1-Dimethyl-propyl)-benzoylamino]-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4,5-dichloro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-5-chloro-indan-2-carboxylic acid,
2-(2-Cyclobutoxy-3-methyl-benzoylamino)-4-fluoro-indan-2-carboxylic acid,
2-(2-cyclobutyloxy-3-methylbenzoylamino)indan-2-acetic acid,
2-(3-bromo-2-methylbenzoylamino)indan-2-carboxylic acid,
2-(5-Bromo-2-cyclobutoxy-3-methyl-benzoylamino)-indan-2-carboxylic acid,
2-(2-Isopropylsulfanyl-benzoylamino)-indan-2-carboxylic acid,
2-(5-Chloro-2-cyclobutoxy-3-methyl-benzoylamino)-5-fluoro-indan-2-carboxylic acid,
2-{[2-(Ethyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[2-(Allyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[2-(Isopropyl-methyl-amino)-pyridine-3-carbonyl]-amino}-indan-2-carboxylic acid,
2-{[5-Chloro-2-(isopropyl-methyl-amino)-pyridine-3-carbonyl)-amino]-indan-2-carboxylic acid,
4,5-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,5-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid

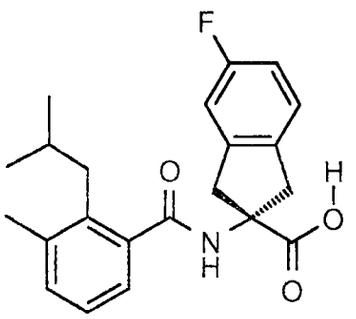
4,7-Difluoro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid,
4,7-Difluoro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid,
5-Chloro-2-(2-isobutyl-3-methyl-benzoylamino)-indan-2-carboxylic acid
5-Chloro-2-[3-methyl-2-(2-methyl-propenyl)-benzoylamino]-indan-2-carboxylic acid
2-(5,6,7,8-Tetrahydro-naphthalen-1-ylcarbamoyl)-indan-2-carboxylic acid,
2-Cyclobutoxy-N-(2-methanesulfonylaminocarbonyl-indan-2-yl)-3-methyl-benzamide,
2-Cyclobutoxy-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,
2-Cyclopent-1-enyl-3-methyl-N-(2-trifluoromethanesulfonylaminocarbonyl-indan-2-yl)-benzamide,
2-Cyclobutoxy-3-methyl-N-[2-(1H-tetrazol-5-yl)-indan-2-yl]-benzamide, and
2-[2-(2-Methyl-propenyl)-3-trifluoromethyl-benzoylamino]-indan-2-carboxylic acid, or

a stereoisomeric form thereof, mixture of stereoisomeric forms thereof in any ratio, or a physiologically acceptable salt thereof.

31. The compound according to claim 1 of the following structure



32. The compound according to claim 1 of the following structure



33. A pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to claim 1 and at least one of a pharmaceutically acceptable excipient and pharmaceutically acceptable carrier.

34. A method for the treatment of a patient suffering from, or subject to, a physiological condition that can be ameliorated by the administration of a pharmaceutically effective amount of an inhibitor of a CXCR5 receptor to the patient comprising administering the compound according to claim 1 to said patient.

35. The method according to claim 34 wherein the physiological condition is an inflammatory disease.

36. The method according to claim 34 wherein the physiological condition is rheumatoid arthritis.

37. The method according to claim 34 wherein the physiological condition is asthma.

38. The method of claim 4 wherein with the administering of the compound of claim 1 and another therapeutic agent is administered at the same time or sequentially.

39. A process for producing a compound according to claim 1 as described herein.

ÁCIDOS BENZOILAMINO-INDAN-2-CARBOXÍLICOS SUSTITUIDOS Y COMPUESTOS RELACIONADOS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a ácidos benzoilamino-indan-2-carboxílicos y a compuestos relacionados e intermedios de los mismos, a su preparación incluyendo procesos sintéticos estereoselectivos para obtener intermedios, a composiciones farmacéuticas que contienen los compuestos y al uso de los compuestos o composiciones de los mismos que tienen la capacidad de bloquear el receptor CXCR5 e inhibir la función de células B asociada con la activación del receptor. Los compuestos que tienen actividad inhibidora de CXCR5 son particularmente útiles en el tratamiento o prevención de diversas enfermedades inflamatorias, tales como artritis reumatoide, esclerosis múltiple, lupus y enfermedad de Crohn, asociadas con la modulación del receptor CXCR5 humano.

ANTECEDENTES DE LA INVENCIÓN

CXCR5 es un receptor de quimioquinas no promiscuo que pertenece a la familia de receptores acoplados a proteína G (GPCR). Específicamente, el receptor CXCR5 interacciona con su ligando CXCL13 - que se expresa constitutivamente en células estromáticas, tales como células dendríticas foliculares, y en tejidos linfoides. El ligando CXCL13 atrae específicamente a las células B y a una pequeña subserie de células T denominada células T foliculares coadyuvantes de B (T_{FH}). Cuando la interacción CXCR5/CXCL13 se bloquea por un antagonista, puede tratarse a pacientes con artritis reumatoide (AR) y otras enfermedades autoinmunes o inflamatorias en las que la regulación positiva de CXCR5 y/o su ligando CXCL13 son responsables de la patogénesis o exacerbación de la enfermedad. Aunque la terapia de reducción de células B con anticuerpo monoclonal anti-CD20 (Rituximab) ha demostrado eficacia en el tratamiento de AR, se sabe que el bloqueo de las células B, tales como células que expresan CXCR5, proporciona efectos terapéuticos beneficiosos en modelos murinos experimentales de artritis.

Además, se sabe que CXCR5 y/o CXCL13 están regulados positivamente en pacientes con artritis reumatoide [*Arthritis Res Ther.* 2005;7(2):R217-29, Epub 2004 Dec 16], síndrome de Sjogren [*Arthritis Rheum.* 2001 Nov; 44(11):2633-41], miastenia grave [*J Neuroimmunol.* 2005 Dec 30;170(1-2):172-8, Epub 2005 Oct 7] y esclerosis múltiple [*Brain.* 2006 Jan;129(Pt 1):200-11, Epub 2005 Nov 9]. También se conoce una asociación entre CXCR5 y el carcinoma pancreático [*Cancer Res.* 2006 Oct 1;66(19): 9576-82]. Por medio del bloqueo de la interacción receptor/ligando con un antagonista de CXCR5, pueden proporcionarse efectos terapéuticos beneficiosos en las enfermedades mencionadas anteriormente, y en otras enfermedades en las que una infiltración de células B (u otras subseries de linfocitos que expresan el receptor CXCR5) es responsable de la patogénesis de la enfermedad [*Front Biosci.* 2007 Jan 1;12:2194-2006, *J Rheumatol Suppl.* 2006 May;77:3-11].

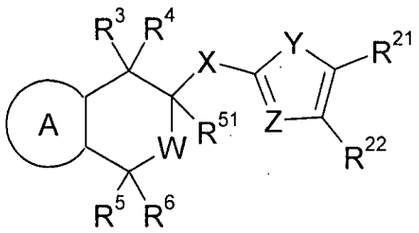
Se sabe que la infiltración de linfocitos en centros germinales ectópicos terciarios (GC) está muy relacionada con un aumento de la gravedad de ciertas enfermedades y la ruptura de la tolerancia. Por medio del uso de modelos murinos *in vivo*, tales como ratones $CXCR5^{-/-}$ y $CXCL13^{-/-}$, por ejemplo, la ausencia del receptor o el ligando ocasiona una alteración de la arquitectura fina de GC producida por el cambio de la localización de las células T y B. Se sabe que estos ratones están protegidos contra el desarrollo de artritis severa inducida por colágeno (CIA). Por lo tanto, como CXCR5 se expresa selectivamente en células B maduras, que están asociadas con la patogénesis de la AR, un antagonista que sea capaz de bloquear este receptor puede modular la respuesta artritogénica en individuos afectados. En el momento actual, el tratamiento de la artritis reumatoide con anticuerpos anti-CD20 ha demostrado ser clínicamente eficaz; tal como con pacientes con una terapia dirigida a las células B, que han demostrado mejorías a largo plazo en los signos clínicos y síntomas. Por lo tanto, no es de esperar que la dirección selectiva a CXCR5, que sólo se expresa en células B maduras y células T auxiliares de B, afecte al desarrollo de las células B ni comprometa al sistema inmune del paciente.

Por lo tanto, existe la necesidad no satisfecha de antagonistas de CXCR5 para el tratamiento de la artritis reumatoide y otras enfermedades inflamatorias, enfermedades autoinmunes y cánceres producidos por la interacción de células B que expresan CXCR5 en respuesta a la expresión de CXCL13.

COMPENDIO DE LA INVENCIÓN

La presente invención se refiere a compuestos antagonistas de la fórmula I, que según se ha descubierto bloquean la migración de las células B en respuesta a un gradiente de ligando, sin reducción de células B periféricas. Por lo tanto, estos compuestos proporcionan un perfil de seguridad para el tratamiento a largo plazo de enfermedades inflamatorias.

La presente invención se refiere a nuevos compuestos de la fórmula I:



(I)

en la que:

el anillo A es un anillo de benceno o un anillo heterocíclico, aromático, de 5 miembros o de 6 miembros, monocíclico, que comprende 1 ó 2 miembros hetero del anillo iguales o diferentes elegidos entre el grupo que consiste en N, $N(R^1)$, O y S, donde todos los anillos pueden estar sustituidos con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-$S(O)_m$-, ciano y nitro;

W se elige entre el grupo que consiste en un enlace o CH2;

X se elige entre el grupo que consiste en $N(R^7)C{=}O$, $N(R^7)S(O)_m$, $N(R^7)CR^8(R^9)$, $C{=}ON(R^7)$, $S(O)_mN(R^7)$, $CR^8(R^9)N(R^7)$, $CR^8(R^9)N(R^7)C{=}O$ y $CR^8(R^9)N(R^7)S(O)_m$;

Y se elige entre el grupo que consiste en $N(R^{11})$, S, O, $C(R^{12}){=}C(R^{13})$, $N{=}C(R^{14})$ y $C(R^{15}){=}N$;

$C(R^{12}){=}C(R^{13})$ puede ser un carbociclo o heterociclo de 5-7 miembros con cualquier sustitución;

Z se elige entre el grupo que consiste en N y $C(R^{16})$;

R^1 se elige entre el grupo que consiste en hidrógeno y alquilo (C_1-C_4);

R^3 y R^4 se eligen independientemente entre sí entre el grupo que consiste en hidrógeno y alquilo (C_1-C_4);

R^5 y R^6 se eligen independientemente entre sí entre el grupo que consiste en hidrógeno y alquilo (C_1-C_4);

R^7 se elige entre el grupo que consiste en hidrógeno, alquilo (C_1-C_4) y cicloalquilo (C_1-C_6);

R^8 y R^9 se eligen independientemente entre sí entre el grupo que consiste en hidrógeno y alquilo (C_1-C_4) o juntos como cicloalquilo (C_1-C_6);

R^{11} se elige entre el grupo que consiste en hidrógeno, alquilo (C_1-C_{10}), hidroxi-alquil (C_1-C_{10})-, alquiloxi (C_1-C_{10}), alquil (C_1-C_{10})-$S(O)_m$-, alquilcarbonil (C_1-C_{10})-, amino, alquilamino (C_1-C_{10}) y di(alquil (C_1-C_{10}))amino;

R^{12}, R^{15} y R^{16} se eligen independientemente entre sí entre el grupo que consiste en hidrógeno, halógeno, alquilo (C_1-C_{10}), hidroxi-alquil (C_1-C_{10})-, alquiloxi (C_1-C_{10}), alquil (C_1-C_{10})-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_{10})-, amino, alquilamino (C_1-C_{10}), di(alquil (C_1-C_{10}))amino y nitro;

R^{13}, R^{14} , R^{21} y R^{22} se eligen independientemente entre sí entre el grupo que consiste en hidrógeno, halógeno, alquilo (C_1-C_4), hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino y nitro;

con la condición de que el número total de átomos de C, N, O y S que estén presentes en uno cualquiera de los grupos R^{13}, R^{14} , R^{21} y R^{22} no supere 4;

R^{51} se elige entre el grupo que consiste en $COOR^{52}$, $CONR^{53}(R^{54})$ y heterociclos de 5-6 miembros que contienen 3 o más heteroátomos;

R^{52} se elige entre el grupo que consiste en hidrógeno y alquilo (C_1-C_4);

R^{53} se elige entre el grupo que consiste en hidrógeno, hidroxilo, alquiloxi (C_1-C_4), alquilo (C_1-C_4), ciano y R^{55}-SO_2-;

R^{54} se elige entre el grupo que consiste en hidrógeno, alquilo (C_1-C_4), alquilcarbonil (C_1-C_2)- y alquil (C_1-C_3)-$S(O)_m$-;

R^{55} se elige entre el grupo que consiste en alquilo (C_1-C_4) y fenilo;

R^{61} se elige entre el grupo que consiste en hidrógeno y alquilo (C_1-C_4);

R^{62} se elige entre el grupo que consiste en hidrógeno y alquilo (C_1-C_4);

heteroarilo es un anillo heterocíclico, aromático, de 5 miembros o de 6 miembros, monocíclico, que comprende 1, 2 ó 3 miembros hetero del anillo iguales o diferentes elegidos entre el grupo que consiste en N, N(R^{61}), O y S;

heterociclilo es un anillo heterocíclico, de 4 miembros a 7 miembros, monocíclico, que comprende 1 ó 2 miembros hetero del anillo iguales o diferentes elegidos entre el grupo que consiste en N, N(R^{62}), O, S, SO y SO_2 pero dos miembros hetero del anillo de la serie que consiste en N(R^{62}), O y S no pueden estar presentes en posiciones adyacentes del anillo, donde el anillo está saturado o parcialmente insaturado y puede estar sustituido con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en alquilo (C_1-C_4);

m es un número entero elegido entre el grupo que consiste en 0, 1 y 2, donde todos los números m son independientes entre sí y pueden ser iguales o diferentes;

todos los grupos fenilo y heteroarilo del compuesto de la fórmula Ia pueden estar sustituidos independientemente entre sí con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquilsulfonilo (C_1-C_4) y ciano;

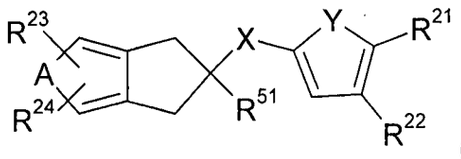
todos los grupos alquilo del compuesto de la fórmula Ia pueden estar sustituidos independientemente entre sí con uno o más átomos de flúor;

en cualquiera de sus formas estereoisoméricas o una mezcla de formas estereoisoméricas en cualquier proporción, o una sal fisiológicamente aceptable de los mismos.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

El contenido de cada uno de los documentos de patente y otras referencias citadas en la presente memoria se incorpora en la presente memoria como referencia en su totalidad.

En una realización particular, la presente invención incluye el compuesto de fórmula Ia:



(Ia)

en la que:

A es CH=CH o S;

R^{23} es hidrógeno, halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-S- o nitro;

R^{24} es hidrógeno o halógeno cuando A es CH=CH, o es hidrógeno, halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-S-, o nitro cuando A es S;

X es N(H)C=O, $N(H)S(O)_2$, C=ON(H) o $S(O)_2N(H)$;

Y es $N(R^{11})$, S, O, $C(R^{12})=C(R^{13})$, $N=C(R^{14})$ o $C(R^{15})=N$, o carbociclilo condensado de 5-7 miembros opcionalmente sustituido;

R^{11} es hidrógeno, alquilo (C_1-C_{10}), hidroxi-alquil (C_1-C_{10})-, alquiloxi (C_1-C_{10}), alquil (C_1-C_{10})-$S(O)_m$-, alquilcarbonil (C_1-C_{10})-, fenilo, amino, alquilamino (C_1-C_{10}) o di(alquil (C_1-C_{10}))amino;

R^{12} es hidrógeno, halógeno, alquilo (C_1-C_{10}), alquenilo (C_2-C_{10}), cicloalquiloxi (C_3-C_6), cicloalqueniloxi (C_3-C_{10}), cicloalquilo (C_3-C_6), cicloalquenilo (C_3-C_{10}), cicloalquil (C_3-C_6)-alquilo[(C_1-C_4) o alquenilo (C_2-C_4)], cicloalquil (C_3-C_6)-alquiloxi(C_1-C_4), hidroxialquilo(C_1-C_{10}), alquiloxi (C_1-C_{10}), alqueniloxi (C_2-C_{10}), alquil (C_1-C_{10})-S-, ciano, alquilcarbonilo (C_1-C_{10}), fenilo o nitro;

R^{13} es hidrógeno, halógeno o alquilo (C_1);

R^{14} es hidrógeno, halógeno, alquilo (C_1-C_4), hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{14} no supere 4;

R^{15} es hidrógeno, halógeno, alquilo (C_1-C_{10}), alquenilo (C_2-C_{10}), cicloalquilo (C_3-C_6), cicloalquenilo (C_3-C_6), cicloalquil (C_3-C_6)-[alquilo (C_1-C_4) o alquenilo (C_2-C_4)], hidroxi-alquil (C_1-C_{10})-, ciano, alquilcarbonil (C_1-C_{10})-, fenilo, amino, [alquil (C_1-C_{10}) o alquenil (C_2-C_{10})-]amino, [alquil (C_1-C_{10}) o alquenil (C_2-C_{10})](alquil (C_1-C_{10}))amino o nitro;

R^{21} es hidrógeno cuando Y es $C(R^{12})=C(R^{13})$, $N=C(R^{14})$ o $C(R^{15})=N$, y es hidrógeno, halógeno, alquilo (C_1-C_4), hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro cuando Y es $N(R^{11})$, S o O, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{21} no supere 4;

R^{22} es hidrógeno, halógeno, alquilo (C_1) cuando Y es $C(R^{12})=C(R^{13})$, $N=C(R^{14})$ o $C(R^{15})=N$, o es hidrógeno, hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro cuando Y es $N(R^{11})$, S o O, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{22} no supere 4;

R^{51} es COOH o $CONH(R^{53})$;

R^{53} es R^{55}-SO_2- o tetrazolilo;

R^{55} es alquilo (C_1-C_4) o fenilo opcionalmente sustituido con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-sulfonilo y ciano; y

m es 0, 1 ó 2;

donde todos los grupos fenilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_{1-4}), alquiloxi (C_{1-4}), alquilsulfonilo (C_{1-4}) y ciano;

donde todos los grupos alquilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más átomos de flúor; o

una forma estereoisomérica del mismo, una mezcla de formas estereoisoméricas del mismo en cualquier proporción o una sal fisiológicamente aceptable del mismo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{23} es hidrógeno, halógeno, alquilo (C_1-C_4) o alquiloxi (C_1-C_4);

R^{24} es hidrógeno o halógeno cuando A es CH=CH, o es hidrógeno, halógeno o alquilo (C_1-C_4) cuando A es S;

X es N(H)C=O, N(H)S(O)$_2$ o C=ON(H);

Y es C(R^{12})=C(R^{13}) o C(R^{15})=N, o carbociclo de 5-6 miembros, opcionalmente sustituido y condensado;

R^{12} es alquilo (C_1-C_6), alquenilo (C_3-C_6), cicloalquiloxi (C_4-C_6), cicloalquilo (C_5-C_6), cicloalquenilo (C_5-C_6), cicloalquil (C_3)-[alquilo (C_2) o alquenilo (C_2)], cicloalquil (C_3)-alquiloxi (C_1), alquiloxi (C_3-C_4), alqueniloxi (C_3), alquil (C_1-C_3)-S-, alquilcarbonilo (C_3), fenilo;

R^{13} es hidrógeno, halógeno o alquilo (C_1);

R^{15} es alquilo (C_1-C_6), alquenilo (C_2-C_6) o [alquil (C_2-C_3) o alquenil (C_3)](alquil (C_1))amino;

R^{21} es hidrógeno cuando Y es $C(R^{12})=C(R^{13})$ o $C(R^{15})=N$;

R^{22} es hidrógeno o halógeno, alquilo (C_1) cuando Y es $C(R^{12})=C(R^{13})$ o $C(R^{15})=N$;

R^{51} es COOH;

donde todos los grupos fenilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_{1-4}), alquiloxi (C_{1-4}), alquilsulfonilo (C_{1-4}) y ciano;

donde todos los grupos alquilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más átomos de flúor; o

una forma estereoisomérica del mismo, una mezcla de formas estereoisoméricas del mismo en cualquier proporción o una sal fisiológicamente aceptable del mismo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

A es CH=CH.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{23} es hidrógeno o halógeno.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{24} es hidrógeno o halógeno cuando A es CH=CH;

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

X es N(H)C=O.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

Y es $C(R^{12})=C(R^{13})$.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

Y es $C(R^{15})=N$.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

Y es carbociclilo de 5-6 miembros, opcionalmente sustituido y condensado.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es alquilo (C_4-C_6) o más particularmente isobutilo o propilo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es alquenilo (C_{3-5}, o más particularmente penten-1-ilo, isobuteno-1-ilo o propen-1-ilo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es cicloalquiloxi (C_4)-(ciclobutiloxi).

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es cicloalquilo (C_5-C_6).

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es cicloalquenilo (C_5-C_6), o más particularmente ciclopenten-1-ilo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es cicloalquil (C_3)-alquilo [(C_2) o alquenilo (C_2), o más particularmente ciclopropiletilo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es cicloalquil (C_3)-alquiloxi (C_1)-(ciclopropilmetilo).

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es alquiloxi (C_3-C_4).

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es alqueniloxi (C_3).

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{12} es fenilo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{13} es halógeno o alquilo (C_1).

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{13} es alquilo (C_1), donde el alquilo está sustituido opcionalmente con 1-3 átomos de flúor, o más particularmente trifluorometililo.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{13} es alquilo (C_1) (metilo).

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{13} es alquilo (C_1) que está sustituido con 2-3 átomos de flúor.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{13} es halógeno.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{15} es [alquil (C_2-C_3) o alquenil (C_3)](alquil (C_1-C_{10}))amino.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{15} es alquil (C_2-C_3)-alquilo(C_1))amino, o más particularmente isopropilmetilamino.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{21} es hidrógeno.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{22} es hidrógeno o halógeno o alquilo (C_1) cuando Y es $C(R^{12})=C(R^{13})$.

Otra realización particular de acuerdo con la invención es el compuesto de acuerdo con la fórmula Ia, en la que

R^{51} es COOH.

Las realizaciones específicas de la presente invención se seleccionan entre el grupo que consiste en

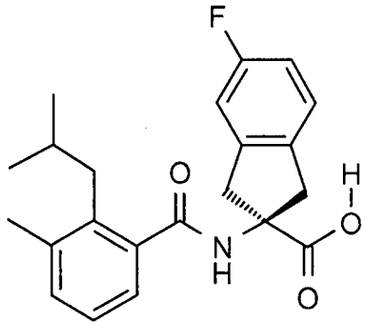
ácido 2-(2-aliloxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclopropilmetoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-sec-butoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(3-cloro-2-isopropoxi-benzoilamino)-indan-2-carboxílico
ácido 2-(2-aliloxi-3-cloro-benzoilamino)-indan-2-carboxílico,
ácido 2-(3,5-dicloro-2-ciclobutoxi-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 2-(3,5-dicloro-2-isopropoxi-bencenosulfonilamino)-indan-2-carboxílico,
ácido 2-(2-aliloxi-3,5-dicloro-bencenosulfonilamino)-indan-2-carboxílico,
ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico,
ácido 1,3-dimetil-5-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico,
ácido 5-metoxi-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico,
ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5-trifluorometil-indan-2-carboxílico
ácido 5-fluoro-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico,
ácido 5-(2-isopropoxi-3-metil-benzoilamino)-1,3-dimetil-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico,
ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-metoxi-indan-2-carboxílico,
ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-trifluorometil-indan-2-carboxílico,
ácido 5-fluoro-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-trifluoro-indan-2-carboxílico,
ácido 5-bromo-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5,6-difluoro-indan-2-carboxílico,

ácido 2-[3-metil-2-((Z)-pent-1-enil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(3-metil-2-pentil-benzoilamino)-indan-2-carboxílico,
ácido 2-[2-(1-etil-but-1-enil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-[2-(1-etil-butil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclopentil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-[2-(-2-ciclopropil-vinil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-[2-(2-ciclopropil-etil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-ciclohex-1-enil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-[3-metil-2-(1-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(3-metil-2-propil-benzoilamino)-indan-2-carboxílico,
ácido 2-[3-metil-2-((E)-pent-1-enil)-benzoilamino]-indan-2-carboxílico,
ácido 5-fluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 5-fluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 5-fluoro-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 5-fluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5,6-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 5,6-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5,6-difluoro-2-(3-metil-2-propenil-benzoilamino)-indan-2-carboxílico,
ácido 5,6-difluoro-2-(3-metil-2-propil-benzoilamino)-indan-2-carboxílico,
ácido 5-bromo-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-[(2-cloro-6-metil-benzoil)-amino]-indan-2-carboxílico,
ácido 2-[(2-metiltiolbencen-1-carbonil)-amino]-indan-2-carboxílico,
ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-isobutiril-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2,3-dimetil-benzoilamino)-indan-2-carboxílico,
ácido 2-(3-ciano-2-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-[(bifenil-2-carbonil)-amino]-indan-2-carboxílico,
ácido 2-[2-(1,1-dimetil-propil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4,5-dicloro-indan-2-carboxílico,

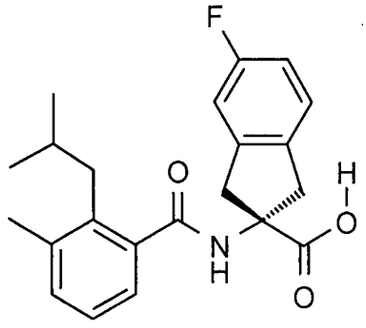
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-cloro-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4-fluoro-indan-2-carboxílico,
ácido 2-(2-ciclobutiloxi-3-metilbenzoilamino)indan-2-acético,
ácido 2-(3-bromo-2-metilbenzoilamino)indan-2-carboxílico,
ácido 2-(5-bromo-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-isopropilsulfanil-benzoilamino)-indan-2-carboxílico,
ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 2-{[2-(etil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,
ácido 2-{[2-(alil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,
ácido 2-{[2-(isopropil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,
ácido 2-{[5-cloro-2-(isopropil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,
ácido 4,5-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 4,5-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 4,7-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 4,7-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5-cloro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5-cloro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(5,6,7,8-tetrahidro-naftalen-1-ilcarbamoil)-indan-2-carboxílico,
2-ciclobutoxi-N-(2-metanosulfonilaminocarbonil-indan-2-il)-3-metil-benzamida,
2-ciclobutoxi-3-metil-N-(2-trifluorometanosulfonilaminocarbonil-indan-2-il)-benzamida,
2-ciclopent-1-enil-3-metil-N-(2-trifluorometanosulfonilaminocarbonil-indan-2-il)-benzamida,
2-ciclobutoxi-3-metil-N-[2-(1H-tetrazol-5-il)-indan-2-il]-benzamida, y
ácido 2-[2-(2-Metil-propenil)-3-trifluorometil-benzoilamino]-indan-2-carboxílico, o

una forma estereoisomérica del mismo, una mezcla de formas estereoisoméricas del mismo en cualquier proporción o una sal fisiológicamente aceptable del mismo.

Otra realización particular según la invención es el compuesto de la siguiente estructura



Otra realización particular según la invención es el compuesto de la siguiente estructura



Otra realización particular según la invención es un compuesto seleccionado entre ejemplo 232, 150, 231, 149, 136, 158, 152, 159, 144, 397, 135, 161, 155, 132, 139, 125, 329, 262, 154, 143, 160, 163, 21, 87, 212, 103, 352, 395, 392, o 388.

Otra realización particular de acuerdo con la invención es una composición farmacéutica que comprende una cantidad farmacéuticamente aceptable de un compuesto de acuerdo con la fórmula Ia y al menos uno de un excipiente farmacéuticamente aceptable y un vehículo farmacéuticamente aceptable.

Otra realización particular de acuerdo con la invención es un método para el tratamiento de un paciente que padece, o que es propenso a, una afección fisiológica que puede mejorarse mediante la administración de una cantidad farmacéuticamente eficaz de un inhibidor de un receptor CXCR5 al paciente, que comprende administrar el compuesto de acuerdo con la fórmula Ia a dicho paciente.

Otra realización particular de acuerdo con la invención es el método de tratamiento en el que la afección fisiológica es una enfermedad inflamatoria.

Otra realización particular de acuerdo con la invención es el método de tratamiento en el que la afección fisiológica es artritis reumatoide.

Otra realización particular de acuerdo con la invención es el método de tratamiento en el que la afección fisiológica es asma.

Otra realización particular de acuerdo con la invención es el método de tratamiento con la administración del compuesto de la reivindicación 1 y otro agente terapéutico que se administra al mismo tiempo o secuencialmente.

Otra realización particular de acuerdo con la invención es un proceso para producir un compuesto de acuerdo con la fórmula Ia como se describe en la presente memoria.

La presente invención también se refiere a una composición farmacéutica que comprende un compuesto de fórmula 1, y a un método para usar el compuesto de fórmula I o de fórmula Ia para prevenir y/o tratar enfermedades inflamatorias, tales como artritis reumatoide, esclerosis múltiple, lupus o enfermedad de Crohn, asociado con la modulación del receptor CXCR5 humano en un paciente.

La invención también se refiere a un proceso para preparar un compuesto que es un intermedio útil en la preparación de un compuesto de fórmula I o de fórmula Ia.

Otro aspecto de la invención son métodos para tratar o prevenir una afección fisiológica o una patología en un paciente que lo necesita, que comprende administrar a dicho paciente una cantidad farmacéuticamente eficaz de uno o más compuestos de fórmula I o de fórmula Ia.

La cantidad de los compuestos de fórmula I o de fórmula Ia u otros compuestos adecuados para una afección fisiológica o una patología en cualquiera de las aplicaciones anteriores puede ser una cantidad farmacéuticamente eficaz, una cantidad subclínica eficaz o

combinaciones de las mismas, siempre que la combinación final para la afección o patología comprenda una cantidad farmacéuticamente eficaz de compuestos que sea eficaz para prevenir y/o tratar enfermedades inflamatorias, tales como artritis reumatoide, esclerosis múltiple, lupus o enfermedad de Crohn, asociada con la modulación del receptor CXCR5 humano en un paciente.

Lista de Abreviaturas

Como se ha usado anteriormente, y a lo largo de la descripción de la invención, debe entenderse que las siguientes abreviaturas, a menos que se indique lo contrario, tienen los siguientes significados:

ACN	acetonitrilo
AIBN	2,2'-azobisisobutironitrilo
BOC o Boc	carbamato de *terc*-butilo
BOP	benzotriazol-1-il-oxitris(dimetilamino)fosfonio
n-Bu_3SnH	hidruro de tri-n-butilestaño
t-Bu	terc-butilo
Cbz	carbamato de bencilo
$CsCO_3$	carbonato de cesio
DAST	trifluoruro de (dietilamino)azufre (Et_2NSF_3)
DCC	diciclohexilcarbodiimida
DCM	diclorometano (CH_2Cl_2) o cloruro de metileno
DIC	1,3-diisopropilcarbodiimida
DIPEA	diisopropiletilamina
DMAP	4-(N,N-dimetilamino)piridina
reactivo DMP	reactivo de peryodinano de Dess-Martin
DMF	dimetilformamida
DMSO	dimetilsulfóxido
EDCI	1-etil-3-(3-dimetilaminopropil)carbodiimida HCl
equiv.	equivalente(s)
Et	etilo
Et_2O	éter dietílico
EtOH	etanol

EtOAc	acetato de etilo
FMOC	9-fluorenilmetoxicarbonilo
HATU	O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio PF_6
HOAt	1-hidroxi-7-azabensotriazol
HOBT	1-hidroxibenzotriazol
HOSu	N-hidroxisuccinamida
HBTU	Hexafluorofosfato de O-benzotriazol-N,N,N',N'-tetrametil-uronio
HPLC	cromatografía líquida de alta resolución
LAH	anhídrido de litio y aluminio
$MgSO_4$	sulfato de magnesio
Me	metilo
MeI	yoduro de metilo
MeOH	metanol
MeOC(O)	cloroformiato de metilo
MOMCI	cloruro de metoximetilo
MOM	metoximetilo
MS	espectroscopía de masas
$NaBH_4$	borohidruro sódico
$NaHCO_3$	bicarbonato sódico
$Na_2C_4H_4O_6$	tartrato sódico
RMN	resonancia magnética nuclear
PTC	catalizador de transferencia de fases
iPrOH	iso-propanol
P	unión a polímero
$KMnO_4$	permanganato potásico
K_2SO_4	carbonato potásico
PyBOP	hexafluorofosfato de benzotriazol-1-il-oxitris-pirrolidino-fosfonio
Na_2SO_4	Sulfato sódico
TBD	1,5,7-triazabiciclo[4.4.0]-dec-5-eno
RP-HPLC	cromatografía líquida de fase inversa a alta presión

TA	temperatura ambiente
TBSCI	cloruro de *terc*-butildimetilsililo
TCA	ácido tricloroacético
TFA	ácido trifluoroacético
Tf_2O	anhídrido de triflato
THF	tetrahidrofurano
THP	tetrahidropirano
TLC	cromatografía de capa fina

Definiciones

Tal como se ha usado anteriormente y a lo largo de la descripción de la invención, debe entenderse que los siguientes términos y expresiones, a menos que se indique lo contrario, tienen los siguientes significados:-

La expresión "bioisóstero ácido" se refiere a un grupo que tiene similitudes químicas y físicas que producen, en términos generales, propiedades biológicas similares a un grupo carboxi (véase Lipinski, Annual Reports en Medicinal Chemistry, "Bioisosterism In Drug Design", 21, 283 (1986); Yun, Hwahak Sekye, "Application of Bioisosterism To New Drug Design" 33, 576-579, (1933); Zhao, Huaxue Tongbao, "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design", 34-38, (1995); Graham, Theochem, "Theoretical Studies Applied To Drug Design ab initio Electronic Distributions In Bioisosteres" 343, 105-109, (1995)). Los bioisósteros ácidos ejemplares incluyen -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, fosfono, alquilsulfonilcarbamoílo, tetrazolilo, arilsulfonilcarbamoílo, N-metoxicarbamoílo, heteroarilsulfonilcarbamoílo, 3-hidroxi-3-ciclobuteno-1,2-diona, 3,5-dioxo-1,2,4-oxadiazolidinilo o hidroxiheteroarilo, tal como 3-hidroxiisoxazolilo, 3-hidroxi-1-metilpirazolilo y similares.

La expresión "grupo funcional ácido" se refiere a un resto que tiene un hidrógeno ácido. Los grupos funcionales ácidos ejemplares incluyen carboxilo (-C(O)OH), -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, fosfono, alquilsulfonilcarbamoiltetrazolilo, arilsulfonilcarbamoílo, N-metoxicarbamoílo, heteroarilsulfonilcarbamoílo o 3-hidroxi-3-ciclobuteno-1,2-diona, imidazolilmercapto y similares, y un grupo hidroxi apropiado, tal como un hidroxi aromático, por ejemplo, hidroxifenilo, hidroxiheteroarilo, tal como 3,5-dioxo-1,2,4-oxadiazolidinilo, 3-hidroxisoxazolilo o 3-hidroxi-1-metilpirazolilo.

La expresión "grupo protector de ácidos" se refiere a un grupo que puede retirarse fácilmente que se conoce en la técnica por proteger a un hidrógeno ácido de un grupo carboxilo frente a una reacción indeseable durante procedimientos sintéticos, por ejemplo, para bloquear o proteger la funcionalidad ácida mientras se realizan las reacciones que implican otros sitios funcionales del compuesto, y porque puede retirarse selectivamente. Tales grupos protectores ácidos son bien conocidos por los especialistas en la técnica y se han usado mucho en la protección de grupos carboxilo, como se describe en las Patentes de Estados Unidos N° 3.840.556 y 3.719.66, cuyas descripciones se incorporan en la presente memoria como referencia. Para más información acerca de grupos protectores ácidos, véase T.W. Green y P.G.M. Wuts en "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. El grupo protector de ácidos también incluye la hidrogenación del grupo protector lábil como se define en la presente memoria. Los grupos protectores de ácidos ejemplares incluyen ésteres, tales como alquilo C_{1-8} inferior sustituido y sin sustituir, por ejemplo, metilo, etilo, *t*-butilo, metoximetilo, metiltiometilo, 2,2,2-tricloroetilo y similares, tetrahidropiranilo, fenilalquilo sustituido y sin sustituir, tal como bencilo y derivados sustituidos del mismo, tales como grupos alcoxibencilo o nitrobencilo y similares, cinnamilo, dialquilaminoalquilo, por ejemplo, dimetilaminoetilo y similares, trimetilsililo, amidas e hidrazidas sustituidas y sin sustituir, por ejemplo, amidas e hidrazidas en N,N-dimetilamina, 7-nitroindol, hidrazina, N-fenilhidrazina y similares, grupos aciloxialquilo, tales como pivaloiloximetilo o propioniloximetilo y similares, aroiloxialquilo, tal como benzoíloxietilo y similares, alcoxicarbonilalquilo, tal como metoxicarbonilmetilo, ciclohexiloxicarbonilmetilo y similares, alcoxicarboniloxialquilo, tal como *t*-butiloxicarboniloximetilo y similares, alcoxicarbonilaminoalquilo, tal como *t*-butiloxicarbonilaminometilo y similares, alquilaminocarbonilaminoalquilo, tal como metilaminocarbonilaminometilo y similares, acilaminoalquilo, tal como acetilaminometilo y similares, heterociclilcarboniloxialquilo, tal como 4-metilpiperazinil-carboniloximetilo y similares, dialquilaminocarbonilalquilo, tal como dimetilaminocarbonil-metilo y similares, (5-(alquil inferior)-2-oxo-1,3-dioxolen-4-il)alquilo, tal como (5-*t*-butil-2-oxo-1,3-dioxolen-4-il)metilo y similares, y (5-fenil-2-oxo-1,3-dioxolen-4-il)alquilo, tal como (5-fenil-2-oxo-1,3-dioxolen-4-il)metilo y similares.

La expresión "grupo protector de amina lábil frente a ácidos" se refiere a un grupo protector de amina como se define en la presente memoria que puede eliminarse fácilmente por tratamiento con un ácido, aunque se mantiene relativamente estable frente a otros agentes. Un grupo protector de amina lábil frente a ácidos preferido es BOC.

El término "alifático" se refiere a alquilo, alquenilo o alquinilo como se define en la presente memoria.

La expresión "sustituyente(s) del grupo alifático" se refiere a sustituyentes unidos a un grupo alifático, como se define en la presente memoria, inclusive, o arilo, heteroarilo, hidroxi, alcoxi, cicliloxi, ariloxi, heteroariloxi, acilo o su análogo tioxo, ciclilcarbonilo o su análogo tioxo, aroílo o su análogo tioxo, heteroaroílo o su análogo tioxo, aciloxi, ciclilcarboniloxi, aroiloxi, heteroaroiloxi, halo, nitro, ciano, carboxi (ácido), -C(O)-NHOH,-C(O)-CH_2OH,-C(O)-CH_2SH,-C(O)-NH-CN-sulfo, fosfono, alquilsulfonilcarbamoílo, tetrazolilo, arilsulfonilcarbamoílo, tetrazolilo, arilsulfonilcarbamoílo, N-metoxicarbamoílo, heteroarilsulfonilcarbamoílo, 3-hidroxi-3-ciclobuteno-1,2-diona, hidroxiheteroarilo, tal como 3-hidroxiisoxazolilo, 3,5-dioxo-1,2,4-oxadiazolidinilo o 3-hidroxi-1-metilpirazolilo, alcoxicarbonilo, cicliloxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilsulfonilo, ciclilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, ciclilsulfinilo, arilsulfinilo, heteroarilsulfinilo, alquiltio, cicliltio, ariltio, heteroariltio, ciclilo, arildiazo, heteroarildiazo, tiol, metileno (H_2C=), oxo (O=), tioxo (S=), Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$-, $Y^1Y^2NSO_2$- o $Y^3SO_2NY^1$-, donde R^2 es como se define en la presente memoria, Y^1 e Y^2 son independientemente hidrógeno, alquilo, arilo o heteroarilo, e Y^3 es alquilo, cicloalquilo arilo o heteroarilo, o para cuando el sustituyente es Y^1Y^2N-, entonces uno de Y^1 e Y^2 puede ser acilo, ciclilcarbonilo, aroílo, heteroaroílo, alcoxicarbonilo, cicliloxicarbonilo, ariloxicarbonilo o heteroariloxicarbonilo, como se define en la presente memoria, y el otro de Y^1 e Y^2 es como se ha definido previamente, o para cuando el sustituyente es $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- o $Y^1Y^2NSO_2$-, Y^1 e Y^2 también pueden tomarse junto con el átomo de N a través del cual Y^1 e Y^2 están unidos para formar un azaheterociclilo o azaheterociclenilo de 4 a 7 miembros. Los sustituyentes del grupo alifático ácido/amida son carboxi (ácido), -C(O)-NHOH, -$C(O)CH_2OH$, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo?), fosfono?), alquilsulfonilcarbamoílo, tetrazolilo, arilsulfonilcarbamoílo, N-metoxicarbamoílo, heteroarilsulfonilcarbamoílo, 3-hidroxi-3-ciclobuteno-1,2-diona, hidroxiheteroarilo, tal como 3-hidroxiisoxazolilo, 3,5-dioxo-1,2,4-oxadiazolidinilo o 3-hidroxi-1-metilpirazolilo e Y^1Y^2NCO-. Los sustituyentes del grupo alifático polar no ácido son hidroxi, oxo (O=), tioxo (S=), acilo o su análogo tioxo, ciclilcarbonilo o su análogo tioxo, aroílo o su análogo tioxo, heteroaroílo o su análogo tioxo, alcoxicarbonilo, cicliloxicarbonilo,

ariloxicarbonilo, heteroariloxicarbonilo, aciloxi, ciclilcarboniloxi, aroiloxi, heteroaroiloxi, alquilsulfonilo, ciclilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, ciclilsulfinilo, arilsulfinilo, heteroarilsulfinilo, tiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- o $Y^1Y^2NSO_2$-. Los grupos alifáticos ejemplares que tienen un sustituyente del grupo alifático incluyen metoximetoxi, metoxietoxi, etoxietoxi, (metoxi-, benciloxi-, fenoxi- o etoxi-) carbonil(metilo o etilo), benciloxicarbonilo, piridilmetiloxi-carbonilmetilo, metoxietilo, etoximetilo, *n*-butoximetilo, ciclopentilmetiloxietilo, fenoxipropilo, fenoxialilo, trifluorometilo, ciclopropil-metilo, ciclopentilmetilo, carboxi(metilo o etilo), 2-fenetenilo, benciloxi, 1- o 2-naftil-metoxi, 4-piridil-metiloxi, benciloxietilo, 3-benciloxialilo, 4-piridilmetil-oxietilo, 4-piridilmetiloxialilo, bencilo, 2-fenetilo, naftilmetilo, estirilo, 4-fenil-1,3-pentadienilo, fenil-propinilo, 3-fenilbut-2-inilo, pirid-3-ilacetilenilo y quinolin-3-ilacetilenilo, 4-piridil-etinilo, 4-piridilvinilo, tieniletenilo, piridiletenilo, imidazolil-etenilo, pirazinil etenilo, piridilpentenilo, piridilhexenilo y piridilheptenilo, tienil-metilo, piridilmetilo, imidazolilmetilo, pirazinilmetilo, tetrahidropiranilmetilo, tetrahidropiranil-metoximetilo y similares.

El término "acilo" se refiere a un grupo H-CO- o (alifático o ciclil)-CO- en el que el grupo alifático es como se ha descrito en la presente memoria. Los acilos preferidos contienen un alquilo inferior. Los grupos acilo ejemplares incluyen formilo, acetilo, propanoílo, 2-metilpropanoílo, butanoílo, palmitoílo, acriloílo, propinoílo, ciclohexilcarbonilo y similares.

El término "alquenoílo" se refiere a un grupo alquenil-CO- en el que el alquenilo es como se define en la presente memoria.

El término "alquenilo" se refiere a un grupo hidrocarburo alifático que contiene en la cadena de aproximadamente 2 a aproximadamente 15 átomos de carbono, un doble enlace carbono-carbono y que puede ser lineal o ramificado. Los grupos alquenilo preferidos tienen de 2 a aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente de aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más de los grupos alquilo inferior tales como metilo, etilo o propilo, se unen a una cadena alquenilo lineal. La expresión "alquenilo inferior" significa de aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena, que puede ser lineal o ramificada. Los grupos alquenilo ejemplares incluyen etenilo, propenilo, *n*-butenilo, *i*-butenilo, 3-metilbut-2-enilo, *n*-pentenilo, heptenilo, octenilo, ciclohexilbutenilo, decenilo y similares. La expresión "alquenilo sustituido" se refiere a un grupo alquenilo como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo alifático"

(preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. Los sustituyentes de los grupos alquenilo alifáticos ejemplares incluyen grupos halo o cicloalquilo.

El término "alqueniloxi" se refiere a un grupo alquenil-O- en el que el grupo alquenilo es como se ha descrito en la presente memoria. Los ejemplos de grupos alqueniloxi incluyen aliloxi, 3-buteniloxi y similares.

El término "alcoxi" se refiere a un grupo alquil-O- en el que el grupo alquilo es como se ha descrito en la presente memoria. Los grupos alcoxi ejemplares incluyen metoxi, etoxi, *n*-propoxi, *i*-propoxi, *n*-butoxi, heptoxi y similares.

El término "alcoxicarbonilo" se refiere a un grupo alquil-O-CO-, en el que el grupo alquilo es como se define en la presente memoria. Los grupos alcoxicarbonilo ejemplares incluyen metoxicarbonilo, etoxicarbonilo, *t*-butiloxicarbonilo y similares.

El término "alquilo" se refiere a un grupo de hidrocarburo alifático que puede ser lineal o ramificado, que tiene de aproximadamente de 1 a aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos tienen de 1 a aproximadamente 12 átomos de carbono en la cadena, más preferiblemente alquilo inferior como se define en la presente memoria. Ramificado significa que uno o más de los grupos alquilo inferior, tales como metilo, etilo o propilo, se unen a una cadena alquilo lineal. La expresión "alquilo inferior" significa de aproximadamente 1 a aproximadamente 4 átomos de carbono en la cadena, que puede ser lineal o ramificada. La expresión "alquilo sustituido" se refiere a un grupo alquilo como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo alifático" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria.

El término "alquilsulfinilo" se refiere a un grupo alquil-SO- en el que el grupo alquilo es como se ha definido anteriormente. Los grupos preferidos son aquellos en los que el grupo alquilo es alquilo inferior.

La expresión "alquilsulfonilo" se refiere a un grupo alquil-SO2- en el que el grupo alquilo es como se ha definido anteriormente. Los grupos preferidos son aquellos en los que el grupo alquilo es alquilo inferior.

La expresión "alquilsulfonilcarbamoílo" se refiere a un grupo alquil-SO_2-NH-C(=O)- en el que el grupo alquilo es como se ha descrito en la presente memoria. Los grupos alquilsulfonilcarbamoílo preferidos son aquellos en los que el grupo alquilo es alquilo inferior.

El término "alquiltio" se refiere a un grupo alquil-S- en el que el grupo alquilo es como se ha descrito en la presente memoria. Los grupos alquiltio ejemplares incluyen metiltio, etiltio, *i*-propiltio y heptiltio.

El término "alquinilo" se refiere a un grupo hidrocarburo alifático que contiene en la cadena de aproximadamente 2 a aproximadamente 15 átomos de carbono, un triple enlace carbono-carbono y que puede ser lineal o ramificado. Los grupos alquinilo preferidos tienen de 2 a aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente de aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más de los grupos alquilo inferiores, tales como el grupo metilo, el grupo etilo o el grupo propilo, están unidos a una cadena alquinilo lineal. La expresión "alquinilo inferior" significa de aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena, que puede ser lineal o ramificada. El grupo alquinilo puede estar sustituido con uno o más halo. Los grupos alquinilo ejemplares incluyen etinilo, propinilo, *n*-butinilo, 2-butinilo, 3-metilbutinilo, *n*-pentinilo, heptinilo, octinilo, decinilo y similares. La expresión "alquinilo sustituido" se refiere a un grupo alquinilo como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo alifático" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria.

La expresión "grupo protector de amina" se refiere a un grupo que puede retirarse fácilmente que es conocido en la técnica por proteger a un resto de nitrógeno de un grupo amino frente a una reacción no deseada durante procedimientos sintéticos y, preferiblemente, por ser retirable de forma selectiva. El uso de grupos protectores de amina es bien conocido en la técnica para proteger grupos frente a reacciones indeseables durante un procedimiento sintético y muchos de estos grupos protectores son conocidos, por ejemplo, en T.W. Greene y P.G.M. Wuts, Protective Groups in Organic Synthesis, 2ª edición, John Wiley and Sons, New York (1991), incorporado en la presente memoria como referencia. Grupo protector de amina también incluye "grupo protector de amina lábil frente a ácidos" y "grupo protector de amina lábil frente a hidrogenación". Son grupos protectores de amina ejemplares acilo, incluyendo formilo, acetilo, cloroacetilo, tricloroacetilo, o-nitrofenilacetilo, o-nitrofenoxi-acetilo, trifluoroacetilo, acetoacetilo, 4-clorobutirilo, isobutirilo, o-nitrocinnamoílo, picolinoílo, acilisotiocianato, aminocaproílo, benzoílo y similares, y aciloxi, incluyendo metoxi-carbonilo, 9-fluorenilmetoxicarbonilo, 2,2,2-trifluoroetoxicarbonilo, 2-trimetilsililetoxi-carbonilo, viniloxicarbonilo, aliloxicarbonilo, *t*-butiloxicarbonilo (BOC), 1,1-dimetil-

propiniloxicarbonilo, benciloxicarbonilo (CBZ), p-nitrobenciloxicarbonilo, 2,4-dicloro-benciloxicarbonilo y similares.

La expresión "grupo protector de amida" se refiere a un grupo que puede retirarse fácilmente que se conoce en la técnica por proteger a un resto nitrógeno de un grupo amida frente a una reacción indeseable durante procedimientos sintéticos y porque puede retirarse de forma selectiva después de su conversión en la amida. El uso de grupos protectores de amida es bien conocido en la técnica para proteger grupos frente a reacciones indeseables durante un procedimiento sintético y muchos de estos grupos protectores son conocidos, por ejemplo, en T.W. Greene y P.G.M. Wuts, Protective Groups in Organic Synthesis, 2ª edición, John Wiley and Sons, New York (1991), incorporado en la presente memoria como referencia. Grupo protector de amida también incluye "grupo protector de amida lábil frente a ácidos" y "grupo protector de amida lábil frente a hidrogenación". Son grupos protectores de amida ejemplares o-nitrocinnamoílo, picolinoílo, aminocaproílo, benzoílo y similares, y aciloxi, incluyendo metoxi-carbonilo, 9-fluorenilmetoxicarbonilo, 2,2,2-trifluoroetoxicarbonilo, 2-trimetilsililetoxi-carbonilo, viniloxicarbonilo, aliloxicarbonilo, *t*-butiloxicarbonilo (BOC), 1,1-dimetil-propiniloxicarbonilo, benciloxicarbonilo (CBZ), p-nitrobenciloxicarbonilo, 2,4-dicloro-benciloxicarbonilo y similares.

Un "aminoácido", como se define en la presente memoria, se selecciona entre el grupo que consiste en aminoácidos naturales y no naturales. Un aminoácido también pretende incluir aminoácidos que tienen estereoquímica L o D en el carbono α. Los aminoácidos preferidos son los que poseen un grupo α-amino. Los aminoácidos pueden ser neutros, positivos o negativos, dependiendo de los sustituyentes de la cadena lateral. La expresión "aminoácido neutro" se refiere a un aminoácido que contiene sustituyentes de la cadena lateral no cargados. Los aminoácidos neutros ejemplares incluyen alanina, valina, leucina, isoleucina, prolina, fenilalanina, triptófano, metionina, glicina, serina, treonina y cisteína. La expresión "aminoácido positivo" se refiere a un aminoácido en el que los sustituyentes de la cadena lateral están cargados positivamente a pH fisiológico. Los aminoácidos positivos ejemplares incluyen lisina, arginina e histidina. La expresión "aminoácido negativo" se refiere a un aminoácido en el que los sustituyentes de la cadena lateral tienen una carga neta negativa a pH fisiológico. Los aminoácidos negativos ejemplares incluyen ácido aspártico y ácido glutámico. Son aminoácidos naturales ejemplares isoleucina, prolina, fenilalanina, triptófano, metionina, glicina, serina, treonina, cisteína, tirosina, asparagina, glutamina, lisina, arginina, histidina, ácido aspártico y ácido glutámico. La expresión "aminoácido no natural" se refiere a un

aminoácido para el que no existe un codón de ácido nucleico. Los aminoácidos no naturales ejemplares incluyen, por ejemplo, los D-isómeros de los α-aminoácidos naturales, como se ha indicado anteriormente; Aib (ácido aminobutírico), βAib (ácido 3-amino-isobutírico) Nva (norvalina), β-Ala, Aad (ácido 2-aminoadípico), βAad (ácido 3-aminoadípico), Abu (ácido 2-aminobutírico), Gaba (ácido γ-aminobutírico), Acp (ácido 6-aminocaproico), Dbu (ácido 2,4-diaminopropiónico), ácido α-aminopimélico, TMSA (trimetilsilil-Ala), alle (alloisoleucina), Nle (norleucina), *teri*-Leu, Cit (citrulina), Orn, Dpm (ácido 2,2'-diaminopimélico), α -o β- Nal, Cha (ciclohexil-Ala), hidroxiprolina, Sar (sarcosina) y similares; aminoácidos cíclicos; aminoácidos N^{a}-alquilados, tales como MeGly, (Na-metilglicina), EtGly (N^{a}-etilglicina) y EtAsn (Na-etilasparagina); y aminoácidos en los que el carbono α tiene dos sustituyentes en la cadena lateral. Los nombres de los aminoácidos naturales y no naturales y restos de los mismos usados en la presente memoria siguen las convenciones de nomenclatura sugeridas por la IUPAC Commission on the Nomenclature of Organic chemistry y la IUPAC-IUB Commission on Biochemical Nomenclature como se expone en "Nomenclature of a-Amino Acids (Recommendations, 1974)" Biochemistry, 14(2), (1975). Cuando los nombres y abreviaturas de aminoácidos y sus restos empleados en esta memoria descriptiva y en las reivindicaciones adjuntas difieran de los indicados, se proporcionarán nombres y abreviaturas diferentes.

La expresión "grupo protector de aminoácidos" se refiere a un grupo que protege a un resto de ácido o amina del aminoácido u otro resto reactivo en la cadena lateral de un aminoácido, por ejemplo, hidroxi o tiol. En relación con los ejemplos de "derivados protegidos correspondientes" de cadenas laterales de aminoácidos, véase T.W. Greene y P.G.M. Wuts en "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. En la presente memoria se describen grupos protectores para un grupo ácido en un aminoácido, por ejemplo, en las secciones "grupo funcional ácido" y "grupo protector de ácido lábil frente a hidrogenación". En la presente memoria se describen grupos protectores para un grupo amina de un aminoácido, por ejemplo, en las secciones "grupo protector de amina", "grupo protector de amina lábil frente a ácidos" y "grupo protector de amina lábil frente a hidrogenación".

La expresión "resto aminoacídico" se refiere a las unidades de aminoácidos individuales del compuesto de la invención.

La expresión "cadena lateral de aminoácidos" se refiere al sustituyente que se encuentra en el carbono situado entre los grupos amino y carboxi en α-aminoácidos. Las cadenas laterales de aminoácidos ejemplares incluyen isopropilo, metilo, y carboximetilo para valina, alanina y ácido aspártico, respectivamente.

La expresión "equivalente de aminoácido" se refiere a un aminoácido que puede usarse en vez de otro amionoácido en los péptidos de acuerdo con la invención sin ninguna pérdida de función apreciable. En la realización de tales cambios, se efectúan sustituciones de aminoácidos similares basándose en la relativa similitud de los sustituyentes de cadena lateral, por ejemplo, con respecto al tamaño, carga, hidrofilia, hidropatía e hidrofobia, como se describe en la presente memoria.

La expresión "grupo aromático" se refiere a arilo o heteroarilo, como se definen en la presente memoria. Los grupos aromáticos ejemplares incluyen fenilo, fenilo sustituido con halo, azaheteroarilo y similares.

El término "aroílo" se refiere a un grupo aril-CO, en el que el grupo arilo es como se describe en la presente memoria. Los grupos aroílo ejemplares incluyen benzoílo, 1- y 2-naftoílo y similares.

El término "arilo" se refiere a un sistema de anillos monocíclico o multicíclico, aromático, de aproximadamente 6 a aproximadamente 14 átomos de carbono, preferiblemente de aproximadamente 6 a 10 átomos de carbono. En el término arilo se incluyen cicloalquenilarilo condensado, cicloalquilarilo condensado, heterociclenilarilo condensado y heterociclilarilo condensado, como se define en la presente memoria, cuando se unen a través del resto arilo de los mismos. El arilo está opcionalmente sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3 sustituyentes, que pueden ser iguales o diferentes, y son como se definen en la presente memoria. Un "arilo sustituido" se refiere a un grupo arilo que está sustituido como se ha definido anteriormente. Los grupos arilo ejemplares incluyen fenilo o naftilo, o fenilo sustituido o naftilo sustituido.

El término "arildiazo" se refiere a un grupo aril-diazo en el que los grupos arilo y diazo son como se definen en la presente memoria.

El término "arileno" se refiere a un grupo arilo bivalente, 1,2-, 1,3-, 1,4-, opcionalmente sustituido, donde el grupo arilo es como se define en la presente memoria. La expresión "arileno sustituido" se refiere a un grupo arileno como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. Los grupos arileno ejemplares incluyen fenileno, naftileno e indanileno opcionalmente sustituidos. Un arileno particular es fenileno opcionalmente sustituido.

El término "ariloxi" se refiere a un grupo aril-O, en el que el grupo arilo es como se define en la presente memoria. Los grupos ariloxi ejemplares incluyen fenoxi y 2-naftiloxi.

El término "ariloxicarbonilo" se refiere a un grupo aril-O-CO- en el que el grupo arilo es como se define en la presente memoria. Los grupos ariloxicarbonilo ejemplares incluyen fenoxicarbonilo y naftoxicarbonilo.

El término "arilsulfonilo" se refiere a un grupo aril-SO_2- en el que el grupo arilo es como se define en la presente memoria.

El término "arilsulfonilcarbamoílo" se refiere a un grupo aril-SO_2-NH-C(=O)- en el que el grupo arilo es como se describe en la presente memoria. Un grupo arilsulfonilcarbamoílo ejemplar es fenilsulfonilcarbamoílo.

El término "arilsulfinilo" se refiere a un grupo aril-SO– en el que el grupo arilo es como se define en la presente memoria.

El término "ariltio" se refiere a un grupo aril-S-, en el que el grupo arilo es como se describe en la presente memoria.
Los grupos ariltio ejemplares incluyen feniltio y naftiltio.

La expresión "átomo de nitrógeno básico" se refiere a un átomo de nitrógeno hibridado sp^2 o sp^3 que tiene un par de electrones no unidos y que puede protonarse. Los átomos de

nitrógeno básicos ejemplares incluyen grupos imino opcionalmente sustituidos, amino opcionalmente sustituidos y amidino opcionalmente sustituidos.

El término "carboxi" se refiere a un grupo HO(O)C-(ácido carboxílico).

La expresión "agente de acoplamiento" se refiere a un compuesto que reacciona con el resto hidroxilo de un resto carboxi, haciendo que éste sea sensible al ataque nucleófilo. Los agentes de acoplamiento ejemplares incluyen DIC, EDCI, DCC y similares.

El término "cicloalquenilo" se refiere a un sistema de anillos mono- o multicíclico, no aromático, opcionalmente sustituido, de aproximadamente 3 a aproximadamente 10 átomos de carbono, preferiblemente de aproximadamente 5 a aproximadamente 10 átomos de carbono, y que contiene al menos un doble enlace carbono-carbono y que puede estar opcionalmente condensado con un grupo aromático como se define en la presente memoria. La expresión "cicloalquenilo condensado (aromático)" se refiere a arilcicloalquenilo condensado y heteroarilcicloalquenilo condensado, como se define en la presente memoria, unido a través del resto cicloalquenilo del mismo. Los tamaños preferidos de los anillos del sistema de anillos son de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo preferidos se denominan también "inferiores". La expresión "cicloalquenilo sustituido" se refiere a un grupo cicloalquenilo como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. Los grupos cicloalquenilo monocíclico ejemplares incluyen ciclopentenilo, ciclohexenilo, cicloheptenilo y similares. Un ejemplo de cicloalquenilo multicíclico es norbornilenilo.

El término "cicloalquilo" se refiere a un sistema de anillos mono- o multicíclico, no aromático, de aproximadamente 3 a aproximadamente 10 átomos de carbono, preferiblemente de aproximadamente 5 a aproximadamente 10 átomos de carbono, y que puede estar opcionalmente condensado con un grupo aromático como se define en la presente memoria. Los tamaños preferidos de los anillos del sistema de anillos incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo preferidos se denominan también "inferiores". La expresión "cicloalquilo condensado (aromático)" se refiere a arilcicloalquilo condensado y heteroarilcicloalquilo condensado, como se define en la presente

memoria, unido a través del resto cicloalquilo del mismo. La expresión "cicloalquilo sustituido" se refiere a un grupo cicloalquilo como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. Los anillos cicloalquilo monocíclicos ejemplares incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Los grupos cicloalquilo multicíclico ejemplares incluyen 1-decalina, norbornilo, adamant-(1- o 2-)ilo y similares.

El término "cicloalquileno" se refiere a un grupo cicloalquilo bivalente como se define en la presente memoria que tiene de aproximadamente 4 a aproximadamente 8 átomos de carbono. Los tamaños de anillo preferidos del cicloalquileno incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo preferidos se denominan también "inferiores". Los puntos de unión del grupo cicloalquileno incluyen patrones de unión 1,1-, 1,2-, 1,3- o 1,4- y cuando puede aplicarse la relación estereoquímica de los puntos de unión es cis o trans. Los grupos cicloalquileno monocíclico ejemplares incluyen (1,1-, 1,2- o 1,3-)ciclohexileno y (1,1- o 1,2-)ciclopentileno. La expresión "cicloalquileno sustituido" se refiere a un grupo cicloalquileno como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria.

El término "cíclico" o "ciclilo" se refiere a cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo, como se definen en la presente memoria. El término "inferior", como se usa con respecto al término cíclico, es el mismo que se ha indicado anteriormente con respecto a cicloalquilo, cicloalquenilo, heterociclilo o heterociclenilo.

El término "cicliloxi" se refiere a un grupo ciclil-O- en el que el grupo ciclilo es como se ha descrito en la presente memoria. Los grupos cicloalcoxi ejemplares incluyen ciclopentiloxi, ciclohexiloxi, quinuclidiloxi, pentametilenosulfidoxi, tetrahidropiraniloxi, tetrahidrotiofeniloxi, pirrolidiniloxi, tetrahidrofuranoiloxi o 7-oxabiciclo[2.2.1]heptaniloxi, hidroxitetrahidropiraniloxi, hidroxi-7-oxabiciclo[2.2.1]heptaniloxi y similares.

El término "ciclilsulfinilo" se refiere a un grupo ciclil-S(O)- en el que el grupo ciclilo es como se ha descrito en la presente memoria.

El término "ciclilsulfonilo" se refiere a un grupo ciclil-$S(O)_2$- en el que el grupo ciclilo es como se ha descrito en la presente memoria.

El término "cicliltio" se refiere a un grupo ciclil-S- en el que el grupo ciclilo es como se ha descrito en la presente memoria.

El término "diazo" se refiere a un radical -N=N- bivalente.

La expresión "resto desplazable" se refiere a un grupo que cuando está asociado con L, como se define en la presente memoria, es propenso a un posible desplazamiento por ataque nucleófilo por parte de un resto amina mono- o di-disustituido con o sin presencia de un agente que facilite dicho ataque, por ejemplo, un agente de acoplamiento. Los restos desplazables ejemplares incluyen hidroxi, oxi alifático, halo, N-oxisuccinimida, aciloxi y similares.

La expresión "cantidad eficaz" se refiere a una cantidad de un compuesto/composición de acuerdo con la presente invención que es eficaz para producir el efecto terapéutico deseado.

La expresión "arilcicloalquenilo condensado" se refiere a un arilo y cicloalquenilo condensados como se define en la presente memoria. Son arilcicloalquenilos condensados preferidos aquellos en los que el grupo arilo de los mismos es fenilo y el cicloalquenilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un arilcicloalquenilo condensado como una variable puede unirse a través de cualquier átomo de su sistema de anillos que sea capaz de ello. La expresión "arilcicloalquenilo condensado sustituido" se refiere a un grupo arilcicloalquenilo condensado como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. Los grupos arilcicloalquenilo condensado ejemplares incluyen 1,2-dihidronaftileno, indeno y similares.

La expresión "arilcicloalquilo condensado" se refiere a un arilo y cicloalquilo condensados como se define en la presente memoria. Los arilcicloalquilos condensados preferidos son

aquellos en los que el grupo arilo de los mismos es fenilo y el cicloalquilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un arilcicloalquilo condensado como una variable puede unirse a través de cualquier átomo de su sistema de anillos que sea capaz de ello. La expresión "arilcicloalquilo condensado sustituido" se refiere a un grupo arilcicloalquilo condensado como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. El arilcicloalquilo condensado ejemplar incluye 1,2,3,4-tetrahidro-naftileno y similares.

La expresión "arilheterociclenilo condensado" se refiere a un arilo y heterociclenilo condensados como se define en la presente memoria. Los arilheterociclenilos condensados preferidos son aquellos en los que el grupo arilo de los mismos es fenilo y el heterociclenilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un arilheterociclenilo condensado como una variable puede unirse a través de cualquier átomo de su sistema de anillos que sea capaz de ello. La designación de aza, oxa o tia como prefijo antes de la porción heterociclenilo del arilheterociclenilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. La expresión "arilheterociclenilo condensado sustituido" se refiere a un grupo arilheterociclenilo condensado como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. El átomo de nitrógeno de un arilheterociclenilo condensado puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heterociclenilo del arilheterociclenilo condensado también puede oxidarse opcionalmente en el N-óxido, S-óxido o S,S-dióxido correspondiente. Los ejemplos de arilheterociclenilo condensado incluyen 3H-indolinilo, 1H-2-oxoquinolilo, 2H-1-oxoisoquinolilo, 1,2-di-hidroquinolinilo, 3,4-dihidroquinolinilo, 1,2-dihidroisoquinolinilo, 3,4-dihidroisoquinolinilo y similares.

La expresión "arilheterociclilo condensado" se refiere a un arilo y heterociclilo condensados como se define en la presente memoria. Son arilheterociclilos condensados preferidos aquellos en los que el grupo arilo de los mismos es fenilo y el heterociclilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un arilheterociclilo condensado como una variable puede unirse a través de cualquier átomo de su sistema de

anillos que sea capaz de ello. La designación de aza, oxa o tia como prefijo antes de la porción heterociclilo del arilheterociclilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. La expresión "arilheterociclilo condensado sustituido" se refiere a un grupo arilheterociclilo condensado como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. El átomo de nitrógeno de un arilheterociclilo condensado puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heterociclilo del arilheterociclilo condensado también puede oxidarse opcionalmente para dar el N-óxido, S-óxido o S,S-dióxido correspondiente. Los sistemas de anillos arilheterociclilo condensado ejemplares incluyen indolinilo, 1,2,3,4-tetrahidroisoquinolina, 1,2,3,4- tetrahidroquinolina, 1H -2,3-dihidroisoindol- 2-ilo, 2,3-dihidrobenz[f]isoindol-2-ilo, 1,2,3,4- tetrahidrobenz[g]-isoquinolin-2-ilo y similares.

La expresión "heteroarilcicloalquenilo condensado" se refiere a un heteroarilo y cicloalquenilo condensados como se define en la presente memoria. Son heteroarilcicloalquenilos condensados preferidos aquellos en los que el grupo heteroarilo de los mismos es fenilo y el cicloalquenilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heteroaril-cicloalquenilo condensado como una variable puede unirse a través de cualquier átomo de su sistema de anillos que sea capaz de ello. La designación de aza, oxa o tia como prefijo antes de la porción heteroarilo del heteroarilcicloalquenilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. La expresión "heteroarilcicloalquenilo condensado sustituido" se refiere a un grupo heteroarilcicloalquenilo condensado como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 30) que pueden ser iguales o diferentes y son como se definen en la presente memoria. El átomo de nitrógeno de un heteroarilcicloalquenilo condensado puede ser un átomo de nitrógeno básico. El átomo de nitrógeno de la porción heteroarilo del heteroarilcicloalquenilo condensado también puede oxidarse opcionalmente para dar el N-óxido correspondiente. Los heteroarilcicloalquenilos condensados ejemplares incluyen 5,6-dihidroquinolilo, 5,6-dihidroisoquinolilo, 5,6-dihidroquinoxalinilo, 5,6-dihidroquinazolinilo, 4,5-dihidro-1H -bencimidazolilo, 4,5-dihidrobenzoxazolilo y similares.

La expresión "heteroarilcicloalquilo condensado" se refiere a un heteroarilo y cicloalquilo condensados como se define en la presente memoria. Los heteroarilcicloalquilos condensados preferidos son aquellos en los que el heteroarilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo y el cicloalquilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heteroarilcicloalquilo condensado como una variable puede unirse a través de cualquier átomo de su sistema de anillos que sea capaz de ello. La designación de aza, oxa o tia como prefijo antes de la porción heteroarilo del heteroarilcicloalquilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. La expresión "heteroarilcicloalquilo condensado sustituido" se refiere a un grupo heteroarilcicloalquilo condensado como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. El átomo de nitrógeno de un heteroarilcicloalquilo condensado puede ser un átomo de nitrógeno básico. El átomo de nitrógeno de la porción heteroarilo del heteroarilcicloalquilo condensado también puede oxidarse opcionalmente para dar el N-óxido correspondiente. Los heteroarilcicloalquilo condensado ejemplares incluyen 5,6,7,8-tetrahidroquinolinilo, 5,6,7,8-tetra-hidroisoquinolilo, 5,6,7,8-tetrahidroquinoxalinilo, 5,6,7,8- tetrahidroquinazolilo, 4,5,6,7-tetrahidro-1H-bencimidazolilo, 4,5,6,7-tetrahidrobenzoxazolilo, 1H-4-oxa-1,5- diazanaftalen-2-onilo, 1,3-dihidroimidizol-[4,5]-piridin-2-onilo y similares.

La expresión "heteroarilheterociclenilo condensado" se refiere a un heteroarilo y heterociclenilo condensados como se define en la presente memoria. Son heteroarilheterociclenilos condensados preferidos aquellos en los que el heteroarilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo y el heterociclenilo consiste en aproximadamente 5 a aproximadamente 6 átomos en el anillo. Un heteroarilheterociclenilo condensado como una variable puede unirse a través de cualquier átomo de su sistema de anillos que sea capaz de ello. La designación del aza, oxa o tia como prefijo antes de la porción heteroarilo o heterociclenilo del heteroarilheterociclenilo condensado define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. La expresión "heteroarilheterociclenilo condensado sustituido" se refiere a un grupo heteroarilheterociclenilo condensado como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente 1 a 3) que pueden ser

iguales o diferentes y son como se definen en la presente memoria. El átomo de nitrógeno de un heteroarilazaheterociclenilo condensado puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre de la porción heteroarilo del heteroarilheterociclilo condensado puede oxidarse también opcionalmente hasta el N-óxido correspondiente. El átomo de nitrógeno o azufre de la porción heteroarilo o heterociclilo del heteroarilheterociclilo condensado puede oxidarse también opcionalmente hasta el N-óxido, S- óxido o S,S-dióxido correspondiente. Los grupos heteroarilheterociclenilo condensado ejemplares incluyen 7,8-dihidro[1,7]naftiridinilo, 1,2-dihidro[2,7]-naftiridinilo, 6,7-dihidro-3H-imidazo[4,5-c]piridilo, 1,2-dihidro-1,5-naftiridinilo, 1,2-dihidro-1,6-naftiridinilo, 1,2-dihidro-1,7-naftiridinilo, 1,2-dihidro-1,8-naftiridinilo, 1,2-dihidro-2,6-naftiridinilo y similares.

"Halo" o "halógeno" significa flúor, cloro, bromo o yodo. Se prefieren flúor, cloro o bromo, y se prefieren más flúor o cloro.

El término "heteroaroílo" se refiere a un grupo heteroaril-CO-, en el que el grupo heteroarilo es como se ha descrito en la presente memoria. Los grupos heteroaroílo ejemplares incluyen tiofenoílo, nicotinoílo, pirrol-2-ilcarbonilo, 1- y 2-naftoílo, piridinoílo y similares.

El término "heteroarilo" se refiere a un sistema de anillos aromáticos monocíclicos o multicíclicos de aproximadamente 5 a aproximadamente 14 átomos de carbono, preferiblemente de aproximadamente 5 a aproximadamente 10 átomos de carbono, donde uno o más de los átomos del sistema de anillos es/son elemento(s) distintos de carbono, por ejemplo, nitrógeno, oxígeno o azufre. Preferiblemente, el sistema de anillos incluye de 1 a 3 heteroátomos. Los tamaños de anillo preferidos del sistema de anillos incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo. En el término heteroarilo se incluyen heteroarilcicloalquenilo condensado, heteroarilcicloalquilo condensado, heteroarilheterociclenilo condensado y heteroarilheterociclilo condensado, como se definen en la presente memoria, cuando se unen a través del resto heteroarilo de los mismos. La expresión "heteroarilo sustituido" se refiere a un grupo heteroarilo como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. La designación de aza, oxa o tia como prefijo antes del heteroarilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como

un átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede ser un átomo de nitrógeno básico y también puede oxidarse opcionalmente hasta el N-óxido correspondiente. Los grupos heteroarilo y heteroarilo sustituido ejemplares incluyen pirazinilo, tienilo, isotiazolilo, oxazolilo, pirazolilo, furazanilo, pirrolilo, 1,2,4-tiadiazolilo, piridazinilo, quinoxalinilo, ftalazinilo, imidazo[1,2-a]piridina, imidazo[2,1-b]tiazolilo, benzofurazanilo, azaindolilo, bencimidazolilo, benzotienilo, tienopiridilo, tienopirimidilo, pirrolopiridilo. imidazopiridilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo, furanilo, imidazolilo, indolilo, indolizinilo, isoxazolilo, isoquinolinilo, isotiazolilo, oxadiazolilo, pirazinilo, piridazinilo, pirazolilo, piridilo, pirimidinilo, pirrolilo, quinazolinilo, quinolinilo, 1,3,4-tiadiazolilo, tiazolilo, tienilo, triazolilo y similares. Un grupo heteroarilo preferido es pirazinilo.

El término "heteroarildiilo" se refiere a un radical bivalente obtenido a partir de un heteroarilo, donde el heteroarilo es como se ha descrito en la presente memoria. Un radical heteroarildiilo ejemplar es piridinadiilo opcionalmente sustituido.

El término "heteroarilsulfonilcarbamoílo" se refiere a un grupo heteroaril-SO_2-NH-C(=O)- en el que el grupo heteroarilo es como se ha descrito en la presente memoria.

El término "heterociclenilo" se refiere a un sistema de anillos de hidrocarburo monocíclico o multicíclico, no aromático, de aproximadamente 3 a aproximadamente 10 átomos de carbono, preferiblemente de aproximadamente 5 a aproximadamente 10 átomos de carbono, en el que uno o más de los átomos de carbono del sistema de anillos es/son heteroelemento(s) distinto(s) de carbono, por ejemplo átomos de nitrógeno, oxígeno o azufre, y que contiene al menos un doble enlace carbono-carbono o un doble enlace carbono-nitrógeno. Preferiblemente, el anillo incluye de 1 a 3 heteroátomos. Los tamaños de anillo preferidos de los anillos del sistema de anillos incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo preferidos se denominan también "inferiores". El término heterociclenilo incluye arilheterociclenilo condensado y heteroarilheterociclenilo condensado, como se define en la presente memoria, cuando se unen a través de su resto heterociclenilo. La designación de aza, oxa o tia como prefijo antes del heterociclenilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. La expresión "heterociclenilo sustituido" se refiere a un grupo heterociclenilo como se ha

definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. El átomo de nitrógeno de un heterociclenilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre del heterociclenilo puede oxidarse también opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los grupos azaheterociclenilo monocíclico ejemplares incluyen 1,2,3,4-tetrahidrohidropiridina, 1,2-dihidropiridilo, 1,4-dihidropiridilo, 1,2,3,6-tetra-hidropiridina, 1,4,5,6-tetrahidro-pirimidina, 2-pirrolinilo, 3-pirrolinilo, 2-imidazolinilo, 2-pirazolinilo y similares. Los grupos oxaheterociclenilo ejemplares incluyen 3,4-dihidro-2H-pirano, dihidrofuranilo y fluorodihidro-furanilo. Un grupo oxaheterociclenilo multicíclico ejemplar es 7-oxabiciclo[2.2.1]heptenilo. Los anillos tiaheterociclenilo monocíclico ejemplares incluyen dihidrotiofenilo y dihidrotiopiranilo.

El término "heterociclilo" se refiere a un sistema de anillos monocíclico o multicíclico, saturado, no aromático, de aproximadamente 3 a aproximadamente 10 átomos de carbono, preferiblemente de aproximadamente 5 a aproximadamente 10 átomos de carbono, donde uno o más de los átomos del sistema de anillos es/son heteroelemento(s) distintos de carbono, por ejemplo, nitrógeno, oxígeno o azufre. Preferiblemente, el sistema de anillos contiene de 1 a 3 heteroátomos. Los tamaños de anillo preferidos de los anillos del sistema de anillos incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo preferidos se denominan también "inferiores". El término heterociclilo incluye arilheterociclilo condensado y heteroarilheterociclilo condensado, como se define en la presente memoria, cuando se unen a través de su resto heterociclilo. La designación de aza, oxa o tia como prefijo antes del heterociclilo define que está presente al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, como un átomo del anillo. La expresión "heterociclilo sustituido" se refiere a un grupo heterociclilo como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria. El átomo de nitrógeno de un heterociclilo puede ser un átomo de nitrógeno básico. El átomo de nitrógeno o azufre del heterociclilo también puede oxidarse opcionalmente hasta el N-óxido, S-óxido o S,S-dióxido correspondiente. Los anillos heterociclilo monocíclico ejemplares incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,3-

dioxolanilo, 1,4-dioxanilo, tetrahidrofuranoílo, tetrahidrotiofenilo, tetrahidrotiopiranilo y similares.

El término "heterociclileno" se refiere a un grupo heterociclilo bivalente como se define en la presente memoria que tiene de aproximadamente 4 a aproximadamente 8 átomos de carbono. Los tamaños de anillo preferidos del heterociclileno incluyen de aproximadamente 5 a aproximadamente 6 átomos en el anillo; y tales tamaños de anillo preferidos se denominan también "inferiores". Los puntos de unión del grupo cicloalquileno incluyen patrones de unión 1,1-, 1,2-, 1,3- o 1,4- y cuando puede aplicarse la relación estereoquímica de los puntos de unión es cis o trans. Los grupos heterociclileno ejemplares incluyen (1,1-, 1,2- o 1,3-)piperidinileno y (1,1- o 1,2-)tetrahidrofuranileno. La expresión "heterociclileno sustituido" se refiere a un grupo heterociclileno como se ha definido anteriormente que está sustituido con uno o más "sustituyentes del grupo del anillo" (preferiblemente de 1 a 3) que pueden ser iguales o diferentes y son como se definen en la presente memoria.

El término "hidrato" se refiere a un solvato en el que la molécula o moléculas de disolvente es/son H_2O.

El término "N-óxido" se refiere a un resto de la siguiente estructura.

El término "paciente" incluye tanto seres humanos como otros mamíferos.

La expresión "éster farmacéuticamente aceptable" se refiere a ésteres que se hidrolizan *in vivo* e incluyen los que se rompen fácilmente en el cuerpo humano para dejar el compuesto parental o una sal del mismo. Los grupos éster adecuados incluyen, por ejemplo, los obtenidos a partir de ácidos carboxílicos alifáticos farmacéuticamente aceptables, particularmente ácidos alcanoico, alquenoico, cicloalcanoico y alcanodioico, en los que cada resto alquilo o alquenilo tiene ventajosamente no más de 6 átomos de carbono. Los ésteres ejemplares incluyen formiatos, acetatos, propionatos, butiratos, acrilatos, etilsuccinatos y similares.

La expresión "profármacos farmacéuticamente aceptables", como se usa en la presente memoria, se refiere a los profármacos de los compuestos de la presente invención que son, dentro del alcance de un criterio médico razonable, adecuados para el uso en contacto con los

tejidos de pacientes sin toxicidad indebida, irritación, respuesta alérgica y similares, en proporción con una relación beneficio/riesgo razonable y eficaces para el uso deseado de los compuestos de la invención. El término "profármaco" se refiere a compuestos que se transforman rápidamente in vivo para producir un compuesto parental de la fórmula anterior, por ejemplo por hidrólisis en la sangre. Los grupos funcionales que pueden transformarse rápidamente, por escisión metabólica, in vivo forman una clase de grupos reactivos con el grupo carboxilo de los compuestos de esta invención. Incluyen, pero sin limitación, grupos tales como alcanoílo (tales como acetilo, propanoílo, butanoílo y similares), aroílo no sustituido y sustituido (tales como benzoílo y benzoílo sustituido), alcoxicarbonilo (tales como etoxicarbonilo), trialquilsililo (tales como trimetilo y trietilsililo), monoésteres formados con ácidos dicarboxílicos (tales como succinilo) y similares. Gracias a la facilidad con la que los grupos escindibles metabólicamente de los compuestos de esta invención se escinden in vivo, los compuestos que llevan tales grupos actúan como profármacos. Los compuestos que llevan los grupos escindibles metabólicamente tienen la ventaja de que pueden mostrar una mejor biodisponibilidad como resultado de la mayor solubilidad y/o velocidad de absorción otorgada por el compuesto parental en virtud de la presencia del grupo metabólicamente escindible. Se proporciona un análisis minucioso en Design of Prodrugs, H. Bundgaard, ed., Elsevier (1985); Methods en Enzymology; K. Widder et al, Ed., Academic Press, 42, 309-396 (1985); Textbook of Drug Design and Development, Krogsgaard-Larsen y H. Bandaged, ed., capítulo 5; "Design and Applications of Prodrugs" 113-191 (1991); Advanced Drug Delivery Reviews, H. Bundgard, 8, 1-38, (1992); J. Pharm. Sci., 77, 285 (1988); Chem. Pharm. Bull., N. Nakeya et al, 32, 692 (1984); Pro-drugs as Novel Delivery Systems, T. Higuchi y V. Stella, 14 A.C.S. Symposium Series and Bioreversible Carriers en Drug Design, E.B. Roche, ed., American Pharmaceutical Association and Pergamon Press, 1987, que se incorporan en la presente memoria como referencia.

La expresión "sales farmacéuticamente aceptables" se refiere a las sales de adición de ácidos orgánicos e inorgánicos y a las sales de adición de bases, relativamente no tóxicas, de los compuestos de la presente invención. Estas sales pueden prepararse *in situ* durante el aislamiento y purificación final de los compuestos. En particular, las sales de adición de ácidos pueden prepararse haciendo reaccionar de forma separada el compuesto purificado en su forma de base libre con un ácido orgánico o inorgánico adecuado y aislando la sal formada de esta manera. Los ejemplos de sales de adición de ácidos incluyen las sales hidrobromuro,

hidrocloruro, sulfato, bisulfato, fosfato, nitrato, acetato, oxalato, valerato, oleato, palmitato, estearato, laurato, borato, benzoato, lactato, fosfato, tosilato, citrato, maleato, fumarato, succinato, tartrato, naftilato, mesilato, glucoheptonato, lactiobionato, sulfamatos, malonatos, salicilatos, propionatos, metileno-bis-ß-hidroxinaftoatos, gentisatos, isetionatos, di-p-toluoiltartratos, metanosulfonatos, etanosulfonatos, bencenosulfonatos, p-toluenosulfonatos, ciclohexilsulfamatos, laurilsulfonato y similares. Véase, por ejemplo, S.M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 66, 1-19 (1977) que se incorpora en la presente memoria como referencia. También pueden prepararse sales de adición de bases haciendo reaccionar por separado el compuesto purificado en su forma de ácido con una base orgánica o inorgánica adecuada y aislando la sal formada de esta manera. Las sales de adición de bases incluyen sales de metales y sales de aminas farmacéuticamente aceptables. Las sales de metales adecuadas incluyen las sales de sodio, potasio, calcio, bario, cinc, magnesio y aluminio. Se prefieren las sales de sodio y potasio. Las sales de adición de bases inorgánicas adecuadas se preparan a partir de bases de metales que incluyen hidruro sódico, hidróxido sódico, hidróxido potásico, hidróxido cálcico, hidróxido de aluminio, hidróxido de litio, hidróxido de magnesio, hidróxido de cinc y similares. Las sales de adición de bases de amina adecuadas se preparan a partir de aminas que tienen suficiente basicidad para formar una sal estable, y preferiblemente incluyen las aminas que se usan con frecuencia en la química medicinal debido a su baja toxicidad y aceptabilidad para uso en medicina, amoniaco, etilendiamina, N-metil-glucamina, lisina, arginina, ornitina, colina, N,N'-dibenciletilendiamina, cloroprocaína, dietanolamina, procaína, N-bencilfenetilamina, dietilamina, piperazina, tris(hidroximetil)-aminometano, hidróxido de tetrametilamonio, trietilamina, dibencilamina, efenamina, deshidroabietilamina, N-etilpiperidina, bencilamina, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, etilamina, aminoácidos básicos, por ejemplo, lisina y arginina, diciclohexilamina y similares.

La expresión "sustituyentes del grupo del anillo" se refiere a sustituyentes unidos a sistemas de anillos aromáticos o no aromáticos, incluyendo arilo, heteroarilo, hidroxi, alcoxi, cicliloxi, ariloxi, heteroariloxi, acilo o su análogo tioxo, ciclilcarbonilo o su análogo tioxo, aroílo o su análogo tioxo, heteroaroílo o su análogo tioxo, aciloxi, ciclilcarboniloxi, aroiloxi, heteroaroiloxi, halo, nitro, ciano, carboxi (ácido), -C(O)-NHOH -C(O)-CH_2OH, -C(O)-CH_2SH -C(O)-NH-CN, sulfo, fosfono, alquilsulfonilcarbamoílo, tetrazolilo, arilsulfonilcarbamoílo, N-metoxicarbamoílo, heteroarilsulfonilcarbamoílo, 3-hidroxi-3-

ciclobuteno-1,2-diona, 3,5-dioxo-1,2,4-oxadiazolidinilo o hidroxiheteroarilo, tal como 3-hidroxiisoxazolilo, 3-hidroxi-1-metilpirazolilo, alcoxicarbonilo, cicliloxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilsulfonilo, ciclilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, ciclilsulfinilo, arilsulfinilo, heteroarilsulfinilo, alquiltio, cicliltio, ariltio, heteroariltio, ciclilo, arildiazo, heteroarildiazo, tiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- o $Y^1Y^2NSO_2$-, donde Y^1, Y^2 e Y^3 son independientemente hidrógeno, alquilo, arilo o heteroarilo, o cuando el sustituyente es Y^1Y^2N-, entonces uno de Y^1 e Y^2 puede ser acilo, ciclilcarbonilo, aroílo, heteroaroílo, alcoxicarbonilo, cicliloxicarbonilo, ariloxicarbonilo o heteroariloxicarbonilo, como se define en la presente memoria, y el otro de Y^1 e Y^2 es como se ha definido previamente, o cuando el sustituyente es $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- o $Y^1Y^2NSO_2$-, Y^1 e Y^2 también pueden tomarse junto con el átomo de N a través del que Y^1 e Y^2 están unidos para formar un azaheterociclilo o azaheterociclenilo de 4 a 7 miembros. Cuando un sistema de anillos está saturado o parcialmente saturado, los "sustituyentes del grupo del anillo" incluyen además metileno (H2C=), oxo (O=) y tioxo (S=). Son sustituyentes del grupo del anillo ácido/amida carboxi (ácido), -C(O)-NHOH, -C(O)-CH_2OH, -C(O)-CH_2SH, -C(O)-NH-CN, sulfo, fosfono, alquilsulfonilcarbamoílo, tetrazolilo, arilsulfonilcarbamoílo, N-metoxicarbamoílo, heteroarilsulfonilcarbamoílo, 3-hidroxi-3-ciclobuteno-1,2-diona, 3,5-dioxo-1,2,4-oxadiazolidinilo o hidroxiheteroarilo, tal como 3-hidroxiisoxazolilo, 3-hidroxi-1-metilpirazolilo e Y^1Y^2NCO-. Son sustituyentes del grupo del anillo polar no ácido hidroxi, oxo (O=), tioxo (S=), acilo o su análogo tioxo, ciclilcarbonilo o su análogo tioxo, aroílo o su análogo tioxo, heteroaroílo o su análogo tioxo, alcoxicarbonilo, cicliloxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, aciloxi, ciclilcarboniloxi, aroiloxi, heteroaroiloxi, alquilsulfonilo, ciclilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquilsulfinilo, ciclilsulfinilo, arilsulfinilo, heteroarilsulfinilo, tiol, Y^1Y^2N-, $Y^1Y^2NC(O)$-, $Y^1Y^2NC(O)O$-, $Y^1Y^2NC(O)NY^3$- o $Y^1Y^2NSO_2$-.

La expresión "solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de disolvente. Esta asociación física incluye enlaces de hidrógeno. En ciertos casos, el solvato podrá aislarse, por ejemplo, cuando una o más de las moléculas de disolvente se incorporan en la red cristalina del sólido cristalino. La expresión "solvato"

incluye tanto los solvatos aislables como los solvatos en fase de solución. Los solvatos ejemplares incluyen hidratos, etanolatos, metanolatos y similares.

Farmacología

Métodos Experimentales y/o Ensayos Usados para Determinar la Actividad:

Ensayo FLIPR - CXCR5 humano:

Se miden cambios en los niveles de Ca^{2+} intracelular en la línea celular RBL transfectada de manera estable con ADN de CXCR5 humano. Se cultivan en placas 9.000 células/pocillo y se incuban a 37°C, con 5% de CO_2 20 h antes del ensayo. Al día siguiente, las células se lavan una vez con tampón de ensayo que contiene solución de Hank (Invitrogen, 14025-092) más HEPES 20 mM, pH 7,4 y se cargan con colorante por incubación durante 30 min a 37°C con 2 fluo-4 M/AM 2 μM (Molecular Probes, F14202) en tampón de ensayo más probenecid 2,5 mM. Las células se lavan 3 veces con tampón de ensayo y después se añaden a las células los compuestos en tampón de ensayo más BSA al 0,1%. Las células se lavan 3 veces más con tampón de ensayo y después se estimulan con CXCL13 humano 10 nM (R&D, 801-CX/CF). Los cambios de Ca^{2+} intracelular se registran usando el FLIPR 384-B (Molecular Devices).

Ensayo FLIPR - CXCR5 murino:

Se miden cambios en los niveles de Ca^{2+} intracelular en la línea celular RBL transfectada de manera estable con ADN de CXCR5 murino. Se cultivan en placas 9.000 células/pocillo y se incuban a 37°C, con 5% de CO_2 20 h antes del ensayo. Al día siguiente, las células se lavan una vez con tampón de ensayo que contiene solución de Hank (Invitrogen, 14025-092) más HEPES 20 mM, pH 7,4 y se cargan con colorante por incubación durante 30 min a 37°C con 2 fluo-4 M/AM 2 μM (Molecular Probes, F14202) en tampón de ensayo más probenecid 2,5 mM. Las células se lavan 3 veces con tampón de ensayo y después se añaden a las células los compuestos en tampón de ensayo más BSA al 0,1%. Las células se lavan 3 veces más con tampón de ensayo y después se estimulan con CXCL13 murino 6 nM (R&D,

470-BC). Los cambios de Ca^{2+} intracelular se registran usando el FLIPR 384-B (Molecular Devices).

Ensayo de GTPγS:

El ensayo de unión de [^{35}S]-GTPγS para CXCR5 se realiza usando membranas preparadas a partir de la línea celular RBL transfectada de manera estable con ADN de CXCR5 humano. Se mezclan conjuntamente GDP 2,5 μM, compuesto de ensayo a la concentración deseada (o DMSO en los controles), GTPγS no marcado 10 μM (o tampón en los controles) y 7,5 μg de membrana celular/pocillo (agitador de placas) durante 15 min a TA. Se añaden CXCL13 humano 750 nM y [^{35}S]-GTPγS 400 pM y la placa se agita durante 5 min a TA. Después, se añaden 1,134 mg/pocillo de perlas spa y la placa se agita durante 45 min a TA. La reacción se detiene por centrifugación a 230 g durante 10 minutos y la radiactividad se mide en un contador beta Wallac Microbeta Trilux.

Ensayo de Quimiotaxis:

Los pocillos de la placa de ensayo se recubren previamente con 150 μl de RPMI (sin rojo de fenol) que contenía BSA al 1% durante 2 h a temperatura ambiente. Se desecha el tampón previo al recubrimiento y los pocillos se lavan dos veces con tampón de ensayo CTX (véase más adelante). Se añaden células HS Sultan CXCR5^{+} (N° de Cat. de ATCC CRL 1484) a la cámara superior de la placa Transwell (Millipore, N° de Cat. MAMI C5S 10) a 0,6 x10^{5} células/pocillo y se incuban con compuesto de ensayo durante 15 min a TA. A la cámara inferior se le añade ligando CXCL13 a 100 nM (R&D, n° de cat. 801-cx/cf) o tampón **CTX** (RPMI sin rojo de fenol suplementado con BSA al 0,02%, piruvato Na 1 mM). Las dos cámaras se ensamblan y se incuban a 37°C durante 2 h. Posteriormente, la cámara superior se retira y las células de la cámara inferior se cuentan después de añadir reactivo colorimétrico (Promega N° Cat G3581) y de realizar la lectura a DO_{490}. Migración específica de CXCR5 = células que migraron en total - células que migraron de manera espontánea (pocillos que contenían tampón CTX sin ligando).

Los datos experimentales que se proporcionan a continuación son una representación de la actividad inhibidora indicada por los valores de CI_{50} para los ejemplos de la presente

memoria. Las realizaciones particulares que se presentan más adelante son ilustrativas y no limitan los equivalentes relacionados.

Tabla I

EJEMPLO	**CI50**
5	2,4
	0,493
18	3,65
7	0,844
	0,425
	0,105
38	0,675
9	0,47
11	2,93
13	1,08
24	ND
26	ND
44	~13
42	5,45
52	>30
46	19,6
119	>30
36	>30
56	>30
58	>30
48	>30
121	ND
29	~24
75	2,85
79	ND
87	0,298
81	~9,5
54	>30
77	ND
93	18,2
91	~27
89	17,35
97	0,537
103	0,38
99	~7,8
85	6,1
95	14,75
112	>30
111	~20,5
108	>30
109	>30
107	~30
116	>30
115	~10,15
113	>30
117	>30
123	19,3

125	0,099
127	2,3
129	15,25
132	0,056
21	0,268
135	0,033
130	3,87
133	0,533
32	~16
34	~13
138	8,2
143	0,232
146	0,446
144	0,023
141	1,05
139	0,097
60	>30
149	0,011
62	~30
152	0,013
64	>30
154	0,2
152	0,013
397	0,026
136	0,014
232	0,007
161	0,045
155	0,047
132	0,056
150	0,015
231	0,030
158	0,015
395	0,009
388	0,005
392	0,038
159	0,017

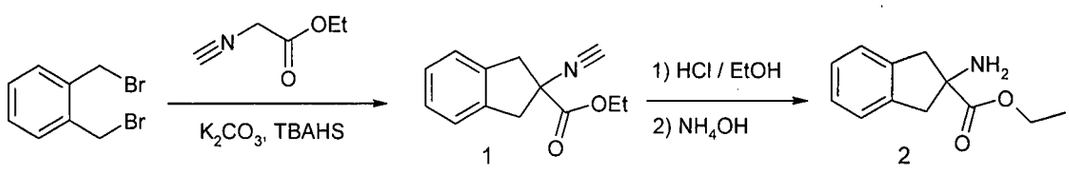
Preparación de compuestos de la invención

Los materiales de partida e intermedios de compuestos de la invención pueden prepararse por la aplicación o adaptación de métodos conocidos que se describen a continuación, sus equivalentes químicos evidentes o, por ejemplo, como se describe en la bibliografía por R.C. Larock en Comprehensive Organic Transformations, VCH publishers (1989).

La purificación por HPLC se refiere a cromatografía líquida preparativa de alta resolución usando las siguientes condiciones: [columna C18, tamaño de partículas de 10 micrómetros, gradiente de elución: CH_3CN al 20-100% (TFA al 0,1%) en H_2O (TFA al 0,1%)].

EJEMPLOS

EJEMPLO 1



Éster etílico del ácido isociano-indan-2-carboxílico (1):

A una solución de isocianoacetato de etilo (4,29 g, 37,9 mmol) en ACN anhidro (400 ml) se le añaden K_2CO_3 anhidro (K_2SO_4, 31,4 g, 227 mmol), TBAHS (hidrogenosulfato de tetrabutilamonio, 2,57 g, 7,58 mmol) y 1,2-bis-bromometil-benceno (10,0 g, 37,9 mmol). La mezcla heterogénea resultante se agita a 75°C durante una noche. La mezcla de reacción se enfría a TA y se filtra para retirar las sales indeseadas. La torta de filtro se lava con ACN (20 ml) y el filtrado se concentra al vacío. El residuo se disuelve en éter etílico (150 ml) y se lava con agua (1 x 10 ml) y salmuera (3 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (400 g de gel de sílice; gradiente de elución: EtOAc al 20-100% en heptano) para dar un producto puro en forma de un sólido de color blanco (8,0 g, 49%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,35 (t, 3H), 3,47 (d, 2H), 3,71 (d, 2H), 4,32 (c, 2H), 7,25 (s, 4H)

LC/MS (ES+) m/z = 449,25

EJEMPLO 2

Éster etílico del ácido 2-amino-indan-2-carboxílico (2):

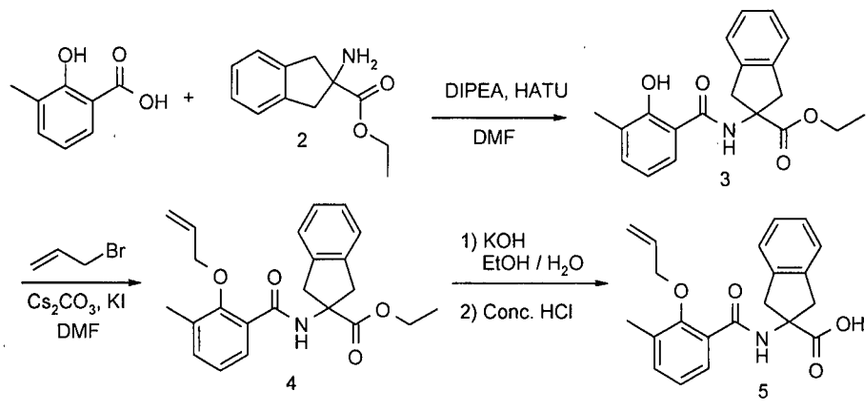
A una solución de éster etílico del ácido 2-isociano-indan-2-carboxílico (1) (8,0 g, 37,2 mmol) en EtOH absoluto (200 ml) se le añade gota a gota HCl concentrado (5 ml). La solución resultante se agita a TA durante 5 h. Después de la retirada del EtOH al vacío, la sal

hidrocloruro restante se disuelve en agua (100 ml) y se extrae con éter etílico (3 x 5 ml) para retirar las impurezas orgánicas indeseadas. La capa acuosa se lleva a un valor de pH = 10 mediante la adición de una solución de NH_4OH y después se extrae con EtOAc (3 x 50 ml). La capa de EtOAc combinada se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 y se concentra al vacío para dar un producto puro en forma de un sólido de color blanco (4,7 g, 62%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 2,88 (d, 2H), 3,57 (d, 2H), 4,23 (c, 2H), 7,16-7,23 (m, 4H)

LC/MS (EZ+) m/z = 206,08

EJEMPLO 3



<u>Éster etílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-indan-2-carboxílico (3):</u>

A una solución de ácido 2-hidroxi-3-metil-benzoico (3,65 g, 24 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (5,00 g, 24 mmol) y HATU [O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio PF_6] (11,0 g, 29 mmol) en DMF anhidra (30 ml) se le añade DIPEA (8,30 ml, 50 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (150 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (400 g de gel de sílice, gradiente de elución: EtOAc al 10-80% en heptano) para dar un producto puro (3) en forma de un sólido de color blanco (5,5 g, 67%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 2,23 (s, 3H), 3,40 (d, 2H), 3,74 (d, 2H), 4,25 (c, 2H), 6,70 (t, 1H), 6,84 (s, 1H), 7,15-7,25 (m, 6H), 12,21 (s, 1H)

LC/MS (ES+) m/z = 340,15

EJEMPLO 4

Éster etílico del ácido 2-(2-aliloxi-3-metil-benzoilamino)-indan-2-carboxílico (4):

A una suspensión de éster etílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-indan-2-carboxílico (3) (300 mg, 0,88 mmol), Cs_2CO_3 anhidro (573 mg, 1,76 mmol) y KI (30 mg, 0,18 mmol) en DMF (8 ml) se le añade 3-bromo-propeno (90 µl, 1,06 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (30 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10-30% en heptano) para dar un producto puro (4) en forma de un sólido de color blanco (303 mg, 91%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,25 (t, 3H), 2,26 (s, 3H), 3,33 (d, 2H), 3,75 (d, 2H), 4,25 (c, 2H), 5,21 (d, 1H), 5,33 (d, 1H), 5,86 (m, 1H), 7,09 (t, 1H), 7,19 (s a, 4H), 7,27 (d, 1H), 7,88 (d, 1H), 8,43 (s, 1H)

LC/MS (ES+) m/z = 380,20

EJEMPLO 5

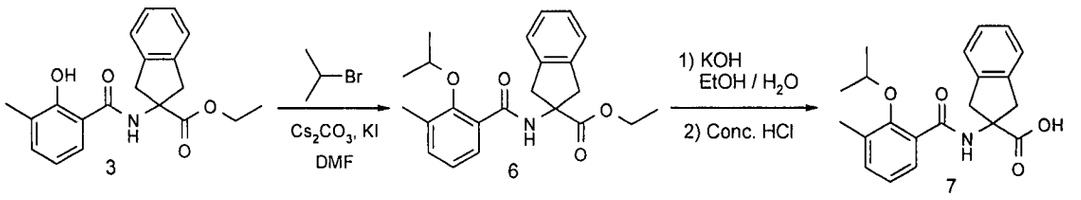
Ácido 2-(2-aliloxi-3-metil-benzoilamino)-indan-2-carboxílico (5):

La mezcla de éster etílico del ácido 2-(2-aliloxi-3-metil-benzoilamino)-indan-2-carboxílico (4) (168 mg, 0,44 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (5) en forma de un sólido de color blanco (150 mg, 97%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 2,26 (s, 3H), 3,34 (d, 2H), 3,77 (d, 2H), 4,23 (d, 2H), 5,20 (d, 1H), 5,32 (d, 1H), 5,84 (m, 1H), 7,10 (t, 1H), 7,16-7,23 (m, 4H), 7,29 (d, 1H), 7,83 (dd, 1H), 8,57 (s, 1H)

LC/MS (ES+) m/z = 352,15

EJEMPLO 6



Éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (6):

A una suspensión de éster etílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-indan-2-carboxílico (3) (300 mg, 0,88 mmol), Cs_2CO_3 anhidro (573 mg, 1,76 mmol) y KI (30 mg, 0,18 mmol) en DMF (10 ml) se le añade 2-bromo-propano (330 µl, 3,52 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10-40% en heptano) para dar un producto puro (6) en forma de un sólido de color blanco (174 mg, 52%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,03 (d, 6H), 1,24 (t, 3H), 2,25 (s, 3H), 3,34 (d, 2H), 3,77 (d, 2H), 4,21 (m, 1H), 4,25 (c, 2H), 7,07 (t, 1H), 7,17-7,26 (m, 5H), 7,85 (dd, 1H), 8,31 (s, 1H)
LC/MS (ES+) m/z = 382,18

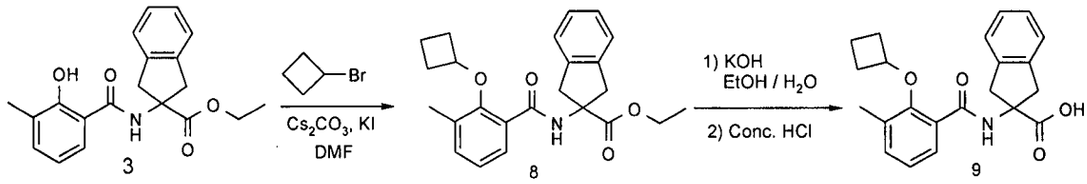
EJEMPLO 7

Ácido 2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (7):

La mezcla de éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (6) (265 mg, 0,69 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (6 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y la solución se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (7) en forma de un sólido de color blanco (244 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,98 (d, 6H), 2,24 (s, 3H), 3,41 (d, 2H), 3,85 (d, 2H), 4,14 (m, 1H), 7,08 (t, 1H), 7,18-7,30 (m, 5H), 7,88 (d, 1H), 8,52 (s, 1H)
LC/MS (ES+) m/z = 354,16

EJEMPLO 8



Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (8):

A una suspensión de éster etílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-indan-2-carboxílico (3) (400 mg, 1,18 mmol), Cs_2CO_3 anhidro (769 mg, 2,36 mmol) y KI (40 mg, 0,24 mmol) en DMF (10 ml) se le añade bromo-ciclobutano (130 µl, 1,42 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10-40% en heptano) para dar un producto puro (8) en forma de un sólido de color blanco (320 mg, 69%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,25 (t, 3H), 1,18-1,34 (m, 1H), 1,41-1,52 (m, 1H), 1,87-2,07 (m, 4H), 2,26 (s, 3H), 3,36 (d, 2H), 3,78 (d, 2H), 4,22 - 4,29 (m, 1H), 4,24 (c, 2H), 7,07 (t, 1H), 7,17-7,27 (m, 5H), 7,86 (dd, 1H), 8,33 (s, 1H)
LC/MS (ES+) m/z = 394,19

EJEMPLO 9

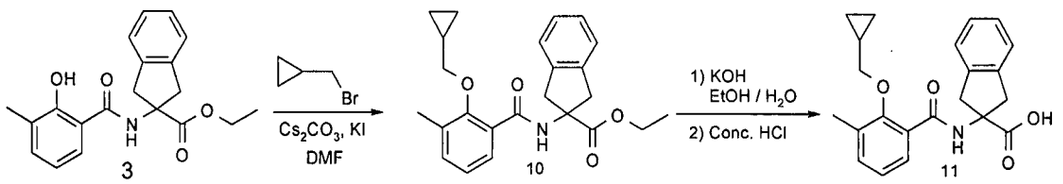
Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (9):

La mezcla de éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (8) (250 mg, 0,64 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y la solución se acidifica con

HCl conc. hasta alcanzar un valor de pH de ~3 para producir un precipitado. El precipitado se filtra para dar un producto puro (9) en forma de un sólido de color blanco (190 mg, 81%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,24 (m, 1H), 1,45 (m, 1H), 1,87-2,01 (m, 4H), 2,26 (s, 3H), 3,40 (d, 2H), 3,81 (d, 2H), 4,26 (m, 1H), 7,08 (t, 1H), 7,18-7,29 (m, 5H), 7,82 (dd, 1H), 8,48 (s, 1H)
LC/MS (ES+) m/z = 366,16

EJEMPLO 10



Éster etílico del ácido 2-(2-ciclopropilmetoxi-3-metil-benzoilamino)-indan-2-carboxílico (10):

A una suspensión de éster etílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-indan-2-carboxílico (3) (400 mg, 1,18 mmol), Cs_2CO_3 anhidro (769 mg, 2,36 mmol) y KI (40 mg, 0,24 mmol) en DMF (10 ml) se le añade bromometilciclopropano (229 µl, 2,36 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (30 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10-40% en heptano) para dar un producto puro (10) en forma de un sólido de color blanco (330 mg, 71%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,17 (m, 2H), 0,50 (m, 2H), 0,91 (m, 1H), 1,24 (t, 3H), 2,26 (s, 3H), 3,36 (d, 2H), 3,54 (d, 2H), 3,79 (d, 2H), 4,24 (c, 2H), 7,08 (t, 1H), 7,15-7,27 (m, 5H), 7,86 (dd, 1H), 8,44 (s, 1H)
LC/MS (ES+) m/z = 394,18

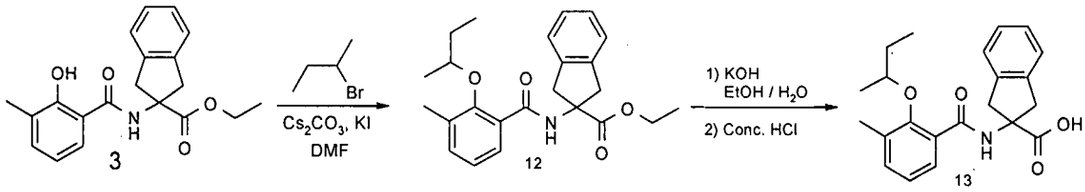
EJEMPLO 11

Ácido 2-(2-ciclopropilmetoxi-3-metil-benzoilamino)-indan-2-carboxílico (11):

La mezcla de éster etílico del ácido 2-(2-ciclopropilmetoxi-3-metil-benzoilamino)-indan-2-carboxílico (10) (240 mg, 0,61 mmol) y KOH (500 mg, 8,93 mmol) se disuelve en EtOH (6 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (11) en forma de un sólido de color blanco (223 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,11 (m, 2H), 0,51 (m, 2H), 0,84 (m, 1H), 2,26 (s, 3H), 3,46 (dd, 4H), 3,88 (d, 2H), 7,11 (t, 1H), 7,17-7,32 (m, 5H), 7,89 (d, 1H), 8,74 (s, 1H)
LC/MS (ES+) m/z = 366,17

EJEMPLO 12



<u>Éster etílico del ácido 2-(2-sec-butoxi-3-metil-benzoilamino)-indan-2-carboxílico (12):</u>

A una suspensión de éster etílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-indan-2-carboxílico (3) (400 mg, 1,18 mmol), Cs_2CO_3 anhidro (574 mg, 2,36 mmol) y KI (40 mg, 0,24 mmol) en DMF (10 ml) se le añade 2-bromobutano (508 µl, 4,72 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (30 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10-40% en heptano) para dar un producto puro (12) en forma de un sólido de color blanco (395 mg, 85%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,80 (t, 3H), 0,93 (d, 3H), 1,22-1,30 (m, 4H), 1,48 (m, 1H), 2,25 (s, 3H), 3,33 (dd, 2H), 3,76 (dd, 2H), 3,97 (m, 1H), 4,25 (c, 2H), 7,01 (t, 1H), 7,17-7,26 (m, 5H), 7,87 (dd, 1H), 8,35 (s, 1H)
LC/MS (ES+) m/z = 396,19

EJEMPLO 13

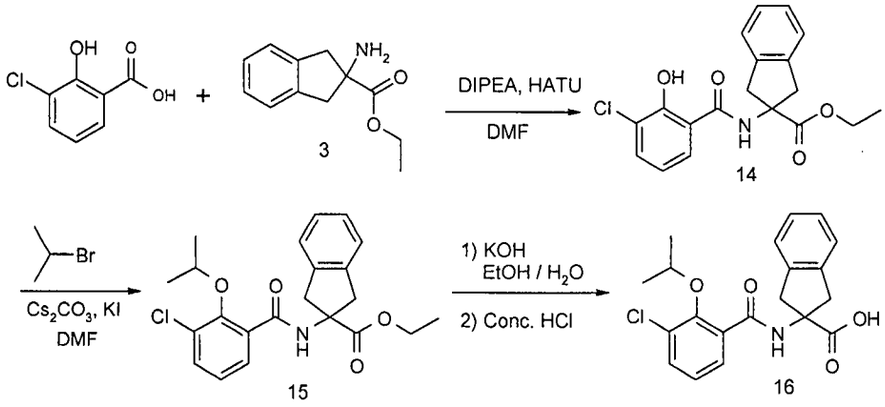
Ácido 2-(2-sec-butoxi-3-metil-benzoilamino)-indan-2-carboxílico (13):

La mezcla de éster etílico del ácido 2-(2-sec-butoxi-3-metil-benzoilamino)-indan-2-carboxílico (12) (176 mg, 0,44 mmol) y KOH (500 mg, 8,93 mmol) se disuelve en EtOH (6 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (13) en forma de un sólido de color blanco (162 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,79 (t, 3H), 0,86 (d, 3H), 1,18 (m, 1H), 1,49 (m, 1H), 2,25 (s, 3H), 3,42 (t, 2H), 3,86 (dd, 2H), 3,91 (m, 1H), 7,09 (t, 1H), 7,19-7,31 (m, 5H), 7,90 (d, 1H), 8,59 (s, 1H)

LC/MS (ES+) m/z = 368,17

EJEMPLO 14



Éster etílico del ácido 2-(3-cloro-2-hidroxi-benzoilamino)-indan-2-carboxílico (14):

A una solución de ácido 3-cloro-2-hidroxi-benzoico (413 mg, 2,4 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (500 mg, 2,4 mmol) y HATU (1,1 g, 2,9 mmol) en DMF anhidra (10 ml) se le añade DIPEA (0,88 ml, 5,3 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10%-80% en heptano) para dar un producto puro (14) en forma de un sólido de color blanco (420 mg, 49%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 3,42 (d, 2H), 3,73 (d, 2H), 4,25 (c, 2H), 6,76 (t, 1H), 6,97 (s, 1H), 7,23-7,29 (m, 5H), 7,47 (dd, 1H), 12,5 (s, 1H)
LC/MS (ES+) m/z = 360,07, 362,08

EJEMPLO 15

Éster etílico del ácido 2-(3-cloro-2-isopropoxi-benzoilamino)-indan-2-carboxílico (15):

A una suspensión de éster etílico del ácido 2-(3-cloro-2-hidroxi-benzoilamino)-indan-2-carboxílico (14) (150 mg, 0,42 mmol), Cs_2CO_3 anhidro (274 mg, 0,84 mmol) y KI (13 mg, 0,08 mmol) en DMF (7 ml) se le añade 3-bromo-propeno (237 µl, 2,52 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (80 g de gel de sílice, gradiente de elución: EtOAc al 10-40% en heptano) para dar un producto puro (15) en forma de un sólido de color blanco (137 mg, 81%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,05 (d, 6H), 1,24 (t, 3H), 3,33 (d, 2H), 3,76 (d, 2H), 4,25 (c, 2H), 4,56 (m, 1H), 7,11 (t, 1H), 7,19-7,26 (m, 4H), 7,46 (dd, 1H), 7,95 (dd, 1H), 8,28 (s, 1H)
LC/MS (ES+) m/z = 404,14

EJEMPLO 16

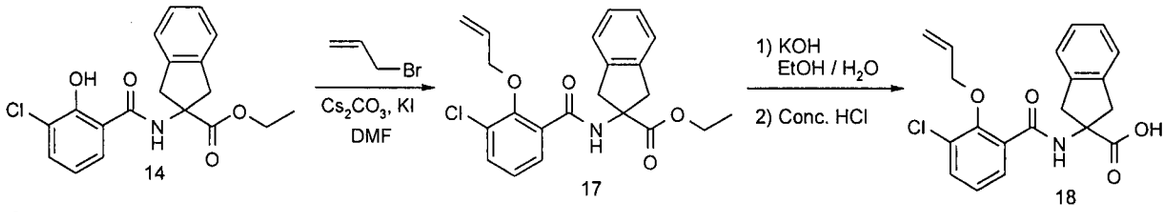
Ácido 2-(3-cloro-2-isopropoxi-benzoilamino)-indan-2-carboxílico (16):

La mezcla de éster etílico del ácido 2-(3-cloro-2-isopropoxi-benzoilamino)-indan-2-carboxílico (15) (122 mg, 0,30 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (16) en forma de un sólido de color blanco (119 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,01 (d, 6H), 3,40 (d, 2H), 3,84 (d, 2H), 4,55 (m, 1H), 7,13 (t, 1H), 7,19-7,26 (m, 4H), 7,48 (dd, 1H), 7,98 (dd, 1H), 8,43 (s, 1H)

LC/MS (ES+) m/z = 376,13

EJEMPLO 17



Éster etílico del ácido 2-(2-aliloxi-3-cloro-benzoilamino)-indan-2-carboxílico (17):

A una suspensión de éster etílico del ácido 2-(3-cloro-2-hidroxi-benzoilamino)-indan-2-carboxílico (14) (250 mg, 0,69 mmol), Cs_2CO_3 anhidro (453 mg, 1,39 mmol) y KI (23 mg, 0,14 mmol) en DMF (10 ml) se le añade 3-bromo-propeno (70 µl, 0,83 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (80 g de gel de sílice, gradiente de elución: EtOAc al 10-40% en heptano) para dar un producto puro (17) en forma de un sólido de color blanco (160 mg, 58%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,25 (t, 3H), 3,32 (d, 2H), 3,75 (d, 2H), 4,25 (c, 2H), 4,41 (d, 2H), 5,20-5,34 (m, 2H), 5,88 (m, 1H), 7,13-7,26 (m, 5H), 7,49 (dd, 1H), 7,97 (dd, 1H), 8,36 (s, 1H)

LC/MS (ES+) m/z = 404,14

EJEMPLO 18

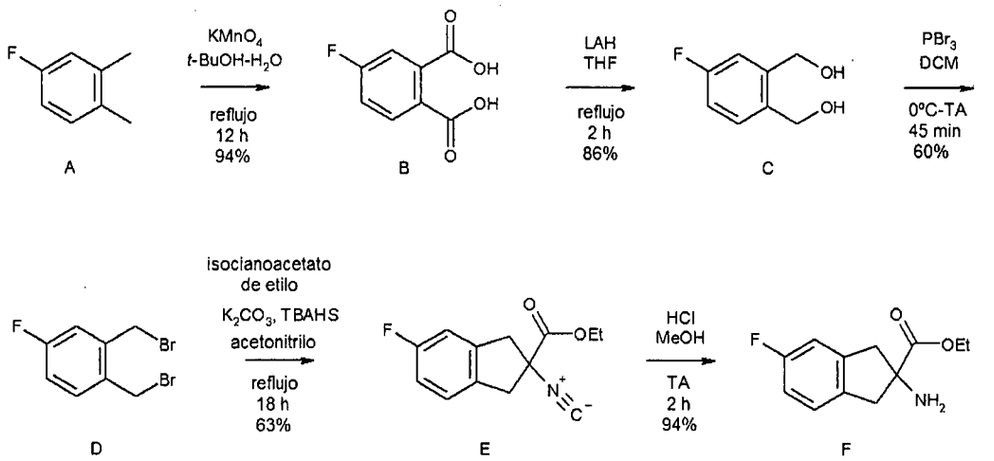
Ácido 2-(2-aliloxi-3-cloro-benzoilamino)-indan-2-carboxílico (18):

La mezcla de éster etílico del ácido 2-(2-aliloxi-3-cloro-benzoilamino)-indan-2-carboxílico (17) (140 mg, 0,35 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~3. Después de la filtración, el sólido se purifica por HPLC para dar un producto puro (18) en forma de un sólido de color blanco (88 mg, 68%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,35 (d, 2H), 3,78 (d, 2H), 4,41 (d, 2H), 5,21-5,34 (m, 2H), 5,87 (m, 1H), 7,13-7,30 (m, 5H), 7,50 (dd, 1H), 7,93 (dd, 1H), 8,49 (s, 1H)
LC/MS (ES+) m/z = 372,09, 374,10

EJEMPLO 19

Éster etílico del ácido 2-amino-5-fluoroindan-2-carboxílico



Preparación de B: Se disuelven 4-fluoro-1,2-dimetilbenceno **A** (50,0 g, 402,7 mmol) y un gran exceso de $KMnO_4$ (400 g, 2,54 mol) en 1500 ml de una mezcla de agua/t-butanol (70/30%, v/v). La mezcla de reacción se calienta a reflujo durante una noche. Se añade EtOH (900 ml) para destruir el $KMnO_4$ que no ha reaccionado y los alcoholes se retiran por destilación. La suspensión de color pardo resultante se filtra a través de una capa de celite. La solución incolora se concentra y se acidifica con HCl conc. a un valor de pH de 1. El producto se filtra y la fase acuosa se extrae con EtOAc y se seca sobre Na_2SO_4. Se obtienen 70,0 g (94%) del sólido de color blanco B después de la evaporación a presión reducida.

^{1}H RMN (400 MHz, DMSO-d_6): δ 7,39 (m, 1H), 7,63 (s a, 1H), 7,99 (s a, 1H).

Preparación de C: Se añade LAH (37,5 g, 989 mmol) a THF (850 ml). La mezcla se enfría en un baño de hielo y se añade gota a gota el ácido 4-fluoroftálico B (70,0 g, 380 mmol) en THF (420 ml). Después de la adición, la mezcla de reacción se calienta a reflujo durante 2 h. La mezcla se enfría en un baño de hielo y se añaden gota a gota agua (35 ml), NaOH acuoso al 15% (35 ml) y agua (70 ml). El material sólido se retira por filtración, se lava con DCM y las

soluciones orgánicas combinadas se secan sobre Na_2SO_4 y se evaporan a presión reducida para dar 51,2 g (86%) de C.

^{1}H RMN (400 MHz, $CDCl_3$): 4,71 (t, J = 4,5 Hz, 4H), 6,98 (m, 1H), 7,08 (m, 1H), 7,29 (m, 1H).

Preparación de D: A una solución de 2-hidroxi-metil-5-fluoro-fenil-metanol C (51,2 g, 327,8 mmol) en 520 ml de DCM se le añade gota a gota tribromuro de fósforo (37,3 ml, 393,5 mmol) en DCM (520 ml) a 0°C en una atmósfera de N_2 y la mezcla se agita durante 45 min. La mezcla de reacción se inactiva con agua (70 ml), que se añade lentamente, se extrae con EtOAc y se lava con agua, con una solución sat. de Na_2SO_4 y salmuera. La capa orgánica se evapora a presión reducida para dar el producto en bruto, que se purifica con una columna de gel de sílice de malla 100-200 eluyendo con hexano para dar 55,8 g (60%) de D.

^{1}H RMN (400 MHz, $CDCl_3$): 4,61 (m, 4H), 6,99 (m, 1H), 7,07 (m, 1H), 7,33 (m, 1H).

Preparación de E: Una solución de 5-fluoro-1,2-bisbromometilbenceno (20,4 g, 72,3 mmol), isocianoacetato de etilo (5,7 ml, 51 mmol), hidrogenosulfato de tetrabutilamonio (6,7 g, 19,7 mmol) y K_2SO_4 seco (41,8 g, 303 mmol) en ACN (1500 ml) se calienta a reflujo durante 18 h. Después de que se complete la reacción, la mezcla se enfría y se filtra. El filtrado se concentra a presión reducida y se disuelve con EtOAc. La capa orgánica se lava con agua y salmuera, se seca sobre Na_2SO_4 y se concentra a presión reducida. La masa en bruto obtenida se purifica con una columna de gel de sílice de malla 100-200 eluyendo con EtOAc al 5%-hexano para dar 10,8 g (63%) de E.

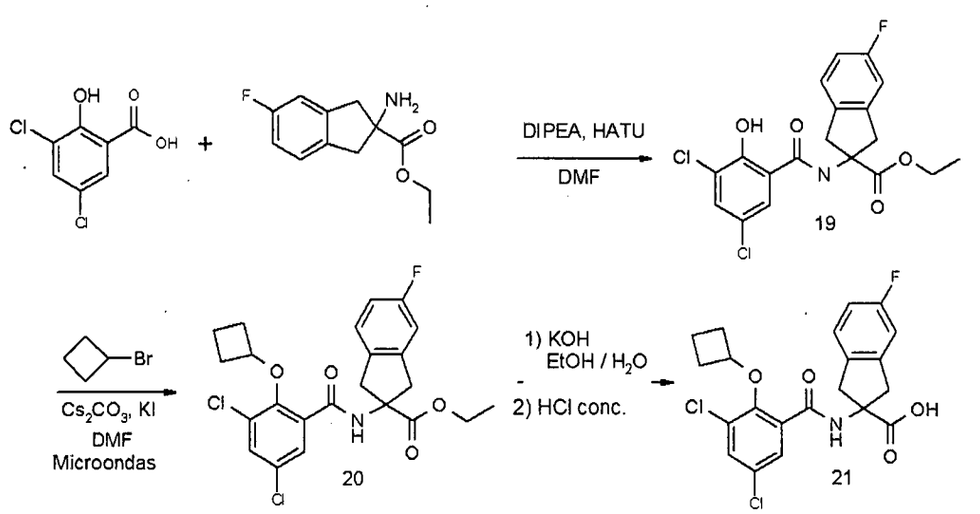
^{1}H RMN (400 MHz, $CDCl_3$): 1,32 (m, 3H), 3,43 (m, 2H), 3,66 (m, 2H), 4,32 (m, 2H), 6,94 (m, 2H), 7,17 (m, 1H).

Preparación de F: una solución metanólica de HCl conc. (al 35%) (9,3 ml en 110 ml de MeOH) se añade gota a gota a una solución metanólica de éster etílico del ácido 5-fluoro-2-isociano-indan-2-carboxílico E (17,6 g, 75,4 mmol) a TA y la mezcla se agita durante 2 h. Después, la mezcla se neutraliza con una solución saturada de $NaHCO_3$ y se extrae con DCM (500 ml). La capa orgánica se lava con agua y salmuera, se seca sobre Na_2SO_4 y se concentra

a presión reducida para obtener 16,0 g (94%) del compuesto F en forma de un semisólido de color amarillento.

^{1}H RMN (400 MHz, $CDCl_3$): 1,26 (c, 3H), 1,62 (s a, 2H), 2,84 (m, 2H), 3,50 (c, 2H), 4,20 (m, 2H), 6,88 (m, 2H), 7,12 (t, J = 7,6 Hz, 1H). ^{1}H RMN (400 MHz, intercambio de D_2O, $CDCl_3$): 1,26 (c, 3H), 2,83 (m, 2H), 3,49 (c, 2H), 4,20 (m, 2H), 6,88 (m, 2H), 7,12 (t, J = 7 Hz, 1H). ^{13}C RMN (100 MHz, $CDCl_3$): 13,98, 45,14, 45,83, 61,21, 65,28, 111,82, 113,59, 125,54, 135,70, 142,44, 163,35, 176,05. IR (Puro): 1728 cm^{-1}. FIA-MS: 234 $[M+H]^+$. La GC-FID cualitativa muestra que la pureza del compuesto 19 es de 96,32% (% por normalización de área).

EJEMPLO 20



<u>Éster etílico del ácido 2-(3,5-dicloro-2-hidroxi-benzoilamino)-5-fluoro-indan-2-carboxílico (19):</u>

A una solución de ácido 3,5-dicloro-2-hidroxi-benzoico (500 mg, 2,42 mmol), éster etílico del ácido 2-amino-5-fluoro-indan-2-carboxílico F (1,08 g, 4,84 mmol) y HATU (1,10 g, 2,89 mmol) en DMF anhidra (15 ml) se le añade DIPEA (599 µl, 3,63 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de

elución: EtOAc al 10%-80% en heptano) para dar un producto puro (A) en forma de un sólido de color blanco (779 mg, 78%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,24 (t, 3H), 3,39 (dd, 2H), 3,68 (dd, 2H), 4,24 (c, 2H), 6,91-6,94 (m, 2H), 7,14-7,18 (m, 1H), 7,46 (d, 1H), 7,52 (d, 1H), 7,92 (s, 1H), LC/MS (ES+) m/z = 412,06, 414,06

EJEMPLO 20

Éster etílico del ácido 2-(3,5-dicloro-2-ciclobutoxi-benzoilamino)-5-fluoro-indan-2-carboxílico (20):

A una suspensión de éster etílico del ácido 2-(3,5-dicloro-2-hidroxi-benzoilamino)-5-fluoro-indan-2-carboxílico (19) (624 mg, 1,51 mmol), Cs_2CO_3 anhidro (984 mg, 3,02 mmol) y KI (50 mg, 0,30 mmol) en DMF (20 ml) se le añade bromociclobutano (711 µl, 7,55 mmol). La suspensión de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 2 h. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10%-50% en heptano) para dar un producto puro (20) en forma de un sólido de color blanco (365 mg, 52%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,23-1,38 (m, 4H), 1,51-1,55 (m, 1H), 1,94-2,07 (m, 4H), 3,32 (t, 2H), 3,73 (dd, 2H), 4,26 (c, 2H), 4,58 (m, 1H), 6,88-6,96 (m, 2H), 7,18 (s a, 1H), 7,47 (s, 1H), 7,93 (s, 1H), 8,27 (s, 1H),
LC/MS (ES+) m/z = 466,12, 468,12

EJEMPLO 21

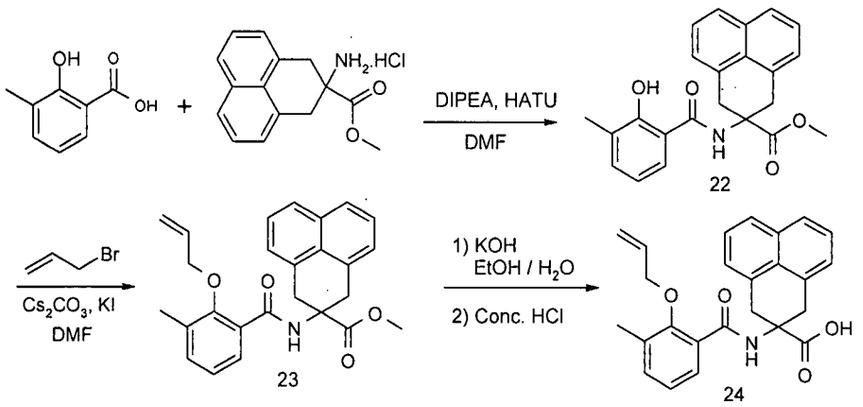
Ácido 2-(3,5-dicloro-2-ciclobutoxi-benzoilamino)-5-fluoro-indan-2-carboxílico (21):

La mezcla de éster etílico del ácido 2-(3,5-dicloro-2-ciclobutoxi-benzoilamino)-5-fluoro-indan-2-carboxílico (20) (300 mg, 0,64 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 6 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con

HCl conc. hasta alcanzar un valor de pH de ~3. El precipitado se filtra para dar un producto puro (21) en forma de un sólido de color blanco (200 mg, 71%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,32 (m, 1H), 1,50 (m, 1H), 1,92-2,09 (m, 4H), 3,36 (t, 2H), 3,75 (dd, 2H), 4,56 (m, 1H), 6,91-6,96 (m, 2H), 7,16-7,20 (m, 1H), 7,48 (dd, 1H), 7,90 (dd, 1H), 8,37 (s, 1H),
LC/MS (ES+) m/z = 438,09, 440,08

EJEMPLO 22



<u>Éster metílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (22):</u>

A una solución de ácido 2-hidroxi-3-metil-benzoico (1,12 g, 7,4 mmol), éster metílico del ácido 2-amino-2,3-dihidro-1H-fenaleno-2-carboxílico (2,05 g, 7,4 mmol) y HATU (3,38 g, 8,9 mmol) en DMF anhidra (28 ml) se le añade DIPEA (4,89 ml, 29,6 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (300 g de gel de sílice, gradiente de elución: EtOAc al 10%-80% en heptano) para dar el producto puro (22) en forma de un sólido de color blanco (353 mg, 13%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,18 (s, 1H), 3,70 (s, 4H), 3,85 (s, 3H), 6,30 (s, 1H), 6,48 (t, 1H), 6,58 (d, 1H), 7,13 (d, 1H), 7,33 (d, 2H), 7,44 (t, 2H), 7,75 (d, 2H), 12,08 (s, 1H)
LC/MS (ES+) m/z = 376,14

EJEMPLO 23

Éster etílico del ácido 2-(2-aliloxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (23):

A una suspensión de éster metílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (22) (175 mg, 0,47 mmol), Cs_2CO_3 anhidro (306 mg, 0,94 mmol) y KI (15,6 mg, 0,09 mmol) en DMF (8 ml) se le añade 3-bromo-propeno (199 µl, 2,35 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5%-40% en heptano) para dar un producto puro (23) en forma de un sólido de color blanco (107 mg, 55%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,08 (s, 3H), 3,68-3,73 (m, 6H), 3,84 (s, 3H), 5,02-5,11 (m, 2H), 5,28-5,40 (m, 1H), 6,70 (t, 1H), 7,16 (dd, 1H), 7,28 (dd, 1H), 7,39 (t, 2H), 7,69 (d, 2H), 7,79 (dd, 1H), 8,10 (s, 1H)

LC/MS (ES+) m/z = 416,23

EJEMPLO 24

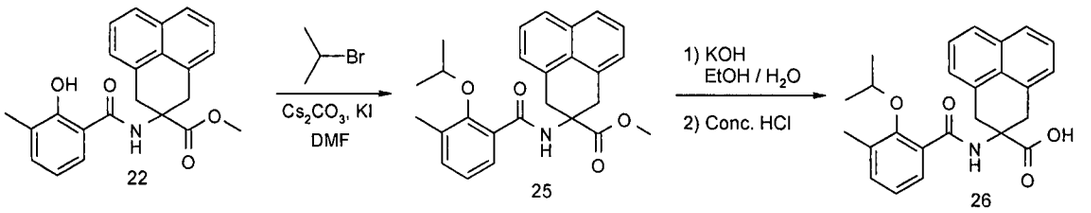
Ácido 2-(2-aliloxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (24):

La mezcla de éster etílico del ácido 2-(2-aliloxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (23) (107 mg, 0,26 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (24) en forma de un sólido de color blanco (98 mg, 94%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 2,09 (s, 3H), 3,71-3,74 (m, 6H), 5,06-5,11 (m, 2H), 5,28-5,41 (m, 1H), 7,01 (t, 1H), 7,18 (dd, 1H), 7,30 (dd, 1H), 7,41 (t, 2H), 7,70 (d, 2H), 7,75 (dd, 1H), 8,20 (s, 1H)

LC/MS (ES+) m/z = 402,16

EJEMPLO 25



Éster metílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (25):

A una suspensión de éster metílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (22) (175 mg, 0,47 mmol), Cs_2CO_3 anhidro (306 mg, 0,94 mmol) y KI (16 mg, 0,09 mmol) en DMF (8 ml) se le añade 2-bromo-propano (220 µl, 2,35 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5%-40% en heptano) para dar el producto puro (25) en forma de un sólido de color blanco (143 mg, 73%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,51 (d, 6H), 2,10 (s, 3H), 3,71 (s, 4H), 3,81 (s, 3H), 3,81-3,89 (m, 1H), 6,98 (t, 1H), 7,16 (dd, 1H), 7,31 (d, 2H), 7,41 (t, 2H), 7,71 (d, 2H), 7,82 (dd, 1H), 8,04 (s, 1H)

LC/MS (ES+) m/z = 418,23

EJEMPLO 26

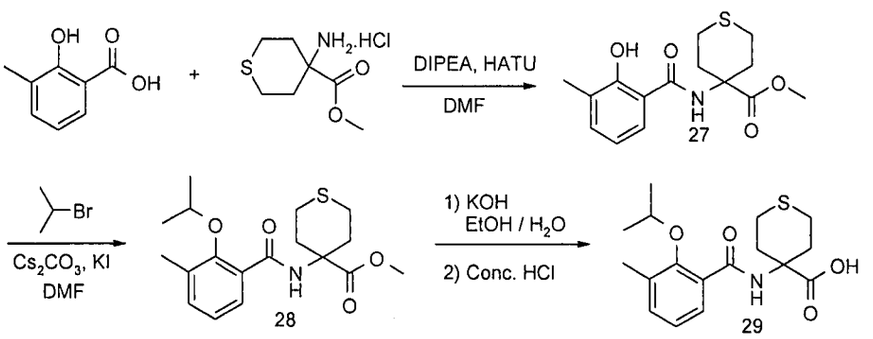
Ácido 2-(2-aliloxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (26):

La mezcla de éster metílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-2,3-dihidro-1H-fenaleno-2-carboxílico (25) (143 mg, 0,34 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (26) en forma de un sólido de color blanco (127 mg, 93%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,49 (d, 6H), 2,10 (s, 3H), 3,71 (s, 4H), 3,81 (m, 1H), 6,99 (t, 1H), 7,16 (d, 1H), 7,33 (d, 2H), 7,42 (t, 2H), 7,72 (d, 2H), 7,79 (dd, 1H), 8,12 (s, 1H)

LC/MS (ES+) m/z = 404,17

EJEMPLO 27



<u>Éster metílico del ácido 4-(2-hidroxi-3-metil-benzoilamino)-tetrahidro-tiopiran-4-carboxílico (27):</u>

A una solución de sal HCl de éster metílico del ácido 4-amino-tetrahidro-tiopiran-4-carboxílico (529 mg, 2,5 mmol), ácido 2-hidroxi-3-metil-benzoico (380 mg, 2,5 mmol) y HATU (1,14 g, 3,0 mmol) en DMF anhidra (20 ml) se le añade DIPEA (1,66 ml, 10 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (30 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 10-80% en heptano) para dar un producto puro (27) en forma de un sólido de color blanco (102 mg, 13%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,41 (m, 4H), 2,72-2,80 (m, 4H), 3,74 (s, 3H), 6,36 (s, 1H), 6,78 (t, 1H), 7,25-7,30 (m, 2H), 12,00 (s, 1H)

LC/MS (ES+) m/z = 310,17

EJEMPLO 28

<u>Éster metílico del ácido 4-(2-isopropoxi-3-metil-benzoilamino)-tetrahidro-tiopiran-4-carboxílico (28):</u>

A una suspensión de éster metílico del ácido 4-(2-hidroxi-3-metil-benzoilamino)-tetrahidro-tiopiran-4-carboxílico (27) (98 mg, 0,32 mmol), Cs_2CO_3 anhidro (208 mg, 0,64 mmol) y KI (11 mg, 0,06 mmol) en DMF (5 ml) se le añade 2-bromopropano (150 µl, 1,6 mmol). La suspensión de reacción resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (80 g de gel de sílice, gradiente de elución: EtOAc al 5-40% en heptano) para dar un producto puro (28) en forma de un sólido de color blanco (92 mg, 81%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,35 (d, 6H), 2,33 (s, 3H), 2,33-2,40 (m, 4H), 2,63-2,69 (m, 2H), 2,76-2,81 (m, 2H), 3,76 (s, 3H), 4,39 (m, 1H), 7,10 (t, 1H), 7,31 (d, 1H), 7,84 (dd, 1H), 8,28 (s, 1H)

LC/MS (ES+) m/z = 352,13

EJEMPLO 29

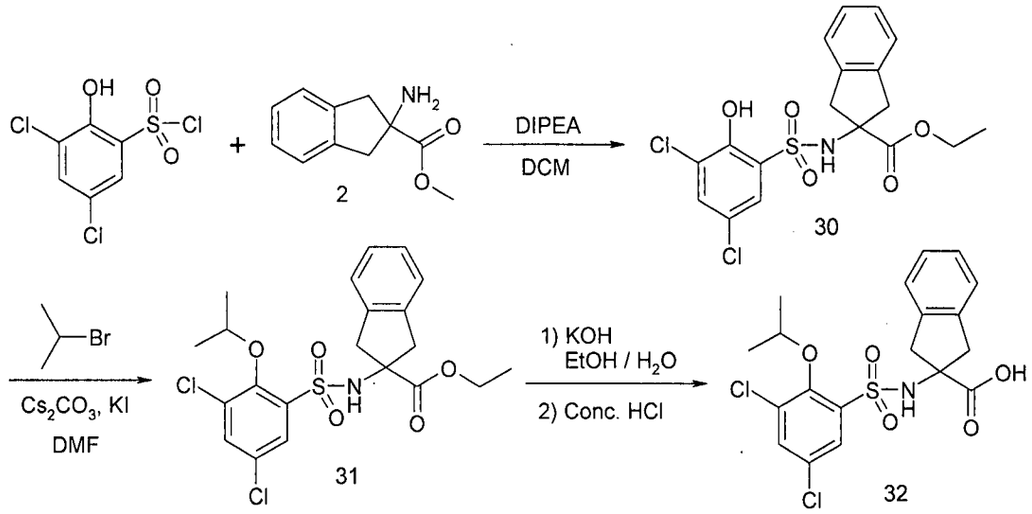
<u>Ácido 4-(2-isopropoxi-3-metil-benzoilamino)-tetrahidro-tiopiran-4-carboxílico (29):</u>

La mezcla de éster metílico del ácido 4-(2-isopropoxi-3-metil-benzoilamino)-tetrahidro-tiopiran-4-carboxílico (28) (75 mg, 0,21 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (29) en forma de un sólido de color amarillo pálido (68 mg, 94%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,32 (d, 6H), 2,33 (s, 3H), 2,41-2,43 (m, 4H), 2,64-2,74 (m, 4H), 4,37 (m, 1H), 7,11 (t, 1H), 7,33 (d, 1H), 7,86 (dd, 1H), 8,42 (s, 1H), 9,07 (s a, 1H)

LC/MS (ES+) m/z = 338,11

EJEMPLO 30



Éster etílico del ácido 2-(3,5-dicloro-2-hidroxi-bencenosulfonilamino)-indan-2-carboxílico (30):

A una solución de éster etílico del ácido 2-amino-indan-2-carboxílico (3,14 g, 15,3 mmol) y cloruro de 3,5-dicloro-2-hidroxi-bencenosulfonilo (1 g, 3,82 mmol) en DCM anhidro (diclorometano, 20 ml) se le añade DIPEA (631 µl, 3,82 mmol). La solución resultante se agita a TA durante 1 hora. La solución de reacción se diluye en DCM (50 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (30) en forma de un sólido de color blanco (450 mg, 27%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 3,25 (d, 2H), 3,57 (d, 2H), 4,18 (c, 2H), 5,60 (s, 1H), 7,04-7,07 (m, 2H), 7,14-7,17 (m, 2H), 7,43 (d, 1H), 7,49 (d, 1H), 8,30 (s a, 1H)
LC/MS (ES+) m/z = 447,04, 449,04, 430,01

EJEMPLO 31

Éster etílico del ácido 2-(3,5-dicloro-2-isopropoxi-bencenosulfonilamino)-indan-2-carboxílico (31):

A una suspensión de éster etílico del ácido 2-(3,5-dicloro-2-hidroxi-bencenosulfonilamino)-indan-2-carboxílico (30) (226 mg, 0,53 mmol), Cs_2CO_3 anhidro (300 mg, 0,92 mmol) y KI (15 mg, 0,09 mmol) en DMF (15 ml) se le añade 2-bromopropano (432 µl, 4,60 mmol). La suspensión de reacción resultante se carga con argón y se somete a una reacción de microondas: 110°C, 2,5 h. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (30 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa

orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10%-60% en heptano) para dar un producto puro (31) en forma de un semi-sólido de color blanco (248 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,23 (t, 3H), 1,27 (d, 6H), 3,19 (d, 2H), 3,50 (d, 2H), 4,10 (c, 2H), 5,12 (m, 1H), 5,75 (s, 1H), 6,98-7,01 (m, 2H), 7,12-7,15 (m, 2H), 7,47 (dd, 1H), 7,58 (dd, 1H), LC/MS (ES+) m/z = 494,0

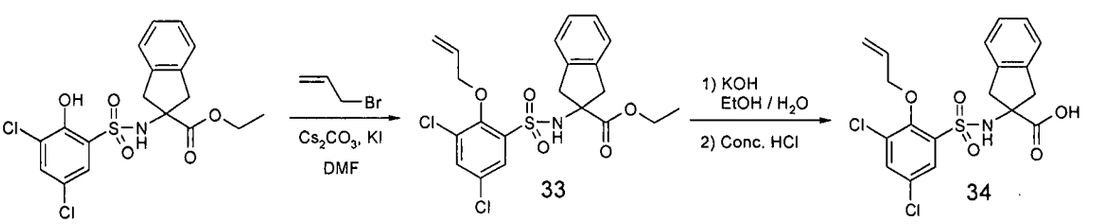
EJEMPLO 32

Ácido 2-(3,5-dicloro-2-isopropoxi-bencenosulfonilamino)-indan-2-carboxílico (32):

La mezcla de éster etílico del ácido 2-(3,5-dicloro-2-isopropoxi-bencenosulfonilamino)-indan-2-carboxílico (31) (248 mg, 0,52 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (10 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (32) en forma de un sólido de color blanco (230 mg, 100%).

^{1}H RMN (CDOD, 300 MHz): δ 1,27 (d, 6H), 3,23 (d, 2H), 3,48 (d, 2H), 5,05 (m, 1H), 6,98-7,01 (m, 2H), 7,08-7,12 (m, 2H), 7,44 (d, 1H), 7,60 (d, 1H)
LC/MS (ES-) m/z = 442,08, 444,08

EJEMPLO 33



Éster etílico del ácido 2-(2-aliloxi-3,5-dicloro-bencenosulfonilamino)-indan-2-carboxílico (33):

A una suspensión de éster etílico del ácido 2-(3,5-dicloro-2-hidroxi-benzoilamino)-indan-2-carboxílico (10) (200 mg, 0,46 mmol), Cs_2CO_3 anhidro (300 mg, 0,92 mmol) y KI (15 mg, 0,09 mmol) en DMF (15 ml) se le añade 3-bromo-propeno (390 µl, 4,6 mmol). La suspensión

de reacción resultante se carga en argón y se somete a una reacción de microondas: 110°C, 2 h. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (20 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10%-60% en heptano) para dar un producto puro (33) en forma de un sólido de color blanco (162 mg, 75%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,22 (t, 3H), 3,21 (d, 2H), 3,52 (d, 2H), 4,09 (c, 2H), 4,55 (d, 2H), 5,36 (dd, 2H), 5,68 (s, 1H), 6,05 (m, 1H), 6,99-7,02 (m, 2H), 7,12-7,14 (m, 2H), 7,52 (d, 1H), 7,58 (d, 1H)

LC/MS (ES-) m/z = 468,10, 470,10

EJEMPLO 34

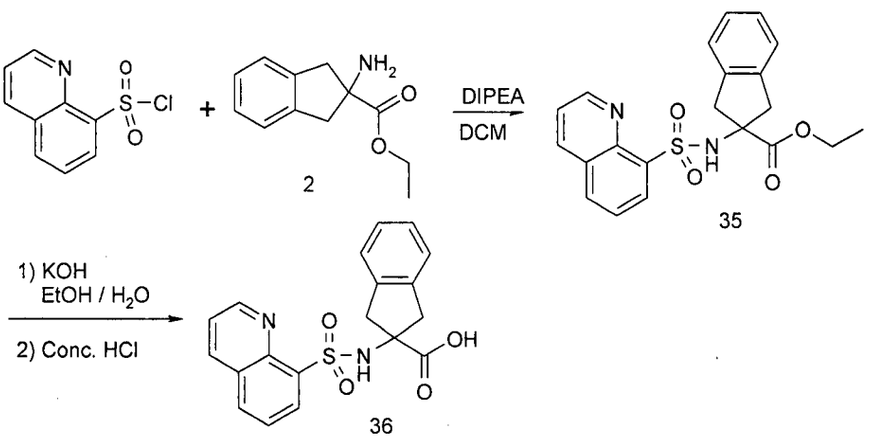
Ácido 2-(2-aliloxi-3,5-dicloro-bencenosulfonilamino)-indan-2-carboxílico (34):

La mezcla de éster etílico del ácido 2-(2-aliloxi-3,5-dicloro-bencenosulfonilamino)-indan-2-carboxílico (33) (143 mg, 0,30 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~3. Después de la filtración, el sólido se purifica por HPLC para dar un producto puro (34) en forma de un sólido de color blanco (91 mg, 69%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 3,24 (d, 2H), 3,58 (d, 2H), 4,53 (d, 2H), 5,36 (dd, 2H), 5,72 (s, 1H), 6,03 (m, 1H), 7,02-7,04 (m, 2H), 7,13-7,17 (m, 2H), 7,34 (d, 1H), 7,60 (d, 1H)

LC/MS (ES+) m/z = 459,03, 461,02, 442,00

EJEMPLO 35



Éster etílico del ácido 2-(quinolina-8-sulfonilamino)-indan-2-carboxílico (35):

A una solución de cloruro de quinolina-8-sulfonilo (400 mg, 1,76 mmol) y éster etílico del ácido 2-amino-indan-2-carboxílico (361 mg, 1,76 mmol) en DCM anhidro (8 ml) se le añade DIPEA (291 µl, 1,76 mmol). La solución resultante se agita a TA durante una noche. La solución de reacción se diluye con DCM (40 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (35) en forma de un sólido de color blanco (245 mg, 35%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,08 (t, 3H), 3,20 (d, 2H), 3,46 (d, 2H), 3,94 (c, 2H), 6,74-6,78 (m, 2H), 6,86-6,90 (m, 2H), 7,32 (s, 1H), 7,39 (dd, 1H), 7,64 (t, 1H), 8,01 (dd, 1H), 8,18 (dd, 1H), 8,34 (dd, 1H), 8,67 (dd, 1H),

LC/MS (ES+) m/z = 397,11

EJEMPLO 36

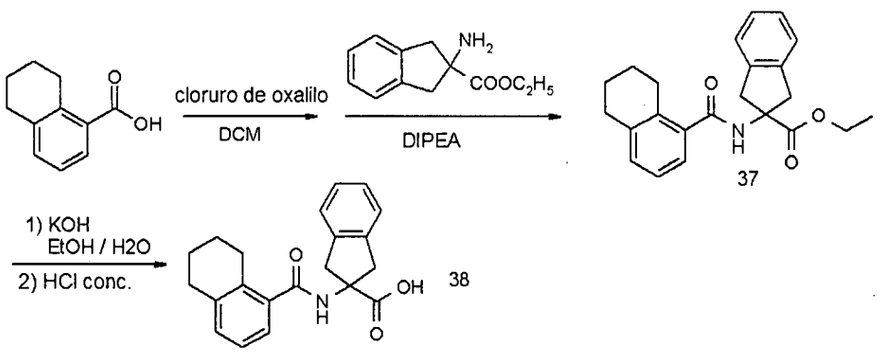
Ácido 2-(quinolina-8-sulfonilamino)-indan-2-carboxílico (36):

La mezcla de éster etílico del ácido 2-(quinolina-8-sulfonilamino)-indan-2-carboxílico (35) (210 mg, 0,53 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (36) en forma de un sólido de color blanco (195 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,18 (d, 2H), 3,46 (d, 2H), 6,66-6,69 (m, 2H), 6,81-6,84 (m, 2H), 7,40 (dd, 1H), 7,65 (t, 1H), 8,02 (d, 1H), 8,18 (dd, 1H), 8,34 (dd, 1H), 8,64 (dd, 1H)

LC/MS (ES+) m/z = 369,10

EJEMPLO 37



Éster etílico del ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (37):

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (500 mg, 2,84 mmol) en DCM (10 ml) se le añade gota a gota cloruro de oxalilo (0,50 ml, 5,68 mmol). La solución resultante se agita a TA durante 2 h. Después de la retirada del DCM y el exceso de cloruro de oxalilo, el residuo, éster etílico del ácido 2-amino-indan-2-carboxílico (583 mg, 2,84 mmol), y DIPEA (1,88 ml, 11,3 mmol) se disuelven en DCM (20 ml). La solución resultante se agita durante una noche. La solución de reacción se diluye con DCM (30 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 0%-20% en heptano) para dar el producto puro (37) en forma de un sólido de color blanco (610 mg, 59%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 1,74 (m, 4H), 2,76 (m, 2H), 2,84 (m, 2H), 3,34 (d, 2H), 3,75 (d, 2H), 4,72 (c, 2H), 6,20 (s, 1H), 7,02-7,12 (m, 3H), 7,18-7,25 (m, 4H)

LC/MS (ES+) m/z = 364,18

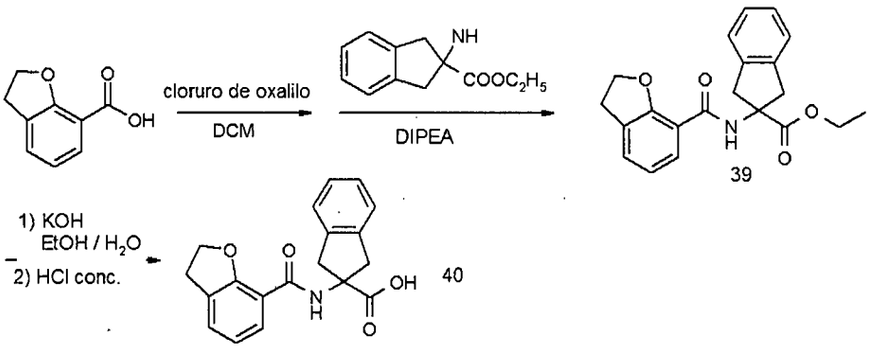
EJEMPLO 38

Ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (38):

La mezcla de éster etílico del ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (37) (400 mg, 1,1 mmol) y KOH (1 g, 17,8 mmol) se disuelve en EtOH (10 ml) y agua (2 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (38) en forma de un sólido de color blanco (300 mg, 82%).

^{1}H RMN (CD_3OD, 300 MHz): δ 1,74 (m, 4H), 2,76 (m, 2H), 3,38 (d, 2H), 3,68 (d, 2H), 4,85 (s, 1H), 7,02-7,08 (m, 3H), 7,14-7,23 (m, 4H)
LC/MS (ES+) m/z = 336,15

EJEMPLO 39



<u>Éster etílico del ácido 2-[(2,3-dihidro-benzofuran-7-carbonil)-amino]-indan-2-carboxílico (39):</u>

A una solución de ácido 2,3-dihidro-benzofuran-7-carboxílico (394 mg, 2,4 mmol) en DCM (10 ml) se le añade cloruro de oxalilo (0,85 ml, 9,6 mmol). La solución resultante se agita a TA durante 2 h. Después de la retirada del DCM y el exceso de cloruro de oxalilo, el residuo, éster etílico del ácido 2-amino-indan-2-carboxílico (500 mg, 2,4 mmol), y DIPEA (3,17 ml, 19,2 mmol) se disuelven en DCM (20 ml). La solución resultante se agita a TA durante una noche. La solución de reacción se diluye con DCM (40 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 0%-20% en heptano) para dar un producto puro (39) en forma de un sólido de color blanco (635 mg, 75%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,23 (t, 3H), 3,22 (t, 2H), 3,40 (d, 2H), 3,77 (d, 2H), 4,26 (c, 2H), 4,67 (t, 2H), 6,93 (t, 1H), 7,17-7,30 (m, 6H), 7,87 (d, 1H), 8,18 (s, H)
LC/MS (ES+) m/z = 352,12

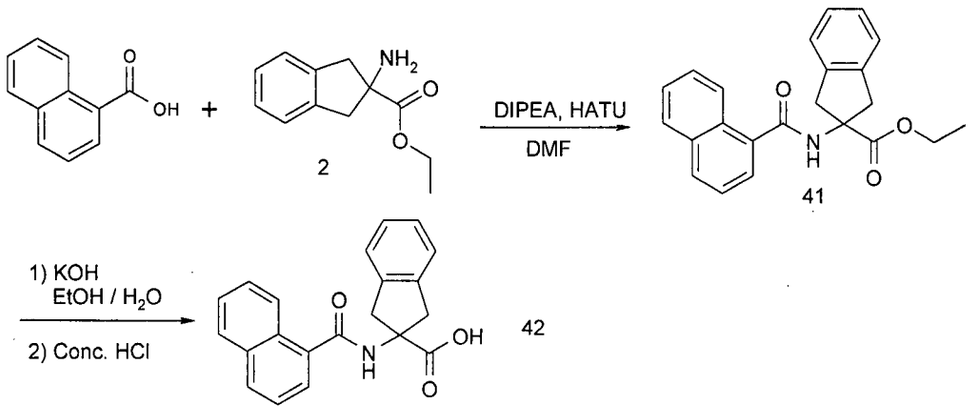
EJEMPLO 40

Ácido 2-[(2,3-dihidro-benzofuran-7-carbonil)-amino]-indan-2-carboxílico (40):

La mezcla de éster etílico del ácido 2-[(2,3-dihidro-benzofuran-7-carbonil)-amino]-indan-2-carboxílico (39) (250 mg, 0,71 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (5 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (40) en forma de un sólido de color blanco (200 mg, 87%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,22 (t, 2H), 3,40 (d, 2H), 3,82 (d, 2H), 4,68 (t, 2H), 6,94 (t, 1H), 7,17-7,25 (m, 4H), 7,30 (d, 1H), 7,83 (d, 1H), 8,28 (s, 1H)
LC/MS (ES+) m/z = 324,11

EJEMPLO 41



Éster etílico del ácido 2-[(naftaleno-1-carbonil)-amino]-indan-2-carboxílico (41):

A una solución de ácido naftaleno-1-carboxílico (300 mg, 1,74 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (357 mg, 1,74 mmol) y HATU (992 mg, 2,61 mmol) en DMF anhidra (8 ml) se le añade DIPEA (431 µl, 2,61 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se

seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (41) en forma de un sólido de color blanco (383 mg, 61%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,30 (t, 3H), 3,40 (d, 2H), 3,77 (d, 2H), 4,29 (c, 2H), 6,59 (s, 1H), 7,20-7,24 (m, 4H), 7,34 (t, 1H), 7,46-7,52 (m, 3H), 7,79-7,85 (m, 2H), 8,28-8,31 (m, 1H)
LC/MS (ES+) m/z = 360,19

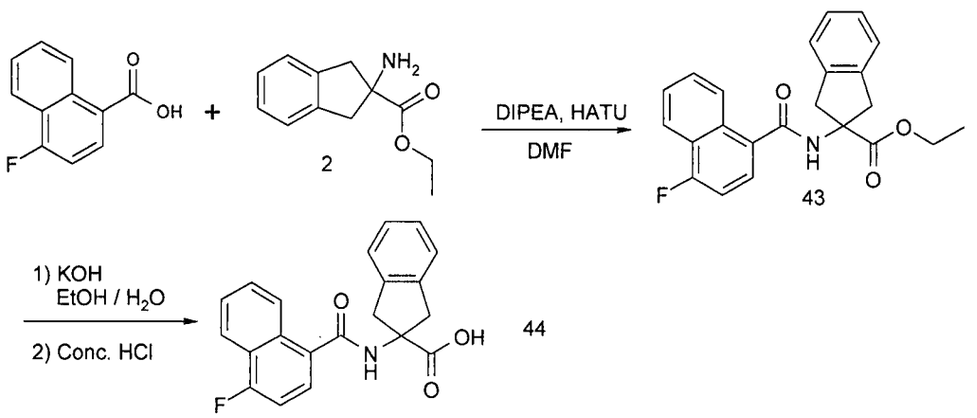
EJEMPLO 42

Ácido 2-[(naftaleno-1-carbonil)-amino]-indan-2-carboxílico (42):

La mezcla de éster etílico del ácido 2-[(naftaleno-1-carbonil)-amino]-indan-2-carboxílico (41) (220 mg, 0,61 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (42) en forma de un sólido de color blanco (196 mg, 97%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,47 (d, 2H), 3,82 (d, 2H), 6,93 (m, 1H), 7,19-7,28 (m, 4H), 7,37-7,50 (m, 4H), 7,81-7,89 (m, 2H), 8,23-8,27 (m, 1H)
LC/MS (ES+) m/z = 332,11

EJEMPLO 43



Éster etílico del ácido 2-[(4-fluoro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (43):

A una solución de ácido 4-fluoro-naftaleno-1-carboxílico (232 mg, 1,22 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (250 mg, 1,22 mmol) y HATU (696 mg, 1,83 mmol) en DMF anhidra (8 ml) se le añade DIPEA (302 µl, 1,83 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (43) en forma de un sólido de color blanco (340 mg, 74%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,31 (t, 3H), 3,42 (d, 2H), 3,80 (d, 2H), 4,31 (c, 2H), 6,53 (s, 1H), 7,03 (dd, 1H), 7,19-7,26 (m, 4H), 7,47-7,82 (m, 3H), 8,07-8,10 (m, 1H), 8,31-8,35 (m, 1H)

LC/MS (ES+) m/z = 378,12

EJEMPLO 44

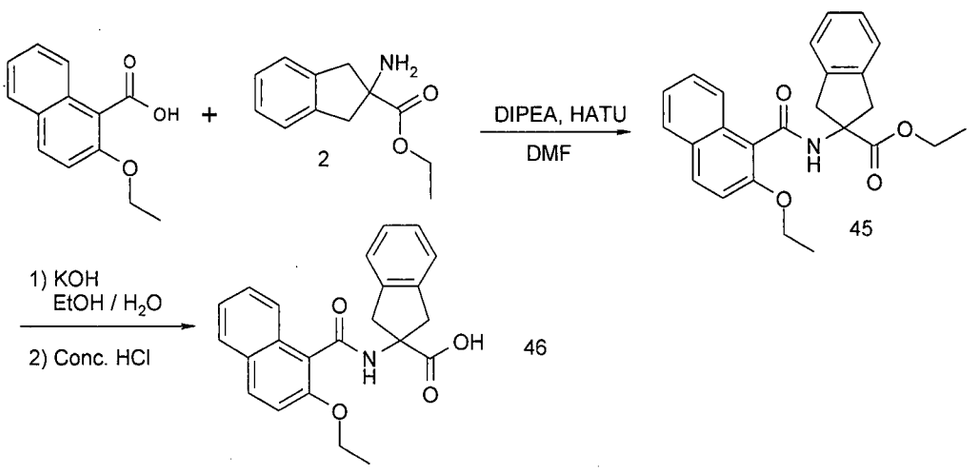
<u>Ácido 2-[(4-fluoro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (44):</u>

La mezcla de éster etílico del ácido 2-[(4-fluoro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (43) (180 mg, 0,48 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 6 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (44) en forma de un sólido de color blanco (174 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,46 (d, 2H), 3,81 (d, 2H), 6,99-7,06 (m, 2H), 7,19-7,26 (m, 4H), 7,48-7,54 (m, 3H), 8,06-8,09 (m, 1H), 8,24-8,28 (m, 1H)

LC/MS (ES+) m/z = 350,09

EJEMPLO 45



Éster etílico del ácido 2-[(2-etoxi-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (45):

A una solución de ácido 2-etoxi-naftaleno-1-carboxílico (335 mg, 1,55 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (318 mg, 1,55 mmol) y HATU (886 mg, 2,33 mmol) en DMF anhidra (8 ml) se le añade DIPEA (385 µl, 2,33 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (45) en forma de un sólido de color blanco (420 mg, 67%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,12 (t, 3H), 1,35 (t, 3H), 3,40 (d, 2H), 3,76 (d, 2H), 3,98 (c, 2H), 4,32 (c, 2H), 6,73 (s, 1H), 7,19 (d, 1H), 7,16-7,23 (m, 4H), 7,29-7,34 (m, 1H), 7,42-7,48 (m, 1H), 7,73 (dd, 2H), 8,16 (d, 1H)
LC/MS (ES+) m/z = 404,18

EJEMPLO 46

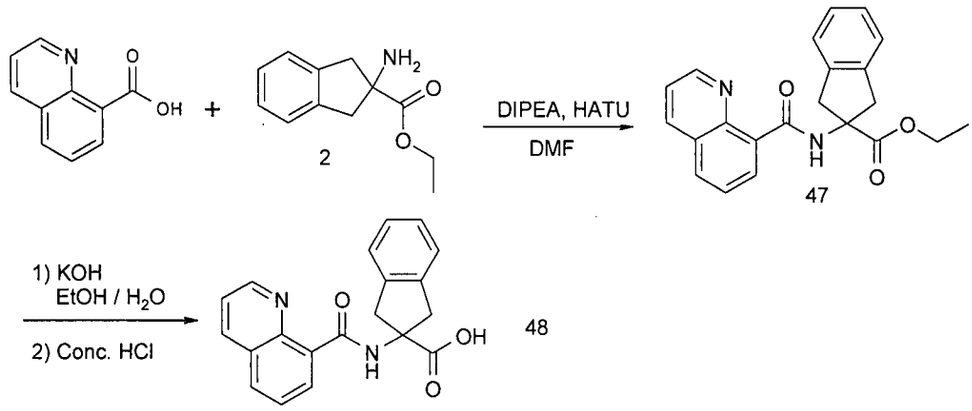
Ácido 2-[(2-etoxi-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (46):

La mezcla de éster etílico del ácido 2-[(2-etoxi-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (45) (270 mg, 0,67 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc.

hasta alcanzar un valor de pH de ~4. El precipitado se filtra para dar un producto puro (46) en forma de un sólido de color blanco (170 mg, 68%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,18 (t, 3H), 3,47 (d, 2H), 3,82 (d, 2H), 4,04 (c, 2H), 7,09 (s, 1H), 7,15-7,37 (m, 7H), 7,47 (t, 1H), 7,78 (dd, 2H), 8,07 (d, 1H)
LC/MS (ES+) m/z = 376,19

EJEMPLO 47



Éster etílico del ácido 2-[(quinolina-8-carbonil)-amino]-indan-2-carboxílico (47):

A una solución de ácido quinolina-8-carboxílico (421 mg, 2,43 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (500 mg, 2,43 mmol) y HATU (1,39 g, 3,65 mmol) en DMF anhidra (15 ml) se le añade DIPEA (603 µl, 3,65 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (47) en forma de un sólido de color blanco (281 mg, 32%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 3,54 (d, 2H), 3,86 (d, 2H), 4,27 (c, 2H), 7,17-7,27 (m, 4H), 7,44 (dd, 1H), 7,65 (t, 1H), 7,94 (dd, 1H), 8,24 (dd, 1H), 8,80-8,84 (m, 2H), 12,00 (s, 1H)
LC/MS (ES+) m/z = 361,13

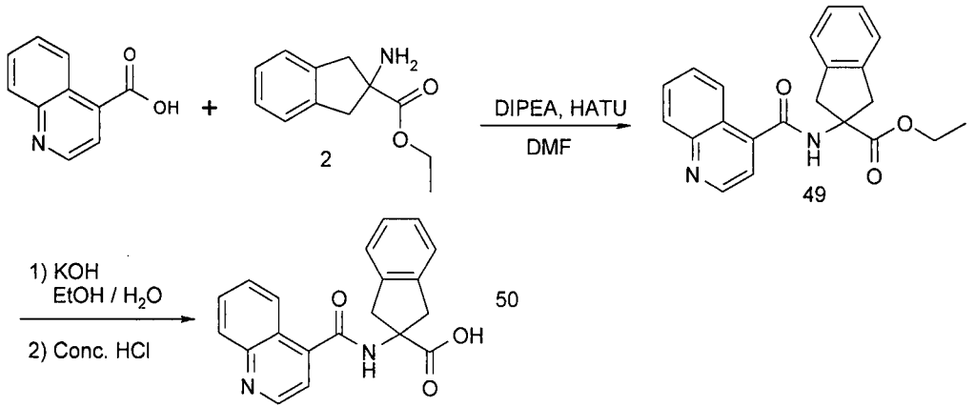
EJEMPLO 48

Ácido 2-[(quinolina-8-carbonil)-amino]-indan-2-carboxílico (48):

La mezcla de éster etílico del ácido 2-[(quinolina-8-carbonil)-amino]-indan-2-carboxílico (47) (190 mg, 0,53 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar el producto puro (48) en forma de un sólido de color blanco (152 mg, 86%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,50 (d, 2H), 3,83 (d, 2H), 7,17-7,24 (m, 4H), 7,44-7,49 (m, 1H), 7,64 (t, 1H), 7,98 (d, 1H), 8,28 (dd, 1H), 8,69 (d, 1H), 8,83 (s, 1H)
LC/MS (ES+) m/z = 333,08

EJEMPLO 49



<u>Éster etílico del ácido 2-[(quinolina-4-carbonil)-amino]-indan-2-carboxílico (49):</u>

A una solución de ácido quinolina-4-carboxílico (301 mg, 1,74 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (357 mg, 1,74 mmol) y HATU (992 mg, 2,61 mmol) en DMF anhidra (8 ml) se le añade DIPEA (431 µl, 2,61 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5-70% en heptano) para dar un producto puro (49) en forma de un sólido de color amarillo pálido (370 mg, 59%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,34 (t, 3H), 3,48 (d, 2H), 3,82 (d, 2H), 4,34 (c, 2H), 6,86 (s, 1H), 7,21-7,29 (m, 5H), 7,51-7,56 (m, 1H), 7,65-7,71 (m, 1H), 7,98 (d, 1H), 8,18 (d, 1H), 8,73 (d, 1H)

LC/MS (ES+) m/z = 361,14

EJEMPLO 50

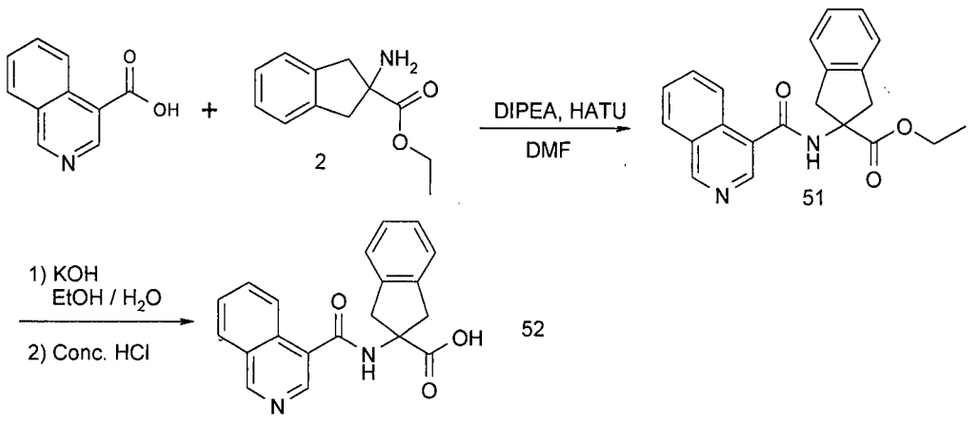
Ácido 2-[(quinolina-4-carbonil)-amino]-indan-2-carboxílico (50):

La mezcla de éster etílico del ácido 2-[(quinolina-4-carbonil)-amino]-indan-2-carboxílico (49) (220 mg, 0,61 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~4. El precipitado se filtra para dar un producto puro (50) en forma de un sólido de color amarillo pálido (98 mg, 48%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,49 (d, 2H), 3,83 (d, 2H), 7,20-7,28 (m, 4H), 7,50 (d, 1H), 7,61 (t, 1H), 7,79 (t, 1H), 8,13 (d, 1H), 8,24 (d, 1H), 8,86 (d, 1H)

LC/MS (ES+) m/z = 333,13

EJEMPLO 51



Éster etílico del ácido 2-[(isoquinolina-4-carbonil)-amino]-indan-2-carboxílico (51):

A una solución de ácido isoquinolina-4-carboxílico (211 mg, 1,22 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (250 mg, 1,22 mmol) y HATU (696 mg, 1,83 mmol) en DMF anhidra (8 ml) se le añade DIPEA (302 µl, 1,83 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se

disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (51) en forma de un sólido de color blanco (359 mg, 82%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 3,49 (d, 2H), 3,79 (d, 2H), 4,28 (c, 2H), 6,96 (s, 1H), 7,20-7,27 (m, 4H), 7,57-7,62 (m, 1H), 7,76-7,82 (m, 1H), 7,86 (d, 1H), 8,12 (d, 1H), 8,54 (d, 1H), 9,22 (d, 1H)

LC/MS (ES+) m/z = 361,15

EJEMPLO 52

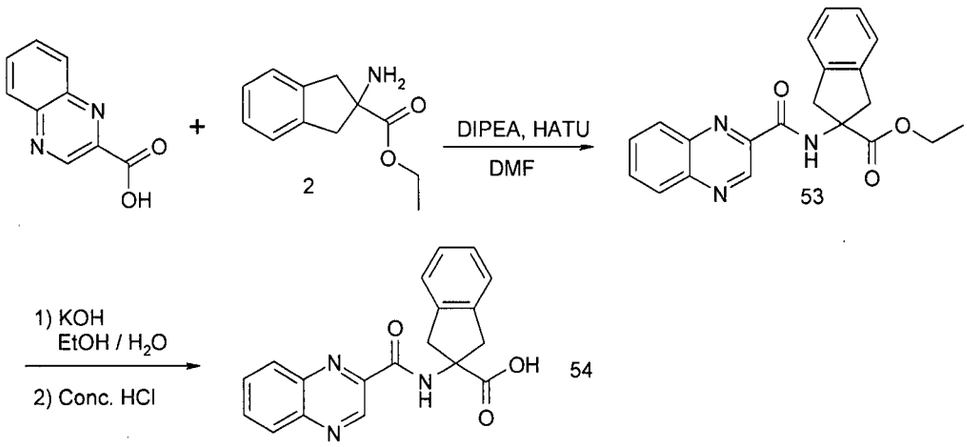
Ácido 2-[(isoquinolina-4-carbonil)-amino]-indan-2-carboxílico (52):

La mezcla de éster etílico del ácido 2-[(isoquinolina-4-carbonil)-amino]-indan-2-carboxílico (51) (200 mg, 0,55 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (52) en forma de un sólido de color blanco (170 mg, 93%).

^{1}H RMN ($CDCl_3$ + CD_3OD, 300 MHz): δ 3,38 (d, 2H), 3,53 (d, 2H), 7,19-7,27 (m, 4H), 7,64 (t, 1H), 7,83 (t, 1H), 7,94 (d, 1H), 8,09 (d, 1H), 8,40 (s, 1H), 8,71 (d, 1H), 9,22 (d, 1H)

LC/MS (ES+) m/z = 333,06

EJEMPLO 53



Éster etílico del ácido 2-[(quinoxalina-2-carbonil)-amino]-indan-2-carboxílico (53):

A una solución de ácido quinoxalina-5-carboxílico (400 mg, 2,3 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (471 mg, 2,3 mmol) y HATU (1,3 g, 3,45 mmol) en DMF anhidra (15 ml) se le añade DIPEA (570 µl, 3,45 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-40% en heptano) para dar un producto puro (56) en forma de un sólido de color naranja (605 mg, 73%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 3,55 (d, 2H), 3,84 (d, 2H), 4,28 (c, 2H), 7,21-7,29 (m, 4H), 7,79-7,89 (m, 2H), 8,08-8,18 (m, 2H), 8,46 (s, 1H), 9,64 (s, 1H)

LC/MS (ES+) m/z = 361,12

EJEMPLO 54

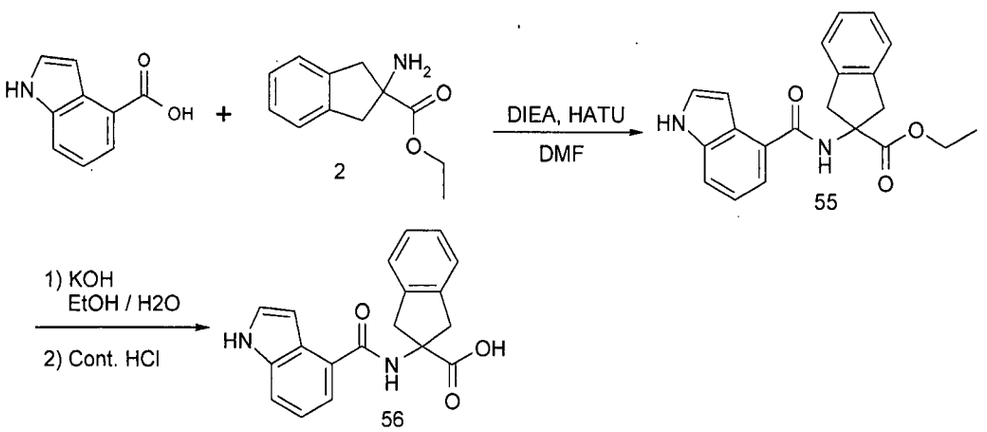
Ácido 2-[(quinoxalina-2-carbonil)-amino]-indan-2-carboxílico (54):

La mezcla de éster etílico del ácido 2-[(quinoxalina-5-carbonil)-amino]-indan-2-carboxílico (56) (480 mg, 1,33 mmol) y KOH (1 mg, 18 mmol) se disuelve en EtOH (13 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (40 ml) y se acidifica gota a gota con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (54) en forma de un sólido de color pardo (444 mg, 100%).

^{1}H RMN ($CDCl_3$ + CD_3OD, 300 MHz): δ 3,58 (d, 2H), 3,86 (d, 2H), 7,21-7,30 (m, 4H), 7,81-7,90 (m, 2H), 8,10-8,18 (m, 2H), 8,58 (s, 1H), 9,61 (s, 1H)

LC/MS (ES+) m/z = 361,12

EJEMPLO 55



Éster etílico del ácido 2-[(1H-indol-4-carbonil)-amino]-indan-2-carboxílico (55):

A una solución de ácido 1H-indol-4-carboxílico (250 mg, 1,55 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (318 mg, 1,55 mmol) y HATU (886 mg, 2,33 mmol) en DMF anhidra (8 ml) se le añade DIPEA (385 µl, 2,33 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-60% en heptano) para dar un producto puro (55) en forma de un sólido de color blanco (278 mg, 52%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 3,46 (d, 2H), 3,78 (d, 2H), 4,26 (c, 2H), 6,78 (m, 1H), 7,14-7,25 (m, 6H), 7,46-7,49 (m, 2H), 8,65 (s, 1H)

LC/MS (ES+) m/z = 349,14

EJEMPLO 56

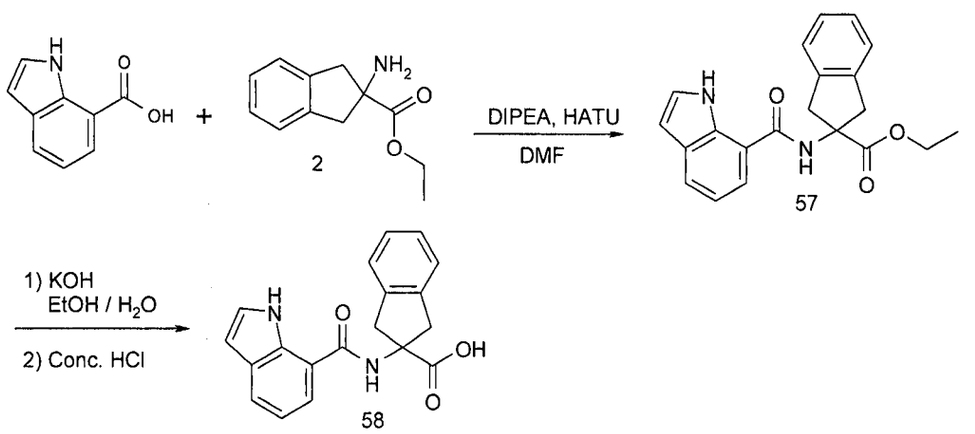
Ácido 2-[(1H-indol-4-carbonil)-amino]-indan-2-carboxílico (56):

La mezcla de éster etílico del ácido 2-[(1H-indol-4-carbonil)-amino]-indan-2-carboxílico (55) (200 mg, 0,57 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (1 ml)

en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (56) en forma de un sólido de color blanco (162 mg, 89%).

^{1}H RMN ($CDCl_3$ = CD_3OD, 300 MHz): δ 3,50 (d, 2H), 3,80 (d, 2H), 6,68 (m, 1H), 7,15-7,29 (m, 6H), 7,46 (d, 1H), 7,53 (dd, 1H), 9,79 (s, 1H)
LC/MS (ES+) m/z = 321,15

EJEMPLO 57



<u>Éster etílico del ácido 2-[(1H-indol-7-carbonil)-amino]-indan-2-carboxílico (57):</u>

A una solución de ácido 1H-indol-7-carboxílico (250 mg, 1,55 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (318 mg, 1,55 mmol) y HATU (886 mg, 2,33 mmol) en DMF anhidra (8 ml) se le añade DIPEA (385 µl, 2,33 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-60% en heptano) para dar un producto puro (57) en forma de un sólido de color blanco (378 mg, 70%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,22 (t, 3H), 3,44 (d, 2H), 3,78 (d, 2H), 4,25 (c, 2H), 6,53 (t, 1H), 6,93 (s, 1H), 7,03 (t, 1H), 7,18-7,27 (m, 5H), 7,32 (d, 1H), 7,77 (d, 1H), 10,25 (s, 1H)
LC/MS (ES+) m/z = 349,21

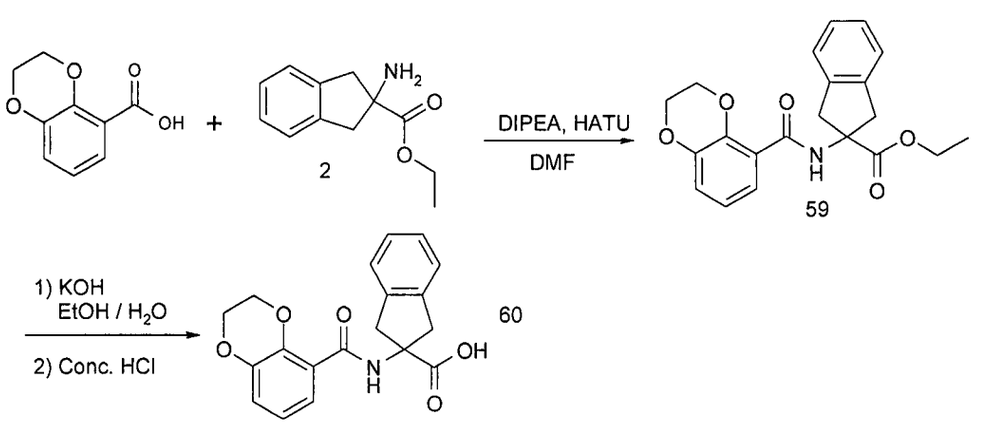
EJEMPLO 58

Ácido 2-[(1H-indol-7-carbonil)-amino]-indan-2-carboxílico (58):

La mezcla de éster etílico del ácido 2-[(1H-indol-7-carbonil)-amino]-indan-2-carboxílico (57) (220 mg, 0,63 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (58) en forma de un sólido de color blanquecino (186 mg, 92%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,50 (d, 2H), 3,79 (d, 2H), 6,54 (m, 2H), 7,06 (t, 1H), 7,19-7,31 (m, 5H), 7,42 (d, 1H), 7,78 (d, 1H), 10,25 (s, 1H)
LC/MS (ES+) m/z = 325,15

EJEMPLO 59



Éster etílico del ácido 2-[(2,3-dihidro-benzo[1,4]dioxino-5-carbonil)-amino]-indan-2-carboxílico (59):

A una solución de ácido 2,3-dihidro-benzo[1,4]dioxino-5-carboxílico (351 mg, 1,95 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (400 mg, 1,95 mmol) y HATU (1,11 g, 2,93 mmol) en DMF anhidra (8 ml) se le añade DIPEA (484 µl, 2,93 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (70 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (59) en forma de un sólido de color blanco (650 mg, 91%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 3,39 (d, 2H), 3,74 (d, 2H), 4,21- 4,33 (m, 6H), 6,90 (t, 1H), 6,98 (dd, 1H), 7,17-7,24 (m, 4H), 7,69 (dd, 1H), 8,25 (s, 1H)
LC/MS (ES+) m/z = 368,15

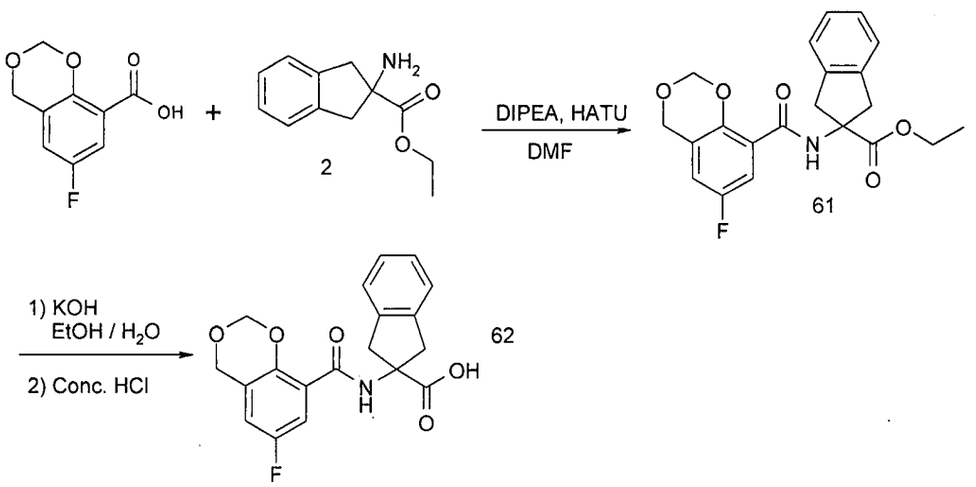
EJEMPLO 60

Ácido 2-[(2,3-dihidro-benzo[1,4]dioxino-5-carbonil)-amino]-indan-2-carboxílico (60):

La mezcla de éster etílico del ácido 2-[(2,3-dihidro-benzo[1,4]dioxino-5-carbonil)-amino]-indan-2-carboxílico (59) (495 mg, 1,35 mmol) y KOH (1 g, 17,9 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (60) en forma de un sólido de color blanco (440 mg, 96%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 3,40 (d, 2H), 3,78 (d, 2H), 4,26- 4,33 (m, 4H), 6,91 (t, 1H), 7,49 (dd, 1H), 7,18-7,25 (m, 4H), 7,65 (dd, 1H), 8,39 (s, 1H)
LC/MS (ES+) m/z = 340,11

EJEMPLO 61



Éster etílico del ácido 2-[(6-fluoro-4H-benzo[1,3]dioxino-8-carbonil)-amino]-indan-2-carboxílico (61):

A una solución de ácido 6-fluoro-4H-benzo[1,3]dioxino-8-carboxílico (386 mg, 1,95 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (400 mg, 1,95 mmol) y HATU (1,11 g, 2,93 mmol) en DMF anhidra (8 ml) se le añade DIPEA (484 µl, 2,93 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (70 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (61) en forma de un sólido de color blanco (720 mg, 6%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 3,38 (d, 2H), 3,74 (d, 2H), 4,24 (c, 2H), 4,90 (s, 2H), 5,27 (s, 2H), 6,79 (dd, 1H), 7,17-7,24 (m, 4H), 7,74 (dd, 1H), 8,25 (s, 1H)
LC/MS (ES+) m/z = 386,11

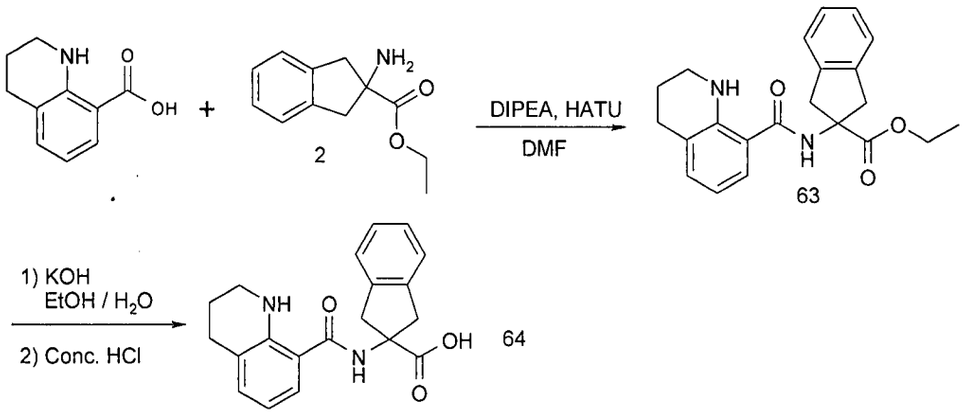
EJEMPLO 62

<u>Ácido 2-[(6-fluoro-4H-benzo[1,3]dioxino-8-carbonil)-amino]-indan-2-carboxílico (62):</u>

La mezcla de éster etílico del ácido 2-[(6-fluoro-4H-benzo[1,3]dioxino-8-carbonil)-amino]-indan-2-carboxílico (61) (560 mg, 1,45 mmol) y KOH (1 g, 17,9 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. Después de la filtración, el sólido se purifica por HPLC para dar un producto puro (62) en forma de un sólido de color blanco (520 mg, 100%).

^{1}H RMN ($CDCl_3$ + CD_3OD, 300 MHz): δ 3,39 (d, 2H), 3,75 (d, 2H), 4,92 (s, 2H), 5,30 (s, 2H), 6,85 (dd, 1H), 7,18-7,25 (m, 4H), 7,64 (dd, 1H), 8,49 (s, 1H)
LC/MS (ES) m/z = 356,10

EJEMPLO 63



Éster etílico del ácido 2-[(1,2,3,4-tetrahidro-quinolina-8-carbonil)-amino]-indan-2-carboxílico (63):

A una solución de ácido 1,2,3,4-tetrahidro-quinolina-8-carboxílico (173 mg, 0,97 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (200 mg, 0,97 mmol) y HATU (553 mg, 1,46 mmol) en DMF anhidra (20 ml) se le añade DIPEA (241 µl, 1,46 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (63) en forma de un sólido de color blanco (300 mg, 85%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 1,87 (m, 2H), 2,74 (t, 2H), 3,31-3,36 (m, 4H), 3,73 (d, 2H), 4,24 (c, 2H), 6,38 (t, 2H), 6,50 (s, 1H), 6,95 (d, 1H), 7,09 (d, 1H), 7,17-7,24 (m, 4H), 7,67 (s a, 1H)

LC/MS (ES+) m/z = 365,18

EJEMPLO 64

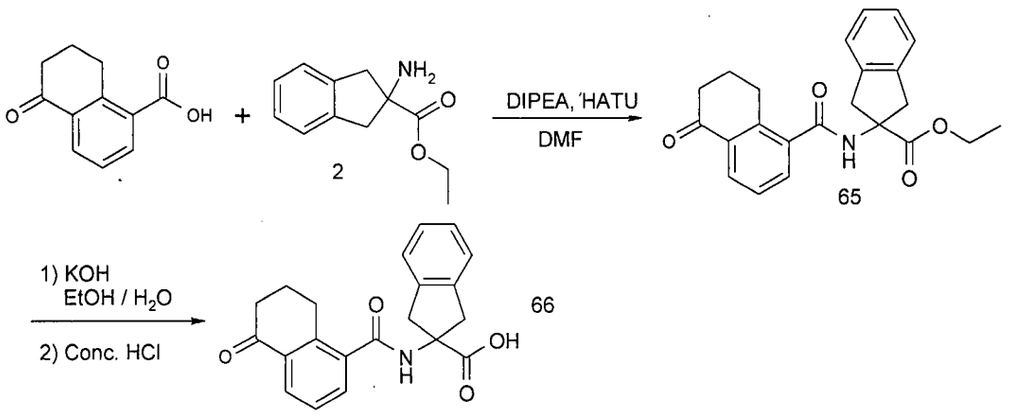
Ácido 2-[(1,2,3,4-tetrahidro-quinolina-8-carbonil)-amino]-indan-2-carboxílico (64):

La mezcla de éster etílico del ácido 2-[(1,2,3,4-tetrahidro-quinolina-8-carbonil)-amino]-indan-2-carboxílico (63) (259 mg, 0,71 mmol) y KOH (1 g, 17,9 mmol) se disuelve en EtOH (15 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica gota a gota con HCl conc. hasta surge el precipitado del agua. Después de la filtración, el sólido se lava con agua y se recoge. El filtrado se acidifica de nuevo cuidadosamente con HCl conc. para

observar si surge o no más cantidad de precipitado. El sólido combinado se seca al vacío para dar un producto puro (64) en forma de un sólido de color amarillo (205 mg, 86%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,87 (m, 2H), 2,74 (t, 2H), 3,40-3,45 (m, 4H), 3,81 (d, 2H), 6,36 (t, 1H), 6,48 (s, 1H), 6,98 (t, 2H), 7,18-7,26 (m, 4H)
LC/MS (ES+) m/z = 337,17

EJEMPLO 65



<u>Éster etílico del ácido 2-[(5-oxo-5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (65):</u>

A una solución de ácido 5-oxo-5,6,7,8-tetrahidro-naftaleno-1-carboxílico (430 mg, 2,26 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (464 mg, 2,26 mmol) y HATU (1 g, 2,70 mmol) en DMF anhidra (20 ml) se le añade DIPEA (446 µl, 2,70 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (65) en forma de un sólido de color blanco (828 mg, 97%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,30 (t, 3H), 2,09 (m, 2H), 2,63 (t, 2H), 3,07 (t, 2H), 3,38 (d, 2H), 3,77 (d, 2H), 4,29 (c, 2H), 6,31 (t, 2H), 7,20-7,26 (m, 4H), 7,30 (d, 1H), 7,50 (dd, 1H), 8,05 (dd, 1H)
LC/MS (ES+) m/z = 378,13

EJEMPLO 66

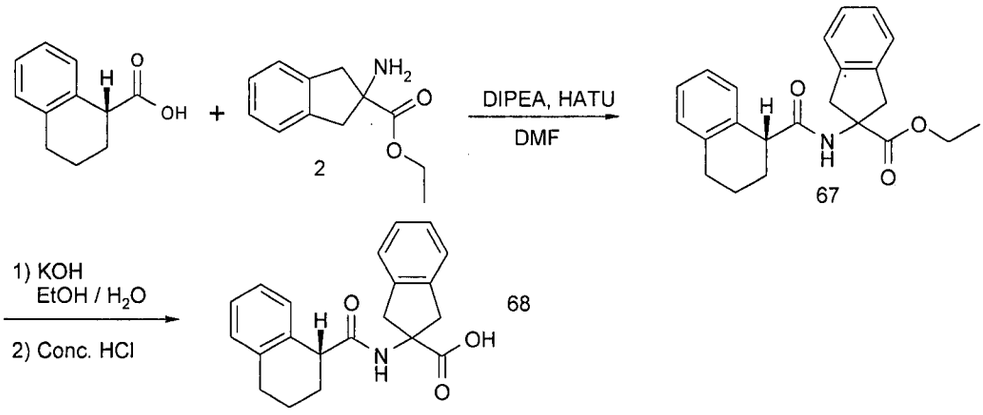
Ácido 2-[(5-oxo-5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (66):

La mezcla de éster etílico del ácido 2-[(5-oxo-5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (65) (250 mg, 0,66 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en etanol (10 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. Después de la filtración, el sólido se purifica por HPLC para dar un producto puro (66) en forma de un sólido de color blanco (150 mg, 65%).

^{1}H RMN ($CDCl_3$ + CD_3OD, 300 MHz): δ 1,98 (m, 2H), 2,60 (t, 2H), 2,97 (t, 2H), 3,34 (d, 2H), 3,58 (d, 2H), 7,15-7,25 (m, 4H), 7,38 (d, 1H), 7,48 (t, 1H), 7,94 (dd, 1H), 9,02 (s, 1H)

LC/MS (ES+) m/z = 350,16

EJEMPLO 67



Éster etílico del ácido 2-[((R)-1,2,3,4-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (67):

A una solución de ácido (R)-1,2,3,4-tetrahidro-naftaleno-1-carboxílico (300 mg, 1,7 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (349 mg, 1,7 mmol) y HATU (760 mg, 2,0 mmol) en DMF anhidra (10 ml) se le añade DIPEA (330 µl, 2 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica

por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-50% en heptano) para dar un producto puro (67) en forma de un sólido de color blanco (615 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 1,57-2,00 (m, 3H), 2,17-2,26 (m, 1H), 2,76 (m, 2H), 3,10 (dd, 2H), 3,57-3,68 (m, 3H), 4,19 (c, 2H), 5,87 (s, 1H), 7,03-7,18 (m, 8H)
LC/MS (ES+) m/z = 364,16

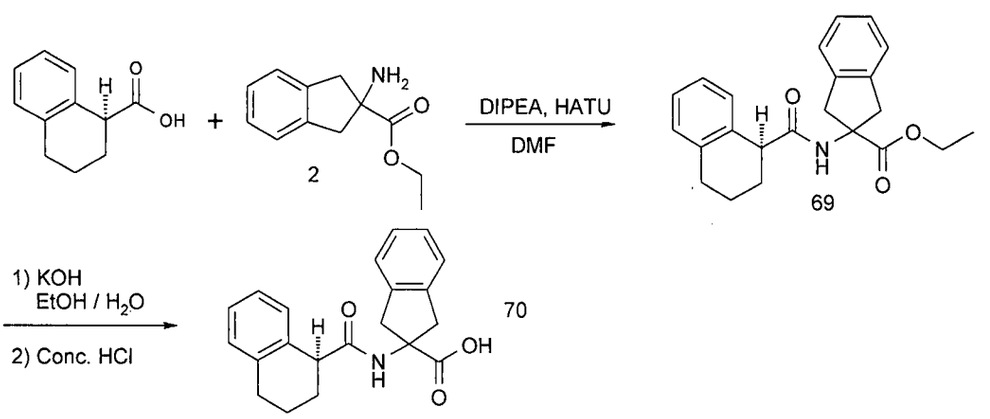
EJEMPLO 68

Ácido 2-[((R)-1,2,3,4-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (68):

La mezcla de éster etílico del ácido 2-[((R)-1,2,3,4-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (67) (440 mg, 1,21 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (10 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (68) en forma de un sólido de color blanco (391 mg, 96%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,65-1,73 (m, 2H), 1,93-1,96 (m, 1H), 2,17-2,27 (m, 1H), 2,69 (t, 2H), 3,12 (t, 2H), 3,63-3,70 (m, 3H), 5,84 (s, 1H), 6,86 (d, 1H), 7,00 (t, 1H), 7,07 (d, 1H), 7,13-7,20 (m, 5H)
LC/MS (ES) m/z = 334,14

EJEMPLO 69



Éster etílico del ácido 2-[((S)-1,2,3,4-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (69):

A una solución de ácido (S)-1,2,3,4-tetrahidro-naftaleno-1-carboxílico (300 mg, 1,7 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (349 mg, 1,7 mmol) y HATU (760 mg, 2 mmol) en DMF anhidra (8 ml) se le añade DIPEA (330 µl, 2 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-50% en heptano) para dar un producto puro (69) en forma de un sólido de color blanco (615 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24 (t, 3H), 1,58-2,00 (m, 3H), 2,17-2,26 (m, 1H), 2,76 (m, 2H), 3,10 (dd, 2H), 3,57-3,68 (m, 3H), 4,19 (c, 2H), 5,87 (s, 1H), 7,05-7,26 (m, 8H)

LC/MS (ES+) m/z = 364,19

EJEMPLO 70

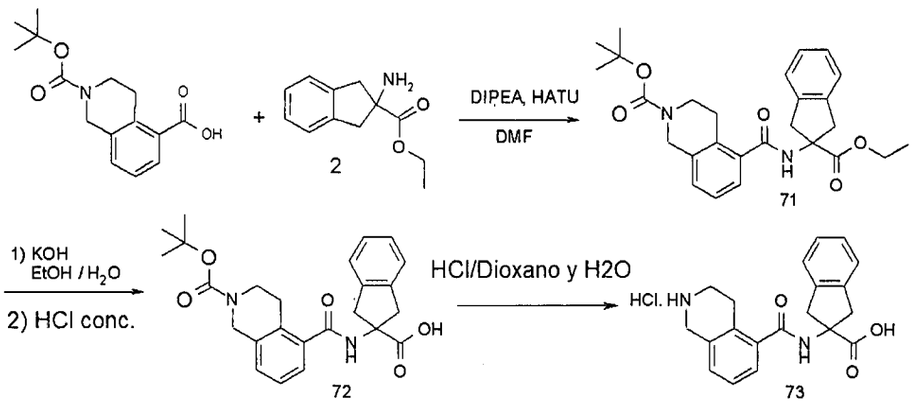
Ácido 2-[((S)-1,2,3,4-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (70):

La mezcla de éster etílico del ácido 2-[((S)-1,2,3,4-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (69) (440 mg, 1,21 mmol) y KOH (800 mg, 14,2 mmol) se disuelve en EtOH (10 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 4 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (70) en forma de un sólido de color blanco (405 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,66-1,73 (m, 2H), 1,93-1,96 (m, 1H), 2,20-2,22 (m, 1H), 2,69 (t, 2H), 3,12 (t, 2H), 3,17-3,71 (m, 3H), 5,82 (s, 1H), 6,87 (d, 1H), 7,01 (t, 1H), 7,07 (d, 1H), 7,13-7,21 (m, 5H)

LC/MS (ES+) m/z = 336,13

EJEMPLO 71



Éster terc-butílico del ácido 5-(2-etoxicarbonil-indan-2-ilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxílico (71):

A una solución de 2-terc-butil éster del ácido 3,4-dihidro-1H-isoquinolina-2,5-dicarboxílico (2 g, 7,2 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (1,5 g, 7,2 mmol) y HATU (3,27 g, 8,6 mmol) en DMF anhidra (20 ml) se le añade DIPEA (1,42 ml, 8,6 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (150 ml) y se lava con agua (1 x 20 ml) y salmuera (2 x 20 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (71) en forma de un sólido de color blanco (1,02 g, 30%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 1,48 (s, 9H), 2,95 (t, 2H), 3,35 (d, 2H), 3,57 (t, 2H), 3,75 (d, 2H), 4,27 (c, 2H), 4,55 (s, 2H), 6,26 (s, 1H), 7,14-7,26 (m, 7H)

LC/MS (ES+) m/z = 465,26

EJEMPLO 72

Éster terc-butílico del ácido 5-(2-carboxi-indan-2-ilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxílico (72):

La mezcla de éster terc-butílico del ácido 5-(2-etoxicarbonil-indan-2-ilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxílico (71) (882 mg, 1,78 mmol) y KOH (1 g, 17,9 mmol) se disuelve en EtOH (15 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (50 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. Después

de la filtración, el sólido se purifica por HPLC para dar un producto puro (72) en forma de un sólido de color blanco (680 mg, 88%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,46 (s, 9H), 2,84 (t, 2H), 3,36 (d, 2H), 3,48 (t, 2H), 3,74 (d, 2H), 4,49 (s, 2H), 6,57 (s a, 1H), 7,10-7,19 (m, 7H)
LC/MS (ES+) m/z = 381,17, 437,23

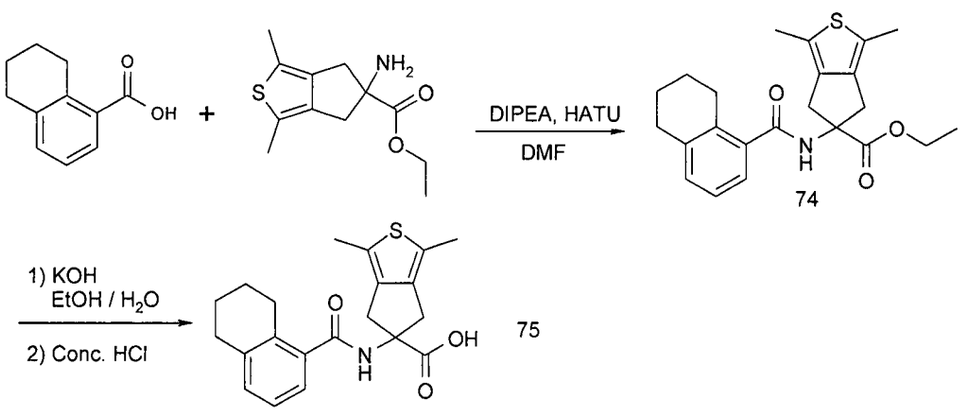
EJEMPLO 73

Sal hidrocloruro del ácido 2-[(1,2,3,4-tetrahidro-isoquinolina-5-carbonil)-amino]-indan-2-carboxílico (73):

Se disuelve éster terc-butílico del ácido 5-(2-carboxi-indan-2-ilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxílico (72) (650 mg, 1,49 mmol) en una solución al 30% de TFA en DCM (10 ml) y la solución resultante se agita a TA durante 2 h. La solución se concentra para dar una sal TFA del ácido 2-[(1,2,3,4-tetrahidro-isoquinolina-5-carbonil)-amino]-indan-2-carboxílico (670 mg, 100%). Esta sal TFA (250 mg, 0,56 mmol) se disuelve en una solución acuosa 6 N de HCl (20 ml). La suspensión resultante se agita durante una noche y se convierte en una solución transparente. La solución se concentra para dar un producto puro (73) en forma de un sólido de color blanco (130 mg, 62%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 3,05 (t, 2H), 3,32-3,37 (m, 4H), 3,57 (d, 2H), 4,27 (s, 2H), 7,15-7,29 (m, 7H), 8,98 (s, 1H), 9,42 (s, 2H), 12,51 (s a, 1H)
LC/MS (ES+) m/z = 337,17

EJEMPLO 74



Éster etílico del ácido 1,3-dimetil-5-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (74):

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (500 mg, 2,84 mmol), éster etílico del ácido 5-amino-1,3-dimetil-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (816 mg, 3,41 mmol) y HATU (1,62 g, 4,26 mmol) en DMF anhidra (15 ml) se le añade DIPEA (704 µl, 4,26 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (74) en forma de un sólido de color blanco (1,10 g, 97%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 1,76 (m, 4H), 2,25 (s, 6H), 2,80 (m, 4H), 2,97 (d, 2H), 3,31 (d, 2H), 4,26 (c, 2H), 6,22 (s, 1H), 7,15-7,15 (m, 3H)

LC/MS (ES+) m/z = 398,16

EJEMPLO 75

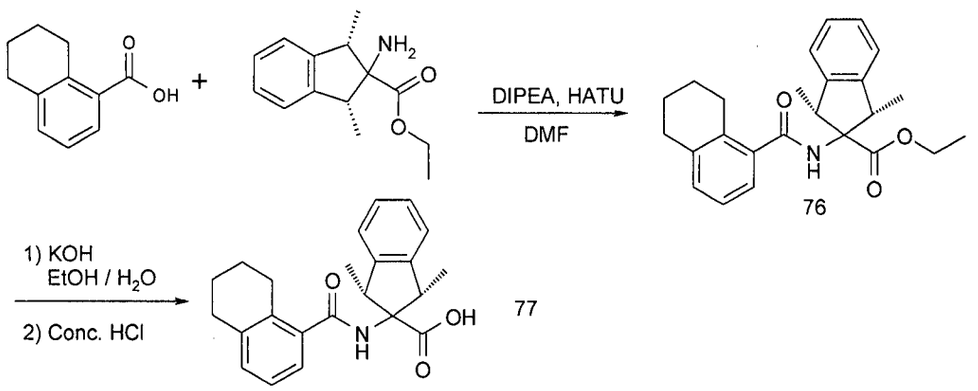
Ácido 1,3-dimetil-5-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (75):

La mezcla de éster etílico del ácido 1,3-dimetil-5-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (74) (942 mg, 2,37 mmol) y KOH (3 g, 23 mmol) se disuelve en EtOH (20 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (75) en forma de un sólido de color pardo pálido (832 mg, 95%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,75 (m, 4H), 2,25 (s, 6H), 2,75 (m, 4H), 3,03 (d, 2H), 3,36 (d, 2H), 6,26 (s, 1H), 7,08-7,16 (m, 3H)

LC/MS (ES+) m/z = 370,12

EJEMPLO 76



Éster etílico del ácido (cis)-1,3-dimetil-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (76):

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (400 mg, 2,27 mmol), éster etílico del ácido (cis)-2-amino-1,3-dimetil-indan-2-carboxílico (636 mg, 2,72 mmol) y HATU (1,3 g, 3,41 mmol) en DMF anhidra (15 ml) se le añade DIPEA (563 µl, 3,41 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 50-50% en heptano) para dar un producto puro (76) en forma de un sólido de color blanco (79 mg, 9%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,32 (t, 3H), 1,50 (d, 6H), 1,75 (m, 4H), 2,75 (s a, 2H), 2,88 (s a, 2H), 3,80 (c, 2H), 4,31 (c, 2H), 5,73 (s, 1H), 7,00-7,25 (m, 7H)
LC/MS (ES+) m/z = 392,22

EJEMPLO 77

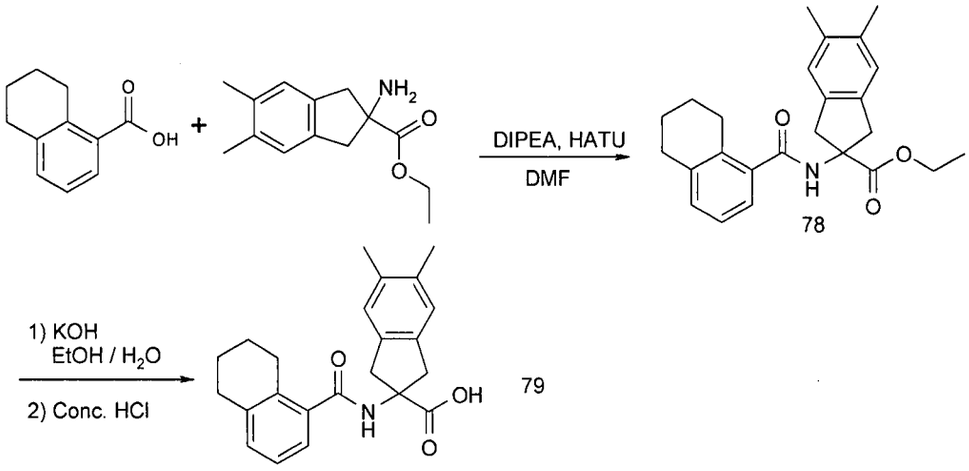
Ácido (cis)-1,3-dimetil-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (77):

La mezcla de éster etílico del ácido (cis)-1,3-dimetil-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (76) (62 mg, 1,2 mmol) y KOH (300 mg, 5,4 mmol) se disuelve en EtOH (3 ml) y agua (0,3 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica

con HCl conc. hasta alcanzar un valor de pH de ~4. El precipitado se filtra para dar un producto puro (77) en forma de un sólido de color blanco (44 mg, 75%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,51 (d, 6H), 1,74 (m, 4H), 2,75 (s a, 2H), 2,86 (s a, 2H), 3,88 (c, 2H), 5,81 (s, 1H), 7,01-7,26 (m, 7H)
LC/MS (ES+) m/z = 364,23

EJEMPLO 78



<u>Éster etílico del ácido 5,6-dimetil-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (78):</u>

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (400 mg, 2,27 mmol), éster etílico del ácido 2-amino-5,6-dimetil-indan-2-carboxílico (636 mg, 2,72 mmol) y HATU (1,30 g, 3,41 mmol) en DMF anhidra (15 ml) se le añade DIPEA (563 µl, 3,41 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (78) en forma de un sólido de color blanco (817 mg, 92%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 1,74 (m, 4H), 2,23 (s, 6H), 2,75 (s a, 2H), 2,84 (s a, 2H), 3,25 (d, 2H), 3,69 (d, 2H), 4,26 (c, 2H), 6,20 (s, 1H), 6,99-7,11 (m, 5H)
LC/MS (ES+) m/z = 392,20

EJEMPLO 79

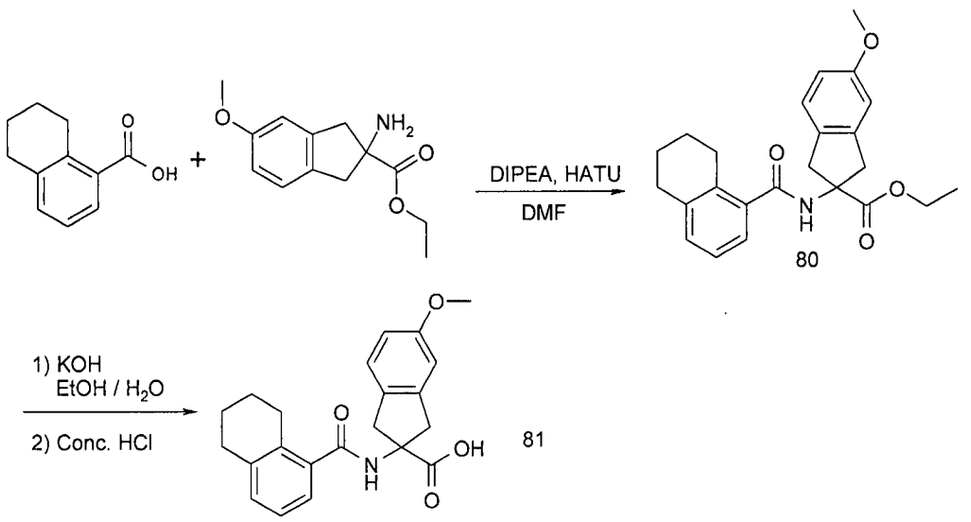
Ácido 5,6-dimetil-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (79):

La mezcla de éster etílico del ácido 5,6-dimetil-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (78) (438 mg, 1,11 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (79) en forma de un sólido de color pardo pálido (390 mg, 97%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,73 (m, 4H), 2,23 (s, 6H), 2,74-2,80 (m, 4H), 3,29 (d, 2H), 3,69 (d, 2H), 6,60 (s, 1H), 6,99-7,08 (m, 5H)

LC/MS (ES+) m/z = 364,23

EJEMPLO 80



Éster etílico del ácido 5-metoxi-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (80):

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (400 mg, 2,27 mmol), éster etílico del ácido 2-amino-5-metoxi-indan-2-carboxílico (639 mg, 2,72 mmol) y HATU (1,3 g, 3,41 mmol) en DMF anhidra (15 ml) se le añade DIPEA (563 µl, 3,41 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x

10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5%-40% en heptano) para dar un producto puro (52) en forma de un sólido de color blanco (622 mg, 70%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,28 (t, 3H), 1,74 (m, 4H), 2,75 (s a, 2H), 2,84 (s a, 2H), 3,27 (dd, 2H), 3,69 (dd, 2H), 3,78 (s, 3H), 4,25 (c, 2H), 6,26 (s, 1H), 6,72-6,76 (m, 2H), 7,01-7,11 (m, 4H),
LC/MS (ES+) m/z = 394,21

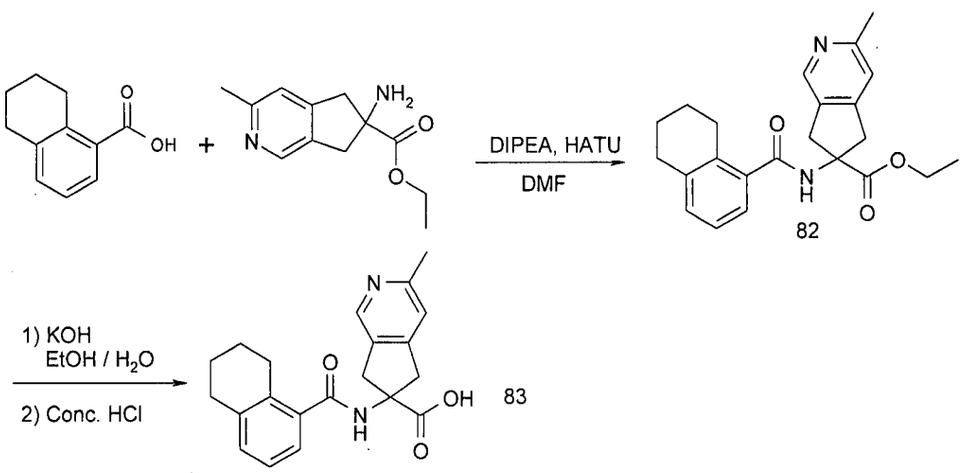
EJEMPLO 81

Ácido 5-metoxi-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (81):

La mezcla de éster etílico del ácido 5-metoxi-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (80) (458 mg, 1,2 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (81) en forma de un sólido de color pardo pálido (448 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,72 (m, 4H), 2,75-2,78 (m, 4H), 3,32 (dd, 2H), 3,78 (dd, 2H), 3,78 (s, 3H), 6,45 (s, 1H), 6,73-6,77 (m, 2H), 7,03-7,11 (m, 4H),
LC/MS (ES+) m/z = 366,20

EJEMPLO 82



Éster etílico del ácido 3-metil-6-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-6,7-dihidro-5H-[2]piridina-6-carboxílico (82):

A una solución de ácido 1,2,3,4-tetrahidro-quinolina-8-carboxílico (240 mg, 1,36 mmol), éster etílico del ácido 6-amino-3-metil-6,7-dihidro-5H-[2]pirimidina-6-carboxílico (no puro, 300 mg, 1,36 mmol) y HATU (608 mg, 1,60 mmol) en DMF anhidra (10 ml) se le añade DIPEA (264 µl, 1,60 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (40 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (82) en forma de un aceite incoloro (100 mg, 19%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 1,75 (s a, 4H), 2,76 (s a, 2H), 3,68 (s, 2H), 3,86 (c, 2H), 4,26 (c, 2H), 7,02-7,12 (m, 3H), 7,32 (s, 1H), 7,52 (s, 1H), 8,51 (s, 1H)

LC/MS (ES+) m/z = 379,22

EJEMPLO 83

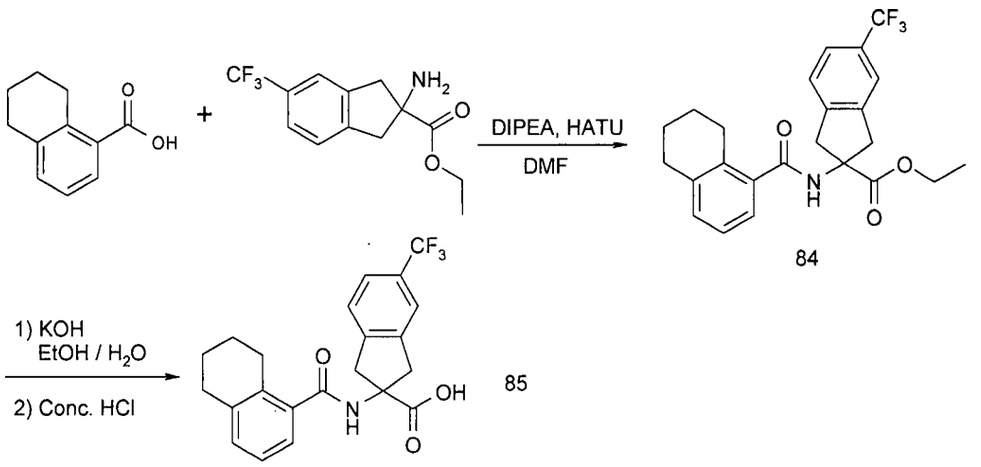
Ácido 3-metil-6-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-6,7-dihidro-5H-[2]piridina-6-carboxílico (83):

La mezcla de éster etílico del ácido 3-metil-6-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-6,7-dihidro-5H-[2]piridina-6-carboxílico (82) y KOH (1 g, 17,9 mmol) en EtOH (5 ml) y agua (0,3 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica gota a gota con HCl conc. hasta que no surge más cantidad de precipitado del agua. Después de la filtración,

el sólido se purifica por HPLC para dar un producto puro (83) en forma de un aceite incoloro (20 mg, 22%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,77 (s a, 4H), 2,79 (s a, 2H), 3,69 (m, 2H), 3,88 (c, 2H), 7,06-7,15 (m, 3H), 7,53 (s, 1H), 8,56 (s, 1H)
LC/MS (ES+) m/z = 351,11

EJEMPLO 84



<u>Éster etílico del ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5-trifluorometil-indan-2-carboxílico (84):</u>

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (306 mg, 1,74 mmol), éster etílico del ácido 2-amino-5-trifluoro-indan-2-carboxílico (583 mg, 2,13 mmol) y HATU (992 mg, 2,61 mmol) en DMF anhidra (15 ml) se le añade DIPEA (431 µl, 2,61 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (80 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-70% en heptano) para dar un producto puro (84) en forma de un sólido de color blanco (589 mg, 78%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,27 (t, 3H), 1,75 (m, 4H), 2,76 (s a, 2H), 2,83 (s a, 2H), 3,44 (dd, 2H), 3,74 (dd, 2H), 4,26 (c, 2H), 6,35 (s, 1H), 7,02-7,12 (m, 3H), 7,32 (d, 1H), 7,46 (s a, 2H) LC/MS (ES+) m/z = 432,17

EJEMPLO 85

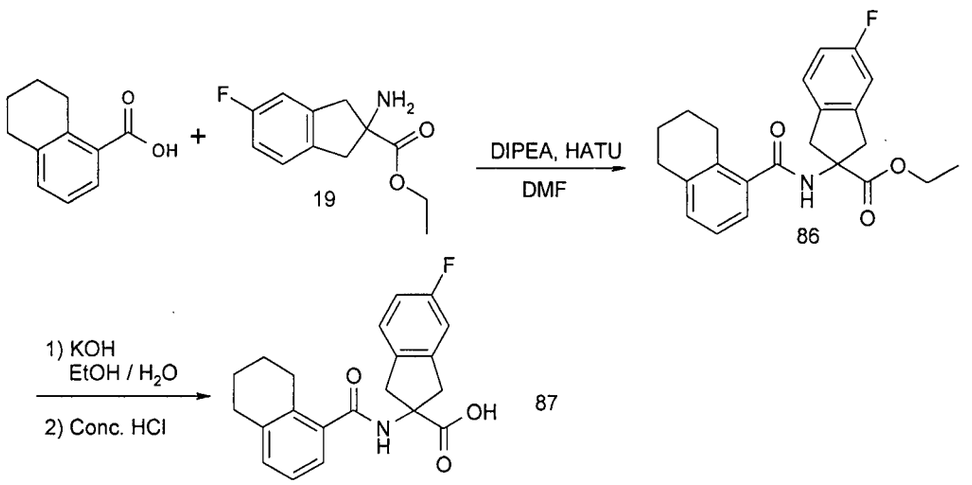
Ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5-trifluorometil-indan-2-carboxílico (85):

La mezcla de éster etílico del ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5-trifluorometil-indan-2-carboxílico (84) (437 mg, 1,0 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (50 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (85) en forma de un sólido de color blanco (408 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,74 (m, 4H), 2,78 (m, 4H), 3,49 (dd, 2H), 3,76 (dd, 2H), 6,69 (s, 1H), 7,03-7,13 (m, 3H), 7,32 (d, 1H), 7,47 (dd, 2H)

LC/MS (ES+) m/z = 404,15

EJEMPLO 86



Éster etílico del ácido 5-fluoro-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (86):

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (400 mg, 2,27 mmol), éster etílico del ácido 2-amino-5-fluoro-indan-2-carboxílico (610 mg, 2,72 mmol) y HATU (1,30 g, 3,41 mmol) en DMF anhidra (15 ml) se le añade DIPEA (563 µl, 3,41 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (70 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se

purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5%-40% en heptano) para dar un producto puro (86) en forma de un sólido de color blanco (345 mg, 40%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,28 (t, 3H), 1,75 (m, 4H), 2,76 (s a, 2H), 2,83 (s a, 2H), 3,33 (dd, 2H), 3,69 (dd, 2H), 4,25 (c, 2H), 6,29 (s, 1H), 6,85-6,93 (m, 2H), 7,02-7,16 (m, 4H)
LC/MS (ES+) m/z = 382,16

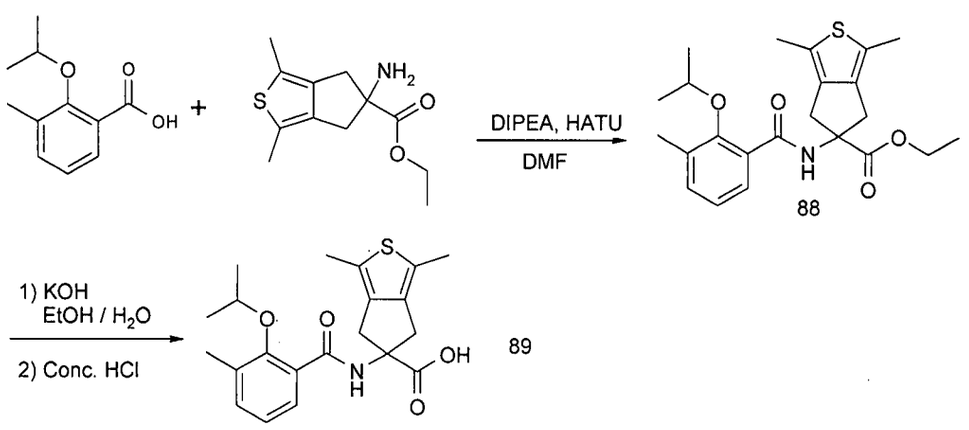
EJEMPLO 87

Ácido 5-fluoro-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (87):

La mezcla de éster etílico del ácido 5-fluoro-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (86) (190 mg, 0,50 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (87) en forma de un sólido de color pardo pálido (178 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,75 (m, 4H), 2,76-2,81 (m, 4H), 3,40 (dd, 2H), 3,72 (dd, 2H), 6,65 (s, 1H), 6,86-6,94 (m, 2H), 7,03-7,18 (m, 4H)
LC/MS (ES+) m/z = 382,16

EJEMPLO 88



Éster etílico del ácido 5-(2-isopropoxi-3-metil-benzoilamino)-1,3-dimetil-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (88):

A una solución de ácido 2-isopropoxi-3-metil-benzoico (300 mg, 1,54 mmol), éster etílico del ácido 5-amino-1,3-dimetil-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (443 mg, 1,85 mmol) y HATU (878 g, 2,31 mmol) en DMF anhidra (10 ml) se le añade DIPEA (382 µl, 2,31 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (70 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5%-50% en heptano) para dar un producto puro (88) en forma de un sólido de color amarillo pálido (599 mg, 95%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,09 (d, 6H), 1,23 (t, 3H), 2,25 (s, 6H), 2,28 (s, 3H), 2,98 (d, 2H), 3,33 (d, 2H), 4,20-4,24 (m, 3H), 7,08 (t, 1H), 7,28 (d, 1H), 7,87 (d, 1H), 8,37 (s, 1H)
LC/MS (ES+) m/z = 416,17

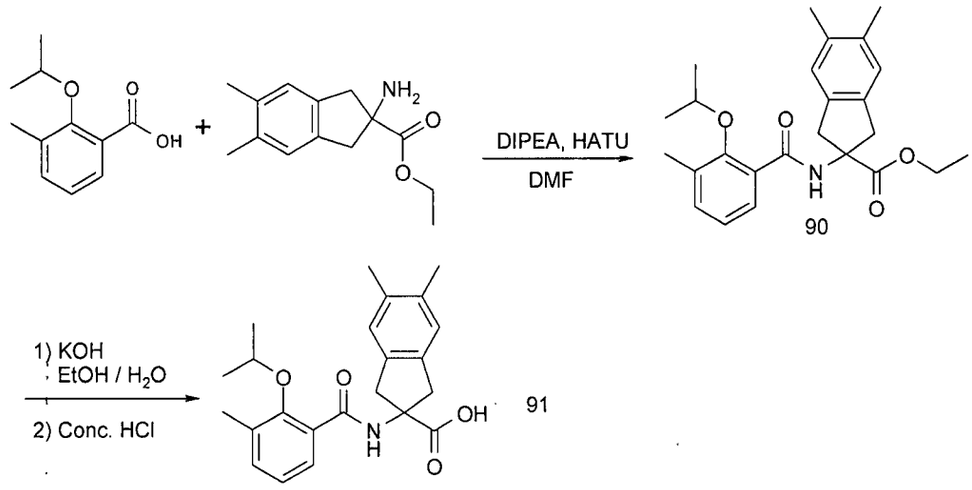
EJEMPLO 89

Ácido 5-(2-isopropoxi-3-metil-benzoilamino)-1,3-dimetil-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (89):

La mezcla de éster etílico del ácido 5-(2-isopropoxi-3-metil-benzoilamino)-1,3-dimetil-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico (88) (448 mg, 1,08 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (89) en forma de un sólido de color pardo (360 mg, 86%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,06 (d, 6H), 2,26 (s, 6H), 2,28 (s, 3H), 3,09 (d, 2H), 3,43 (d, 2H), 4,17 (m, 1H), 7,12 (t, 1H), 7,32 (d, 1H), 7,91 (d, 1H), 8,61 (s, 1H)
LC/MS (ES+) m/z = 388,14

EJEMPLO 90



Éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5,6-dimetil-indan-2-carboxílico (90):

A una solución de ácido 2-isopropoxi-3-metil-benzoico (300 mg, 1,54 mmol), éster etílico del ácido 2-amino-5,6-dimetil-indan-2-carboxílico (432 mg, 1,85 mmol) y HATU (878 g, 2,31 mmol) en DMF anhidra (10 ml) se le añade DIPEA (382 µl, 2,31 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5-40% en heptano) para dar un producto puro (90) en forma de un sólido de color blanco (591 mg, 94%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,08 (d, 6H), 1,24 (t, 3H), 2,22 (s, 6H), 2,24 (s, 3H), 3,25 (d, 2H), 3,70 (d, 2H), 4,20-4,28 (m, 3H), 7,00-7,08 (m, 3H), 7,24 (d, 1H), 7,83 (d, 1H), 8,27 (s, 1H)

LC/MS (ES+) m/z = 410,21

EJEMPLO 91

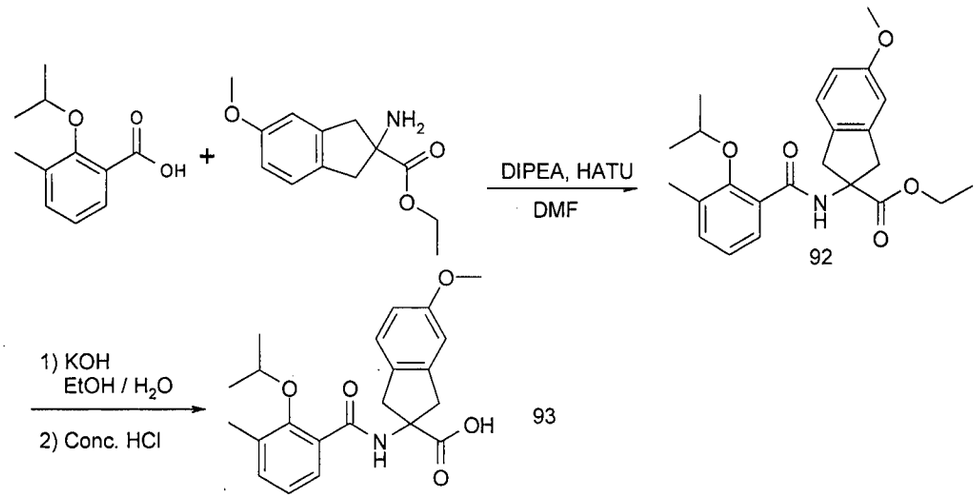
Ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5,6-dimetil-indan-2-carboxílico (91):

La mezcla de éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5,6-dimetil-indan-2-carboxílico (90) (440 mg, 1,07 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc.

hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar el producto puro (91) en forma de un sólido de color pardo pálido (374 mg, 92%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,02 (d, 6H), 2,22 (s, 6H), 2,25 (s, 3H), 3,34 (d, 2H), 3,80 (d, 2H), 4,14 (m, 1H), 7,01 (s, 2H), 7,09 (t, 1H), 7,29 (d, 1H), 7,87 (dd, 1H), 8,52 (s, 1H)
LC/MS (ES+) m/z = 382,19

EJEMPLO 92



<u>Éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-metoxi-indan-2-carboxílico (92):</u>

A una solución de ácido 2-isopropoxi-3-metil-benzoico (300 mg, 1,54 mmol), éster etílico del ácido 2-amino-5-metoxi-indan-2-carboxílico (435 mg, 1,85 mmol) y HATU (878 g, 2,31 mmol) en DMF anhidra (10 ml) se le añade DIPEA (382 µl, 2,31 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5%-40% en heptano) para dar un producto puro (92) en forma de un aceite de color amarillo pálido (569 mg, 90%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,07 (d, 6H), 1,24 (t, 3H), 2,25 (s, 3H), 3,28 (d, 2H), 3,72 (dd, 2H), 3,78 (s, 3H), 4,21-4,25 (m, 3H), 6,73-6,78 (m, 2H), 7,04-7,13 (m, 2H), 7,26 (d, 1H), 7,85 (d, 1H), 8,32 (s, 1H)

LC/MS (ES+) m/z = 412,18

EJEMPLO 93

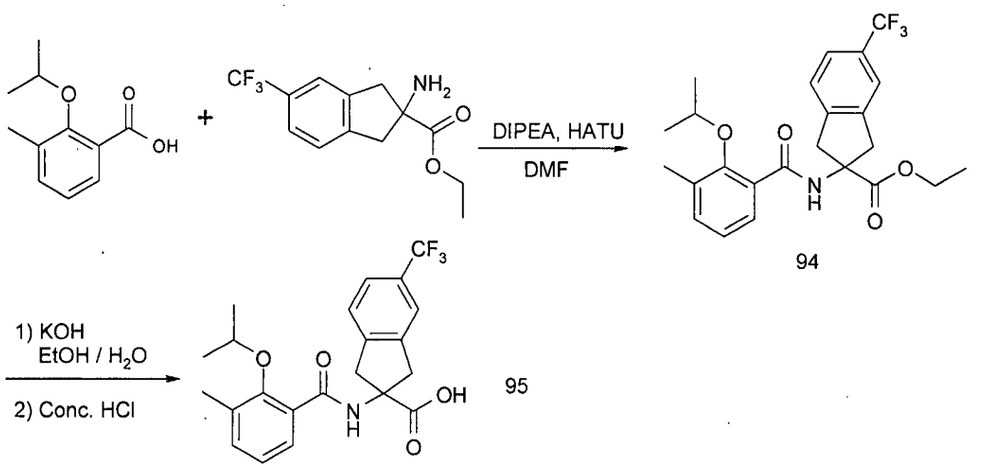
Ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-metoxi-indan-2-carboxílico (93):

La mezcla de éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-metoxi-indan-2-carboxílico (92) (410 mg, 1 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (93) en forma de un sólido de color blanco (400 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,02 (m, 6H), 2,25 (s, 3H), 3,34 (d, 2H), 3,78 (s, 3H), 3,80 (dd, 2H), 4,16 (m, 1H), 6,73-6,78 (m, 2H), 7,05-7,14 (m, 2H), 7,27-7,30 (m, 1H), 7,88 (dd, 1H), 8,51 (s, 1H)

LC/MS (ES+) m/z = 384,17

EJEMPLO 94



Éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-trifluorometil-indan-2-carboxílico (94):

A una solución de ácido 2-isopropoxi-3-metil-benzoico (377 mg, 1,94 mmol), éster etílico del ácido 2-amino-5-trifluoro-indan-2-carboxílico (650 mg, 2,38 mmol) y HATU (1,11 g, 2,91 mmol) en DMF anhidra (15 ml) se le añade DIPEA (480 µl, 2,91 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el

residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-70% en heptano) para dar un producto puro (94) en forma de un sólido de color blanco (842 mg, 97%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,06 (d, 6H), 1,24 (t, 3H), 2,26 (s, 3H), 3,43 (d, 2H), 3,78 (dd, 2H), 4,16-4,29 (m, 1H), 4,25 (c, 2H), 7,08 (t, 1H), 7,26-7,35 (m, 2H), 7,47 (d, 2H), 7,85 (dd, 1H), 8,39 (s, 1H)
LC/MS (ES+) m/z = 450,18

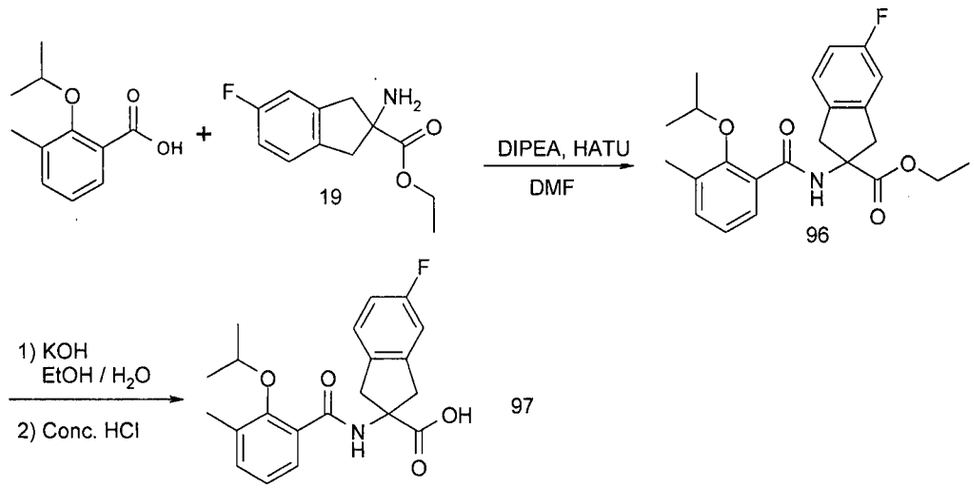
EJEMPLO 95

Ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-trifluorometil-indan-2-carboxílico (95):

La mezcla de éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-trifluorometil-indan-2-carboxílico (94) (690 mg, 1,5 mmol) y KOH (1,5 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente. La reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~4. El precipitado se filtra para dar un producto puro (95) en forma de un sólido de color pardo pálido (495 mg, 78%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,99 (d, 6H), 2,25 (s, 3H), 3,48 (d, 2H), 3,89 (d, 2H), 4,15 (m, 1H), 7,10 (t, 1H), 7,29-7,37 (m, 2H), 7,49 (d, 2H), 7,88 (dd, 1H), 8,57 (s, 1H)
LC/MS (ES+) m/z = 422,15

EJEMPLO 96



Éster etílico del ácido 5-fluoro-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (96):

A una solución de ácido 2-isopropoxi-3-metil-benzoico (400 mg, 2,06 mmol), éster etílico del ácido 2-amino-5-fluoro-indan-2-carboxílico (554 mg, 2,47 mmol) y HATU (1,17 g, 3,09 mmol) en DMF anhidra (10 ml) se le añade DIPEA (511 µl, 3,09 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-50% en heptano) para dar un producto puro (96) en forma de un sólido de color blanco (709 mg, 86%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,07 (m, 6H), 1,24 (t, 3H), 2,26 (s, 3H), 3,32 (t, 2H), 3,72 (dd, 2H), 4,23 (m, 3H), 6,85-6,94 (m, 2H), 7,05-7,28 (m, 3H), 7,85 (dd, 1H), 8,36 (s, 1H)
LC/MS (ES+) m/z = 400,18

EJEMPLO 97

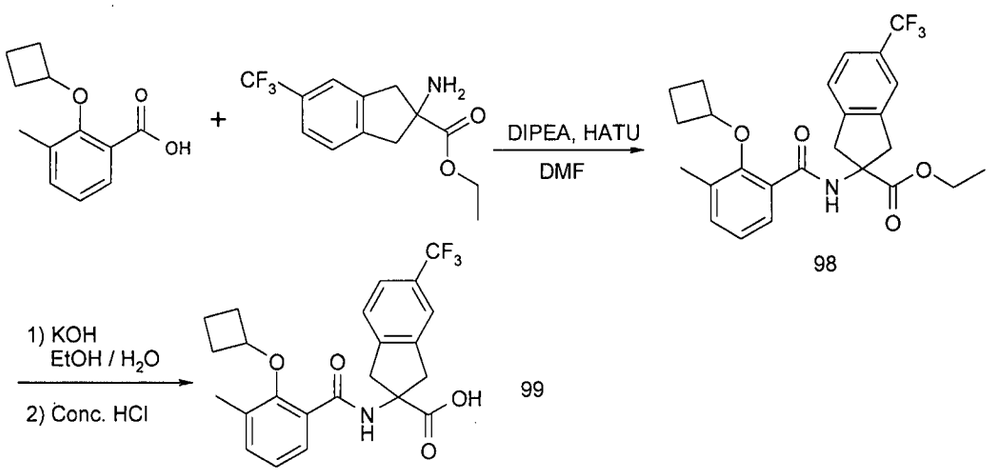
Ácido 5-fluoro-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (97):

La mezcla de éster etílico del ácido 5-fluoro-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (96) (544 mg, 1,36 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc.

hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (97) en forma de un sólido de color blanco (460 mg, 91%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,02 (m, 6H), 2,26 (s, 3H), 3,38 (dd, 2H), 3,82 (dd, 2H), 4,16 (m, 1H), 6,87-6,95 (m, 2H), 7,07-7,31 (m, 3H), 7,88 (dd, 1H), 8,56 (s, 1H)
LC/MS (ES+) m/z = 372,16

EJEMPLO 98



<u>Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-trifluoro-indan-2-carboxílico (98):</u>

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (400 mg, 1,94 mmol), éster etílico del ácido 2-amino-5-trifluoro-indan-2-carboxílico (650 mg, 2,38 mmol) y HATU (1,11 g, 2,91 mmol) en DMF anhidra (15 ml) se le añade DIPEA (480 µl, 2,91 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-60% en heptano) para dar un producto puro (98) en forma de un sólido de color blanco (800 mg, 89%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,25 (t, 3H), 1,26-1,38 (m, 1H), 1,45-1,55 (m, 1H), 1,89-2,17 (s, 3H), 2,27 (s, 3H), 3,44 (dd, 2H), 3,80 (dd, 2H), 4,22-4,35 (m, 3H), 7,08 (t, 1H), 7,27 (d, 1H), 7,34 (d, 1H), 7,47 (d, 2H), 7,85 (d, 1H), 8,41 (s, 1H)
LC/MS (ES+) m/z = 462,18

EJEMPLO 99

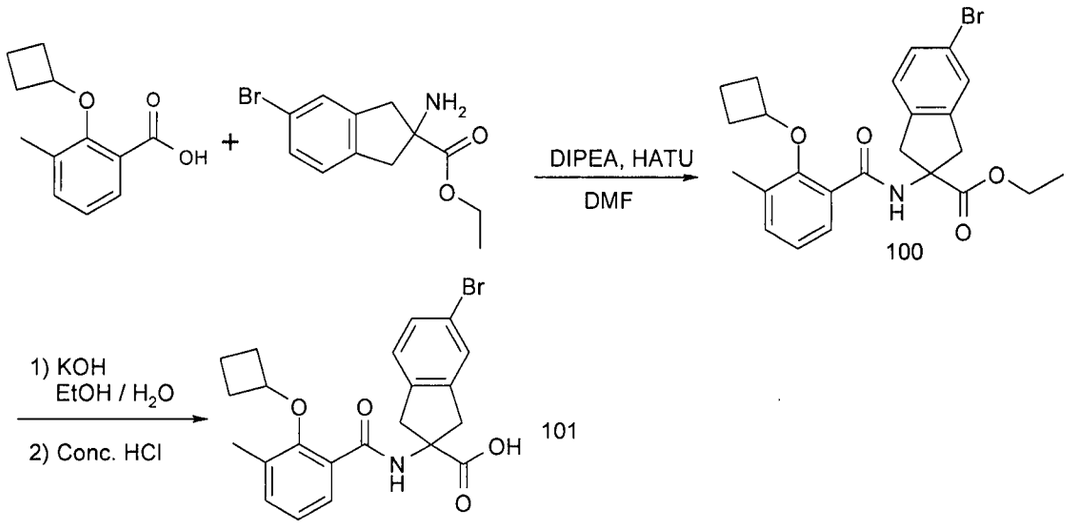
Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-trifluoro-indan-2-carboxílico (99):

La mezcla de éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-trifluoro-indan-2-carboxílico (98) (648 mg, 1,4 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (99) en forma de un sólido de color pardo pálido (595 mg, 98%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,21-1,32 (m, 1H), 1,41-1,51 (m, 1H), 1,85-2,08 (s, 3H), 2,25 (s, 3H), 3,48 (dd, 2H), 3,89 (dd, 2H), 4,26 (m, 1H), 7,09 (t, 1H), 7,26-7,36 (m, 2H), 7,49 (d, 2H), 7,87 (dd, 1H), 8,55 (s, 1H)

LC/MS (ES+) m/z = 434,16

EJEMPLO 100



Éster etílico del ácido 5-bromo-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (100):

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (250 mg, 1,21 mmol), éster etílico del ácido 2-amino-5-bromo-indan-2-carboxílico (344 mg, 1,21 mmol) y HATU (551 mg, 1,45 mmol) en DMF anhidra (10 ml) se le añade DIPEA (240 µl, 1,45 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el

residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-70% en heptano) para dar un producto puro (100) en forma de un aceite incoloro (520 mg, 91%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,22-1,40 (m, 4H), 1,48-1,63 (m, 1H), 1,90-2,12 (m, 4H), 2,27 (s, 3H), 3,44 (dd, 2H), 3,72 (dd, 2H), 4,21-4,35 (m, 3H), 7,05-7,12 (m, 2H), 7,26-7,27 (m, 3H), 7,85 (dd, 1H), 8,38 (s, 1H)

LC/MS (ES+) m/z = 474,13

EJEMPLO 101

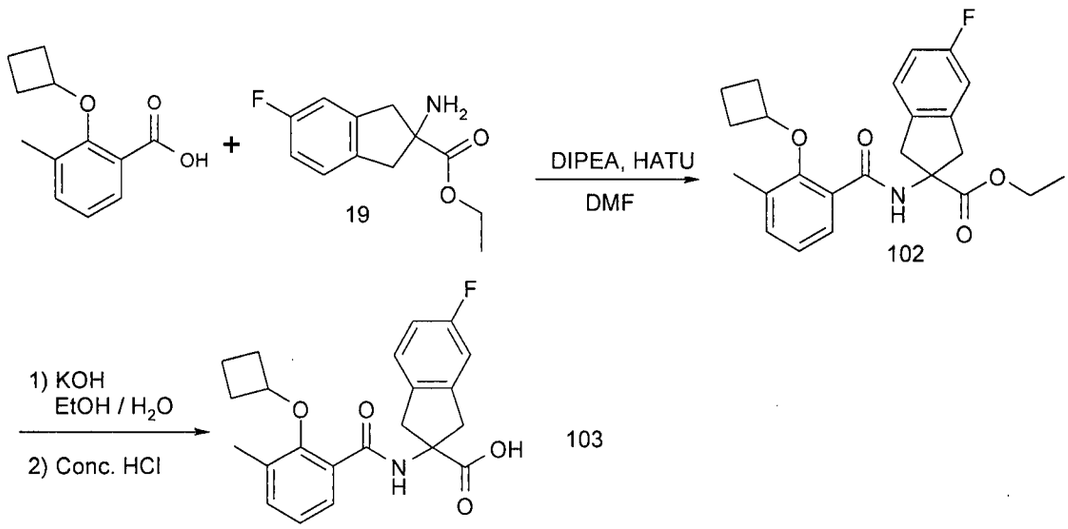
Ácido 5-bromo-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (101):

La mezcla éster etílico del ácido 5-bromo-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (100) (442 mg, 0,94 mmol) y KOH (700 mg, 12 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (101) en forma de un sólido de color blanco (390 mg, 93%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (m, 1H), 1,49 (m, 1H), 1,83-2,00 (m, 4H), 2,22 (s, 3H), 3,31-3,61 (m, 4H), 4,33 (m, 1H), 7,04 (t, 1H), 7,21 (d, 1H), 7,28-7,37 (m, 3H), 7,46 (s, 1H), 8,67 (s, 1H), 12,65 (s, 1H)

LC/MS (ES+) m/z = 444,07, 446,06

EJEMPLO 102



Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (102):

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (400 mg, 1,94 mmol), éster etílico del ácido 2-amino-5-fluoro-indan-2-carboxílico (523 mg, 2,33 mmol) y HATU (1,11 g, 2,91 mmol) en DMF anhidra (18 ml) se le añade DIPEA (480 µl, 2,91 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 5%-40% en heptano) para dar un producto puro (102) en forma de un sólido de color blanco (681 mg, 85%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,21-1,36 (m, 4H), 1,50-1,56 (m, 1H), 1,96-2,09 (m, 4H), 2,27 (s, 3H), 3,44 (t, 2H), 3,73 (dd, 2H), 4,21- 4,33 (m, 3H), 6,85-6,94 (m, 2H), 7,08 (t, 1H), 7,14-7,19 (m, 1H), 7,27 (d, 1H), 7,85 (dd, 1H), 8,37 (s, 1H)
LC/MS (ES+) m/z = 412,19

EJEMPLO 103

Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (103):

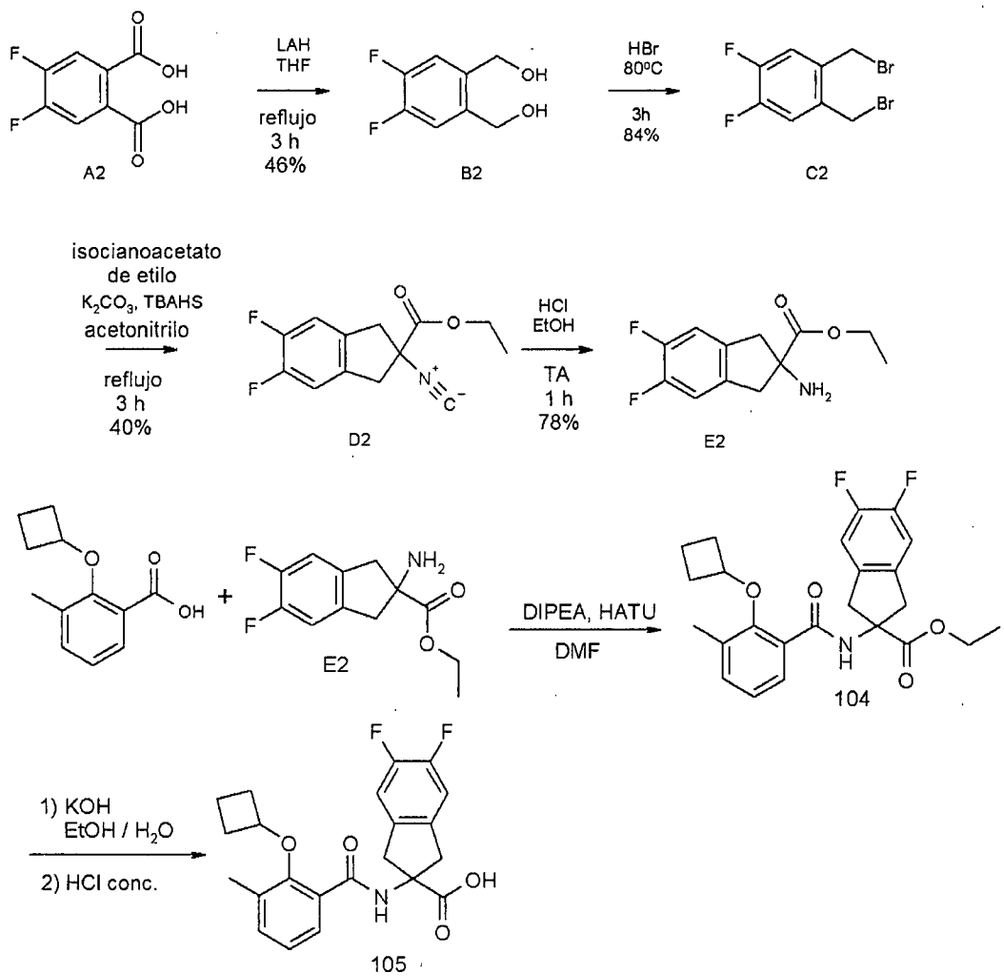
La mezcla de éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (102) (510 mg, 1,24 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la

concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (103) en forma de un sólido de color blanco (469 mg, 99%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,21-1,36 (m, 1H), 1,50 (m, 1H), 1,92-2,14 (m, 4H), 2,26 (s, 3H), 3,38 (t, 2H), 3,73 (dd, 2H), 4,29 (m, 1H), 6,86-6,95 (m, 2H), 7,11 (t, 1H), 7,15-7,20 (m, 1H), 7,29 (d, 1H), 7,83 (dd, 1H), 8,51 (s, 1H)
LC/MS (ES+) m/z = 384,15

Ejemplo 104

<u>Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5,6-difluoro-indan-2-carboxílico (104):</u>



Preparación de B2: A una suspensión de LAH (375 mg, 9,9 mmol) en THF (5 ml) se le añade gota a gota una solución del ácido 4,5-difluoroftálico **A2** (1 g, 4,95 mmol) en THF (15 ml) a 0°C. La mezcla resultante se calienta a reflujo durante 3 h seguido de refrigeración a 0°C e inactivación mediante la lenta adición de EtOAc. La masa de reacción se filtra a través de una capa de celite y el lecho de filtro se lava con metanol. El filtrado combinado se concentra para producir el producto en bruto que se purifica sobre sílice eluyendo con MeOH al 5% en DCM para producir el compuesto B2 (400 mg, 46%).

^{1}H RMN (400 MHz, $CDCl_3$): 4,69 (s, 4H), 7,19 (t, J = 9,2 y 2 Hz, 2H); FIA-MS: m/z 173 (M + H).

Preparación de C2: Una suspensión agitada de B2 (1 g, 5,74 mmol) en HBr ac. (al 47%, 10 ml) se agita a 80°C durante 3 h. El progreso de la reacción se controla por tlc. Después de que se complete el consumo del material de partida, la mezcla de reacción se enfría a TA y se extrae con DCM. Los extractos orgánicos combinados se lavan con salmuera, se secan y se concentran para dar el compuesto C2 (1,4 g, 84%). El dibromuro es bastante inestable y se utiliza inmediatamente para la siguiente etapa.

^{1}H RMN (400 MHz, $CDCl_3$): 4,59 (s, 4H), 7,19 (t, J = 9 y 2 Hz, 2H); FIA-MS: m/z 201 (M + H).

Preparación de D2: Una mezcla del dibromuro C2 (5,5 g, 18,33 mmol), cianoacetato de etilo (2,07 g, 18,33 mmol), K_2CO_3 (14 g, 106,3 mmol) e hidrogenosulfato de tetrabutilamonio (1,8 g, 5,33 mmol) en CH_3CN (150 ml) se calienta a reflujo durante 3 h. La mezcla de reacción se enfría a TA, se filtra y se concentra. El residuo se disuelve en éter, se lava con agua y salmuera, se seca y se concentra para conseguir una masa pegajosa que se purifica sobre sílice eluyendo con EtOAc al 10% en hexanos para producir el compuesto D2 (1,8 g, 40%).

^{1}H RMN (400 MHz, $CDCl_3$): 1,32 (t, J = 7,2 y 3 Hz, 3H), 3,40 (d, J = 16,3 Hz, 2H), 3,60 (d, J = 16,3 Hz, 2H), 4,30 (c, J = 7,2 y 2 Hz, 2H), 7,04 (t, J = 8,6 y 2 Hz, 2H).

Preparación de E2: A una solución agitada de D2 (2 g, 7,96 mmol) en EtOH (50 ml) se le añade HCl conc. (1 ml) y mezcla de reacción se agita a TA durante 1 h. La mezcla de reacción

se concentra, se diluye con agua y se extrae con éter. La capa orgánica se desecha y la capa acuosa se lleva a un valor de pH de 9-10 usando una solución ac. de amoniaco, manteniendo la temperatura interna por debajo de 10°C. La solución resultante se extrae con EtOAc (3 x 50 ml). Los extractos orgánicos combinados se lavan con agua y salmuera, se secan y se concentran para conseguir una masa pegajosa que se purifica sobre sílice eluyendo con EtOAc al 10% en hexanos para producir el compuesto E2 (1,5 g, 78%) en forma de un sólido de color blanquecino con p.f. 69-71°C.

^{1}H RMN (400 MHz, $CDCl_3$): 1,26 (t, J = 7,1 y 3 Hz, 3H), 2,80 (d, J = 15,9 Hz, 2H), 4,22 (c, J = 7,1 Hz, 2H), 6,99 (t, J = 8,8 y 2 Hz, 2H). ^{13}C RMN (100 MHz, $CDCl_3$): 175,7, 150,7, 150,5, 148,2, 148,1, 136,3, 136,26, 136,22, 113,24, 113,17, 113,11, 113,05, 65,2, 61,2, 45,2, 13,8; FIA-MS: m/z 242 (M + H). Pureza por HPLC: 94,28% (rendimiento cualitativo).

Preparación de 104:

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (250 mg, 1,21 mmol), éster etílico del ácido 2-amino-5,6-difluoro-indan-2-carboxílico E2 (292 mg, 1,21 mmol) y HATU (551 mg, 1,45 mmol) en DMF anhidra (10 ml) se le añade DIPEA (240 µl, 1,45 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (50 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10%-70% en heptano) para dar un producto puro (104) en forma de un sólido de color blanco (420 mg, 81%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,25 (t, 3H), 1,30-1,41 (m, 1H), 1,52-1,62 (m, 1H), 1,96-2,16 (m, 4H), 2,28 (s, 3H), 3,34 (d, 2H), 3,70 (d, 2H), 4,21- 4,39 (m, 3H), 6,99-7,11 (m, 3H), 7,28 (d, 1H), 7,85 (dd, 1H), 8,43 (s, 1H)
LC/MS (ES+) m/z = 430,22

EJEMPLO 105

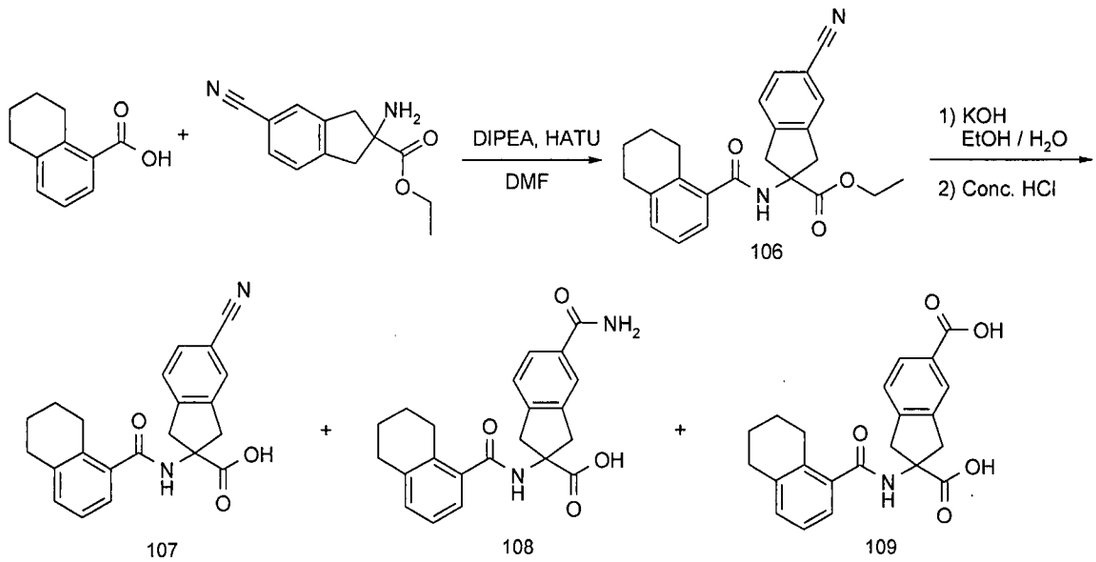
<u>Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5,6-difluoro-indan-2-carboxílico (105):</u>

La mezcla de éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5,6-difluoro-indan-2-carboxílico (104) (367 mg, 0,85 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en

EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. Después de la filtración, el sólido se purifica por HPLC para dar un producto puro (105) en forma de un sólido de color blanco (300 mg, 88%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,28 (m, 1H), 1,48 (m, 1H), 1,85-2,00 (m, 4H), 2,21 (s, 3H), 3,34 (d, 2H), 3,51 (d, 2H), 4,33 (m, 1H), 7,02 (t, 1H), 7,28-7,34 (m, 4H), 8,69 (s, 1H)
LC/MS (ES+) m/z = 430,22

EJEMPLO 106



<u>Éster etílico del ácido 5-ciano-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (106):</u>

A una solución de ácido 5,6,7,8-tetrahidro-naftaleno-1-carboxílico (306 mg, 1,74 mmol), éster etílico del ácido 2-amino-5-ciano-indan-2-carboxílico (601 mg, 2,61 mmol) y HATU (992 mg, 2,61 mmol) en DMF anhidra (15 ml) se le añade DIPEA (431 µl, 2,61 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (70 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de

elución: EtOAc al 5%-80% en heptano) para dar un producto puro (106) en forma de un sólido de color blanco (473 mg, 70%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 1,74 (m, 4H), 2,76 (s a, 2H), 2,82 (s a, 2H), 3,47 (dd, 2H), 3,72 (t, 2H), 4,25 (c, 2H), 6,47 (s, 1H), 7,03-7,12 (m, 3H), 7,31 (d, 1H), 7,49 (d, 2H)
LC/MS (ES+) m/z = 389,18

EJEMPLOS 107, 108, 109

Ácido 5-ciano-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (107):

Ácido 5-carbamoil-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (108):

y Ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2,5-dicarboxílico (109):

La mezcla de éster etílico del ácido 5-ciano-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (106) (320 mg, 0,82 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente. La solución de reacción resultante se calienta a 50°C y se agita a esta temperatura durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~2. Después de la filtración, el sólido se purifica por HPLC para dar 3 productos puros: (107) en forma de un sólido de color blanco (44 mg, 15%), (108) en forma de un sólido de color blanco (154 mg, 50%) y (109) en forma de un sólido de color blanco (28 mg, 9%).

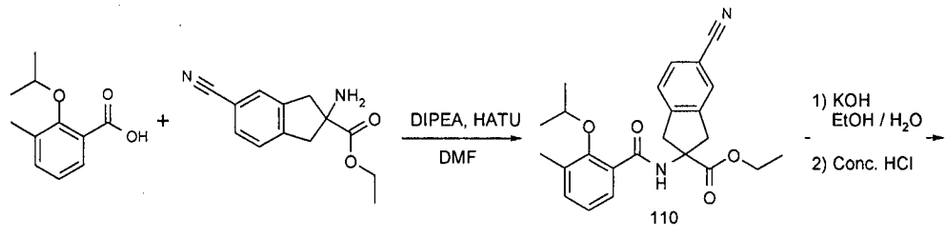
(107): ^{1}H RMN (CD_3OD, 300 MHz): δ 1,75 (m, 4H), 2,77 (s a, 4H), 3,49 (dd, 2H), 3,75 (t, 2H), 7,04-7,12 (m, 3H), 7,41 (d, 1H), 7,54-7,59 (m, 2H), 8,87 (s, 1/3H)
LC/MS (ES+) m/z = 361,15

(108): ^{1}H RMN (CD_3OD, 300 MHz): δ 1,74 (m, 4H), 2,76 (m, 4H), 3,44 (d, 2H), 3,73 (dd, 2H), 7,04-7,11 (m, 3H), 7,32 (d, 1H), 7,72 (d, 2H), 8,87 (s, 1/2H)
LC/MS (ES+) m/z = 379,17

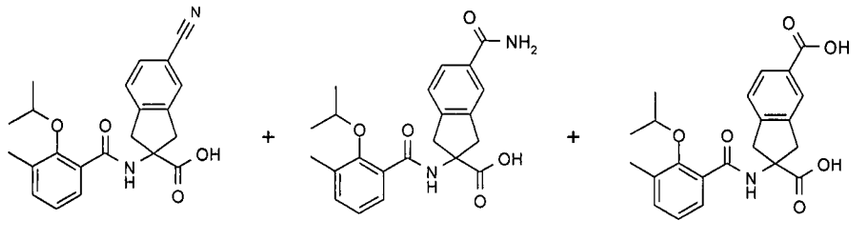
(109): ^{1}H RMN (CD_3OD, 300 MHz): δ 1,74 (m, 4H), 2,77 (m, 4H), 3,45 (dd, 2H), 3,74 (t, 2H), 7,04-7,09 (m, 3H), 7,33 (d, 1H), 7,88 (d, 2H), 8,88 (s, 1/2H)

LC/MS (ES+) m/z = 380,16

EJEMPLO 110



110



111 112 113

<u>Éster etílico del ácido 5-ciano-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (110):</u>

A una solución de ácido 2-isopropoxi-3-metil-benzoico (377 mg, 1,94 mmol), éster etílico del ácido 2-amino-5-ciano-indan-2-carboxílico (670 mg, 2,91 mmol) y HATU (1,11 g, 2,91 mmol) en DMF anhidra (15 ml) se le añade DIPEA (480 µl, 2,91 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-70% en heptano) para dar un producto puro (110) en forma de un semisólido de color blanco (680 mg, 86%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,12 (m, 6H), 1,23 (t, 3H), 2,27 (s, 3H), 3,47 (dd, 2H), 3,77 (t, 2H), 4,21- 4,26 (m, 3H), 7,08 (t, 1H), 7,28-7,35 (m, 2H), 7,51 (d, 2H), 7,84 (d, 1H), 8,47 (s, 1H)

LC/MS (ES+) m/z = 407,19

EJEMPLOS 111, 112, 113

Ácido 5-ciano-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (111):

Ácido 5-carbamoil-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (112):

Ácido 2-(2-isopropoxi-3-metil-benzoilamino)-indan-2,5-dicarboxílico (113):

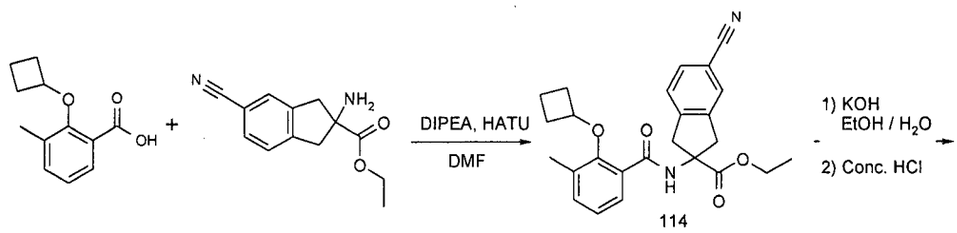
La mezcla de éster etílico del ácido 5-ciano-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (110) (527 mg, 1,3 mmol) y KOH (1,3 g, 23 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente. La solución de reacción resultante se calienta a 50°C y se agita a esta temperatura durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~2. Después de la filtración, el sólido se purifica por HPLC para dar 3 productos puros: (111) en forma de un sólido de color blanco (37 mg, 8%), (112) en forma de un sólido de color blanco (295 mg, 57%) y (113) en forma de un sólido de color blanco (62 mg, 12%).

(111): ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,06 (m, 6H), 2,27 (s, 3H), 3,49 (dd, 2H), 3,90 (dd, 2H), 4,19 (m, 1H), 7,11 (t, 1H), 7,34 (t, 2H), 7,53 (d, 2H), 7,88 (dd, 1H), 8,65 (s, 1H)
LC/MS (ES+) m/z = 379,16

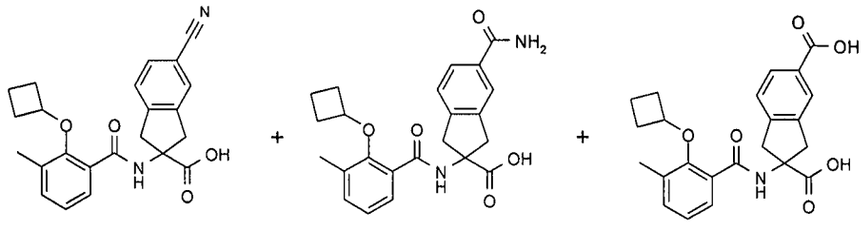
(112): ^{1}H RMN ($CDCl_3$ + gotas de D3OD, 300 MHz): δ 1,08 (dd, 6H), 2,26 (s, 3H), 3,43 (dd, 2H), 3,80 (dd, 2H), 4,20 (m, 1H), 7,08 (t, 1H), 7,28-7,32 (m, 2H), 7,67-7,77 (m, 2H), 7,79 (dd, 1H), 8,58 (s, 1/4H)
LC/MS (ES+) m/z = 397,18

(113): ^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,04 (m, 6H), 2,26 (s, 3H), 3,45 (dd, 2H), 3,81 (t, 2H), 4,18 (m, 1H), 7,08 (t, 1H), 7,27-7,32 (m, 2H), 7,80 (d, 1H), 7,92 (dd, 2H), 8,53 (s, 1H)
LC/MS (ES+) m/z = 398,16

EJEMPLO 114



114



115 116 117

Éster etílico del ácido 5-ciano-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (114):

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (400 mg, 1,94 mmol), éster etílico del ácido 2-amino-5-ciano-indan-2-carboxílico (670 mg, 2,91 mmol) y HATU (1,11 g, 2,91 mmol) en DMF anhidra (15 ml) se le añade DIPEA (480 µl, 2,91 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-60% en heptano) para dar un producto puro (114) en forma de un semisólido de color blanco (682 mg, 84%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,27 (t, 3H), 1,30-1,43 (m, 1H), 1,51-1,65 (m, 1H), 1,98-2,12 (m, 4H), 2,28 (s, 3H), 3,47 (dd, 2H), 3,78 (t, 2H), 4,22- 4,33 (m, 3H), 7,08 (t, 1H), 7,27-7,35 (m, 2H), 7,51 (d, 2H), 7,85 (d, 1H), 8,47 (s, 1H)
LC/MS (ES+) m/z = 419,19

EJEMPLOS 115, 116, 117

Ácido 5-ciano-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (115):

Ácido 5-carbamoil-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (116):

Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2,5-dicarboxílico (117):

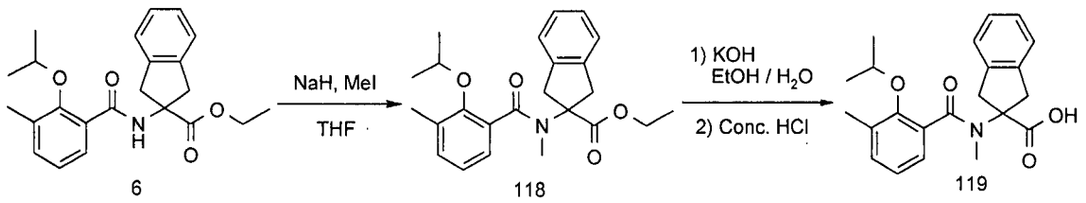
La mezcla de éster etílico del ácido 5-ciano-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (114) (530 mg, 1,3 mmol) y KOH (1,3 g, 23 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente. La solución de reacción resultante se calienta a 50°C y se agita a esta temperatura durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~2. Después de la filtración, el sólido obtenido se purifica por HPLC para dar tres productos puros: (115) en forma de un sólido de color blanco (167 mg, 33%), (116) en forma de un sólido de color blanco (239 mg, 45%) y (117) en forma de un sólido de color blanco (21 mg, 4%).

(115): ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,24-1,39 (m, 1H), 1,46-1,56 (m, 1H), 1,89-2,13 (m, 4H), 2,10 (s, 3H), 3,47 (dd, 2H), 3,89 (dd, 2H), 4,29 (m, 1H), 7,09 (t, 1H), 7,26-7,36 (m, 2H), 7,52 (d, 2H), 7,85 (d, 2H), 8,60 (s, 1H)
LC/MS (ES+) m/z = 391,13

(116): ^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,22-1,38 (m, 1H), 1,46-1,56 (m, 1H), 1,92-2,09 (m, 4H), 2,26 (s, 3H), 3,47 (dd, 2H), 3,82 (dd, 2H), 4,30 (m, 1H), 7,08 (t, 1H), 7,27-7,32 (m, 2H), 7,66-7,72 (m, 2H), 7,81 (d, 1H), 8,57 (s, 1H)
LC/MS (ES+) m/z = 409,14

(117): ^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,22-1,35 (m, 1H), 1,42-1,52 (m, 1H), 1,87-2,06 (m, 4H), 2,26 (s, 3H), 3,47 (dd, 2H), 3,83 (dd, 2H), 4,28 (m, 1H), 7,08 (t, 1H), 7,27-7,33 (m, 2H), 7,82 (d, 1H), 7,93 (d, 2H), 8,53 (s, 1H)
LC/MS (ES+) m/z = 410,17

EJEMPLO 118



6 118 119

Éster etílico del ácido 2-[(2-isopropoxi-3-metil-benzoil)-metil-amino]-indan-2-carboxílico (118):

A una solución de NaH (hidruro sódico, dispersión al 60%, 86,0 mg, 2,15 mmol) en THF anhidro (20 ml) se le añade gota a gota la solución de éster etílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico (6) (410 mg, 1,07 mmol) en THF (5 ml) a 0°C. Después de agitar durante 20 min, se añade gota a gota yoduro de metilo (452 µl, 7,26 mmol) y la suspensión resultante se calienta a TA y continua en agitación durante una noche. Después de inactivarse con una solución acuosa saturada de cloruro de amonio (5 ml), la mezcla de reacción se diluye en EtOAc (50 ml). La capa orgánica se separa, se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml), se seca sobre anhidro Na_2SO_4 y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 0%-30% en heptano) para dar el producto puro (118) en forma de un aceite incoloro (240 mg, 57%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,18 (d a, 6H), 1,28 (t, 3H), 2,24 (s, 3H), 2,85 (s, 3H), 3,44 (d, 2H), 3,62 (d a, 1H), 4,02 (d a, 1H), 4,18-4,36 (m, 3H), 7,00 (t, 1H), 7,09 (d, 1H), 7,18-7,20 (m, 5H)

LC/MS (ES+) m/z = 396,21

EJEMPLO 119

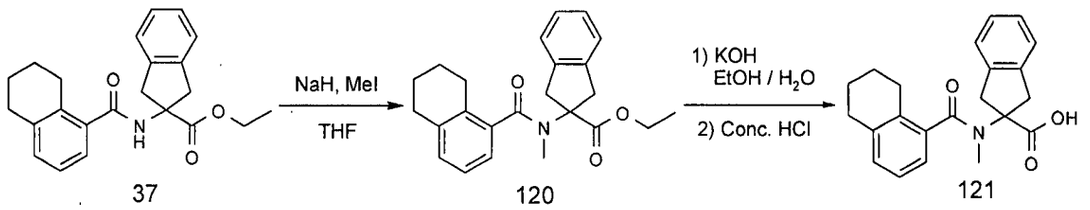
Ácido 2-[(2-isopropoxi-3-metil-benzoil)-metil-amino]-indan-2-carboxílico (119):

La mezcla de éster etílico del ácido 2-[(2-isopropoxi-3-metil-benzoil)-metil-amino]-indan-2-carboxílico (118') (200 mg, 0,51 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (119) en forma de un sólido de color naranja pálido (170 mg, 91%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,15 (d a, 6H), 2,24 (s, 3H), 2,86 (s, 3H), 3,46 (d, 2H), 3,74 (d a, 1H), 4,02 (d a, 1H), 4,26 (m, 1H), 6,99 (t, 1H), 7,15-7,26 (m, 6H), 8,79 (s a, 1H)

LC/MS (ES+) m/z = 368,20

EJEMPLO 120



37 120 121

Éster etílico del ácido 2-[metil-(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (120):

A una solución de NaH (hidruro sódico, dispersión al 60%, 124 mg, 3,08 mmol) en THF anhidro (20 ml) se le añade gota a gota la solución de éster etílico del ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (37) (280 mg, 0,77 mmol) en THF (5 ml) a 0°C. Después de agitar durante 20 min, se añade gota a gota yoduro de metilo (377 µl, 6,05 mmol) y la suspensión resultante se calienta a TA y continua en agitación durante una noche. Después de inactivarse con una solución acuosa saturada de cloruro de amonio (5 ml), la mezcla de reacción se diluye en EtOAc (50 ml). La capa orgánica se separa, se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml), se seca sobre anhidro Na_2SO_4 y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 0%-30% en heptano) para dar un producto puro (120) en forma de un semisólido incoloro (250 mg, 86%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 1,76 (s a, 4H), 2,47 (s a, 1H), 2,76 (s a, 2H), 2,82 (s, 3H), 2,82 (s a, 1H), 3,45 (d, 2H), 3,83 (d, 2H), 4,24 (m, 2H), 6,92 (d, 1H), 7,05-7,08 (m, 2H), 7,17-7,23 (m, 4H)

LC/MS (ES+) m/z = 378,22

EJEMPLO 121

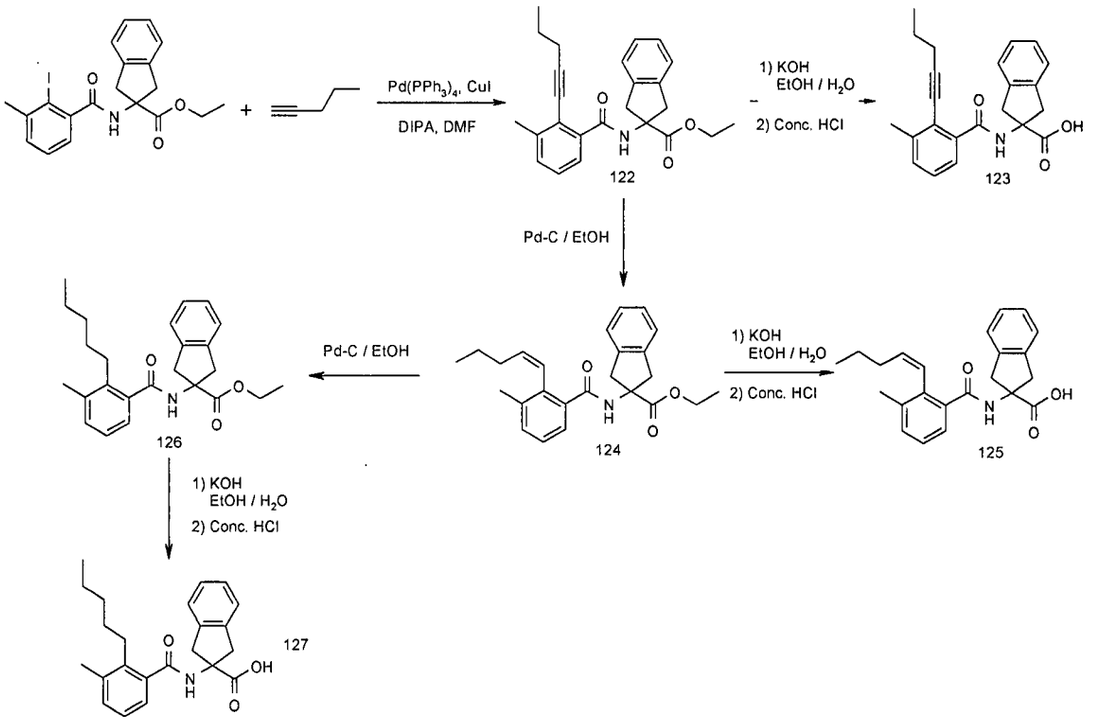
Ácido 2-[metil-(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (121):

La mezcla de éster etílico del ácido 2-[metil-(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico (120) (226 mg, 0,60 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (5 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~3. El precipitado se filtra para dar un producto puro (121) en forma de un sólido de color naranja pálido (150 mg, 72%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,74 (s a, 4H), 2,45 (s a, 1H), 2,76-2,84 (m, 3H), 2,85 (s, 3H), 3,48 (d, 2H), 3,90 (d, 2H), 4,24 (m, 2H), 6,96-7,26 (m, 7H)

LC/MS (ES+) m/z = 350,16

EJEMPLO 122



<u>Éster etílico del ácido 2-(3-metil-2-pent-1-inil-benzoilamino)-indan-2-carboxílico (122):</u>

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (693 mg, 1,54 mmol) en DMF anhidra (5 ml) y DIPA (diisopropilamina, 10 ml) se le añaden $Pd(PPh_3)_4$ (89 mg, al 7,7% en mmol), CuI (29 mg, 0,154 mmol) y pent-1-ina (1,5 ml, 15,4 mmol). La solución resultante se cubre en argón y se somete a una reacción de microondas: 110°C, 35 minutos. Después de la retirada de la DMF y el DIPA al vacío, el residuo obtenido se disuelve en EtOAc (100 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 0%-40% en heptano) para dar un producto puro (122) en forma de un sólido de color amarillo pálido (144 mg, 24%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,99 (t, 3H), 1,25 (t, 3H), 1,51 (m, 2H), 2,14 (t, 1H), 2,39 (s, 3H), 3,35 (d, 2H), 3,77 (d, 2H), 4,25 (c, 2H), 7,17-7,30 (m, 6H), 7,84 (d, 1H), 8,21 (s, 1H)
LC/MS (ES+) m/z = 390,18

EJEMPLO 123

Ácido 2-(3-metil-2-pent-1-inil-benzoilamino)-indan-2-carboxílico (123):

La mezcla de éster etílico del ácido 2-(3-metil-2-pent-1-inil-benzoilamino)-indan-2-carboxílico (122) (180 mg, 0,46 mmol) y KOH (1 g, 18 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~4. Después de la filtración, el sólido se purifica por HPLC para dar un producto puro (123) en forma de un sólido de color blanco (114 mg, 69%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,99 (t, 3H), 1,53 (m, 2H), 2,14 (t, 1H), 2,40 (s, 3H), 3,39 (d, 2H), 3,82 (d, 2H), 7,18-7,32 (m, 6H), 7,83 (d, 1H), 8,39 (s, 1H)
LC/MS (ES+) m/z = 362,17

EJEMPLO 124

Éster etílico del ácido 2-[3-metil-2-((Z)-pent-1-enil)-benzoilamino]-indan-2-carboxílico (124):

A una solución de éster etílico del ácido 2-(3-metil-2-pent-1-inil-benzoilamino)-indan-2-carboxílico (122) (300 mg, 0,77 mmol) en EtOH absoluto (18 ml) se le añade el catalizador, Pd-C (polvo humedecido al 50%, Pd al 10%, 30 mg, al 1,4% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), temperatura ambiente, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución de EtOH combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro en forma de un sólido de color blanco (168 mg, 56%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,72 (t, 3H), 1,13-1,30 (m, 5H), 1,64 (m, 2H), 2,16 (s, 3H), 3,29 (d, 2H), 3,69 (d, 2H), 4,25 (c, 2H), 5,56 (dt, 1H), 6,29 (d, 1H), 6,78 (s, 1H), 7,17-7,26 (m, 6H), 7,57 (d, 1H)

LC/MS (ES+) m/z = 392,12

EJEMPLO 125

Ácido 2-[3-metil-2-((Z)-pent-1-enil)-benzoilamino]-indan-2-carboxílico (125):

La mezcla de éster etílico del ácido 2-[3-metil-2-((Z)-pent-1-enil)-benzoilamino]-indan-2-carboxílico (124) (69 mg, 0,18 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (8 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 5 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~4. El precipitado se filtra para dar un producto puro (125) en forma de un sólido de color blanco (42 mg, 64%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,73 (t, 3H), 1,11-1,25 (m, 2H), 1,62 (c, 2H), 2,16 (s, 3H), 3,33 (d, 2H), 3,72 (d, 2H), 5,54 (dt, 1H), 6,25 (d, 1H), 7,01 (s, 1H), 7,18-7,28 (m, 6H), 7,57 (d, 1H)

LC/MS (ES+) m/z = 364,18

EJEMPLO 126

Éster etílico del ácido 2-(3-metil-2-pentil-benzoilamino)-indan-2-carboxílico (126):

A una solución de éster etílico del ácido 2-[3-metil-2-((Z)-pent-1)-enil-benzoilamino]-indan-2-carboxílico (124) (92 mg, 0,23 mmol) en EtOH absoluto (10 ml) se le añade el catalizador, Pd-C (polvo humedecido al 50%, Pd al 10%, 30 mg, al 1,4% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), temperatura ambiente, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución de EtOH combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (126) en forma de un sólido de color blanco (80 mg, 89%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,88 (t, 3H), 1,26-1,33 (m, 7H), 1,42-1,47 (m, 2H), 2,29 (s, 3H), 2,64-2,69 (m, 2H), 3,34 (d, 2H), 3,74 (d, 2H), 4,28 (c, 2H), 6,18 (s, 1H), 7,02-7,26 (m, 7H)

LC/MS (ES+) m/z = 394,23

EJEMPLO 127

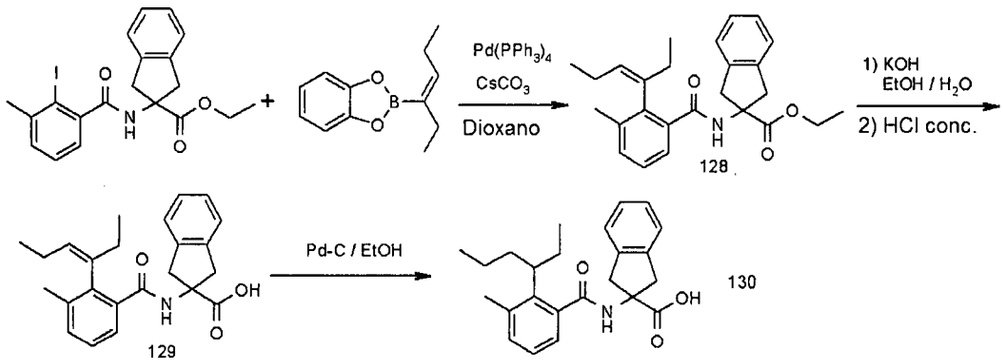
Ácido 2-(3-metil-2-pentil-benzoilamino)-indan-2-carboxílico (127):

La mezcla de éster etílico del ácido 2-(3-metil-2-pentil-benzoilamino)-indan-2-carboxílico (126) (68 mg, 0,17 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (8 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (127) en forma de un sólido de color pardo pálido (63 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,88 (t, 3H), 1,26-1,30 (m, 4H), 1,41-1,43 (m, 2H), 2,30 (s, 3H), 2,62-2,67 (m, 2H), 3,40 (d, 2H), 3,83 (d, 2H), 6,22 (s, 1H), 7,01-7,07 (m, 2H), 7,17-7,26 (m, 5H)

LC/MS (ES+) m/z = 366,20

EJEMPLO 128



Éster etílico del ácido 2-[2-(1-etil-but-1-enil)-3-metil-benzoilamino]-indan-2-carboxílico (128):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,89 mmol) y 2-(1-etil-but-1-enil)-benzo[1,3,2]dioxaborol (709 µl, 3,56 mmol) en dioxano (15 ml) se le añaden $Pd(PPh_3)_4$ (103 mg, al 8,9% en mmol) y una solución acuosa 2 M de $CsCO_3$ (1,34 ml, 2,67 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 2 h. Después de la concentración al vacío, el residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5%-50% en heptano) para dar un producto puro (128) en forma de un semi-sólido de color pardo (530 mg, 73%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,71 (t, 3H), 0,99 (t, 3H), 1,27 (t, 3H), 1,75-2,05 (m, 3H), 2,11-2,25 (m, 1H), 2,21 (s, 3H), 3,11 (d, 1H), 3,33 (d, 1H), 3,37 (dd, 2H), 4,25 (c, 2H), 5,54 (t, 1H), 7,16-7,27 (m, 6H), 7,66 (d, 1H)

LC/MS (ES+) m/z = 406,25

EJEMPLO 129

Ácido 2-[2-(1-etil-but-1-enil)-3-metil-benzoilamino]-indan-2-carboxílico (129):

La mezcla de éster etílico del ácido 2-[2-(1-etil-but-1-enil)-3-metil-benzoilamino]-indan-2-carboxílico (128) (503 mg, 1,24 mmol) y KOH (1 g, 17,9 mmol) se disuelve en EtOH (10 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (40 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~3. El precipitado se filtra para dar un producto puro (129) en forma de un sólido de color pardo (452 mg, 97%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,68 (t, 3H), 0,99 (t, 3H), 1,83 (m, 2H), 1,95-2,18 (m, 2H), 2,20 (s, 3H), 3,11 (d, 1H), 3,39 (d, 1H), 3,72 (dd, 2H), 5,54 (t, 1H), 7,16-7,35 (m, 6H), 7,63 (d, 1H)

LC/MS (ES+) m/z = 378,21

EJEMPLO 130

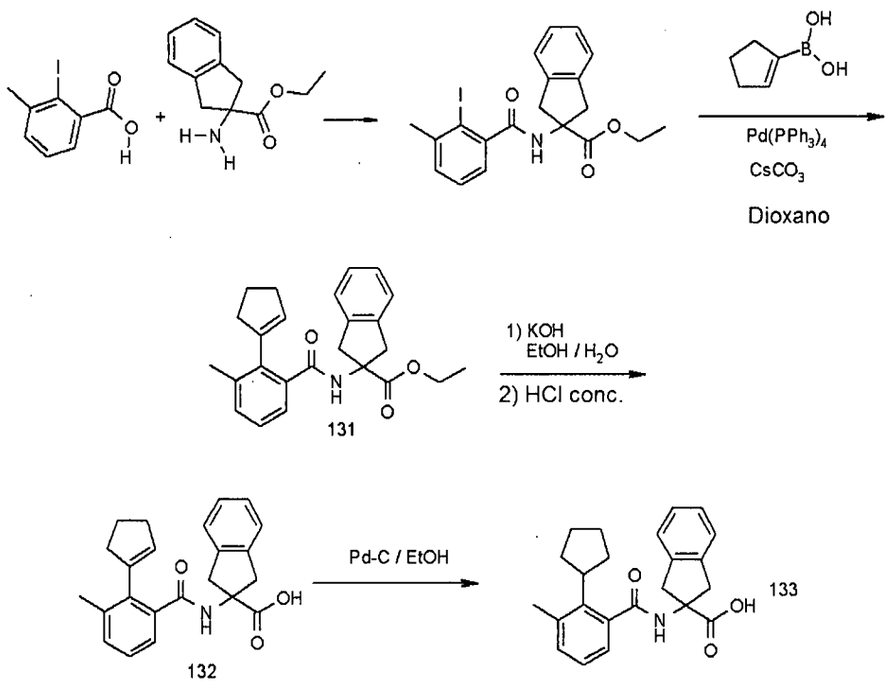
Ácido 2-[2-(1-etil-butil)-3-metil-benzoilamino]-indan-2-carboxílico (130):

A una solución de éster etílico del ácido 2-[2-(1-etil-but-1-enil)-3-metil-benzoilamino]-indan-2-carboxílico (129) (270 mg, 0,72 mmol) en EtOH absoluto (15 ml) se le añade el catalizador, Pd-C (polvo humedecido al 50%, Pd al 10%, 46 mg, al 2,2% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), 70°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución de EtOH combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (130) en forma de un sólido de color blanco (75 mg, 28%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,66-0,75 (m, 6H), 0,83-1,26 (m, 2H), 1,56-1,69 (m, 4H), 2,34 (s, 3H), 2,87 (m, 1H), 3,34-3,43 (m, 2H), 3,72 (d, 2H), 6,15 (s, 1H), 7,00-7,25 (m, 7H), 8,83 (s a, 1H)

LC/MS (ES+) m/z = 380,22

EJEMPLO 131



<u>Éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico</u>

Un matraz de fondo redondo de 100 ml se carga con ácido 2-yodo-3-metilbenzoico (1,92 g, 7,31 mmol) y DCM seco (25 ml). Se añade una barra de agitación y se inicia la agitación. Después de 5 min, se añade HTBU (2,37 g, 7,31 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (1,50 g, 7,31 mmol) seguido de DIPEA (3,2 ml, 18,37 mmol). La reacción se deja en agitación durante 118 horas. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 15%/diclorometano) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (70 ml). Se lava con HCl acuoso diluido (al 3%, 2 x 30 ml), $NaHCO_3$ acuoso saturado (2 x 30 ml) y salmuera (30 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 2,04 g de un sólido de color blanco. Este material se disuelve en DCM (15 ml). Este material se purifica utilizando un ISCO Companion con un

cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% durante 10 volúmenes de columna. Se recogen fracciones de 27 ml del eluyente activo por UV. Las fracciones 10 a 15 se combinan y se evaporan al vacío hasta alcanzar un peso constante, para dar éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico, 1,04 g de sólido de color blanco.

Éster etílico del ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (131):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (800 mg, 1,78 mmol) y ácido ciclopenten-1-ilborónico (796 mg, 7,11 mmol) en dioxano (20 ml) se le añaden $Pd(PPh_3)_4$ (412 mg, 0,36 mmol) y una solución acuosa 2 M de $CsCO_3$ (5,34 ml, 10,7 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 2,7 h. Después de la concentración al vacío, el residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5-40% en heptano) para dar un producto puro (131) en forma de un sólido de color pardo (589 mg, 85%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,27 (t, 3H), 1,72 (m, 2H), 2,19 (s, 3H), 2,33-2,43 (m, 4H), 3,23 (d, 2H), 3,70 (dd, 2H), 4,25 (c, 2H), 5,57 (m, 1H), 6,99 (s, 1H), 7,16-7,26 (m, 6H), 7,58 (d, 1H)
LC/MS (ES+) m/z = 390,22

EJEMPLO 132

Ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (132):

La mezcla de éster etílico del ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (131) (560 mg, 1,43 mmol) y KOH (1 g, 17,9 mmol) se disuelve en EtOH (8 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de ~3. El precipitado se filtra para dar un producto puro (132) en forma de un sólido de color amarillo pálido (518 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,73 (m, 2H), 2,19 (s, 3H), 2,36-2,39 (m, 4H), 3,27 (d, 2H), 3,73 (dd, 2H), 5,57 (m, 1H), 7,16-7,29 (m, 6H), 7,53 (d, 1H)
LC/MS (ES+) m/z = 362,17

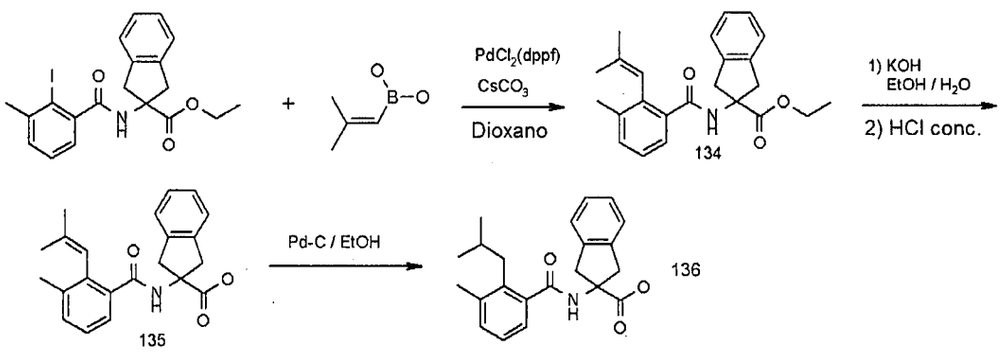
EJEMPLO 133

Ácido 2-(2-ciclopentil-3-metil-benzoilamino)-indan-2-carboxílico (133):

A una solución de ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (132) (365 mg, 1,01 mmol) en EtOH absoluto (15 ml) se le añade el catalizador, Pd-C (polvo humedecido al 50%, Pd al 10%, 192 mg, al 9% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), 50°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución de EtOH combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (133) en forma de un sólido de color blanco (184 mg, 50%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,55-1,77 (m, 8H), 2,33 (s, 3H), 3,22 (m, 1H), 3,27 (d, 2H), 3,77 (dd, 2H), 6,22 (m, 1H), 7,101-7,26 (m, 7H)
LC/MS (ES+) m/z = 364,22

EJEMPLO 134



Éster etílico del ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (134):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,89 mmol) y ácido 2,2-dimetiletilenoborónico (133 mg, 1,34 mmol) en dioxano (15 ml) se le añaden $PdCl_2$(dppf) ([1,1'-bis(difenilfosfina)ferroceno]-dicloropaladio (II), 73 mg, al

8,9% en mmol) y una solución acuosa 2 M de $CsCO_3$ (1,34 ml, 2,67 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 2 h. Después de la concentración al vacío, el residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (134) en forma de un sólido de color amarillo pálido (523 mg, 78%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,27 (t, 3H), 1,30 (s, 3H), 1,65 (s, 3H), 2,14 (s, 3H), 3,24 (d a, 2H), 3,70 (d a, 2H), 4,25 (c, 2H), 6,10 (s, 1H), 7,02 (s, 1H), 7,17-7,26 (m, 6H), 7,69 (d, 1H)
LC/MS (ES+) m/z = 378,22

EJEMPLO 135

Ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (135):

La mezcla de éster etílico del ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (134) (283 mg, 0,75 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. El precipitado se filtra para dar un producto puro (135) en forma de un sólido de color blanco (250 mg, 95%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,28 (t, 3H), 1,68 (s, 3H), 2,14 (s, 3H), 3,28 (d, 2H), 3,74 (d, 2H), 6,09 (s, 1H), 7,17-7,29 (m, 6H), 7,66 (d, 1H)
LC/MS (ES+) m/z = 350,19

EJEMPLO 136

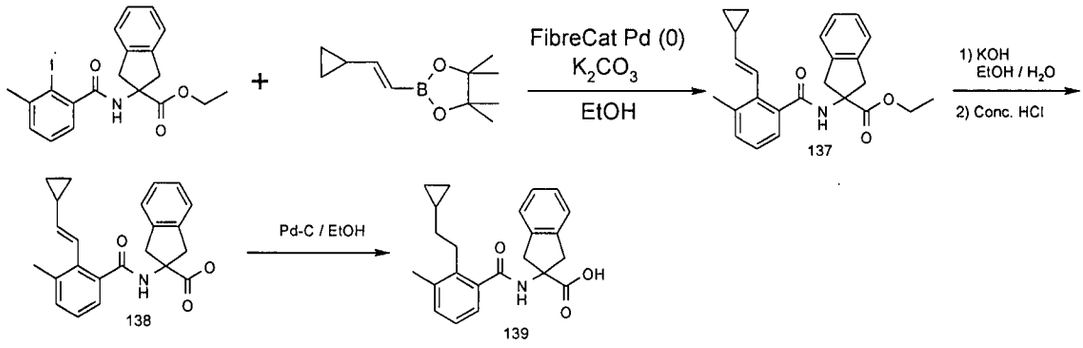
Ácido 2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico (136):

A una solución de ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (135) (120 mg, 0,34 mmol) en ácido acético (15 ml) se le añade el catalizador, Pd-C (Pd al 5% en peso, 72 mg, al 3,4% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (95 psi), 50°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución orgánica combinada se concentra al vacío. El

residuo se purifica por HPLC para dar un producto puro (136) en forma de un sólido de color blanco (65 mg, 54%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,80 (d, 6H), 1,75-1,78 (m, 1H), 2,30 (s, 3H), 2,68 (d, 2H), 3,38 (d, 2H), 3,76 (d, 2H), 6,53 (s, 1H), 7,03-7,25 (m, 7H)
LC/MS (ES+) m/z = 352,15

EJEMPLO 137



Éster etílico del ácido 2-[2-(2-ciclopropil-vinil)-3-metil-benzoilamino]-indan-2-carboxílico (137):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (600 mg, 1,34 mmol) y 2-(2-ciclopropil-vinil)-4,4,5,5-tetrametil-[1,3,2]dioxaborolano (1,11 ml, 5,36 mmol) en EtOH (10 ml) y dioxano (10 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0), (Pd al 4,84%, 285 mg, 0,13 mmol), y una solución acuosa 2 M de K_2SO_4 (2,68 ml, 5,36 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 8 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar un producto puro (137) en forma de un sólido de color blanco (250 mg, 49%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,47-0,50 (m, 2H), 0,76-0,82 (m, 2H), 1,29 (t, 3H), 1,45 (m, 1H), 2,27 (s, 3H), 3,32 (d, 2H), 3,72 (d, 2H), 4,27 (c, 2H), 5,30 (dd, 1H), 6,45 (dd, 1H), 6,52 (s, 1H), 7,09-7,23 (m, 6H), 7,39 (d, 1H)
LC/MS (ES+) m/z = 390,20

EJEMPLO 138

Ácido 2-[2-(2-ciclopropil-vinil)-3-metil-benzoilamino]-indan-2-carboxílico (138):

La mezcla de éster etílico del ácido 2-[2-(2-ciclopropil-vinil)-3-metil-benzoilamino]-indan-2-carboxílico (137) (220 mg, 0,56 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (138) en forma de un sólido de color blanco (209 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,47-0,50 (m, 2H), 0,78-0,84 (m, 2H), 1,43 (m, 1H), 2,26 (s, 3H), 3,38 (d, 2H), 3,83 (d, 2H), 5,24 (dd, 1H), 6,34 (d, 1H), 6,68 (s, 1H), 7,11-7,26 (m, 6H), 7,41 (d, 1H)

LC/MS (ES+) m/z = 362,17

EJEMPLO 139

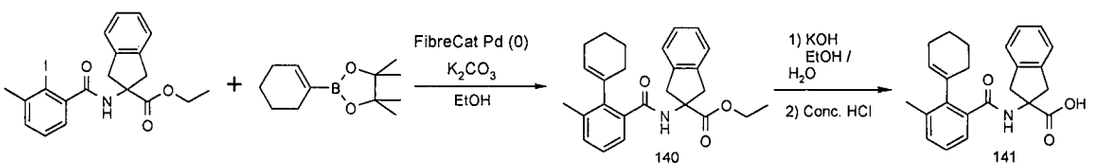
<u>Ácido 2-[2-(2-ciclopropil-etil)-3-metil-benzoilamino]-indan-2-carboxílico (139):</u>

A una solución de ácido 2-[2-((E)-2-ciclopropil-vinil)-3-metil-benzoilamino]-indan-2-carboxílico (138) (120 mg, 0,33 mmol) en EtOH absoluto (10 ml) se le añade el catalizador, Pd-C (Pd al 5% en peso, 28 mg, al 1,3% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), temperatura ambiente, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (139) en forma de un sólido de color blanco (30 mg, 25%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,00 (m, 2H), 0,35-0,41 (m, 2H), 0,66 (m, 1H), 1,32-1,39 (m, 2H), 2,30 (s, 3H), 2,76-2,82 (m, 2H), 3,40 (d, 2H), 3,82 (d, 2H), 6,23 (s, 1H), 7,03-7,04 (m, 2H), 7,16-7,26 (m, 4H)

LC/MS (ES+) m/z = 364,13

EJEMPLO 140



Éster etílico del ácido 2-(2-ciclohex-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (140):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (491 mg, 1,09 mmol) y 2-ciclohex-1-enil-4,4,5,5-tetrametil-[1,3,2]dioxaborolano (937 µl, 4,36 mmol) en EtOH (10 ml) y dioxano (10 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 240 mg, 0,11 mmol), y una solución acuosa 2 M de K_2SO_4 (2,18 ml, 4,36 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 8 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar un producto puro (140) en forma de un sólido de color blanco (95 mg, 22%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 1,55 (t a, 4H), 2,01-2,34 (m, 4H), 2,21 (s, 3H), 3,27 (t a, 2H), 3,74 (d a, 2H), 4,22-4,27 (m, 2H), 5,56 (s, 1H), 7,16-7,29 (m, 7H), 7,63 (d, 1H)
LC/MS (ES+) m/z = 404,22

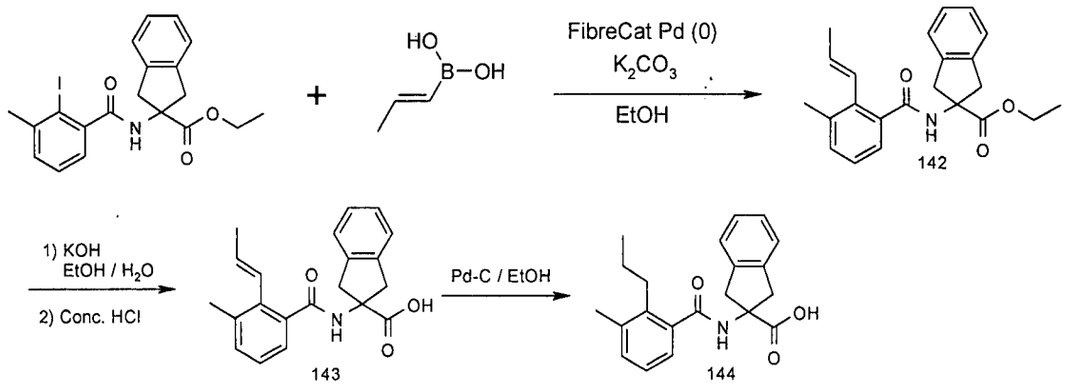
EJEMPLO 141

Ácido 2-(2-ciclohex-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (141):

La mezcla de éster etílico del ácido 2-(2-ciclohex-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (141) (80 mg, 0,20 mmol) y KOH (300 mg, 5,36 mmol) se disuelve en EtOH (8 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (141) en forma de un sólido de color blanco (71 mg, 95%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,41-1,56 (m, 4H), 2,03-2,24 (m, 4H), 2,21 (s, 3H), 3,32 (m, 2H), 3,83 (d, 2H), 5,56 (s, 1H), 7,16-7,34 (m, 6H), 7,61 (d, 1H)
LC/MS (ES+) m/z = 376,22

EJEMPLO 142



Éster etílico del ácido 2-[3-metil-2-(1-propenil)-benzoilamino]-indan-2-carboxílico (142):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (600 mg, 1,34 mmol) y ácido trans-1-propen-1-ilborónico (460 mg, 5,36 mmol) en EtOH (10 ml) y dioxano (10 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0), (Pd al 4,84%, 285 mg, 0,13 mmol), y una solución acuosa 2 M de K_2SO_4 (2,68 ml, 5,36 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 8 h. Después de la concentración al vacío y el residuo se purifica por HPLC para dar un producto puro (142) en forma de un sólido de color blanco (300 mg, 63%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 1,74 (dd, 3H), 2,25 (s, 3H), 3,28 (d, 2H), 3,71 (d, 2H), 4,27 (c, 2H), 5,75 (dc, 1H), 6,37 (d, 1H), 7,10-7,26 (m, 6H), 7,36 (d, 1H)
LC/MS (ES+) m/z = 364,18

EJEMPLO 143

Ácido 2-[3-metil-2-(1-propenil)-benzoilamino]-indan-2-carboxílico (143):

La mezcla de éster etílico del ácido 2-[3-metil-2-(1-propenil)-benzoilamino]-indan-2-carboxílico (142) (340 mg, 0,94 mmol) y KOH (700 mg, 12,5 mmol) se disuelve en EtOH (8 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (143) en forma de un sólido de color blanco (315 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,75 (dd, 3H), 2,25 (s, 3H), 3,32 (d, 2H), 3,73 (d, 2H), 5,75 (dc, 1H), 6,36 (dd, 1H), 6,76 (s, 1H), 7,10-7,24 (m, 6H), 7,31 (d, 1H)
LC/MS (ES+) m/z = 336,16

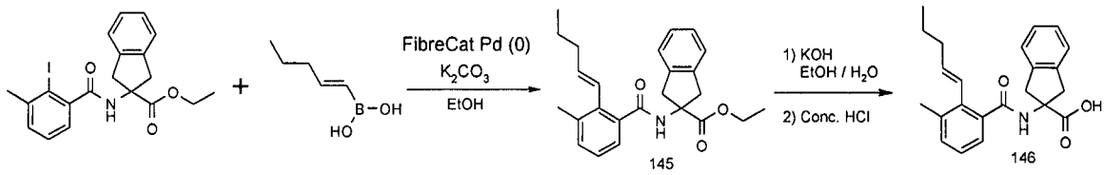
EJEMPLO 144

Ácido 2-(3-metil-2-propil-benzoilamino)-indan-2-carboxílico (144):

A una solución de ácido 2-[3-metil-2-(1-propenil)-benzoilamino]-indan-2-carboxílico (143) (220 mg, 0,65 mmol) en EtOH absoluto (10 ml) se le añade el catalizador, Pd-C (Pd al 5% en peso, 55 mg, al 2,6% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), temperatura ambiente, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (144) en forma de un sólido de color blanco (128 mg, 58%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,91 (t, 3H), 1,45 (m, 2H), 2,45 (s, 3H), 2,61-2,66 (d, 2H), 3,40 (d, 2H), 3,82 (d, 2H), 6,22 (s, 1H), 7,04 (d, 2H), 7,17-7,26 (m, 5H)
LC/MS (ES+) m/z = 338,17

EJEMPLOS 145-146



Éster etílico del ácido 2-[3-metil-2-((E)-pent-1-enil)-benzoilamino]-indan-2-carboxílico (145):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (200 mg, 0,45 mmol) y ácido trans-1-penten-1-ilborónico (205 mg, 1,80 mmol) en EtOH (10 ml) y dioxano (10 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 96 mg, 0,045 mmol), y una solución acuosa 2 M de K_2SO_4 (0,90 ml, 1,80 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 8 h. Después de la concentración al vacío, el residuo se

purifica por HPLC para dar un producto puro (145) en forma de un sólido de color blanco (107 mg, 60%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,93 (t, 3H), 1,28 (t, 3H), 1,42 (m, 2H), 2,03 (c, 3H), 2,26 (s, 3H), 3,29 (d, 2H), 3,70 (d, 2H), 4,25 (c, 2H), 5,75 (dt, 1H), 6,37 (d, 1H), 6,43 (s, 1H), 7,09-7,25 (m, 6H), 7,37 (d, 1H)
LC/MS (ES+) m/z = 392,0

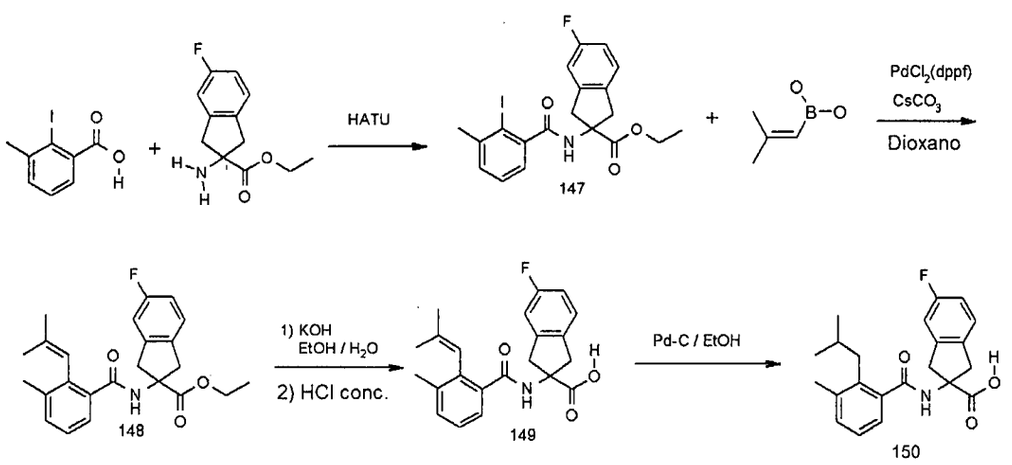
EJEMPLO 146

Ácido 2-[3-metil-2-((E)-pent-1-enil)-benzoilamino]-indan-2-carboxílico (146):

La mezcla de éster etílico del ácido 2-[3-metil-2-((E)-pent-1-enil)-benzoilamino]-indan-2-carboxílico (145) (170 mg, 0,43 mmol) y KOH (60 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (146) en forma de un sólido de color blanco (160 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,93 (t, 3H), 1,42 (m, 2H), 2,05 (c, 3H), 2,26 (s, 3H), 3,33 (d, 2H), 3,74 (d, 2H), 4,25 (c, 2H), 5,73 (dt, 1H), 6,35 (d, 1H), 6,68 (s, 1H), 7,11-7,21 (m, 6H), 7,34 (d, 1H)
LC/MS (ES+) m/z = 364,18

EJEMPLOS 147-150



EJEMPLO 147

Éster etílico del ácido 5-fluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (147):

A una solución de ácido 2-yodo-3-metil-benzoico (3,85 g, 14,7 mmol), éster etílico del ácido 2-amino-5-fluoro-indan-2-carboxílico (3,00 g, 13,4 mmol) y HATU (6,10 g, 16,1 mmol) en DMF anhidra (6 ml) se le añade DIPEA (3,30 ml, 20,1 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo se recristaliza en EtOAc para dar un producto puro (147) en forma de un sólido de color blanco (3,90 g, 62%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 2,44 (s, 3H), 3,45-3,67 (m, 4H), 4,28 (c, 2H), 6,32 (s, 1H), 6,85-6,94 (m, 2H), 7,12-7,26 (m, 4H)

LC/MS (ES+) m/z = 468,03

EJEMPLO 148

Éster etílico del ácido 5-fluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (148):

A una solución de éster etílico del ácido 5-fluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,85 mmol) y 2,2-ácido dimetiletilenborónico (342 mg, 3,42 mmol) en EtOH (10 ml) y dioxano (5 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 186 mg, al 8,5% en mmol), y una solución acuosa 2 M de K_2SO_4 (1,71 ml, 3,42 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 120°C, 7 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar un producto puro (148) en forma de un aceite incoloro (245 mg, 73%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 1,34 (d, 3H), 1,71 (dd, 3H), 2,15 (s, 3H), 3,25(dd a, 2H), 3,65(dd a, 2H), 4,24 (c, 2H), 6,12 (s, 1H), 6,86-6,92 (m, 2H), 7,19-7,26 (m, 4H), 7,65 (d, 1H)

LC/MS (ES+) m/z = 396,18

EJEMPLO 149

Ácido 5-fluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (149):

La mezcla de éster etílico del ácido 5-fluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (148) (245 mg, 0,62 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (10 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (149) en forma de un sólido de color blanco (230 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,32 (s, 3H), 1,73 (s, 3H), 2,15 (s, 3H), 3,27 (t, 2H), 3,68 (dd, 2H), 6,12 (s, 1H), 6,86-6,93 (m, 2H), 7,13-7,30 (m, 4H), 7,61 (d, 1H)
LC/MS (ES+) m/z = 368,10

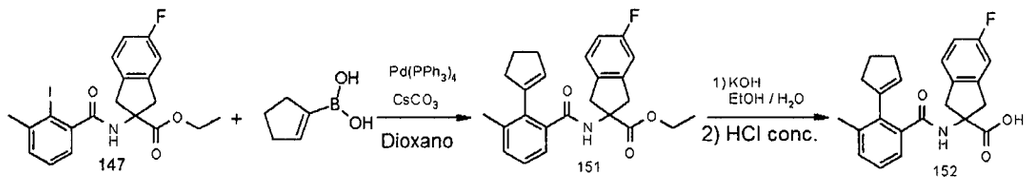
EJEMPLO 150

<u>Ácido 5-fluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico (150):</u>

A una solución de ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (149) (230 mg, 0,63 mmol) en ácido acético (10 ml) se le añade el catalizador, Pd-C (Pd al 5% en peso, 134 mg, al 6,3% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 379,21 kPa (55 psi), 95°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución orgánica combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (150) en forma de un sólido de color blanco (200 mg, 86%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,81 (dd, 6H), 1,78 (m, 1H), 2,30 (s, 3H), 2,68 (d, 2H), 3,37 (t, 2H), 3,69 (dd, 2H), 6,88-6,93 (m, 3H), 7,13-7,30 (m, 4H), 7,32 (s, 1H)
LC/MS (ES+) m/z = 370,19

EJEMPLO 151-152



Éster etílico del ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (151):

A una solución de éster etílico del ácido 5-fluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,85 mmol), ácido ciclopenten-1-ilborónico (383 mg, 3,42 mmol) en EtOH (10 ml) y dioxano (5 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 186 mg, al 8,5% en mmol), y una solución acuosa 2 M de K_2SO_4 (1,71 ml, 3,42 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 8 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar un producto puro (151) en forma de un sólido de color blanco (240 mg, 69%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,27 (t, 3H), 1,76 (m, 2H), 2,20 (s, 3H), 2,38-2,41 (m, 4H), 3,25 (dd, 2H), 3,66 (dd, 2H), 4,25 (c, 2H), 5,62 (t, 1H), 6,87-6,93 (m, 2H), 7,12-7,30 (m, 4H), 7,53 (d, 1H), 8,39 (s a, 1H)

LC/MS (ES+) m/z = 408,22

EJEMPLO 152

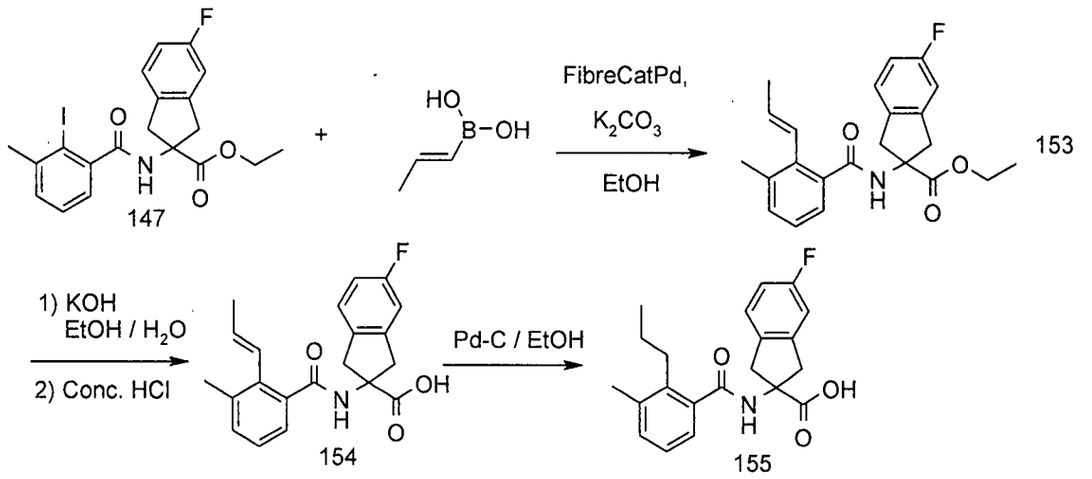
Ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (152):

La mezcla de éster etílico del ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (151) (190 mg, 0,47 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (10 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado. El precipitado se filtra para dar un producto puro (152) en forma de un sólido de color blanco (182 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,72 (m, 2H), 2,18 (s, 3H), 2,34 (t, 4H), 3,20 (t, 2H), 3,66 (dd, 2H), 5,55 (s, 1H), 6,84-6,89 (m, 2H), 7,07-7,26 (m, 4H), 7,56 (d, 1H)

LC/MS (ES+) m/z = 380,19

EJEMPLO 153



Éster etílico del ácido 5-fluoro-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico (153):

A una solución de éster etílico del ácido 5-fluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,85 mmol) y ácido trans-1-propen-1-ilborónico (294 mg, 3,42 mmol) en EtOH (10 ml) y dioxano (5 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 186 mg, al 8,5% en mmol), y una solución acuosa 2 M de K_2SO_4 (1,71 ml, 3,42 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 7 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar un producto puro (153) en forma de un sólido de color blanco (165 mg, 51%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,28 (t, 3H), 1,75 (m, 3H), 2,26 (s, 3H), 3,27 (dd, 2H), 3,62 (dd, 2H), 4,26 (c, 2H), 5,76 (dc, 1H), 6,38 (d, 1H), 6,44 (s, 1H), 6,85-6,91 (m, 2H), 7,11-7,22 (m, 3H), 7,35 (d, 1H)

LC/MS (ES+) m/z = 382,21

EJEMPLO 154

Ácido 5-fluoro-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico (154):

La mezcla de éster etílico del ácido 5-fluoro-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico (153) (260 mg, 0,68 mmol) y KOH (600 mg, 10,7 mmol) se disuelve en EtOH (8 ml) y agua (0,2 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 2,5 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El compuesto filtrado se

purifica por HPLC para dar un producto puro (154) en forma de un sólido de color blanco (267 mg, 100%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,76 (m, 3H), 2,26 (s, 3H), 3,31 (t, 2H), 3,65 (dd, 2H), 5,76 (dc, 1H), 6,38 (d, 1H), 6,80 (s, 1H), 6,85-6,93 (m, 2H), 7,10-7,22 (m, 3H), 7,31 (d, 1H)

LC/MS (ES+) m/z = 354,18

EJEMPLO 155

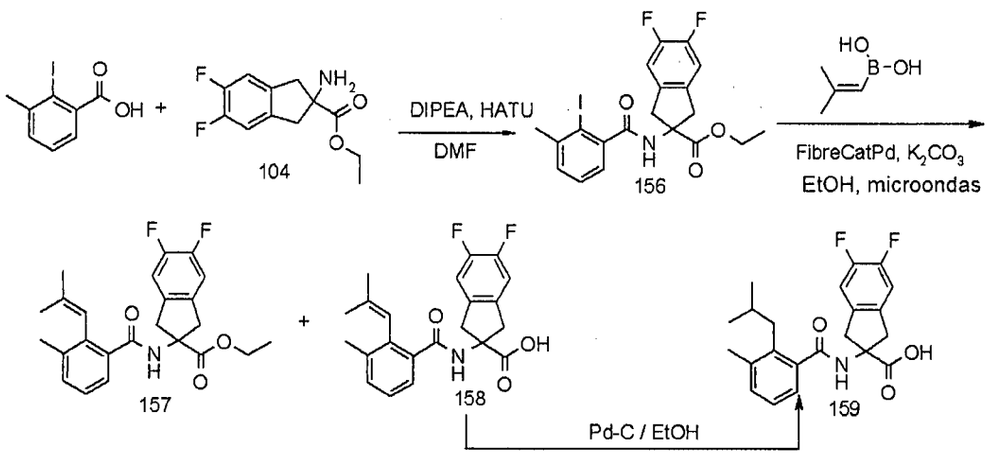
<u>Ácido 5-fluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico (155):</u>

Se disuelve ácido 5-fluoro-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico (154) (270 mg, 0,76 mmol) en EtOH absoluto (15 ml) con calentamiento. La solución resultante se enfría a TA en una atmósfera de argón y después se añade el catalizador, Pd-C (Pd al 5% en peso, 125 mg, al 5,9% en mmol). La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), 50°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución orgánica combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (155) en forma de un sólido de color blanco (210 mg, 78%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,92 (t, 3H), 1,46 (m, 2H), 2,30 (s, 3H), 2,65-2,68 (m, 2H), 3,36 (t, 2H), 3,71 (dd, 2H), 6,85-6,93 (m, 2H), 7,03-7,18 (m, 4H)

LC/MS (ES+) m/z = 356,14

EJEMPLO 156



Éster etílico del ácido 5,6-difluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (156):

A una solución de ácido 2-yodo-3-metil-benzoico (1,50 g, 5,75 mmol), éster etílico del ácido 2-amino-5,6-difluoro-indan-2-carboxílico (1,39 g, 5,75 mmol) y HATU (2,63 g, 6,90 mmol) en DMF anhidra (6 ml) se le añade DIPEA (1,14 ml, 6,90 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (200 ml) y se lava con agua (1 x 20 ml) y salmuera (2 x 20 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (400 g de gel de sílice, gradiente de elución: EtOAc al 10%-80% en heptano) para dar un producto puro (156) en forma de un sólido de color blanco (2,32 g, 83%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ ,29 (t, 3H), 2,45 (s, 3H), 3,48 (d, 2H), 3,63 (d, 2H), 4,27 (c, 2H), 6,38 (s, 1H), 7,04 (t, 2H), 7,10-7,13 (m, 1H), 7,24-7,27 (m, 2H)
LC/MS (ES+) m/z = 486,02

EJEMPLOS 157 y 158

Éster etílico del ácido 5,6-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (157) y Ácido 5,6-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (158):

A una solución de éster etílico del ácido 5,6-difluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,82 mmol) y ácido 2,2-dimetiletilenborónico (328 mg, 3,28 mmol) en EtOH (10 ml) y dioxano (5 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 180 mg, al 8,2% en mmol), y una solución acuosa 2 M de K_2SO_4 (1,64 ml, 3,28 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 120°C, 6 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar dos productos puros: (157) en forma de un sólido de color blanco (100 mg, 29%) y (158) también en forma de un sólido de color blanco (120 mg, 38%).

(157): ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 1,38 (d, 3H), 1,76 (s, 3H), 2,15 (s, 3H), 3,27 (d, 2H), 3,59 (d, 2H), 4,24 (c, 2H), 6,14 (s, 1H), 6,98-7,31 (m, 5H), 7,61 (d, 1H)
LC/MS (ES+) m/z = 414,20

(158): ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,34 (d, 3H), 1,79 (s, 3H), 2,15 (s, 3H), 3,26 (d, 2H), 3,75 (d, 2H), 6,09 (s, 1H), 7,02 (t, 2H), 7,21-7,34 (m, 3H), 7,77 (d, 1H)
LC/MS (ES+) m/z = 386,19

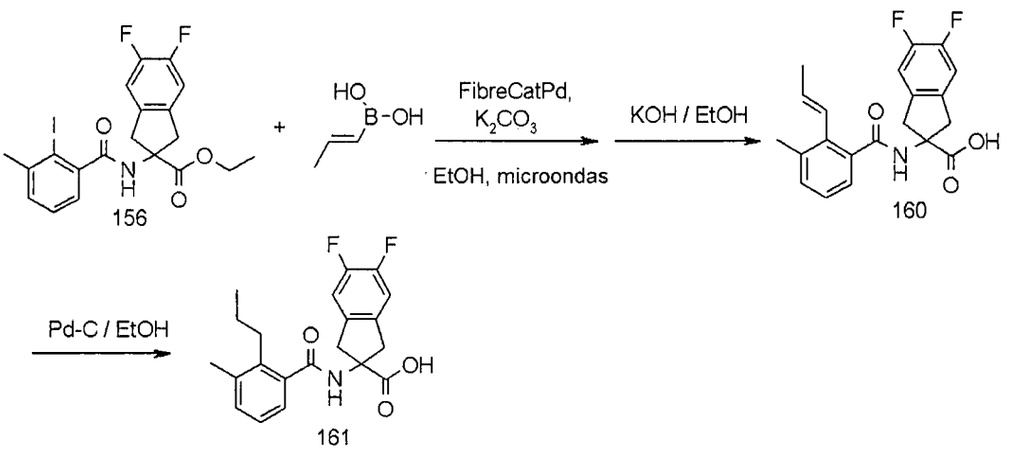
EJEMPLO 159

Ácido 5,6-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico (159):

Se disuelve ácido 5,6-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (158) (200 mg, 0,63 mmol) en ácido acético (15 ml) con calentamiento. La solución resultante se enfría a TA y después se añade el catalizador, Pd-C (Pd al 5% en peso, 134 mg, al 6,3% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 379,21 kPa (55 psi), 95°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución orgánica combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (159) en forma de un sólido de color blanco (170 mg, 84%).

(159): ^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,83 (d, 6H), 1,80 (m, 1H), 2,32 (s, 3H), 2,68 (d, 2H), 3,39 (d, 2H), 7,00-7,20 (m, 5H), 7,44 (s, 1H)
LC/MS (ES+) m/z = 388,17

EJEMPLOS 160-161



Ácido 5,6-difluoro-2-(3-metil-2-propenil-benzoilamino)-indan-2-carboxílico (160):

A una solución de éster etílico del ácido 5,6-difluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,82 mmol) y ácido trans-1-propen-1-ilborónico (282 mg, 3,28 mmol)

en EtOH (10 ml) y dioxano (5 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 180 mg, al 8,2% en mmol), y una solución acuosa 2 M de K_2SO_4 (1,64 ml, 3,28 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 120°C, 5 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar un sólido de color blanco (160 mg), que se disuelve en EtOH (5 ml) y agua (0,2 ml) junto con KOH (600 mg, 10,7 mmol) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El filtrado se purifica por HPLC para dar un producto puro (160) en forma de un sólido de color blanco (127 mg, rendimiento global de 42%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,80 (dd, 3H), 2,27 (s, 3H), 3,36 (d, 2H), 3,63 (d, 2H), 5,77 (dc, 1H), 6,40 (d, 1H), 7,01 (t, 2H), 7,10-7,29 (m, 4H)
LC/MS (ES+) m/z = 372,15

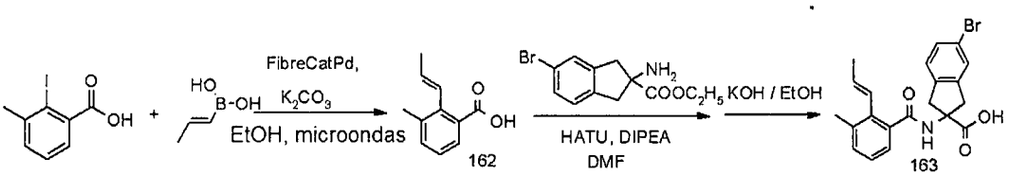
EJEMPLO 161

Ácido 5,6-difluoro-2-(3-metil-2-propil-benzoilamino)-indan-2-carboxílico (161):

Se disuelve ácido 5,6-difluoro-2-[3-metil-2-(-propenil)-benzoilamino]-indan-2-carboxílico (160) (110 mg, 0,30 mmol) en EtOH absoluto (15 ml) con calentamiento. La solución resultante se enfría a TA y se añade el catalizador, Pd-C (Pd al 5% en peso, 64 mg, al 3,0% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), 50°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución de EtOH combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (161) en forma de un sólido de color blanco (80 mg, 71%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 0,86 (c, 3H), 1,40 (m, 2H), 2,27 (s, 3H), 2,58 (m, 2H), 3,29 (d, 2H), 3,52 (d, 2H), 7,00 (d, 1H), 7,08 (t, 1H), 7,18 (d, 1H), 7,29 (t, 2H), 8,87 (s, 1H), 12,58 (s, 1H)
LC/MS (ES+) m/z = 374,14

EJEMPLO 162



Ácido 3-metil-2-((E)-propenil)-benzoico (162):

A una solución de ácido 2-yodo-3-metil-benzoico (708 mg, 2,70 mmol) y ácido trans-1-propen-1-ilborónico (526 mg, 6,12 mmol) en EtOH (10 ml) se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0) (Pd al 4,84%, 235 mg, 0,15 mmol), y una solución acuosa 2 M de K_2SO_4 (3,06 ml, 6,12 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 7 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar un producto puro (162) en forma de un sólido de color amarillo pálido (500 mg, 93%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,90 (dd, 3H), 2,34 (s, 3H), 5,68 (dc, 1H), 6,67 (d, 1H), 7,20 (t, 1H), 7,35 (d, 1H), 7,70 (d, 1H)

LC/MS (ES+) m/z = 177,10, 218,13

EJEMPLO 163

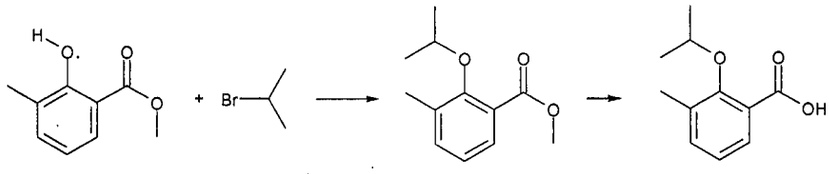
Ácido 5-bromo-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico (163):

A una solución de ácido 3-metil-2-((E)-propenil)-benzoico (162) (470 mg, 2,67 mmol), éster etílico del ácido 2-amino-5-bromo-indan-2-carboxílico (835 mg, 2,94 mmol) y HATU (1,22 mg, 3,20 mmol) en DMF anhidra (12 ml) se le añade DIPEA (529 µl, 3,20 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (150 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (300 g de gel de sílice, gradiente de elución: EtOAc al 5-60% en heptano) para dar un sólido de color blanco (1,12 g), que se disuelve en EtOH (15 ml) y agua (1 ml) junto con KOH (1,20 g, 21 mmol) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 4 h. Después de la concentración al vacío, el residuo se disuelve en agua (100 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El compuesto filtrado se purifica por HPLC para dar un producto puro (163) en forma de un sólido de color blanco (1,03 g, rendimiento global de 93%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,74 (dd, 3H), 2,25 (s, 3H), 3,30 (dd, 2H), 3,74 (dd, 2H), 5,73 (dc, 1H), 6,32 (d, 1H), 6,51 (s, 1H), 7,08-7,38 (m, 6H)

LC/MS (ES+) m/z = 414,09, 416,09

EJEMPLO 164



164

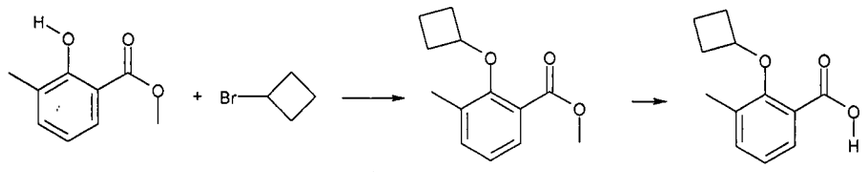
<u>Ácido 2-isopropoxi-3-metil-benzoico (164):</u>

Un matraz de fondo redondo de 250 ml se carga con 2-hidroxi-3-metilbenzoato de metilo (10g, 60,18 mmol) y N,N-dimetilformamida seca (DMF, 120 ml). Se añade una barra de agitación y se inicia la agitación. Después de 2 minutos, se añade 2-bromopropano (8,1ml, 86,65 mmol) mediante una jeringa. Se añaden en orden KI (20 mg, cat.) y $CsCO_3$ (44,42 g, 136,32 mmol). La reacción se cubre. El matraz de reacción se equipa con un manto de calentamiento que se calienta a 43°C. Después de 4 días, el análisis por tlc (sílice, 1:3 de EtOAc:heptanos) indica que el fenol de partida se ha consumido y se ha convertido en una única mancha tal como se visualiza por análisis UV. La fuente de calor se retira del matraz de reacción. Después de agitar durante 2 h más a temperatura ambiente, el contenido del matraz de reacción se filtra a través de una capa de Celite. La capa de Celite se lava con EtOAc:heptanos (1:1, 200 ml). El filtrado se transfiere a un embudo de decantación y se lava con salmuera (100 ml), agua (100 ml) y $NaHCO_3$ acuso saturado (100 ml). Esta secuencia de lavado se repite (1 vez) seguido de un lavado final con salmuera (50 ml). La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra al vacío. Después de bombear hasta alcanzar un peso constante, se proporcionan 11,88 g de un aceite de color amarillo pálido. El matraz de 250 ml que contiene el material anterior se carga con 1,4-dioxano (50 ml) y MeOH (100 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (50 ml) seguido de LiOH hidrato (5,7 g, 135,8 mmol). Después de 18 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, 55 ml). El contenido del matraz se transfiere a un embudo de decantación que contiene EtOAc (100 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (50 ml).

Los extractos orgánicos combinados se lavan con agua (50 ml) y salmuera (50 ml), se secan sobre $MgSO_4$, se filtran y se concentran a presión reducida. Después de bombear hasta alcanzar un peso constante da 10,19 g (52,46 mmol, 87,18%) de un sólido de color blanquecino.

^1H RMN (300 MHz, DMSO-d_6): δ 1,18 (d, 6H), 2,22, (s, 3H), 4,19 (m, 1H), 7,03 (dd, 1H), 7,38, (dd, 1H), 7,48 (dd, 1H).
LC/MS m/z = 195.

EJEMPLO 165



165

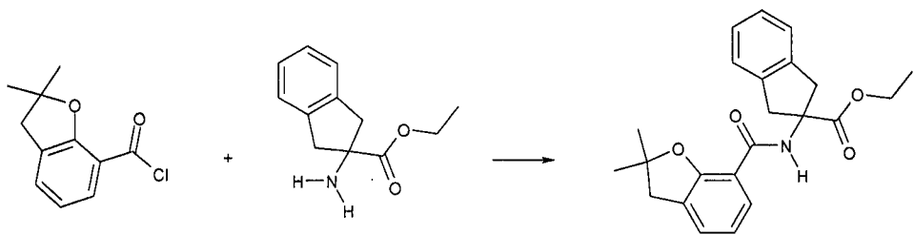
Ácido 2-ciclobutoxi-3-metil-benzoico (165):

Un matraz de fondo redondo de 100 ml se carga con 2-hidroxi-3-metilbenzoato de metilo (5g, 30,09 mmol) y N,N-dimetilformamida seca (DMF, 60 ml). Se añade una barra de agitación y se inicia la agitación. Después de 2 min, se añade bromociclobutano (5 g, 37,04 mmol) mediante una jeringa. Se añaden en orden yoduro potásico (10 mg, cat.) y $CsCO_3$ (22,21 g, 68,16 mmol). La reacción se cubre. El matraz de reacción se equipa con un manto de calentamiento que se calienta a 43°C. Después de 4 días, el análisis por tlc (sílice, 1:3 de EtOAc:heptanos) indica que el fenol de partida se ha consumido y se ha convertido en una única mancha tal como se visualiza mediante análisis UV. La fuente de calor se retira del matraz de reacción. Después de agitar durante 16 h más a temperatura ambiente, el contenido del matraz de reacción se filtra a través de una capa de Celite. La capa de Celite se lava con EtOAc:heptanos (1:1, 200 ml). El filtrado se transfiere a un embudo de decantación y se lava con salmuera (50 ml), agua (50 ml) y $NaHCO_3$ acuso saturado (50 ml). Esta secuencia de lavado se repite (1 vez) seguido de un lavado final con salmuera (50 ml). La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra al vacío. Después de bombear hasta alcanzar un peso constante, se dan 5,94 g de un aceite de color amarillo pálido. El matraz de 100 ml que contiene el material anterior se carga con 1,4-dioxano (30 ml) y MeOH (30 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (10 ml) seguido de LiOH hidrato (2,80 g, 66,78 mmol). Después de 18 h, el análisis por tlc (sílice,

MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, 30 ml). El contenido del matraz se transfiere a un embudo de decantación que contiene EtOAc (80 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (40 ml). Los extractos orgánicos combinados se lavan con agua (50 ml) y salmuera (50 ml), se secan sobre $MgSO_4$, se filtran y se concentran a presión reducida. Después de bombear hasta alcanzar un peso constante, se dan 5,3 g (25,70 mmol, 85,40%) de un sólido de color blanquecino.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,37 (m, 1H), 1,42 (m, 1H), 2,02 - 2,26, (m, 4H), 2,22 (s, 3H), 4,35 (m, 1H), 7,03 (dd, 1H), 7,36, (dd, 1H), 7,47 (dd, 1H).
LC/MS m/z = 207.

EJEMPLO 166



2 166

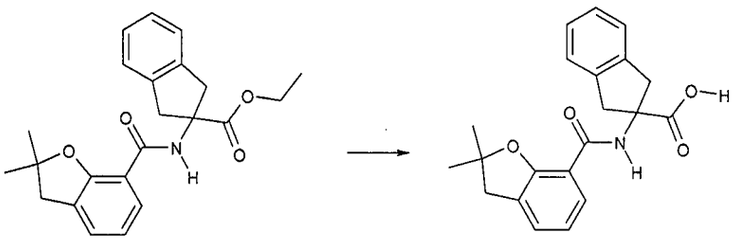
<u>Éster etílico del ácido 2-[(2,2-dimetil-2,3-dihidro-benzofuran-7-carbonil)-amino]-indan-2-carboxílico (166):</u>

Un tubo de ensayo (25 x 150 mm) que contiene una barra de agitación y éster etílico del ácido 2-amino-indan-2-carboxílico (0,5 g, 2,436 mmol) se carga con DCM seco (3 ml). Se inicia la agitación. Después de la disolución, se añaden DIPEA (1,50 ml; 8,6 mmol) y 4-dimetilaminopiridina (2 mg, 17 μmol). Al tubo de reacción se le añade una solución de cloruro de 2,2-dimetil-2,3-dihidro-1-benzofuran-7-carbonilo (0,73 g, 3,47 mmol) en DCM seco (4 ml). Después de agitar durante 18 h, el análisis por tlc (sílice, CH_3OH al 10% en DCM) indica el consumo completo de la amina de partida. La mezcla de reacción se diluye con DCM (10 ml), se lava con HCl acuoso al 5% (2 x 5 ml) y salmuera (5 ml), se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar 0,72 g de una goma de color pardo claro. Este material se purifica por cromatografía (sílice, EtOAc de 0% a 20% en diclorometano) en el ISCO Companion usando un cartucho de 40 g (sílice). Las fracciones 17

- 22 se combinan, se evaporan y se bombean hasta alcanzar un peso constante, para proporcionar 0,62 g (67%) de un sólido vidrioso.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,14 (t, 3H), 1,37 (s, 6 H) 3,03, (s, 2H), 3,43 (dd, 4H), 4,12 (c, 2H), 6,91 (dd, 1H), 7,16 - 7,27 (m, 4H), 7,35 (dd, 1H), 7,56 (d, 1H), 8,32 (s, 1H).
LC/MS m/z = 380,

EJEMPLO 167



167

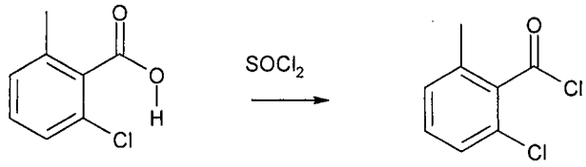
Ácido 2-[(2,2-dimetil-2,3-dihidro-benzofuran-7-carbonil)-amino]-indan-2-carboxílico (167):

Un matraz de fondo redondo de 50 ml que contiene el éster etílico del ácido 2-[(2,2-dimetil-2,3-dihidro-benzofuran-7-carbonil)-amino]-indan-2-carboxílico (0,45 g, 1,179 mmol) se carga con MeOH (25 ml) y se añade una barra de agitación. Se inicia la agitación. Después de la disolución, se añaden agua (8 ml) y el LiOH (108 mg, 2,58 mmol). Después de 56 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 3 mediante la adición lenta de HCl acuoso diluido (al 3%, ~20 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (30 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 460 mg de material. La muestra se purifica por cromatografía en columna (sílice, CH_3OH de 2% a 15% en DCM) usando un ISCO Companion y un cartucho de 12 g. La fracción 3 se recoge y se evapora. Después de bombear hasta alcanzar un peso constante, se obtienen 375 mg (90%) de un polvo seco de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,36 (s, 6 H) 2,99, (s, 2H), 3,40 (dd, 4H), 6,88 (dd, 1H), 7,11 - 7,20 (m, 4H), 7,30 (dd, 1H), 7,57 (d, 1H), 8,34 (s, 1H).

LC/MS m/z = 352,

EJEMPLO 168

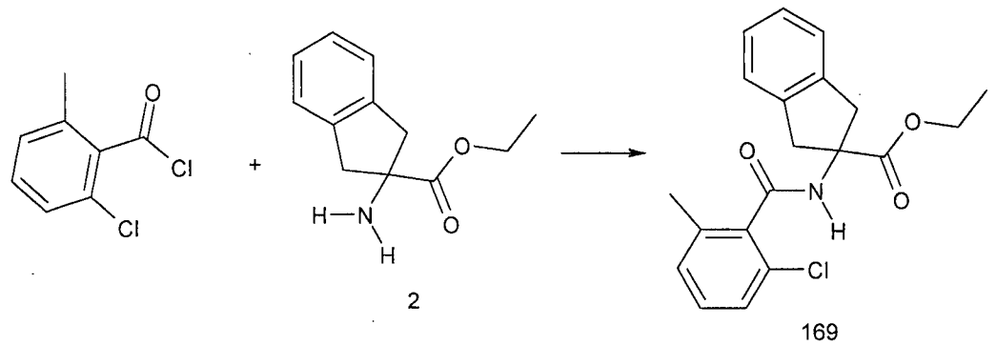


168

Cloruro de 2-cloro-6-metilbenzoílo (168):

Un matraz de fondo redondo que contiene el ácido 2-cloro-6-metil-benzoico (1,5 g, 8,79 mmol) y una barra de agitación se carga con DCM seco (10 ml). Se inicia la agitación. Después de varios min, se añade una solución de cloruro de tionilo (en DCM (2 M), 6,6 ml, 13,2 mmol) mediante una jeringa. Después, se añaden 2 gotas de DMF. La reacción comienza a burbujear inmediatamente de forma suave. Después de 2 h, cesa la formación de burbujas. Después de 3 h, el disolvente se retira de la mezcla de reacción al vacío. El residuo oleoso se disuelve de nuevo en DCM (6 ml) y el disolvente se retira de nuevo una vez más al vacío. El residuo se disuelve en DCM seco (6 ml) y se usa sin purificación adicional en la siguiente secuencia de reacción.

EJEMPLO 169



169

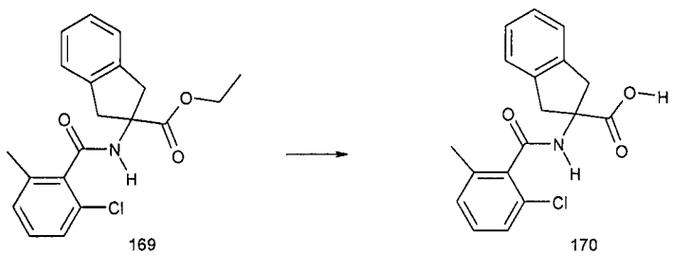
Éster etílico del ácido 2-[(2-cloro-6-metil-benzoil)-amino]-indan-2-carboxílico (169):

Un tubo de ensayo (25 x 150 mm) que contiene una barra de agitación y éster etílico del ácido 2-amino-indan-2-carboxílico (0,53 g, 2,58 mmol) se carga con DCM seco (3 ml). Se inicia la agitación. Después de la disolución, se añaden DIPEA (1,50 ml, 8,6 mmol) y 4-dimetilaminopiridina (2 mg, 17 µmol). Al tubo de reacción se le añade una solución de cloruro de 2-cloro-6-metilbenzoílo (5,8 mmol) en DCM seco (4 ml), como se ha preparado anteriormente. Después de agitar durante 18 h, el análisis por tlc (sílice, CH_3OH al 10% en

DCM) indica el consumo completo de la amina. La mezcla de reacción se diluye con DCM (10 ml), se lava con HCl acuoso al 5% (2 x 5 ml) y salmuera (5 ml), se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar 1,07 g de un sólido de color pardo claro. Este material se purifica por cromatografía (sílice, EtOAc de 2% a 20% en diclorometano) en el ISCO Companion usando un cartucho de 40 g. Las fracciones 6 - 10 se combinan, se evaporan y se bombean para producir un peso constante, 550 mg de un sólido amorfo de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,19 (t, 3H), 3,33, (s, 3H), 3,45 (dd, 4H), 4,13 (c, 2H), 6,88 (dd, 1H), 7,12 - 7,47 (m, 7H), 9,11 (s, 1H).
LC/MS m/z = 358.

EJEMPLO 170



169 170

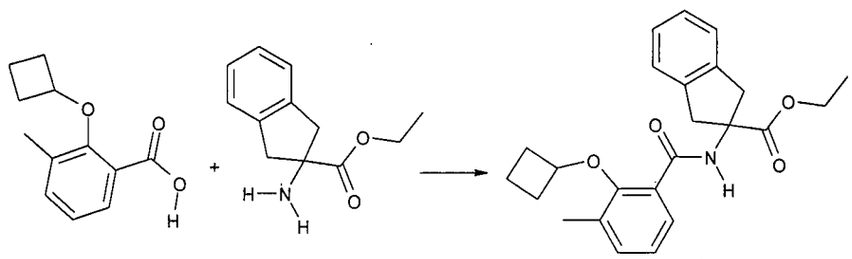
<u>Ácido 2-[(2-cloro-6-metil-benzoil)-amino]-indan-2-carboxílico (170):</u>

Un matraz de fondo redondo de 100 ml que contiene el éster etílico del ácido 2-(2-cloro-6-metil-benzoilamino)-indan-2-carboxílico (0,255 g, 0,712 mmol) se carga con MeOH (15 ml) y se añade una barra de agitación. Se inicia la agitación. Después de la disolución, se añade agua (5 ml) y el material de partida comienza a precipitar. Se añade tetrahidrofurano para disolver de nuevo el material de partida. Se añade LiOH (90 mg, 2,14 mmol). Después de 16 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 3 mediante la adición lenta de HCl acuoso diluido (al 3%, ~20 ml). El contenido del matraz se vierte en un embudo de adición que contiene DCM (30 ml). Las capas se separan. La capa acuosa se extrae con DCM (20 ml). Los extractos orgánicos combinados se lavan con agua (30 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran para producir 280 mg de material. El material se purifica por cromatografía en columna (sílice, CH_3OH de 2% a 15% en DCM) usando un ISCO Companion y un cartucho de 12 g. La fracción 2 se

recoge y se evapora. Después de bombear hasta alcanzar un peso constante, se obtienen 130 mg de un polvo seco de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 2,27, (s, 3H), 3,45 (dd, 4H), 7,14 - 7,39 (m, 7H), 8,96 (s, 1H). LC/MS m/z = 330.

EJEMPLO 171

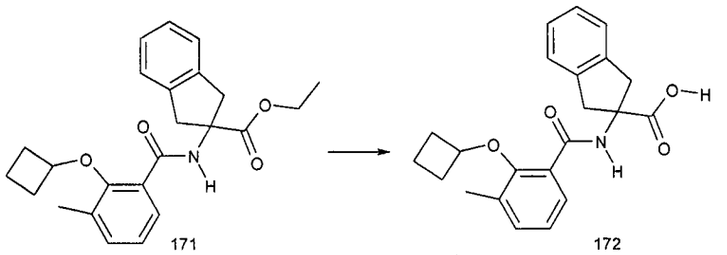


165 2 171

Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (171):

Un vial de 25 ml que contiene una barra de agitación se carga con ácido 2-ciclobutoxi-3-metil-benzoico (1,01 g, 4,87 mmol) y DCM seco (14 ml). Se inicia la agitación. Se añade HBTU (1,84 g, 4,86 mmol). Después de 5 min, se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (1 g, 4,87 mmol) seguido del DIPEA (1,9 ml, 10,92 mmol). La reacción se deja en agitación durante 12 días. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. Los contenidos del matraz de reacción se diluyen con EtOAc (70 ml) y se transfieren a un embudo de decantación. Se lava consecutivamente con HCl acuoso diluido (al 3%, 35 ml), $NaHCO_3$ acuoso saturado (35 ml) y salmuera (35 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 2,56 g de un sólido de color blanquecino. Este material se disuelve en 15 ml de DCM. Se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 10 volúmenes de columna y después EtOAc al 100% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 7 a 22 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 1,73 g de un sólido amorfo de color blanco.

EJEMPLO 172



171 172

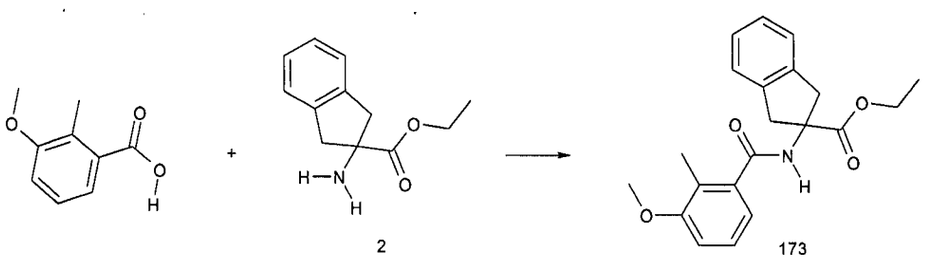
Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (172):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(2-ciclobutoxi-3-metil-benzoil)-amino]-indan-2-carboxílico (1,72 g, 4,37 mmol) se carga con 1,4-dioxano (16 ml) y MeOH (16 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (8 ml) seguido de LiOH (458 mg, 10,91 mmol). Después de 20 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~25 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (60 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (30 ml). Los extractos orgánicos combinados se lavan con agua (35 ml) y salmuera (35 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 1,58 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,16 - 1,27 (m, 1H), 1,38 - 1,53 (m, 1H), 1,78 - 2,03 (m, 4H), 2,23, (s, 3H), 3,44 (dd, 4H), 4,34 (m, 1H), 7,03 (dd, 1H), 7,17 - 7,37 (m, 6H), 8,64 (s, 1H), 12,59 (s a, 1H).

LC/MS m/z = 364,

EJEMPLO 173



2 173

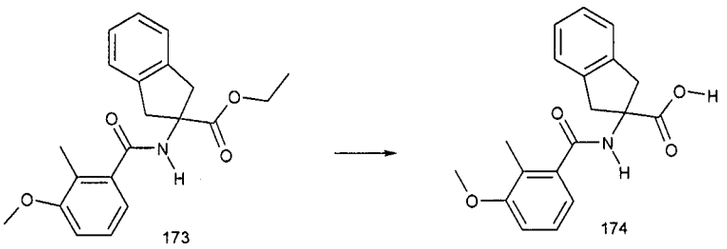
Éster etílico del ácido 2-(3-metoxi-2-metil-benzoilamino)-indan-2-carboxílico (173):

Un matraz de fondo redondo de 100 ml se carga con éster etílico del ácido 2-amino-indan-2-carboxílico (750 mg, 3,65 mmol) y DCM seco (10 ml). Se añade una barra de agitación y se inicia la agitación. Se añade HBTU (1,38 g, 3,65 mmol). Después de 2 min, se añaden ácido

2-metil-3-metoxi-benzoico (0,61 g, 3,65 mmol) y DIPEA (1,5 ml, 8,6 mmol). La reacción se deja en agitación durante 36 h. El análisis por tlc de la mezcla de reacción (sílice, EtOAc al 50%/heptanos) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,1 g de una goma espesa de color parduzco. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 15% en heptanos durante 2 volúmenes de columna seguido de un gradiente por etapas a EtOAc al 30%, después al 50% y después EtOAc al 70% durante 3 volúmenes de columna, cada una de ellas con una rampa de 1 volumen de columna. Se recogen fracciones de 35 ml. Las fracciones 15 a 21 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se da un sólido de color blanco (1,15 g).

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,19 (t, 3H), 2,12 (s, 3H), 3,54 (dd, 4H), 3,78 (s, 3H), 4,12 (c, 2H), 6,79 (d, 1H), 6,99 (d, 1H), 7,14 - 7,24 (m, 6H), 8,97 (s, 1H).
LC/MS m/z = 354.

EJEMPLO 174



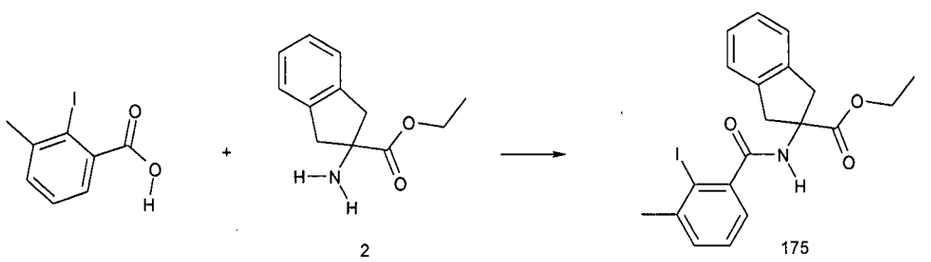
<u>Ácido 2-(3-metoxi-2-metil-benzoilamino)-indan-2-carboxílico (174):</u>

Un vial de 40 ml que contiene el éster etílico del ácido 2-(3-metoxi-2-metil-benzoilamino)-indan-2-carboxílico (0,65 g, 1,84 mmol) se carga con THF (10 ml) y MeOH (10 ml) y se añade una barra de agitación. Se inicia la agitación. Después de la disolución, se añade agua (5 ml) seguido de LiOH (267 mg, 6,36 mmol). Después de 36 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de adición que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20

ml), se secan sobre $MgSO_4$, se filtran y se concentran para producir 620 mg de un sólido amorfo de color blanco. La muestra se purifica por cromatografía en columna (sílice, CH_3OH de 2% a 15% en DCM) usando un ISCO Companion y un cartucho de 40 g. Las fracciones 14-16 se recogen y se evaporan, bombeando hasta alcanzar un peso constante, para dar 380 mg de un polvo seco de color blanco.

^1H RMN (300 MHz, DMSO-d_6): δ 2,11, (s, 3H), 3,44 (dd, 4H), 3,77, (s, 3H), 6,79 (d, 1H), 6,97 (d, 1H), 7,13-7,23 (m, 5H), 8,82 (s, 1H), 12,49 (s, 1H).
LC/MS m/z = 326.

EJEMPLO 175

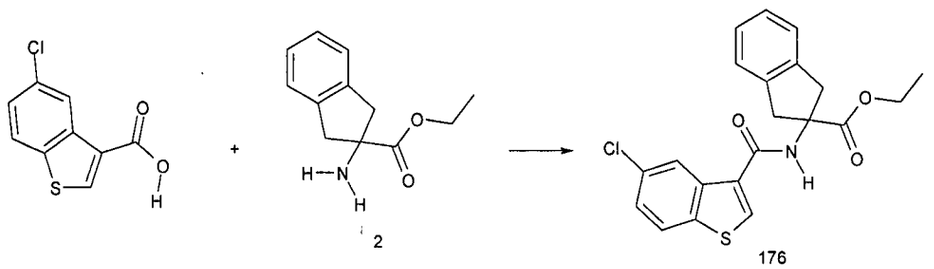


<u>Éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (175):</u>

Un matraz de fondo redondo de 100 ml se carga con ácido 2-yodo-3-metilbenzoico (1,92 g, 7,31 mmol) y DCM seco (25 ml). Se añade una barra de agitación y se inicia la agitación. Después de 5 min, se añade el HBTU (2,37 g, 7,31 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (1,5 g, 7,31 mmol) seguido de N,N-diisopropiletil-amina (3,2 ml, 18,37 mmol). La reacción se deja en agitación durante 118 h. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 15%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (70 ml). Se lava con HCl acuoso diluido (al 3%, 2 x 30 ml), $NaHCO_3$ acuoso saturado (2 x 30 ml) y salmuera (30 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 2,04 g de un sólido de color blanco. Este material se disuelve en 15 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% durante 10 volúmenes de columna. Se recogen fracciones de 27 ml del eluyente activo por UV. Las fracciones 10 a 15 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 1,04 g de un material sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,20 (t, 3H), 2,39 (s, 3H), 3,52 (dd, 4H), 4,15 (c, 2H), 6,79 (d, 1H), 6,97 (d, 1H), 7,16 - 7,24 (m, 4H), 7,28 - 7,38 (m, 2H), 9,15 (s, 1H).
LC/MS m/z = 450.

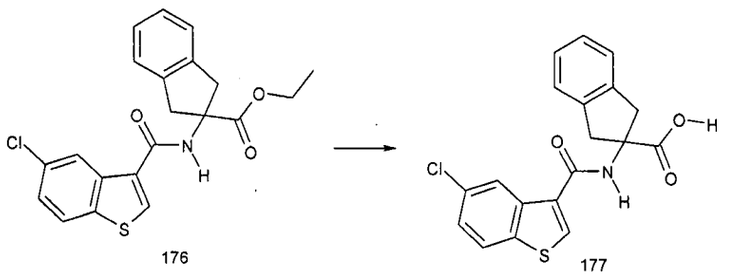
EJEMPLO 176



Éster etílico del ácido 2-[(5-cloro-benzo[b]tiofeno-3-carbonil)-amino]-indan-2-carboxílico (176):

En un vial de 40 ml que contiene una barra de agitación se carga ácido 5-cloro-benzo[b]tiofeno-3-carboxílico (518 g, 2,44 mmol) con DCM seco (7 ml). Se inicia la agitación. Se añaden HBTU (922 mg, 2,43 mmol) y DIPEA (0,95 ml, 8,0 mmol). Después, se añade éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol). La reacción se deja en agitación durante 20 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,64 g de un sólido de color blanquecino. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 20% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 8 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 7 a 31 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,94 g de un sólido amorfo de color blanco.

EJEMPLO 177



176 177

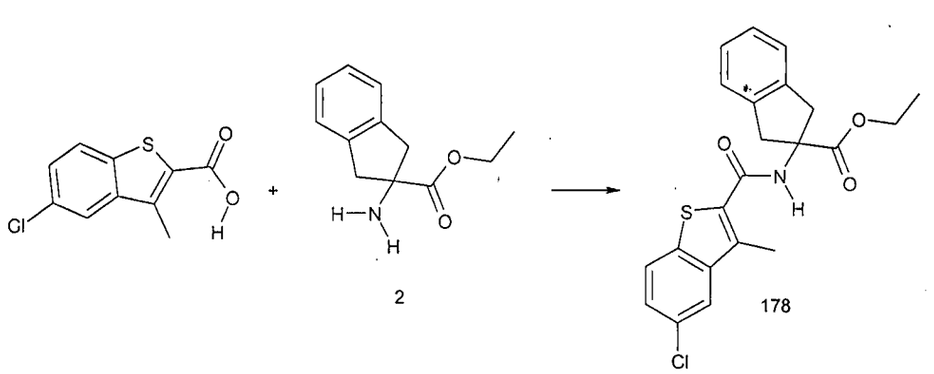
Ácido 2-[(5-cloro-benzo[b]tiofeno-3-carbonil)-amino]-indan-2-carboxílico (177):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(5-cloro-3-benzo[b]tiofeno-3-carbonil)-amino]-indan-2-carboxílico (0,66 g, 1,65 mmol) se carga con 1,4-dioxano (10 ml) y MeOH 10 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (5 ml) seguido de LiOH (173 mg, 4,13 mmol). Después de 15 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 590 mg de un polvo seco de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 3,52 (dd, 4H), 7,15 - 7,27 (m, 4H), 7,46 (dd, 1H), 8,09 (d, 1H), 8,44 (d, 1H), 8,52 (s, 1H), 8,99 (s, 1H), 12,55 (s a, 1H).

LC/MS m/z = 372.

EJEMPLO 178

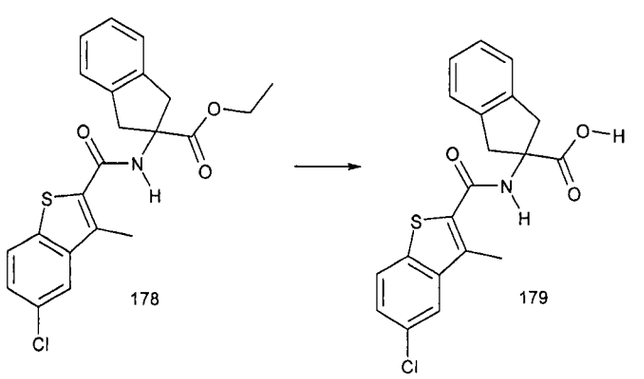


2 178

Éster etílico del ácido 2-[(5-cloro-3-metil-benzo[b]tiofeno-2-carbonil)-amino]-indan-2-carboxílico (178):

Un vial de 40 ml que contiene una barra de agitación y ácido 5-cloro-3-metil-benzo[b]tiofeno-2-carboxílico ([50451-84-8], 0,81 g, 3,53 mmol) se carga con DCM seco (10 ml). Se inicia la agitación. Se añaden HBTU (1,34 g, 3,54 mmol) y el DIPEA (1,4 ml, 8,0 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (0,725 g, 3,53 mmol). La reacción se deja en agitación durante 240 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (80 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,26 g de un sólido de color blanquecino. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 20% en heptanos durante 3 volúmenes de columna seguido de un gradiente por etapas a EtOAc al 30%, después al 50% y después EtOAc al 70% durante 2 volúmenes de columna, cada una de ellas con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 22 a 60 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,78 g de un sólido amorfo de color blanco.

EJEMPLO 179



<u>Ácido 2-[(5-cloro-3-metil-benzo[b]tiofeno-2-carbonil)-amino]-indan-2-carboxílico (179):</u>

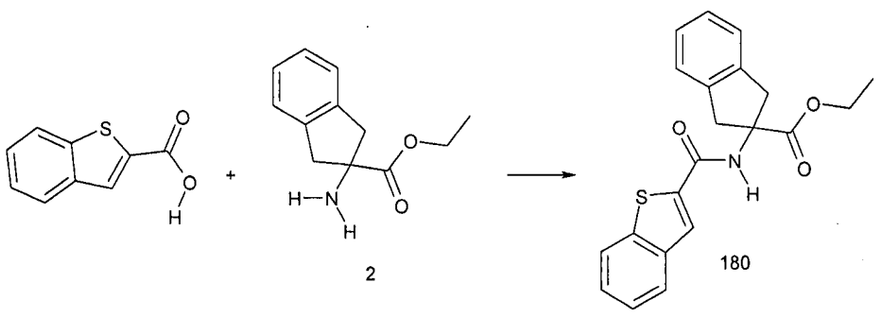
Un vial de 40 ml que contiene el éster etílico del ácido 2-[(5-cloro-3-metil-benzo[b]tiofeno-2-carbonil)-amino]-indan-2-carboxílico (0,53 g, 1,28 mmol) se carga con MeOH (7,5 ml) y se añade una barra de agitación. Se inicia la agitación. Después de la disolución, se añade agua (3,8 ml) seguido de LiOH (134 mg, 3,20 mmol). Después de 36 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de

decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran para producir 360 mg de un sólido amorfo de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 2,45 (s, 3H) 3,49 (dd, 4H), 7,15 - 7,29 (m, 4H), 7,48 (dd, 1H), 7,92 (d, 1H), 8,02 (d, 1H), 8,96 (s, 1H).

LC/MS m/z = 386.

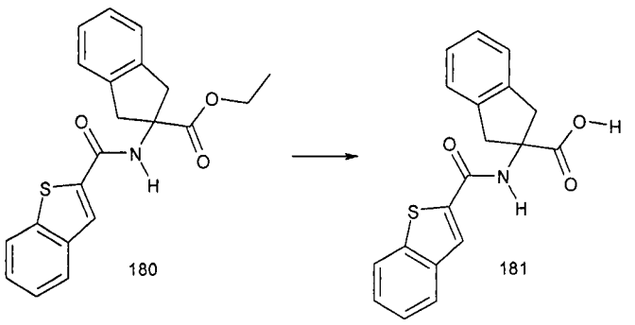
EJEMPLO 180



Éster etílico del ácido 2-[(benzo[b]tiofeno-2-carbonil)-amino]-indan-2-carboxílico (180):

Un vial de 40 ml que contiene una barra de agitación y ácido benzo[b]tiofeno-2-carboxílico (518 g, 2,44 mmol) se carga con DCM seco (7 ml). Se inicia la agitación. Se añaden HBTU (922 mg, 2,43 mmol) y el DIPEA (0,95 ml, 8,0 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol). La reacción se deja en agitación durante 110 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,54 g de un sólido de color blanquecino. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 20% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 10 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 13 a 27 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,62 g de un sólido amorfo de color blanco.

EJEMPLO 181

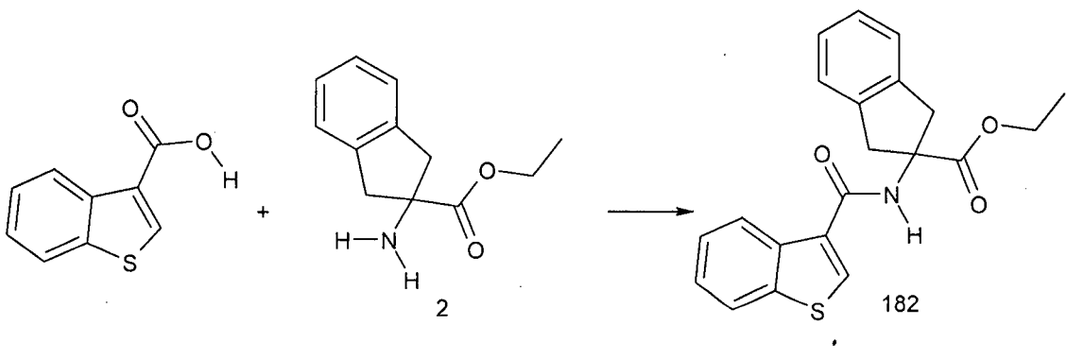


Ácido 2-[(benzo[b]tiofeno-2-carbonil)-amino]-indan-2-carboxílico (181):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(benzo[b]tiofeno-2-carbonil)-amino]-indan-2-carboxílico (0,37 g, 1,01 mmol) se carga con 1,4-dioxano (6 ml) y MeOH (6 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (3,0 ml) seguido de LiOH (106 mg, 2,53 mmol). Después de 18 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 290 mg (89%) de un polvo seco de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 3,57 (dd, 4H), 7,15 - 7,32 (m, 4H), 7,45 - 7,48 (m, 2H) 7,91 (dd, 1H), 8,01 (dd, 1H), 8,18 (s, 1H), 9,11 (s, 1H), 12,58 (s a, 1H).
LC/MS m/z = 338.

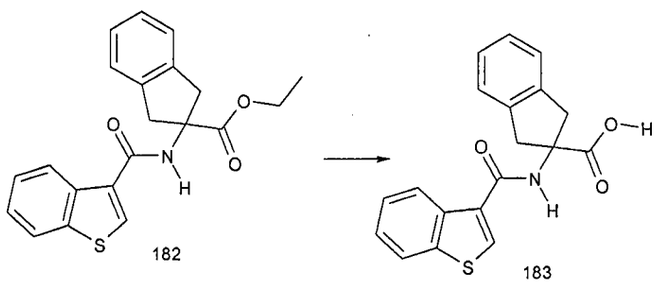
EJEMPLO 182



Éster etílico del ácido 2-[(benzo[b]tiofeno-3-carbonil)-amino]-indan-2-carboxílico (182):

Un vial de 40 ml que contiene una barra de agitación y ácido benzo[b]tiofeno-3-carboxílico ([5381-25-9], 434 g, 2,44 mmol) se carga con DCM seco (7 ml). Se inicia la agitación. Se añaden HBTU (922 mg, 2,43 mmol) y DIPEA (0,95 ml, 8,0 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol). La reacción se deja en agitación durante 20 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,64 g de un sólido de color blanquecino. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 20% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 8 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 4 a 16 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,69 g de un sólido amorfo de color blanco.

EJEMPLO 183



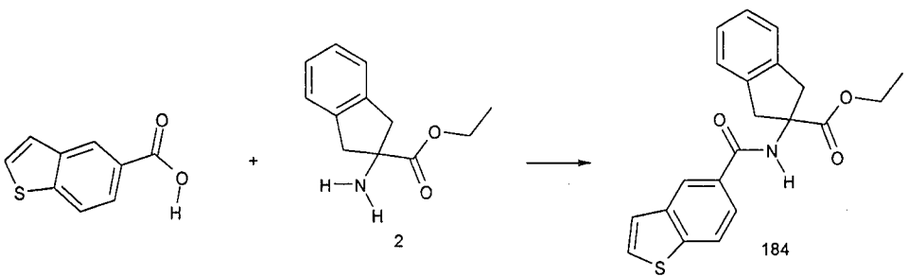
Ácido 2-[(benzo[b]tiofeno-3-carbonil)-amino]-indan-2-carboxílico (183):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(benzo[b]tiofeno-3-carbonil)-amino]-indan-2-carboxílico (182, 0,40 g, 1,10 mmol) se carga con 1,4-dioxano (10 ml) y MeOH (10 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (5,0 ml) seguido de LiOH (115 mg, 2,74 mmol). Después de 18 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al matraz de reacción se le añaden HCl acuoso diluido (al 3%, ~15 ml) y EtOAc (25 ml). Después de agitar durante 10 min, el contenido del matraz se vierte en un embudo de decantación. Las capas se separan. La capa acuosa se extrae con EtOAc (30

ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 450 mg de un polvo seco de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 3,52 (dd, 4H), 7,18 - 7,28 (m, 4H), 7,38 - 7,43 (m, 2H) 8,03X (dd, 1H), 8,37 - 8,41 (m, 2H), 8,92 (s, 1H), 13,53 (s a, 1H).
LC/MS m/z = 338.

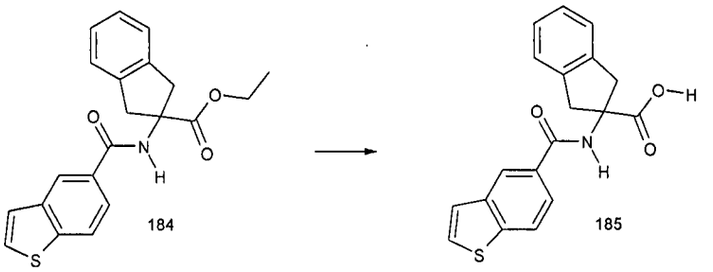
EJEMPLO 184



Éster etílico del ácido 2-[(benzo[b]tiofeno-5-carbonil)-amino]-indan-2-carboxílico (184):

Un vial de 40 ml que contiene una barra de agitación y ácido benzo[b]tiofeno-5-carboxílico (434 g, 2,44 mmol) se carga con DCM seco (7 ml). Se inicia la agitación. Se añaden HBTU (922 mg, 2,43 mmol) y DIPEA (0,95 ml, 8 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol). La reacción se deja en agitación durante 64 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,4 g de un sólido de color blanquecino. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 8 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 4 a 16 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,79 g de un sólido amorfo de color blanco.

EJEMPLO 185



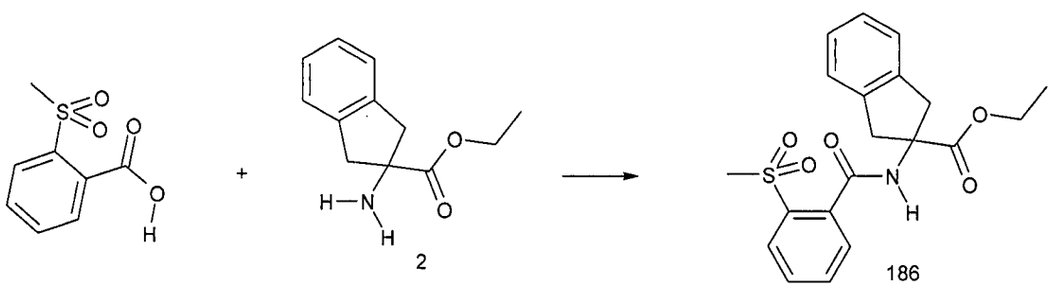
Ácido 2-[(benzo[b]tiofeno-5-carbonil)-amino]-indan-2-carboxílico (185):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(benzo[b]tiofeno-5-carbonil)-amino]-indan-2-carboxílico (184, 0,45 g, 1,25 mmol) se carga con 1,4-dioxano (8 ml) y MeOH (8 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (4,0 ml) seguido de LiOH (131 mg, 3,11 mmol). Después de 114 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~12 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 0,42 g de un sólido de color blanquecino.

^{1}H RMN (300 MHz, DMSO-d_6): δ 3,57 (dd, 4H), 7,18 - 7,28 (m, 5H), 7,59 (d, 1H), 7,78 - 7,93 (m, 2H), 8,08 (d, 1H), 8,41 (s, 1H), 8,91 (s, 1H).

LC/MS m/z = 338.

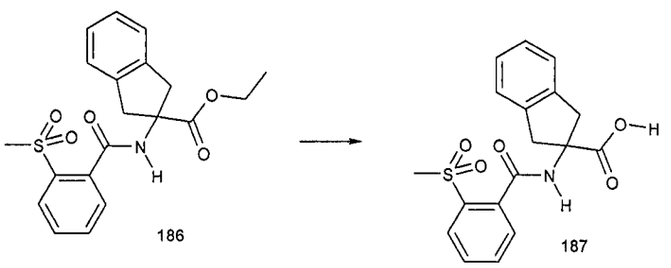
EJEMPLO 186



Éster etílico del ácido 2-[(2-metilsulfonilbenceno-1-carbonil)-amino]-indan-2-carboxílico (186):

Un vial de 40 ml que contiene una barra de agitación y ácido 2-(metilsulfonil)benzoico (0,4 g, 2,88 mmol) se carga con DCM seco (7 ml). Se inicia la agitación. HBTU (922 mg, 2,43 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol) seguido del DIPEA (0,95 ml, 8 mmol). La reacción se deja en agitación durante 36 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,32 g de un sólido de color blanco. Este material se disuelve en 10 ml de DCM y se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 15% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 8 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 5 a 8 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,71 g de un sólido amorfo de color blanco.

EJEMPLO 187



186 187

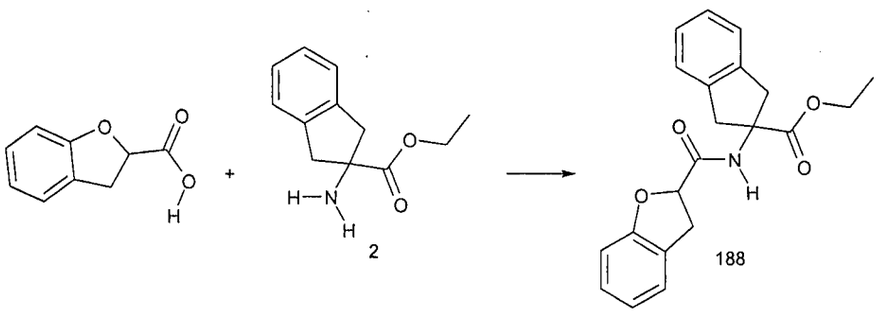
<u>Ácido 2-[(2-metilsulfonilbenceno-1-carbonil)-amino]-indan-2-carboxílico (187):</u>

Un matraz de 50 ml que contiene éster etílico del ácido 2-[(2-metilsulfonilbenceno-1-carbonil)-amino]-indan-2-carboxílico (186, 0,50 g, 1,27 mmol) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH (133 mg, 3,17 mmol). Después de 69 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~12 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con

agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 0,46 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 3,37 - 3,61 (m, 7H), 7,16 - 7,23 (m, 4H), 7,54 (d, 1H), 7,69 (dd, 1H), 7,79 (dd, 1H), 7,93 (d, 1H), 9,25 (s, 1H), 12,55 (s, 1H).
LC/MS m/z = 360.

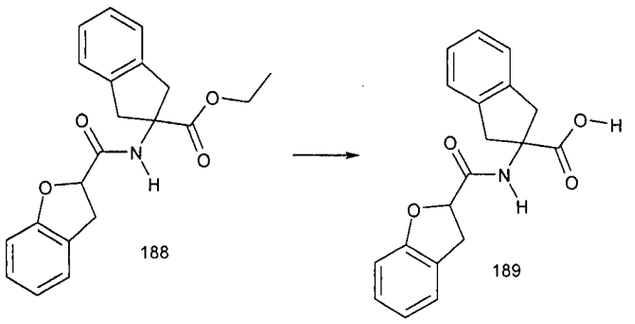
EJEMPLO 188



<u>Éster etílico del ácido 2-[(2,3-dihidrobenzofuran-2-carbonil)-amino]-indan-2-carboxílico (188):</u>

Un vial de 40 ml que contiene una barra de agitación y ácido 2,3-dihidro-1-benzofuran-2-carboxílico (0,4 g, 2,44 mmol) se carga con DCM seco (7 ml). Se inicia la agitación. Se añaden HBTU (922 mg, 2,43 mmol) y el DIPEA (0,95 ml, 8,0 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol). La reacción se deja en agitación durante 16 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,47 g de un aceite viscoso de color amarillo. Este material se disuelve en 10 ml de DCM y se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 15% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 8 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 3 a 6 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,68 g de un sólido amorfo de color blanco.

EJEMPLO 189



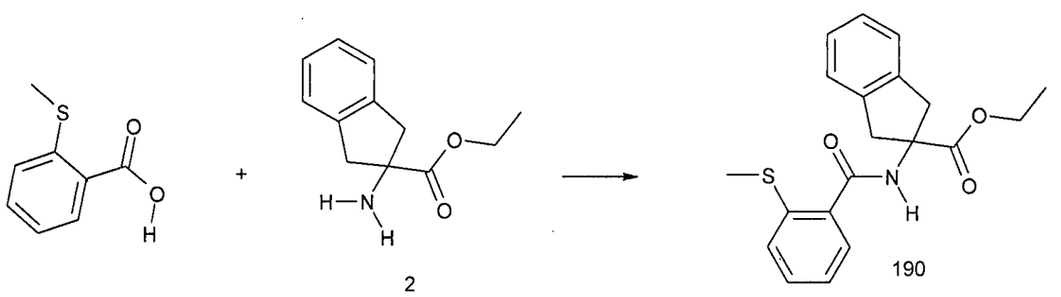
Ácido 2-[(2,3-dihidrobenzofuran-2-carbonil)-amino]-indan-2-carboxílico (189):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(2,3-dihidrobenzofuran-2-carbonil)-amino]-indan-2-carboxílico (0,447 g, 1,39 mmol) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH hidrato (133 mg, 3,17 mmol). Después de 19 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~12 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 0,43 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 3,17 (dd, 1H), 3,21 - 3,58 (m, 5H), 5,13 (dd, 1H), 6,79 (dd, 1H), 6,84 (dd, 1H), 7,03 - 7,28 (m, 6H), 8,64 (s, 1H), 12,55 (s a, 1H).

LC/MS m/z = 324.

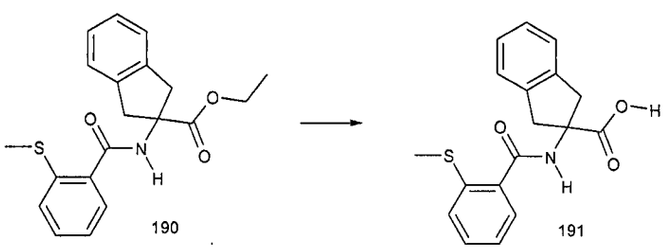
EJEMPLO 190



Éster etílico del ácido 2-[(2-metiltiolbenceno-1-carbonil)-amino]-indan-2-carboxílico (190):

Un vial de 40 ml que contiene una barra de agitación y ácido 2-(metiltiol)benzoico ([3724-10-5], 0,410 g, 2,44 mmol) se carga con DCM seco (7 ml). Se inicia la agitación. Se añade HBTU (922 mg, 2,43 mmol). Después de 2 min, se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol) seguido del DIPEA (0,95 ml, 8,0 mmol). La reacción se deja en agitación durante 38 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con HCl acuoso diluido (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,49 g de un aceite viscoso de color amarillo. Este material se disuelve en 10 ml de DCM y se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 15% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 8 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 8 a 15 se combinan y se evaporan al vacío. Después de bombear hasta alcanzar un peso constante, se dan 0,69 g de un sólido amorfo de color blanco.

EJEMPLO 191



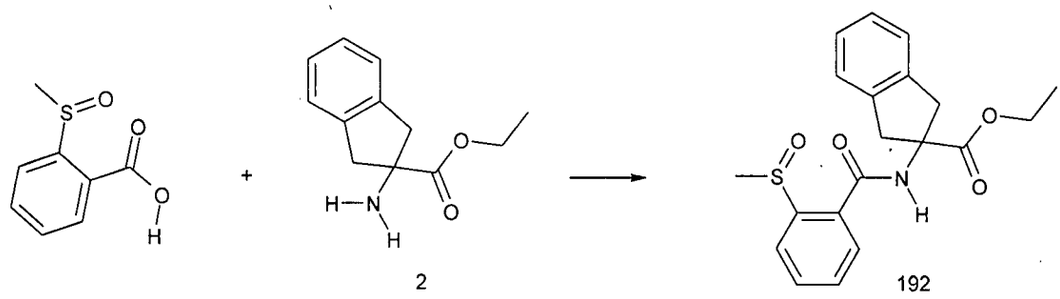
<u>Ácido 2-[(2-metiltiolbenceno-1-carbonil)-amino]-indan-2-carboxílico (191):</u>

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(2-metiltiobenceno-2-carbonil)-amino]-indan-2-carboxílico (0,510 g, 1,44 mmol) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH hidrato (150 mg, 3,58 mmol). Después de 96 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~12 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con

agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 0,34 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 2,37 (s, 3H), 3,47 (dd, 4H), 7,14 - 7,21 (m, 5H), 7,22 - 7,44 (m, 3H), 8,88 (s, 1H), 12,46 (s, 1H).
LC/MS m/z = 328.

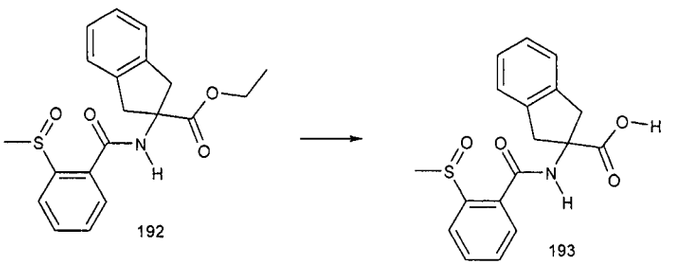
EJEMPLO 192



<u>Éster etílico del ácido 2-[(2-metilsulfinilbenzoil)-amino]-indan-2-carboxílico (192):</u>

Un vial de 40 ml que contiene una barra de agitación y ácido 2-(metilsulfinil)benzoico (0,449 g, 2,44 mmol) se carga con DCM seco (7 ml). Se inicia la agitación. Se añade HBTU (922 mg, 2,43 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (500 mg, 2,44 mmol) seguido del DIPEA (0,95 ml, 8,0 mmol). La reacción se deja en agitación durante 94 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,2 g de una espuma de color amarillo. Este material se disuelve en 10 ml de DCM y se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta acetato de etilo al 100% durante 8 volúmenes de columna y después se mantiene durante 5 volúmenes de columna. Se recogen fracciones de 25 ml. Las fracciones 9 a 18 se combinan y se evaporan al vacío hasta alcanzar un peso constante, para dar 0,75 g de un sólido amorfo de color blanquecino.

EJEMPLO 193



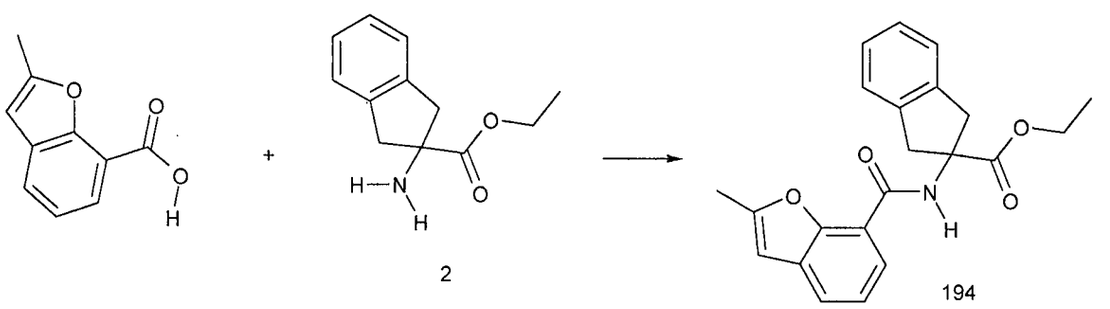
192 193

Ácido 2-[(2-metilsulfinilbenzoil)-amino]-indan-2-carboxílico (193):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-(2-metilsulfinilbenzoil-amino)-indan-2-carboxílico (0,50 g, 1,34 mmol) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH (141 mg, 3,36 mmol). Después de 39 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~12 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran al vacío hasta alcanzar un peso constante de 0,39 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 3,35 (s, 3H), 3,48 (dd, 4H), 7,16 - 7,27 (m, 4H), 7,60 (dd, 1H), 7,67 - 7,84, (m, 2H), 8,07 (d, 1H), 9,22 (s, 1H), 12,63 (s a, 1H).
LC/MS m/z = 344.

EJEMPLO 194



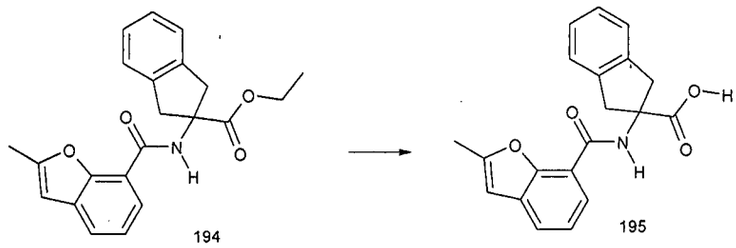
2 194

Éster etílico del ácido 2-[(2-metilbenzofuran-7-carbonil)-amino]-indan-2-carboxílico (194):

Un vial de 25 ml que contiene una barra de agitación y ácido 2-metilbenzofuran-7-carboxílico (0,343 g, 1,95 mmol) se carga con DCM seco (6 ml). Se inicia la agitación. Se añade HBTU

(738 mg, 1,95 mmol). Se añade el éster etílico del ácido 2-aminoindan-2-carboxílico (400 mg, 1,95 mmol) seguido del DIPEA (0,75 ml, 4,31 mmol). La reacción se deja en agitación durante 16 h. El análisis por tlc de la mezcla de reacción (sílice, EtOH al 10%/diclorometano) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con HCl acuoso diluido (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 0,97 g de un aceite viscoso de color amarillo. Este material se disuelve en 10 ml de DCM. Se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 15% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 90% durante 15 volúmenes de columna y después EtOAc al 100% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 2 a 7 se combinan y se evaporan al vacío hasta alcanzar un peso constante, para dar 0,63 g de un sólido amorfo de color blanquecino.

EJEMPLO 195

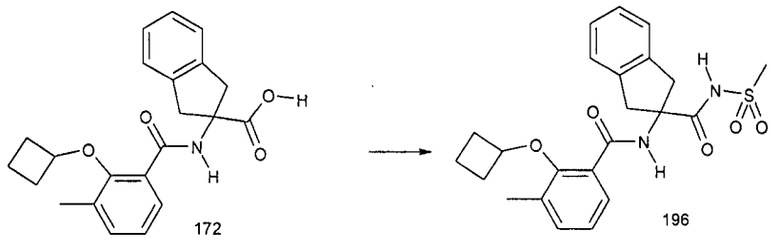


<u>Ácido 2-[(2-metilbenzofuran-7-carbonil)-amino]-indan-2-carboxílico (195):</u>

Un matraz de 50 ml que contiene el éster etílico del ácido 2-[(2-metilbenzofuran-7-carbonil)-amino]-indan-2-carboxílico (0,40 g, 1,10 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH (115 mg, 2,75 mmol). Después de 18 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~12 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran al vacío hasta alcanzar un peso constante, para dar 0,37 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 2,42, (s, 3H), 3,47 (dd, 4H), 6,68, (s, 1H), 7,17-7,27 (m, 5H), 7,57 (dd, 1H), 7,67 (dd, 1H), 8,68 (s, 1H), 12,63 (s, 1H).
LC/MS m/z = 336.

EJEMPLO 196

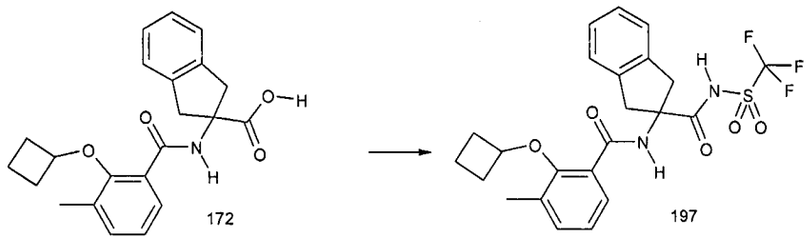


2-Ciclobutoxi-N-(2-metanosulfonilaminocarbonil-indan-2-il)-3-metil-benzamida (196):

Un vial de 30 ml se carga con ácido 2-[(2-ciclobutoxi-3-metil-benzoil)-amino]-indan-2-carboxílico (245 mg, 0,67 mmol) y DCM seco (5,0 ml). Se añade una barra de agitación y se inicia la agitación. Se añade la metanosufonamida (89 mg, 0,936 mmol). A la suspensión resultante se le añaden hidrocloruro de (N-(3-dimetilaminopropil)-N'-etilcarbodiimida (120 mg, 0,624 mmol) y 4-dimetilaminopiridina (76 mg, 0,62 mmol). Después de 6 días, el análisis por tlc (sílice, MeOH al 10% en DCM) indica que el ácido de partida se ha consumido. La mezcla de reacción se diluye con EtOAc (50 ml), se transfiere a un embudo de decantación, se lava con HCl acuoso diluido (3 N, 3 x 20 ml) y salmuera, se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar 0,26 g de una espuma amorfa de color blanco. Este material se disuelve en DCM (5 ml) y se aplica a una columna de 12 g (sílice) en un ISCO Companion. La columna se eluye con iPrOH al 1% en DCM durante 3 volúmenes de columna seguido de un gradiente lineal hasta iPrOH al 30% en DCM durante 15 volúmenes de columna. Se recogen fracciones de 12 ml del eluyente activo por UV. Las fracciones 4 a 9 se combinan y se evaporan al vacío hasta alcanzar un peso constante, para dar 0,2 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,01 - 1,31 (m, 2H), 1,45 - 1,68 (m, 2H), 1,72 - 1,83 (m, 2H), 2,21 (s, 3H), 3,18 (s, 3H), 3,42 (m, 4H), 4,18 (m, 1H), 7,16 (t, 1H), 7,19 - 7,22 (m, 2H), 7,27 - 7,36 (m, 2H), 7,38 (d, 1H), 7,62 (d, 1H), 8,43 (s, 1H), 11,59 (s, 1H).
LC/MS m/z = 441.

EJEMPLO 197



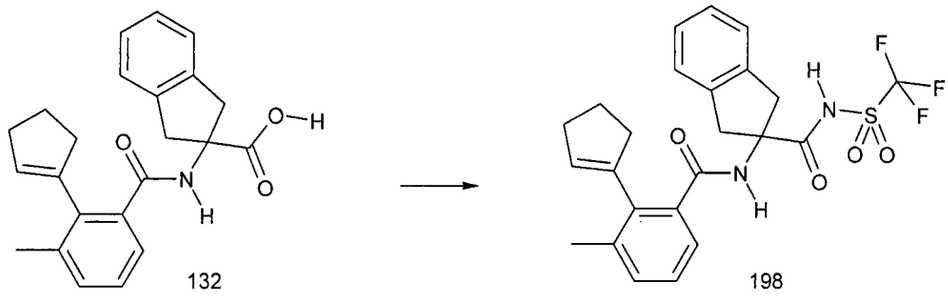
2-Ciclobutoxi-3-metil-N-(2-trifluorometanosulfonilaminocarbonil-indan-2-il)-benzamida (197):

Un vial de 30 ml se carga con ácido 2-[(2-ciclobutoxi-3-metil-benzoil)-amino]-indan-2-carboxílico (323 mg, 0,884 mmol) y DCM seco (7,0 ml). Se añade una barra de agitación, se inicia la agitación y después se añade trifluorometanosulfonamida (198 mg, 1,33 mmol). A la suspensión resultante se le añaden hidrocloruro de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (170 mg, 0,88 mmol) y 4-dimetilaminopiridina (108 mg, 0,88 mmol). Después de 8 días, el análisis por tlc (sílice, MeOH al 10% en DCM) indica que el ácido de partida se ha consumido. La mezcla de reacción se diluye con EtOAc (50 ml), se transfiere a un embudo de decantación, se lava con HCl acuoso diluido (3 N, 2 x 20 ml) y salmuera, se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar 0,51 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,21 - 1,38 (m, 1H), 1,41 - 1,56 (m, 1H), 1,91 - 2,04 (m, 4H), 2,23 (s, 3H), 3,42 (m, 4H), 4,37 (m, 1H), 7,04 (t, 1H), 7,14 - 7,21 (m, 4H), 7,31 (d, 1H), 7,51 (d, 1H), 8,66 (s, 1H), 8,95 (s, 1H).

LC/MS m/z = 497.

EJEMPLO 198

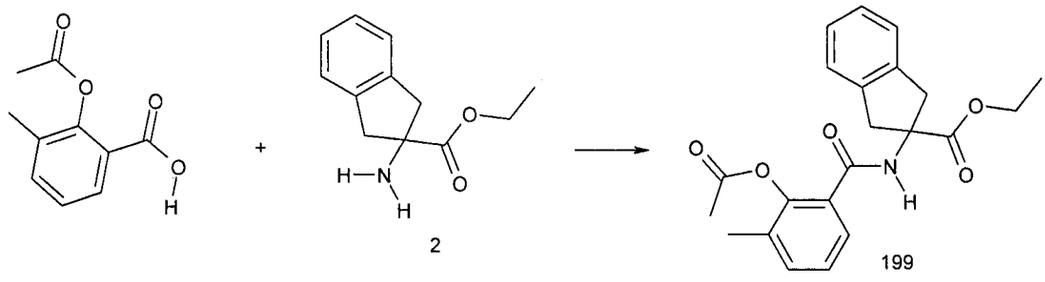


2-Ciclopent-1-enil-3-metil-N-(2-trifluorometanosulfonilaminocarbonil-indan-2-il)-benzamida (198):

Un matraz de 50 ml se carga con ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-indan-2-carboxílico (323 mg, 0,884 mmol) y DCM seco (7,0 ml). Se añade una barra de agitación y se inicia la agitación. Se añade trifluorometanosulfonamida (198 mg, 1,33 mmol). A la suspensión resultante se le añaden hidrocloruro de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (170 mg, 0,88 mmol) y 4-dimetilaminopiridina ([MFCD00006418], 108 mg, 0,88 mmol). Después de 80 h, el análisis por tlc (sílice, MeOH al 10% en DCM) indica que el ácido de partida se ha consumido. La mezcla de reacción se diluye con EtOAc (50 ml), se transfiere a un embudo de decantación, se lava con HCl acuoso diluido (3 N, 2 x 20 ml) y salmuera, se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar 0,50 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,76 (m, 2H), 2,17 (s, 3H), 2,22 - 2,42 (m, 4H), 3,38 (dd, 4H), 5,39, (s, 1H), 7,04 - 7,29 (m, 7H), 8,02 (s, 1H), 8,94 (s, 1H).
LC/MS m/z = 493.

EJEMPLO 199

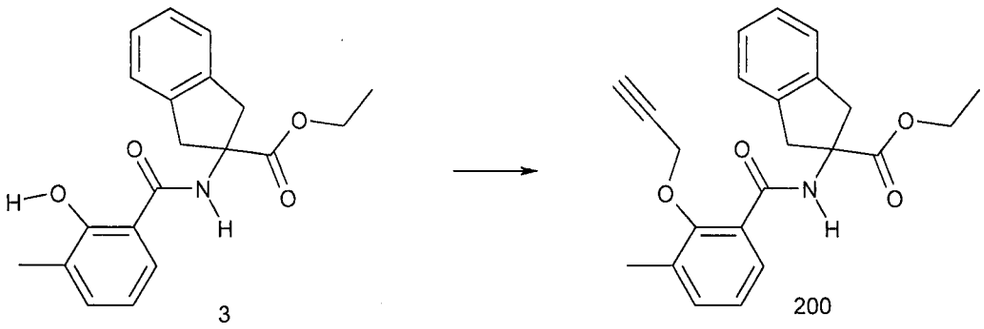


<u>Éster etílico del ácido 2-(2-acetoxi-3-metil-benzoil-amino)-indan-2-carboxílico (199):</u>

Un vial de 40 ml que contiene una barra de agitación se carga con ácido 2-acetoxil-3-metil-benzoico (1 g, 4,87 mmol) y DCM seco (14 ml) y se inicia la agitación. Después de que se complete la disolución, se añade HBTU (1,85 g, 4,87 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (1 g, 4,87 mmol) seguido de DIPEA (2,1 ml, 12,18 mmol). La reacción se deja en agitación durante 110 h. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (100 ml). Se lava consecutivamente con HCl acuoso diluido (al 3%, 40 ml), $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 3 g de un sólido de color naranja claro. Este material se

disuelve en 15 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 80 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% durante 12 volúmenes de columna. Las fracciones 19 a 27 se combinan y se evaporan al vacío para dar 1,38 g de un sólido de color blanco.

EJEMPLO 200

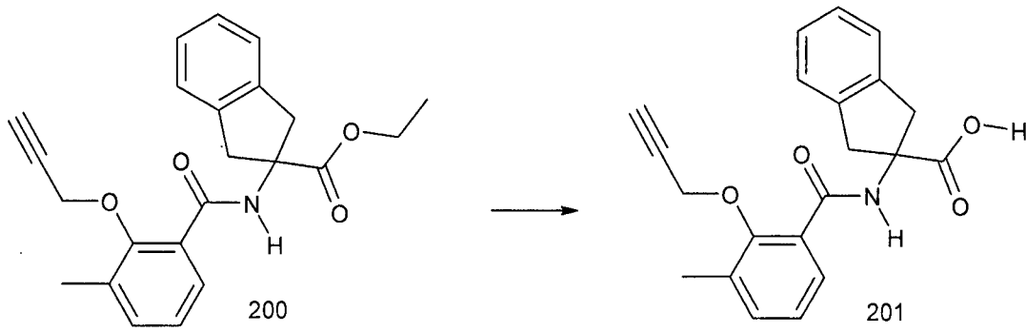


3 200

<u>Éster etílico del ácido 2-(3-metil-2-prop-2-iniloxi-benzoilamino)-indan-2-carboxílico (200):</u>

Un matraz de fondo redondo de 100 ml que contiene el éster etílico del ácido 2-(hidroxi-3-metil-benzoil)-indan-2-carboxílico (3) (0,29 g 0,855 mmol) se carga con DMF (4 ml) y se añade una barra de agitación. Después de la disolución del material de partida, se añade K_2SO_4 (0,3 g, 2,17 mmol) seguido de una solución de bromuro de propargilo en tolueno (11,59 M, 240 µl, 2,78 mmol). Después de agitar durante 62 h, el análisis por tlc (sílice, 1:1 de EtOAc/heptanos) indica que el material de partida se ha consumido. El material se convierte limpiamente en una mancha positiva por UV con un Rf ligeramente inferior. La reacción se diluye con EtOAc (80 ml) y se filtra a través de una capa de Celite. El filtrado se transfiere a un embudo de decantación. Se lava repetidamente con una solución acuosa saturada de $NaHCO_3$ (2 x 50 ml) y salmuera (50 ml), se seca sobre Na_2SO_4, se filtra y se evapora al vacío para producir 2,09 g de un aceite de color pardo claro. Se purifica (sílice, columna ISCO de 40 g, EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% en heptanos durante 10 volúmenes de columna). Se recogen fracciones de 17 ml del eluyente positivo por UV. Las fracciones 4 a 10 se combinan, se evaporan al vacío y se bombean hasta alcanzar un peso constante, para dar 0,21 g de un sólido de color blanco.

EJEMPLO 201

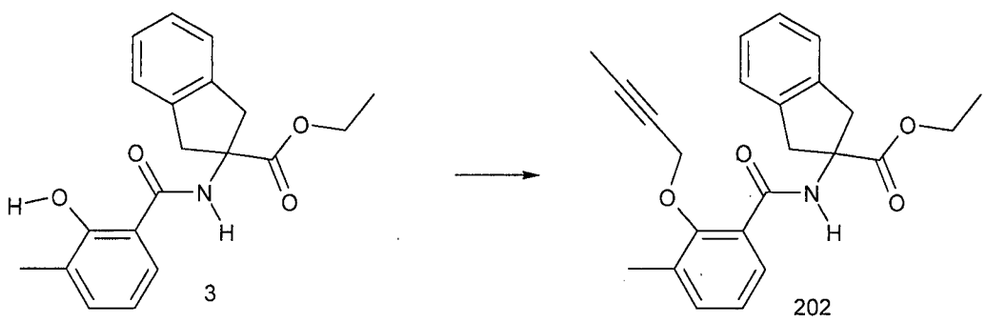


Ácido 2-(3-metil-2-prop-2-iniloxi-benzoilamino)-indan-2-carboxílico (201):

Un matraz de 50 ml que contiene el éster etílico del ácido 2-(3-metil-2-prop-2-iniloxi-benzoilamino)-indan-2-carboxílico (0,20 g, 0,53 mmol) se carga con 1,4-dioxano (3 ml) y MeOH (3 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH (56 mg, 1,35 mmol). Después de 108 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran hasta alcanzar un peso constante, para dar 0,2 g de un sólido de color blanquecino.

^{1}H RMN (300 MHz, DMSO-d_6): δ 2,26 (s, 3H), 3,43 (dd, 4H), 4,52 (s, 2H), 7,08 (dd, 1H), 7,12 - 7,38 (m, 6H), 8,79 (s, 1H), 12,53 (s a, 1H).
LC/MS m/z = 350.

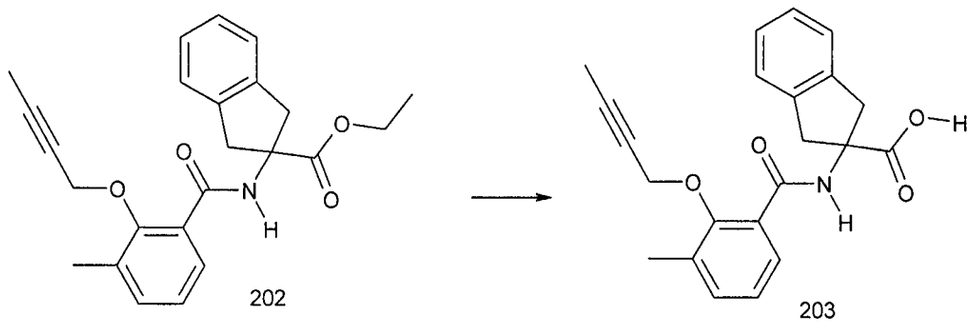
EJEMPLO 202



Éster etílico del ácido 2-(3-metil-2-but-2-iniloxi-benzoilamino)-indan-2-carboxílico (202):

Un matraz de fondo redondo de 100 ml que contiene el éster etílico del ácido 2-(hidroxi-3-metil-benzoil)-indan-2-carboxílico (0,62 g, 1,87 mmol) se carga con DMF (3 ml) y se añade una barra de agitación. Después de la disolución del material de partida, se añade K_2SO_4 (0,791 g, 5,95 mmol) seguido de una solución de 1-bromo-2-butina (537 µl, 5,95 mmol). Después de agitar durante 110 h, el análisis por tlc (sílice, 1:1 de EtOAc/heptanos) indica que el material de partida se ha consumido. El material se convierte limpiamente en una mancha positiva por UV con un Rf ligeramente inferior. La reacción se diluye con EtOAc (80 ml) y se filtra a través de una capa de Celite. El filtrado se transfiere a un embudo de decantación. Se lava repetidamente con una solución acuosa saturada de $NaHCO_3$ (2 x 50 ml) y salmuera (50 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para producir 0,75 g de un aceite de color pardo claro. Se purifica (sílice, columna ISCO de 40 g, EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% en heptanos durante 10 volúmenes de columna). Se recogen fracciones de 17 ml del eluyente positivo por UV. Las fracciones 2 a 8 se combinan, se evaporan al vacío y se bombean en seco para producir 0,79 g de un sólido de color blanco.

EJEMPLO 203



202 203

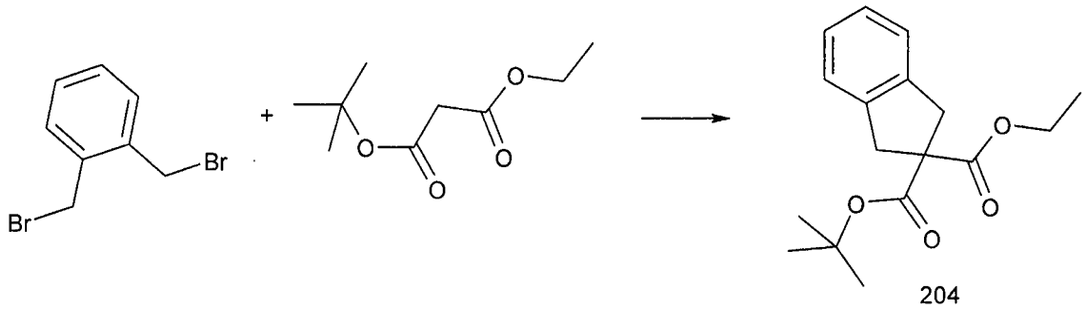
<u>Ácido 2-(3-metil-2-but-2-iniloxi-benzoilamino)-indan-2-carboxílico (203):</u>

Un matraz de 100 ml que contiene el ácido 2-(3-metil-2-but-2-iniloxi-benzoilamino)-indan-2-carboxílico (0,30 g, 0,77 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH (81 mg, 1,93 mmol). Después de 14 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~6 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20

ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran, bombeando hasta alcanzar un peso constante, para dar 0,25 g de un sólido de color blanquecino.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,77 (s, 3H), 2,24 (s, 3H), 3,44 (dd, 4H), 4,42 (s, 2H), 7,08 (dd, 1H), 7,14 - 7,23 (m, 4H), 7,31 (d, 2H), 8,75 (s, 1H), 12,52 (s a, 1H).
LC/MS m/z = 364,

EJEMPLO 204



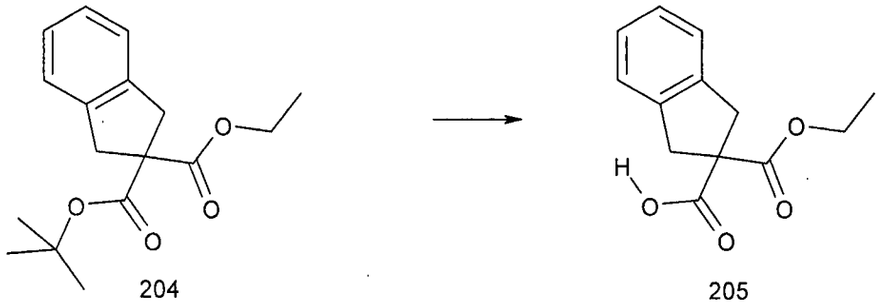
204

<u>Éster etílico de éster *terc*-butílico del ácido indan-2,2-dicarboxílico (204):</u>

Un matraz de 3 bocas que contiene una barra de agitación se equipa con un embudo de adición y se lava abundantemente con nitrógeno. El matraz se carga con NaH (dispersión al 60% en aceite, 3,38 g, 84,48 mmol) y THF seco (50 ml) y después se inicia la agitación. Se añade gota a gota malonato de *t*-butil etilo (8 ml, 42,24 mmol) mediante una jeringa durante un periodo de 5 minutos. Después de 1/2 hora, el embudo de adición se carga con una solución de dibromuro de o-xileno (11,15 g, 42,24 mmol) en tetrahidrofurano seco (THF, 50 ml). A la mezcla de reacción se le añade la solución durante un periodo de 30 minutos. Al final de este tiempo, el embudo de adición se lava con THF seco (10 ml). Esto también se añade a la mezcla de reacción. La mezcla de reacción se deja en agitación durante 6 días. Después, la mezcla de reacción se transfiere a un matraz de fondo redondo y el disolvente se retira a presión reducida. El semi-sólido de color blanco resultante se disuelve en una mezcla de EtOAc (200 ml) y agua (150 ml) y se transfiere a un embudo de decantación. Las capas se separan. La fase acuosa se extrae con EtOAc (150 ml). Los extractos orgánicos se combinan, se lavan con salmuera (150 ml), se secan sobre $MgSO_4$, se filtran y se evaporan hasta alcanzar un peso constante, para dar 12,44 g de un aceite viscoso. Este material se diluye con heptanos (30 ml) y se aplica a una columna de gel de sílice (300 g). El material se eluye con EtOAc/heptanos (al 5% durante 5 volúmenes de columna) con un gradiente hasta EtOAc al

75% en heptanos durante 7 volúmenes de columna. Se recogen fracciones de 43 ml del eluyente positivo por UV. Las fracciones 11- 20 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar 9,82 g de un aceite viscoso transparente.

EJEMPLO 205

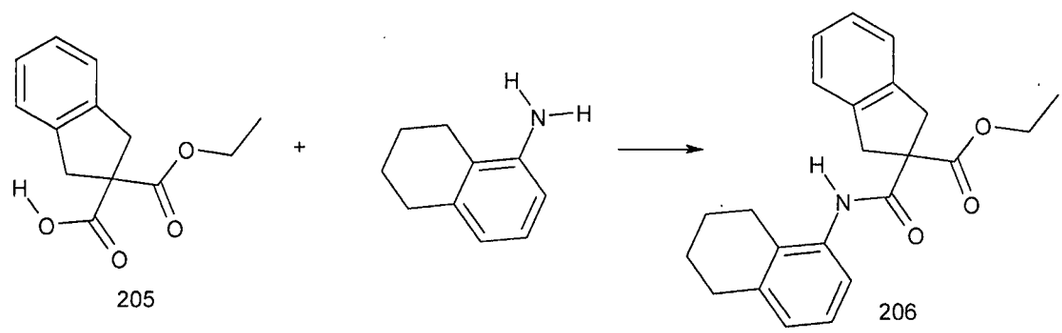


204 205

<u>Éster etílico del ácido indan-2,2-dicarboxílico (205):</u>

Un matraz de fondo redondo de 200 ml se carga con éster etílico de éster terc-butílico del ácido indan-2,2-dicarboxílico (8,69 g, 29,93 mmol). Se añaden DCM (40 ml) y una barra de agitación. Se inicia la agitación. Se añade ácido trifluoroacético (20,0 ml, 269 mmol). Después de 20 h, el análisis por tlc (sílice, 1:1 de acetato de etilo:heptanos) indica el consumo completo de material de partida. La mezcla de reacción se diluye con DCM (50 ml) y se evapora a presión reducida. El aceite resultante se diluye con DCM (55 ml) y se evapora a presión reducida. El aceite resultante se diluye con tolueno (50 ml) y se evapora a presión reducida, bombeando hasta alcanzar un peso constante, para dar 6,78 g de un material sólido de color blanco.

EJEMPLO 206

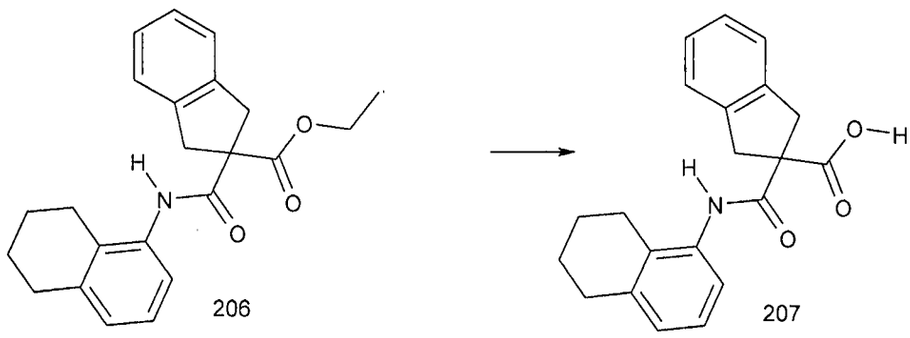


205 206

<u>Éster etílico del ácido 2-(5,6,7,8-tetrahidro-naftalen-1-ilcarbamoil)-indan-2-carboxílico (206):</u>

Un vial de reacción de 25 ml que contiene una barra de agitación se carga con éster etílico del ácido indan-2-carboxílico (0,48 g, 1,79 mmol) y DCM seco (7 ml). Se inicia la agitación. Después de que se complete la disolución, se añade HBTU (0,68 g, 1,79 mmol). Después de 5 min, se añade la 5,6,7,8-tetrahidro-1-naftilamina (0,26 ml, 1,79 mmol) seguido de DIPEA (0,72 ml, 4,12 mmol). La reacción se deja en agitación durante 68 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo del ácido de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (40 ml). Se lava consecutivamente con HCl acuoso diluido (al 3%, 20 ml), $NaHCO_3$ acuoso saturado (20 ml) y salmuera (20 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 0,50 g de un sólido de color púrpura claro. Este material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% durante 12 volúmenes de columna. Se recogen fracciones de 17 ml de eluyente. Las fracciones 11 a 16 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar 0,41 g de un material sólido de color blanco.

EJEMPLO 207



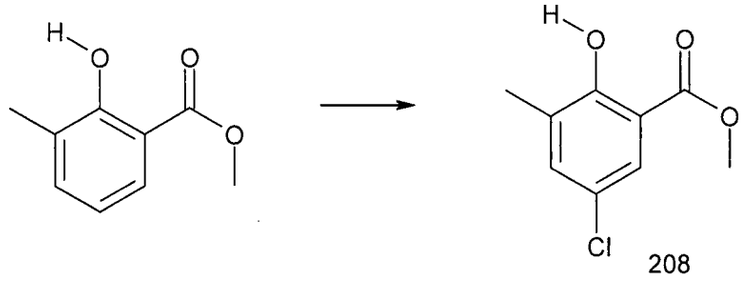
<u>Ácido 2-(5,6,7,8-tetrahidro-naftalen-1-ilcarbamoil)-indan-2-carboxílico (207):</u>

Un matraz de 100 ml que contiene éster etílico del ácido 2-(5,6,7,8-tetrahidro-naftaleno-1-il-carbamoil)-indan-2-carboxílico (0,23 g, 0,63 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH (67 mg, 1,58 mmol). Después de 14 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~6 ml). El contenido del matraz se

vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran al vacío, bombeando hasta alcanzar un peso constante, para dar 0,18 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,58 - 1,78 (m, 4H), 2,43 - 2,58 (m, 2H), 2,63 - 2,78 (m, 2H), 3,57 (dd, 4H), 6,96 (dd, 1H), 6,98 - 7,08 (m, 2H), 7,09 - 7,19 (m, 2H), 7,20 - 7,28 (m, 2H), 9,15 (s, 1H), 12,82 (s a, 1H).
LC/MS m/z = 336.

EJEMPLO 208



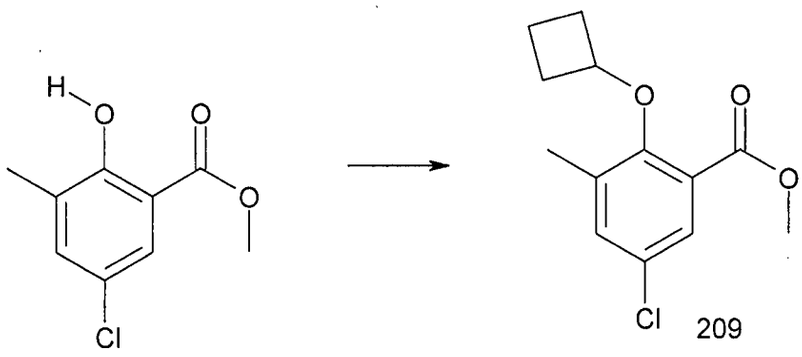
208

<u>Éster metílico del ácido 2-hidroxi-3-metil-5-clorobenzoico (208):</u>

Un matraz de fondo redondo de 3 bocas y 250 ml se carga con éster metílico del ácido 2-hidroxi-3-metil-5-benzoico (5 g, 30,1 mmol) y DCM seco (50 ml). Se añade una barra de agitación y el matraz se sumerge en un baño de hielo/agua. Después de 10 minutos, se añade cloruro de sulfurilo (2,9 ml, 36,1 mmol) mediante una jeringa durante un periodo de 5 minutos. Después de 0,5 h, el baño de hielo-agua se retira. Después de 2 h más, el análisis por tlc (sílice, EtOAc al 40%-heptanos) no indica ninguna reacción.

Después de 27 días, el análisis por tlc (sílice, EtOAc al 40%-heptanos) sigue sin indicar ninguna reacción. A la mezcla de reacción se le añade MeOH (50 ml). Comienza a precipitar un sólido cristalino de color blanco. El precipitado se recoge por filtración por succión para dar 2,1 g de un sólido de color blanco. Se recoge del filtrado una 2ª extracción de 1,25 g más de sólido de color blanco.

EJEMPLO 209

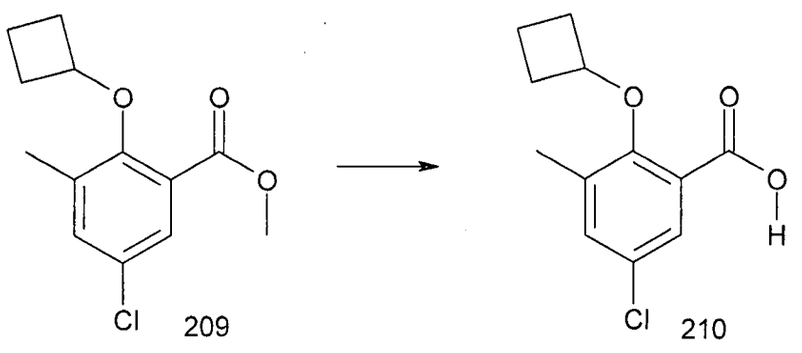


209

Éster metílico del ácido 5-cloro-2-ciclobutoxi-3-metil-benzoico (209):

Un matraz de fondo redondo de 100 ml se carga con éster metílico del ácido 5-cloro-2-hidroxi-3-metil-bezoico (0,92 g, 4,59 mmol). Se añaden N,N-dimetilformamida seca (DMF, 15 ml) y una barra de agitación. Se inicia la agitación. Después de la disolución, se añaden K_2SO_4 (1,90 g, 13,76 mmol) y bromociclobutano (0,65 ml, 6,88 mmol). Después de 12 días, el análisis por tlc (sílice, EtOAc al 25%/heptanos) indica un ligero consumo del material de partida y la aparición de una mancha positiva por UV con un valor de R_f ligeramente mayor. La reacción se equipa con un manto de calentamiento y se calienta a 37°C. Después de 3 días más, el análisis por tlc (sílice, EtOAc al 25%/heptanos) indica un ligero consumo del material de partida y la conversión completa en una mancha positiva por UV con un valor de R_f ligeramente mayor. La mezcla de reacción se filtra a través de una capa de Celite. El filtrado se diluye con EtOAc y (100 ml) y se transfiere a un embudo de decantación. La solución de EtOAc se lava con $NaHCO_3$ saturado (2 x 25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar 0,79 g de material semi-sólido.

EJEMPLO 210

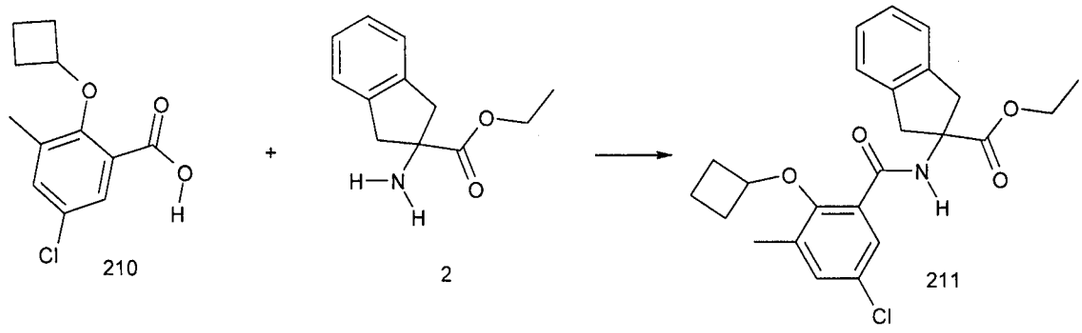


209 210

Ácido 5-cloro-2-ciclobutoxi-3-metil-benzoico (210):

Un matraz de 100 ml que contiene éster metílico del ácido 5-cloro-2-ciclobutoxi-3-metil-benzoico (0,57 g, 2,23 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH (237 mg, 5,65 mmol). Después de 39 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~6 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran al vacío, bombeando hasta alcanzar un peso constante, para dar 0,53 g de un sólido de color blanco.

EJEMPLO 211

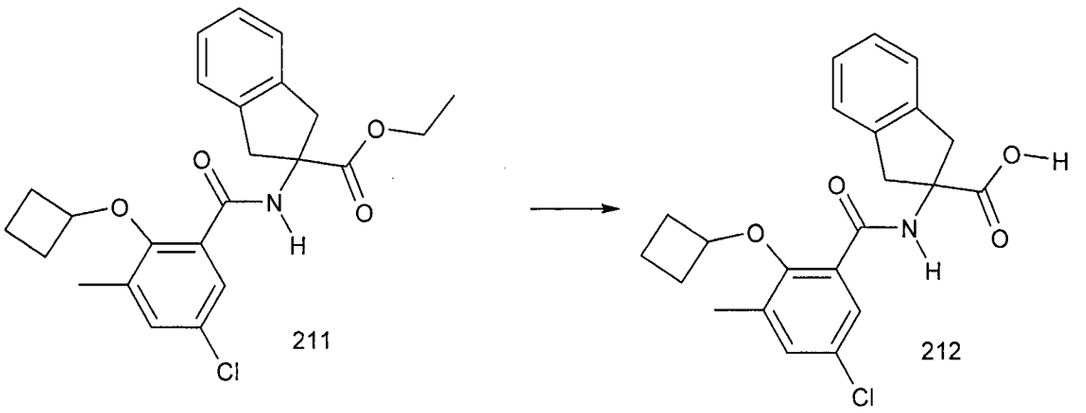


<u>Éster etílico del ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (211):</u>

Un matraz de fondo redondo de 100 ml que contiene una barra de agitación se carga con ácido 2-ciclobutoxil-3-metil-5-cloro-benzoico (0,36 g, 1,5 mmol) y DCM seco (7 ml). Se inicia la agitación. Después de que se complete la disolución, se añade HBTU (567 mg, 1,5 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (307 mg, 1,50 mmol) seguido de DIPEA (0,74 ml, 3,74 mmol). La reacción se deja en agitación durante 39 h. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (100 ml). Se lava consecutivamente con HCl acuoso diluido (al 3%, 40 ml), $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 0,8 g de un sólido de color naranja claro. Este material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en

heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 70% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente activo por UV. Las fracciones 8 a 11 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar 0,48 g de un sólido de color blanco.

EJEMPLO 212



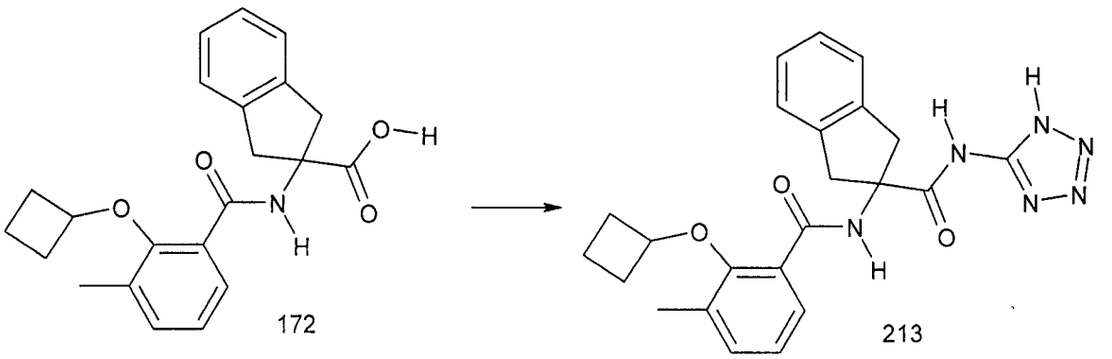
Ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (212):

Un matraz de 100 ml que contiene éster etílico del ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (0,3 g, 0,7 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH (74 mg, 1,77 mmol). Después de 20 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~6 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se dan 0,21 g de un sólido de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,17 - 1,28 (m, 1H), 1,49 (m, 1H), 1,78 - 1,95 (m, 2H), 1,96 - 2,04 (m, 2H), 3,46 (dd, 4H), 4,28 (m, 1H), 7,15 - 7,26 (m, 5H), 7,39 (d, 1H), 8,78 (s, 1H), 12,62 (s a, 1H).

LC/MS m/z = 400.

EJEMPLO 213



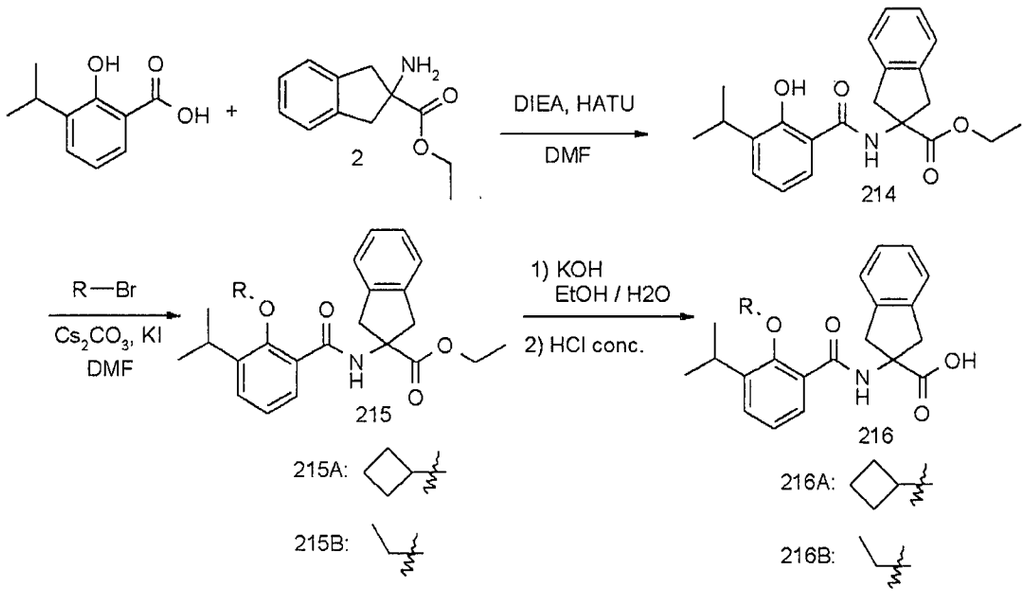
(1H-Tetrazol-5-il)-amida del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (213):

Un tubo de 40 ml se carga con ácido 2-[(2-ciclobutoxi-3-metil-benzoil)-amino]-indan-2-carboxílico (323 mg, 0,884 mmol) y DCM seco (7 ml). Se añade una barra de agitación y se inicia la agitación. Se añade 5-amino-1H-tetrazol (113 mg, 1,33 mmol). A la suspensión resultante se le añaden hidrocloruro de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (170 mg, 0,88 mmol) y 4-dimetilaminopiridina (108 mg, 0,88 mmol). Después de 11 1/2 días, el análisis por tlc (sílice, MeOH al 10% en DCM) indica que el ácido de partida se ha consumido. La mezcla de reacción se diluye con EtOAc (50 ml) y se transfiere a un matraz Erlenmeyer que contiene cloruro de amonio acuoso saturado (50 ml). Esta mezcla se deja en agitación. Después de 16 h de agitación, esta mezcla contiene un sólido de color blanco que se recoge por filtración por succión y se lava con agua (2 x 25 ml). El secado al aire da 0,26 g de un polvo de color blanco.

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,01 - 1,31 (m, 2H), 1,62 (m, 2H), 1,73 - 1,93 (m, 2H), 2,22 (s, 3H), 3,39 (dd, 4H), 4,19 (m, 1H), 7,08 (t, 1H), 7,19 - 7,51 (m, 5H), 7,57 (dd, 1H), 8,61 (s, 1H), 12,01 (s a, 1H).

LC/MS m/z = 433.

EJEMPLO 214



Éster etílico del ácido 2-(2-hidroxi-3-isopropil-benzoilamino)-indan-2-carboxílico (214):

A una solución de ácido 2-hidroxi-3-isopropil-benzoico (539 mg, 2,99 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (737 mg, 3,59 mmol) y HATU (1,36 g, 3,59 mmol) en DMF anhidra (30 ml) se le añade DIPEA (0,59 ml, 3,59 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (150 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (222) en forma de un sólido de color blanco (920 mg, 84%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,21 (d, 6H), 1,24 (t, 3H), 3,32-3,44 (m, 1H), 3,41 (d, 2H), 3,74 (d, 2H), 4,25 (c, 2H), 6,74-6,81 (m, 2H), 7,16 (d, 1H), 7,18-7,25 (m, 3H), 7,32 (d, 1H), 12,26 (s, 1H)

LC/MS (ES+) m/z = 368,17

EJEMPLOS 215A y 215B

Éster etílico del ácido 2-(2-ciclobutoxi-3-isopropil-benzoilamino)-indan-2-carboxílico (215A) y Éster etílico del ácido 2-(2-etoxi-3-isopropil-benzoilamino)-indan-2-carboxílico (215B):

A una suspensión de éster etílico del ácido 2-(2-hidroxi-3-isopropil-benzoilamino)-indan-2-carboxílico (214) (1 equiv., 0,82 mmol), Cs_2CO_3 anhidro (2 equiv., 1,64 mmol) y KI (0,2

equiv., 0,16 mmol) en DMF (15 ml) se le añade RBr (4 equiv., 3,28 mmol). La suspensión de reacción resultante se calienta en un recipiente para microondas (215A: 130°C, 2 h. 215B: 50°C, 30 min). Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (30 ml) y se lava con agua (1 x 5 ml) y salmuera (2 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 10-50% en heptano) para dar un producto puro (215) en forma de un sólido de color blanco (215A: 340 mg, 98%; 215B: 300 mg, 93%).

215A: ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,19 (d, 6H), 1,26 (t, 3H), 1,16-1,57 (m, 2H), 1,87-2,07 (m, 4H), 3,24-3,38 (m, 1H), 3,36 (d, 2H), 3,78 (d, 2H), 4,26 (c, 2H), 4,15-4,30 (m, 1H), 7,12-7,26 (m, 5H), 7,35 (dd, 1H), 7,83 (dd, 1H), 8,20 (s, 1H).
LC/MS (ES+) m/z = 422,24

215B: ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,13 (t, 3H), 1,20 (d, 6H), 1,26 (t, 3H), 3,24 (m, 1H), 3,35 (d, 2H), 3,72 (c, 2H), 3,78 (d, 2H), 4,26 (c, 2H), 7,14-7,26 (m, 5H), 7,36 (dd, 1H), 7,82 (dd, 1H), 8,36 (s, 1H)
LC/MS (ES+) m/z = 396,22

EJEMPLOS 216A y 216B

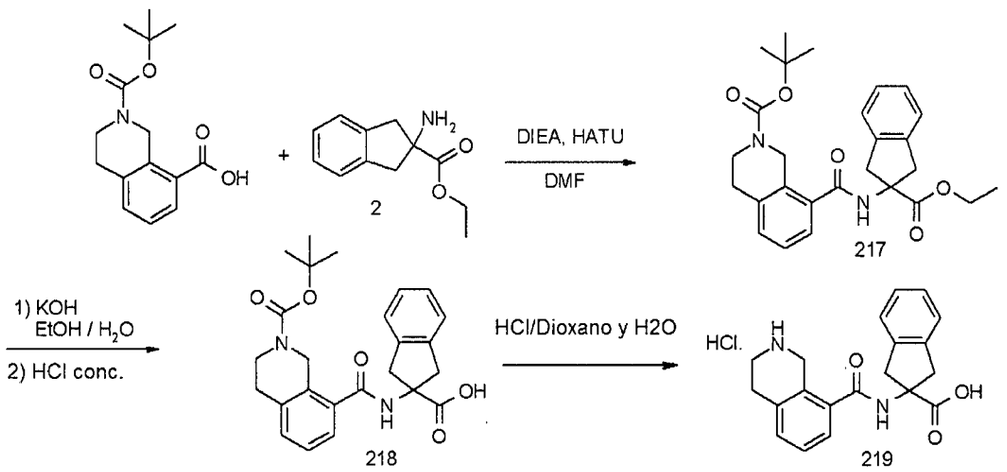
<u>Ácido 2-(2-ciclobutoxi-3-isopropil-benzoilamino)-indan-2-carboxílico (216A) y Ácido 2-(2-etoxi-3-isopropil-benzoilamino)-indan-2-carboxílico (216B):</u>

La mezcla de (215) (1 equiv., 0,69 mmol) y KOH (13 equiv., 8,9 mmol) se disuelve en EtOH (10 ml) y agua (0,5 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 4 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (216) en forma de un sólido de color blanco (216A: 190 mg, 70%; 216B: 220 mg, 91%).

216A: ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,17 (d, 6H), 1,13-1,30 (m, 1H), 1,41 (m, 1H), 1,78-2,02 (m, 4H), 3,27 (m, 1H), 3,38 (d, 2H), 3,81 (d, 2H), 4,13 (m, 1H), 7,09 (t, 1H), 7,13-7,23 (m, 4H), 7,34 (dd, 1H), 7,81(dd, 1H), 8,37 (s, 1H).
LC/MS (ES+) m/z = 394,19

216B: ^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,08 (t, 3H), 1,19 (d, 6H), 3,20 (m, 1H), 3,46 (d, 2H), 3,55 (c, 2H), 3,88 (d, 2H), 7,18-7,27 (m, 5H), 7,42 (dd, 1H), 7,89 (dd, 1H), 8,63 (s, 1H)
LC/MS (ES+) m/z = 368,19

Ejemplo 217



<u>Éster terc-butílico del ácido 8-(2-etoxicarbonil-indan-2-ilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxílico (217):</u>

A una solución de 2-terc-butil éster del ácido 3,4-dihidro-1H-isoquinolina-2,8-dicarboxílico (2,0 g, 7,2 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (1,5 g, 7,2 mmol) y HATU (3,3 g, 8,6 mmol) en DMF anhidra (70 ml) se le añade DIPEA (1,4 ml, 8,6 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (150 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (200 g de gel de sílice, gradiente de elución: EtOAc al 5-50% en heptano) para dar un producto puro (217) en forma de un sólido de color blanco (3,3 g, 99%).

Ejemplo 218

Éster terc-butílico del ácido 8-(2-carboxi-indan-2-ilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxílico (218):

El producto (217) (2,46 g, 5,3 mmol) y KOH (2,5 g, 45 mmol) se disuelven en EtOH (20 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (50 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado de color blanco del agua. El precipitado se filtra para dar un producto puro (218) en forma de un sólido de color blanco (1,4 g, 61%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,40 (s, 9H), 2,79 (t, 2H), 3,34 (d, 2H), 3,52 (t, 2H), 3,57 (d, 2H), 4,59 (s, 2H), 7,10-7,31 (m, 7H), 8,88 (s, 1H), 11,56-12,92 (s a, 1H)
LC/MS (ES+) m/z = 437,26

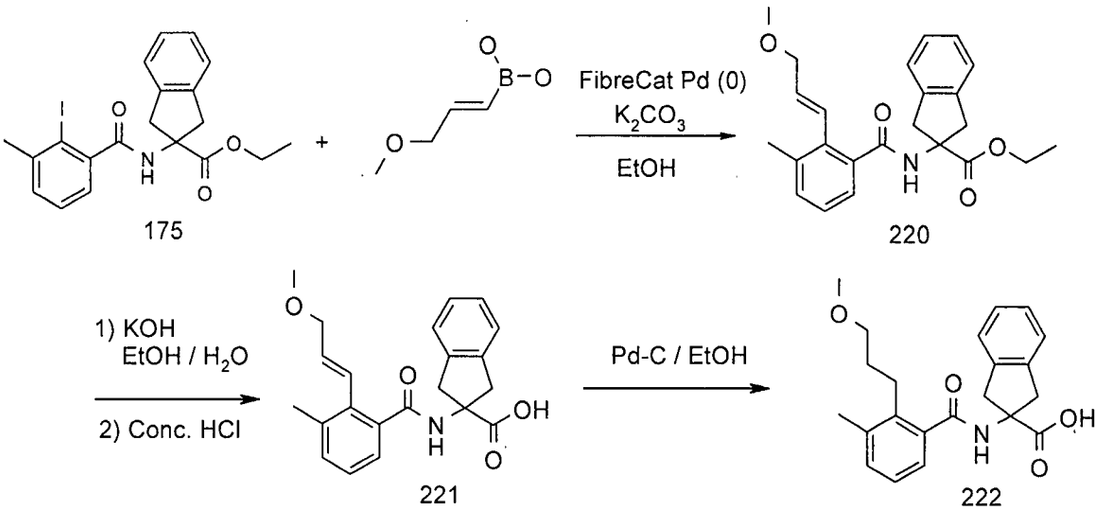
Ejemplo 219

Ácido 2-[(1,2,3,4-tetrahidro-isoquinolina-8-carbonil)-amino]-indan-2-carboxílico (219):

A una solución de éster terc-butílico del ácido 8-(2-carboxi-indan-2-ilcarbamoil)-3,4-dihidro-1H-isoquinolina-2-carboxílico (226) (128 mg, 0,29 mmol) en 6 ml de dioxano se le añade gota a gota una solución 4 N de HCl en dioxano/agua (0,72 ml) y la solución resultante se agita a TA durante 4 h. La concentración da una sal HCl de (219) en forma de un sólido de color blanco (246 mg, 100%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 3,04 (t, 3H), 3,28-3,41 (m, 4H), 3,58 (d, 2H), 4,31 (s, 2H), 7,13-7,27 (m, 4H), 7,32 (s, 3H), 9,05 (s, 1H), 9,30-9,57 (s a, 1H), 12,46-12,77 (s a, 1H)
LC/MS (ES+) m/z = 337,18

Ejemplo 220



175 220 221 222

Éster etílico del ácido 2-[2-(3-metoxi-propenil)-3-metil-benzoilamino]-indan-2-carboxílico (220):

A una solución de éster etílico del ácido 2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (400 mg, 0,89 mmol) y ácido 3-metoxi-1-propenilborónico (206 mg, 1,78 mmol) en 10 ml de EtOH/10 ml de dioxano se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0), (Pd al 4,84%, 195 mg, 0,089 mmol), y una solución acuosa 2 M de K_2SO_4 (1,78 ml, 3,56 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 4 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar el producto (220) en forma de un aceite amarillo pálido.

Ejemplo 221

Ácido 2-[2-(3-metoxi-propenil)-3-metil-benzoilamino]-indan-2-carboxílico (221):

El producto (220) y KOH (1,0 g, 18 mmol) se disuelven en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 3 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. Después de la filtración, el sólido de color pardo obtenido se purifica por HPLC para dar el producto puro (221) en forma de un sólido de color blanco (200 mg, 62%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,28 (s, 3H), 3,31 (s, 1H), 3,37 (s, 4H), 3,78 (d, 2H), 3,93 (dd, 2H), 5,83 (dt, 1H), 6,44 (s, 1H), 6,64 (d, 1H), 7,10-7,35 (m, 7H)

LC/MS (ES+) m/z = 366,15

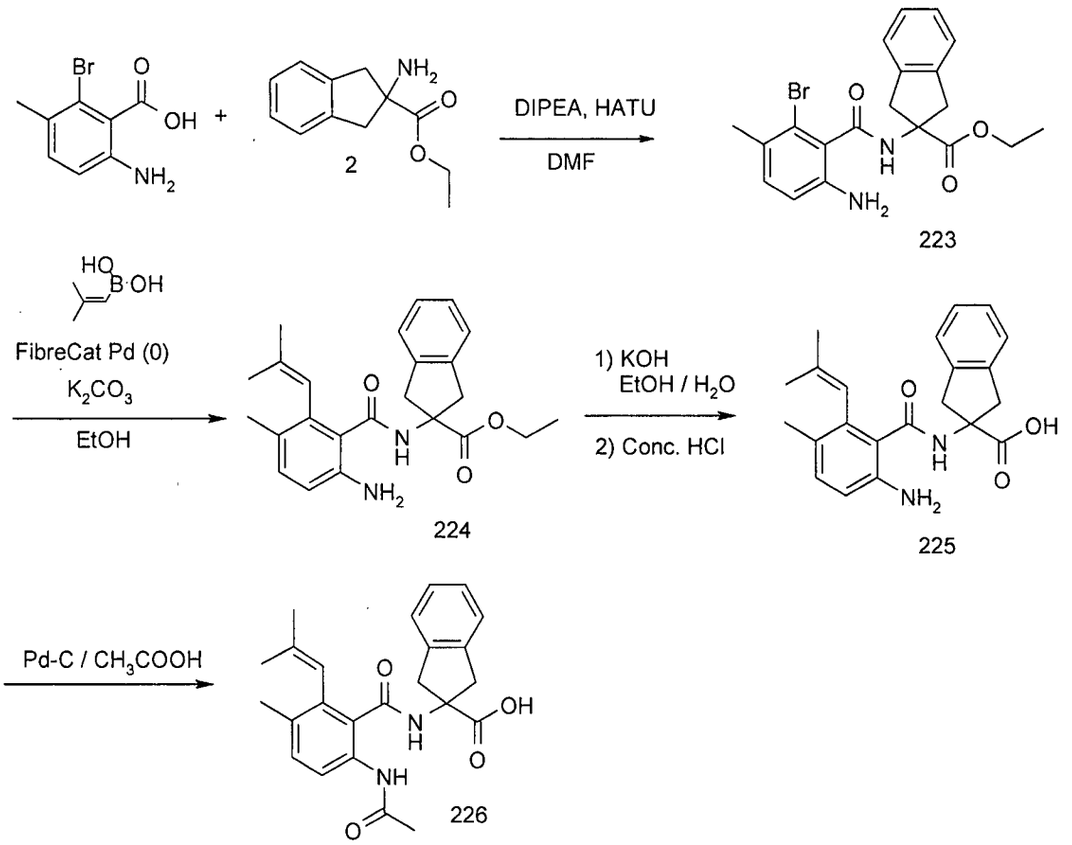
Ejemplo 222

Ácido 2-[2-(3-metoxi-propil)-3-metil-benzoilamino]-indan-2-carboxílico (222):

A una solución de ácido 2-[2-(3-metoxi-propenil)-3-metil-benzoilamino]-indan-2-carboxílico (229) (120 mg, 0,34 mmol) en EtOH absoluto (15 ml) se le añade el catalizador, Pd-C (Pd al 5% en peso, 93 mg, al 4,4% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 344,74 kPa (50 psi), 50°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución orgánica combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (222) en forma de un sólido de color blanco (80 mg, 49%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,64 (m, 2H), 2,27 (s, 3H), 2,59-2,69 (m, 2H), 3,16-3,40 (m, 7H), 3,56 (d, 2H), 6,97-7,24 (m, 7H), 8,84 (s, 1H), 12,48 (s, 1H)
LC/MS (ES+) m/z = 368,18

Ejemplo 223



Ácido 2-[6-acetilamino-3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (223):

A una solución de ácido 6-amino-2-bromo-3-metil-benzoico (688 mg, 2,99 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (737 mg, 3,59 mmol) y HATU (1,36 g, 3,59 mmol) en DMF anhidra (30 ml) se le añade DIPEA (0,59 ml, 3,59 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (150 ml) y se lava con agua (1 x 10 ml) y salmuera (2 x 10 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar 278 mg de un aceite de color pardo (223).

EJEMPLO 224

Éster etílico del ácido 2-[6-amino-3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (224)

A una solución de (223) (278 mg, 0,67 mmol) y ácido 2,2-dimetiletilenoborónico (134 mg, 1,34 mmol) en 10 ml de EtOH se le añaden catalizador homogéneo de paladio soportado, FibreCatPd(0), (Pd al 4,84%, 195 mg, 0,089 mmol), y una solución acuosa 2 M de K_2SO_4

(1,78 ml, 3,56 mmol). La mezcla de reacción resultante se cubre con argón y se somete a una reacción de microondas: 110°C, 5 h. Después de la concentración al vacío, el residuo se purifica por HPLC para dar 380 mg de un semi-sólido de color pardo (224).

EJEMPLO 225

Ácido 2-[6-amino-3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (225)

La mezcla de (224) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (8 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 4 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no se forma más cantidad de precipitado de color blanco. Después de la filtración, el sólido en bruto se purifica por HPLC para dar 48 mg de un sólido de color pardo (225).

EJEMPLO 226

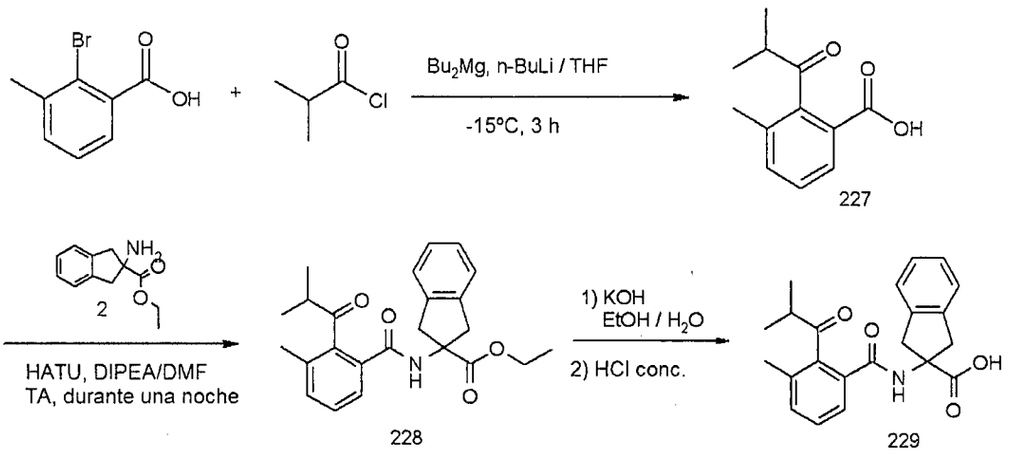
Ácido 2-[6-acetilamino-3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (226)

A una solución de (225) (48 mg, 0,1 mmol) en ácido acético (10 ml) se le añade el catalizador, Pd-C (Pd al 5% en peso, 21 mg, al 1% en mmol), en una atmósfera de argón. La mezcla de reacción resultante se lleva al aparato Parr para realizar la hidrogenación: 379,211 kPa (55 psi), 90°C, durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución orgánica combinada se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (226) en forma de un sólido de color blanco (35 mg, 86%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 1,17 (s, 3H), 1,70 (s, 3H), 2,08 (d, 3H), 2,16 (d, 3H), 3,26 (d, 2H), 3,72 (d, 2H), 5,89 (s, 1H), 7,12-7,25 (m, 5H), 7,48 (s, 1H), 7,74 (d, 1H)

LC/MS (ES+) m/z = 407,18

Ejemplo 227



Ácido 2-isobutiril-3-metil-benzoico (227):

La solución de ácido 2-bromo-3-metil-benzoico (1,5 g, 6,98 mmol) en 10 ml de THF se trata con Bu_2Mg 1 M/heptano a -15°C en una atmósfera de argón. Después de agitar durante 30 min, se añade gota a gota n-BuLi 1,6 M/hexano a -15°C y la mezcla se deja durante 1 h. Después, se añade gota a gota cloruro de isobutirilo (2,95 ml, 27,9 mmol). Después de 30 min más de agitación, la reacción se interrumpe con una solución acuosa 2 N de HCl (2 ml). Después de la concentración, el residuo se purifica por HPLC para dar un producto puro (227) en forma de un sólido de color blanco (840 mg, 58%).

^{1}H RMN ($CDCl_3$ + gotas de CD_3OD, 300 MHz): δ 0,62 (d, 3H), 1,31 (d, 3H), 2,51 (s, 3H), 2,61 (s, 1H), 7,42-7,50 (m, 2H), 7,68 (m, 1H)

LC/MS (ES) m/z = 205,06

Ejemplo 228

Éster etílico del ácido 2-(2-isobutiril-3-metil-benzoilamino)-indan-2-carboxílico (228):

A una solución de ácido 2-isobutiril-3-metil-benzoico (227) (200 mg, 0,97 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (220 mg, 1,07 mmol) y HATU (441 mg, 1,16 mmol) en DMF anhidra (10 ml) se le añade DIPEA (192 µl, 1,16 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en DCM (50 ml) y se lava con agua (1 x 5 ml) y salmuera (1 x 5 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por HPLC para dar un producto puro (228) en forma de un sólido de color amarillo pálido (340 mg, 89%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,06 (d, 6H), 1,25 (t, 3H), 2,24 (s, 3H), 2,86 (m, 1H), 3,30 (d, 2H), 3,72 (d, 2H), 4,23 (c, 2H), 6,47 (s, 1H), 7,14-7,43 (m, 7H)
LC/MS (ES+) m/z = 394,23

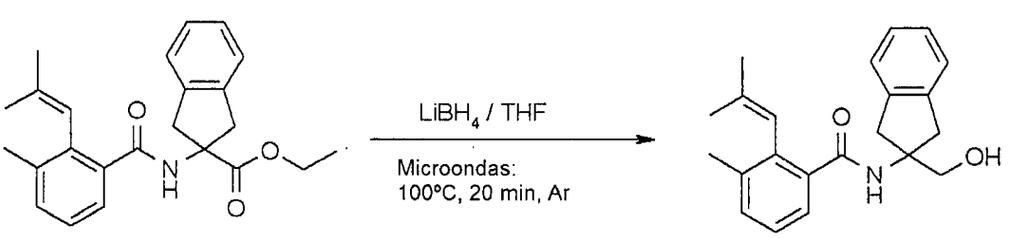
Ejemplo 229

Ácido 2-(2-isobutiril-3-metil-benzoilamino)-indan-2-carboxílico (229):

La mezcla de éster etílico del ácido 2-(2-isobutiril-3-metil-benzoilamino)-indan-2-carboxílico (228) (170 mg, 0,43 mmol) y KOH (500 mg, 8,9 mmol) se disuelve en EtOH (20 ml) y agua (1 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. El precipitado se filtra para dar un producto puro (229) en forma de un sólido de color blanco (140 mg, 89%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,07 (d, 6H), 2,25 (s, 3H), 2,87 (m, 1H), 3,35 (d, 2H), 3,74 (d, 2H), 7,16-7,42 (m, 7H)
LC/MS (ES+) m/z = 366,16

Ejemplo 230



134 230

N-(2-Hidroximetil-indan-2-il)-3-metil-2-(2-metil-propenil)-benzamida (230):

A una solución de éster etílico del ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (80 mg, 0,21 mmol) en THF anhidro (1 ml) se añade gota a gota $LiBH_4$ 2 M/THF (0,84 ml, 1,68 mmol) a TA en una atmósfera de argón. La solución resultante se calienta durante 20 min a 100°C con microondas. Después de enfriar a temperatura ambiente, la solución de reacción se vierte en hielo-agua y una solución ac. saturada de NH_4Cl hasta

alcanzar un valor de pH de 7. La solución se extrae con EtOAc (50 ml x 3). La fase de EtOAc combinada se lava con salmuera (10 ml x 2), se seca sobre Na_2SO_4 y se concentra. El residuo se purifica por HPLC para dar un producto puro (230) en forma de un sólido de color blanco (58 mg, 82%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,38 (s, 3H), 1,80 (s, 1H), 2,16 (s, 1H), 3,11 (d, 2H), 3,33 (d, 2H), 3,88 (s, 2H), 6,11 (s, 1H), 6,71(s a, 1H), 7,13-7,33 (m, 6H), 7,60 (d, 1H)
LC/MS (ES+) m/z = 336,21

EJEMPLOS 231 Y 232

Separación Quiral del Ejemplo 150 en los Ejemplos 231 y 232

1. Condiciones experimentales:

	Instrumento: Americhrom Global Technologies VERSAPrep 100 (Módulo Detector, Módulo de Recolección y Reciclado de Fracciones y de Válvulas de Inyección, Módulo de Bombeo de Inyección de Muestra)
Programa informático:	Chiralpak AD, 20 mm ID x 250 mm, 10 micrómetros
Eluyente:	EtOH/Heptano (20/80) con TFA al 0,1% (Pre-mezclado)
Caudal:	15 ml/min
Detección:	UV 214 nm
Temperatura de Columna:	TA
Volumen de inyección:	1 ml
Concentración:	~10 mg/ml

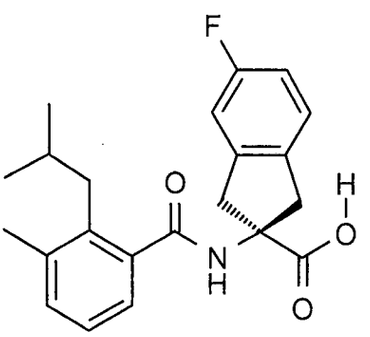
2. Resultados:

Muestra	Enantiómero 1		Enantiómero 2	
	TA (min)	%	TA (min)	%
	Tiempo Máx 6,78	53,8	Tiempo Máx 10,02	46,2
	F1(-) 47,7 mg, sólido de color blanco		F2(+) 45,1 mg, sólido de color blanco	

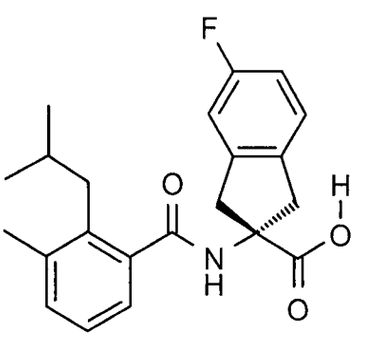
Fracción 1(-) (231):

^{1}H RMN (DMSO-d_6, 300 MHz): δ 0,76 (d, 6H), 1,74 (m, 1H), 2,27 (s, 3H), 2,62 (d, 2H), 3,24-3,38 (m, 2H), 3,43-3,62 (m, 2H), 6,90-7,28 (m, 6H), 8,83 (s, 1H), 12,51 (s, 1H)
LC/MS (ES+) m/z = 370,18

Fracción 2(+) (232):
^{1}H RMN (DMSO-d_6, 300 MHz): δ 0,76 (d, 6H), 1,74 (m, 1H), 2,27 (s, 3H), 2,62 (d, 2H), 3,24-3,38 (m, 2H), 3,43-3,62 (m, 2H), 6,90-7,28 (m, 6H), 8,83 (s, 1H), 12,51 (s, 1H)
LC/MS (ES+) m/z = 370,18
Las estructuras de los enantiómeros son las siguientes:

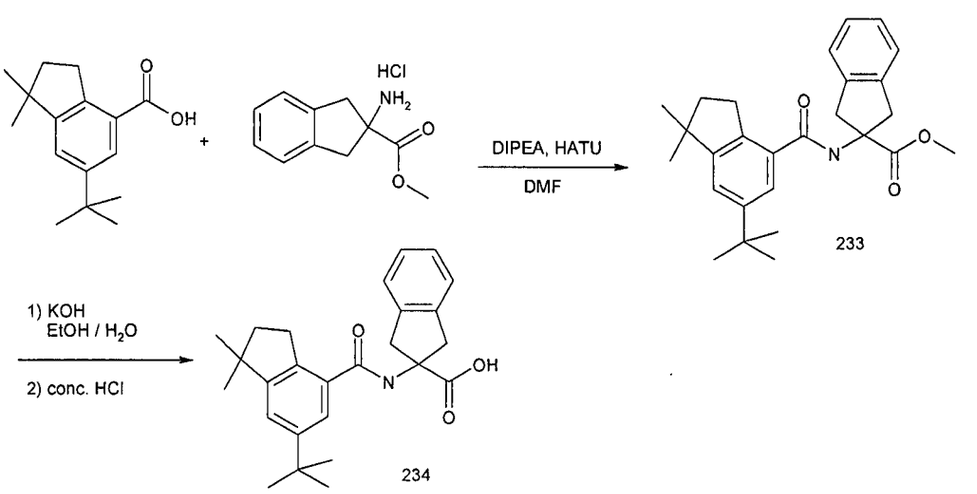


y



. Sin embargo, las estructuras no se asignan a ninguna de la fracción de elución particular.

EJEMPLO 233



<u>Éster metílico del ácido 2-[(6-terc-butil-1,1-dimetil-indan-4-carbonil)-amino]-indan-2-carboxílico (233):</u>

A una solución de ácido 6-*terc*-butil-1,1-dimetil-indan-4-carboxílico (1 g, 4,1 mmol), sal HCl de éster metílico del ácido 2-amino-indan-2-carboxílico (924 mg, 4,1 mmol) y HATU (1,85 g,

4,9 mmol) en DMF anhidra (15 ml) se le añade DIPEA (2,5 ml, 14,4 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo se disuelve en EtOAc (100 ml) y se lava con agua (1 x 100 ml), HCl 1 N (1 x 100 ml) y salmuera (1 x 100 ml). La capa orgánica se seca sobre $MgSO_4$ anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (60 g de gel de sílice, gradiente de elución: EtOAc al 10-60% en heptano) para dar un producto puro en forma de un sólido de color blanco (660 mg, 39%).

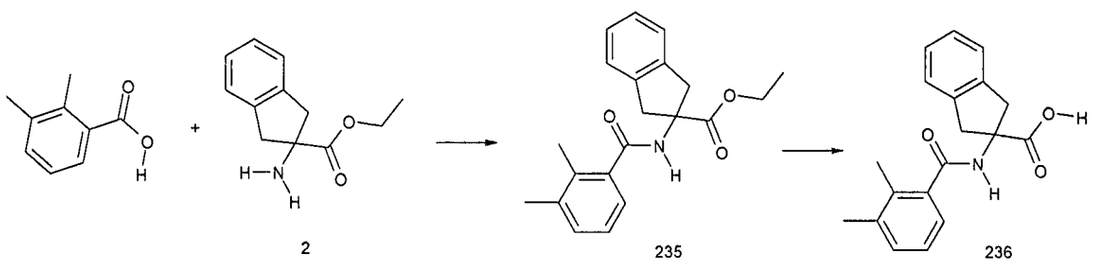
^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,20 (s, 6H), 1,27 (s, 9H), 1,80 (t, 2H), 2,87 (t, 2H), 3,37 (s, 2H), 3,57 (s, 2H), 3,63 (s, 1H), 3,64 (s, 3H), 7,15-7,29 (m, 6H), 8,78 (s, 1H)
LC/MS (ES+) m/z = 420,24

EJEMPLO 234

Ácido 2-[(6-terc-butil-1,1-dimetil-indan-4-carbonil)-amino]-indan-2-carboxílico (234):
Una mezcla de éster metílico del ácido 2-[(6-terc-butil-1,1-dimetil-indan-4-carbonil)-amino]-indan-2-carboxílico (600 mg, 1,4 mmol) y KOH (1,8 g, 30,8 mmol) se disuelve en EtOH (25 ml) y agua (2 ml) en un baño de agua. El baño de agua se retira cuando el KOH se disuelve completamente y la solución de reacción resultante se agita a TA durante 8 h. Después de la concentración al vacío, el residuo se neutraliza con HCl 1 N y se extrae con EtOAc (3 x 150 ml) y los lavados orgánicos se combinan y se concentran al vacío. El residuo se purifica por HPLC preparativa (columna C18 de 10 micrómetros, gradiente de elución: ACN al 20-100%, TFA al 0,1% en H_2O·TFA al 0,1%). El producto cristaliza de las fracciones recogidas después de un periodo de reposo. La filtración y el secado dan el producto puro en forma de un sólido de color blanco (454 mg, 78%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,20 (s, 6H), 1,27 (s, 9H), 1,79 (t, 2H), 2,87 (t, 2H), 3,37 (s, 2H), 3,55 (s, 2H), 3,61 (s, 1H), 7,12-7,29 (m, 6H), 8,62 (s, 1H)
LC/MS (ES+) m/z = 406,22

Ejemplo 235



2 235 236

Éster etílico del ácido 2-(2,3-dimetil-benzoilamino)-indan-2-carboxílico (235):

Se recogen éster etílico del ácido 2-amino-indan-2-carboxílico (250 mg, 1,2 mmol), ácido 2,3-dimetil-benzoico (183 mg, 1,2 mmol) y HATU (555 mg, 1,46 mmol) en un vial, se evacúa y se carga de nuevo con nitrógeno. Se añade DMF anhidra (2 ml) y se inicia la agitación. Después de unos min, se añade DIPEA (0,302 ml, 1,82 mmol) y la mezcla se agita a TA durante una noche. El análisis por tlc de la mezcla de reacción (sílice, EtOAc al 50%/heptanos) indica el consumo completo de la amina de partida. Se añade agua (10 ml), se extrae con EtOAc (3 x 5 ml), se seca sobre Na_2SO_4, se concentra y el producto en bruto se cromatografía sobre una columna de 25 g de gel de sílice usando EtOAc al 20-50% en heptano como gradiente para producir éster etílico del ácido 2-(2,3-dimetil-benzoilamino)-indan-2-carboxílico (350 mg, 87%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,3 (t, 3H), 2,26 (s, 3H), 2,29 (s, 3H), 3,55 (dd, 4H), 4,28 (c, 2H), 6,19 (s, 1H), 7,04 - 7,22 (m, 7H).
LC/MS m/z = 338,17,

EJEMPLO 236

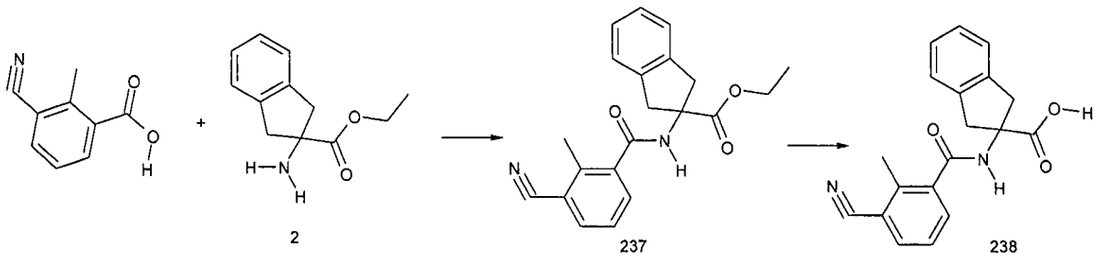
Ácido 2-(2,3-dimetil-benzoilamino)-indan-2-carboxílico (236):

La mezcla de éster etílico del ácido 2-(2,3-dimetil-benzoilamino)-indan-2-carboxílico (235) (290 mg, 0,86 mmol), KOH (solución acuosa al 50%, 1,92 g, 17,2 mmol), EtOH (10 ml) y agua (1 ml) se agita en un vial de 20 ml a 50°C durante 30 min. Después de la concentración al vacío, el residuo se disuelve en agua (5 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. La filtración da ácido 2-(2,3-dimetil-benzoilamino)-indan-2-carboxílico (236) en forma de un sólido de color blanco (240 mg, 90%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,22 (s, 3H), 2,25 (s, 3H), 3,61 (dd, 4H), 6,24 (s, 1H), 7,06 (m, 2H), 7,18 - 7,23 (m, 5H).

LC/MS m/z = 310,13.

EJEMPLO 237



Éster etílico del ácido 2-(3-ciano-2-metil-benzoilamino)-indan-2-carboxílico (237):

Se recogen éster etílico del ácido 2-amino-indan-2-carboxílico (250 mg, 1,2 mmol), ácido 3-ciano-2-metil-benzoico (196 mg, 1,2 mmol) y HATU (555 mg, 1,46 mmol) en un vial, se evacúa y se carga de nuevo con nitrógeno. Se añade DMF anhidra (2 ml) y se inicia la agitación. Después de unos min, se añade DIPEA (0,302 ml, 1,82 mmol) y la mezcla se agita a TA durante una noche. El análisis por tlc de la mezcla de reacción (sílice, EtOAc al 50%/heptanos) indica el consumo completo de la amina de partida. Se añade agua (10 ml), se extrae con EtOAc (3 x 5 ml), se seca sobre Na_2SO_4, se concentra y el producto en bruto se cromatografía sobre una columna de 25 g de gel de sílice usando EtOAc al 20-50% en heptano como gradiente para producir éster etílico del ácido 2-(3-ciano-2-metil-benzoilamino)-indan-2-carboxílico (373 mg, 89%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,3 (t, 3H), 2 6 (s, 3H), 3,57 (dd, 4H), 4,29 (c, 2H), 6,23 (s, 1H), 7,23 - 7,30 (m, 5H), 7,51 (d, 1H), 7,64 (d, 1H).
LC/MS m/z = 349,16.

EJEMPLO 238

Ácido 2-(3-ciano-2-metil-benzoilamino)-indan-2-carboxílico (238):

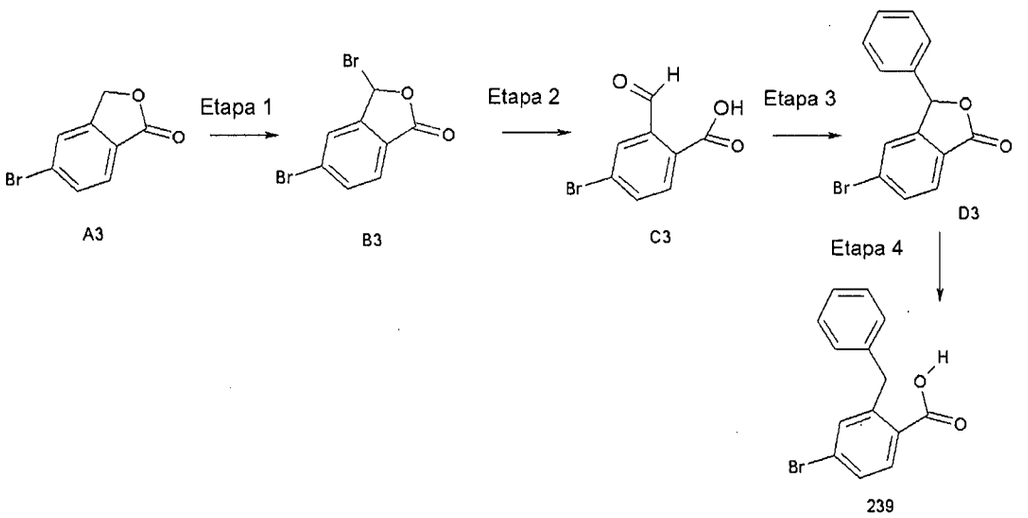
La mezcla de éster etílico del ácido 2-(3-ciano-2-metil-benzoilamino)-indan-2-carboxílico (3) (310 mg, 0,89 mmol), KOH (solución acuosa al 50%, 2 g, 17,8 mmol), EtOH (10 ml) y agua (1 ml) se agita en un vial de 20 ml a 50°C durante 30 min. Después de la concentración al vacío, el residuo se disuelve en agua (5 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. La filtración produce ácido 2-(3-ciano-2-metil-

benzoilamino)-indan-2-carboxílico (238) en forma de un sólido de color blanco (270 mg, 95%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,56 (s, 3H), 3,62 (dd, 4H), 6,30 (s, 1H), 7,22 - 7,31 (m, 5H), 7,51 (d, 1H), 7,65 (d, 1H).
LC/MS m/z = 321,12.

EJEMPLO 239

Ácido 2-bencil-4-bromo-benzoico (239):



Etapa 1

3,5-Dibromo-3H-isobenzofuran-1-ona (B3): La mezcla de 5-bromo-3H-isobenzofuran-1-ona (A3) (51,5 g, 242 mmol) en bromobenceno (100 ml) se calienta a 158°C. A la mezcla se le añade gota a gota bromo (18,8 ml, 363 mmol) durante 2 h. La mezcla se agita durante 30 min más a 158°C. El bromobenceno se retira por destilación al vacío. El residuo se seca al vacío durante 1 hora a 120°C para producir un residuo cristalino de color negro. Recristalización: El residuo se disuelve en éter isopropílico caliente (300 ml). Se añade carbón activado (1 g) y la mezcla se filtra mientras permanece caliente. El filtrado se enfría en un baño de hielo-agua (0°C) durante una noche. El sólido se filtra, se aclara con éter isopropílico frío (2 x 10 ml) y se seca al vacío sobre KOH (KOH) para producir 3,5-dibromo-3H-isobenzofuran-1-ona (B3) (38 g, 54%, p.f.: 100°C).

Etapa 2

Ácido 4-bromo-2-formil-benzoico (C3): La mezcla de 3,5-dibromo-3H-isobenzofuran-1-ona (B3) (38 g, 130 mmol) en una solución de NaOH 10 N (28,6 ml, 286 mmol) y agua (240 ml) se calienta durante 2 h a 80°C. Se añade carbón activado (2 g) y la mezcla se calienta a reflujo durante 1 hora más. La mezcla se filtra mientras permanece caliente y se acidifica con ácido metanosulfónico 2 N (100 ml). La mezcla resultante se enfría en un baño de hielo-agua durante 1 h. El sólido se filtra, se lava con agua (4 x 25 ml) y se seca al vacío en KOH para producir ácido 4-bromo-2-formil-benzoico (C3) (26,5 g, 89%, p.f.: 202°C). Recristalización: Se disuelve ácido 4-bromo-2-formil-benzoico (C3) en EtOH caliente (220 ml) y la mezcla se enfría en un baño de hielo-agua durante 4 h. El sólido se filtra y se aclara con EtOH frío (3 x 20 ml). Después, el sólido se seca al vacío sobre KOH para producir ácido 4-bromo-2-formil-benzoico (16,8 g, 63%, p.f.: 204-205°C).

Etapa 3

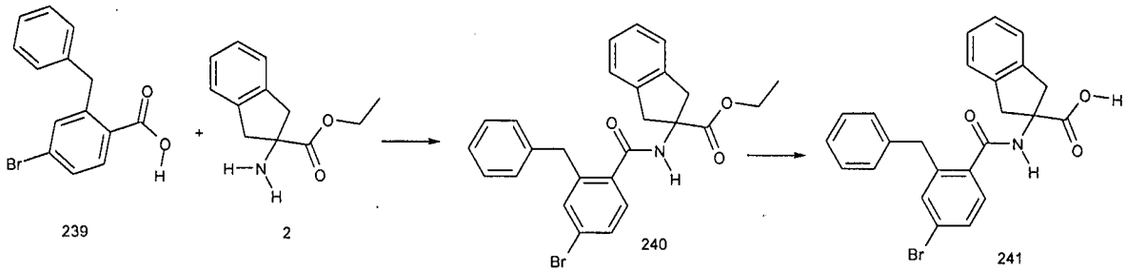
5-bromo-3-fenil-3H-isobenzofuran-1-ona (D3): Un tricol de 1 l con un condensador y un embudo de adición se purga con N_2 y se añaden limaduras de magnesio (5 g, 206 mmol) en tetrahidrofurano (80 ml). Se añade gota a gota bromobenceno (32 g, 206 mmol) en tetrahidrofurano (80 ml) durante 1¼ hora, manteniendo la temperatura de la mezcla a 30°C. La mezcla resultante se agita durante 45 min a 30°C. Se añade gota a gota ácido 4-bromo-2-formil-benzoico (C3) (18,9 g, 83 mmol) en tetrahidrofurano anhidro (200 ml) durante 45 min. La mezcla se agita durante 2 h a 30°C. La mezcla se enfría en un baño de hielo-agua y se añaden agua (120 ml) y una solución 5 N de HCl (80 ml). La mezcla se agita durante una noche. El THF se retira al vacío y se extrae con DCM (3 x 100 ml). Los extractos orgánicos combinados se lavan con agua (2 x 100 ml), se secan sobre Na_2SO_4, se filtran y el disolvente se retira al vacío para producir 5-bromo-3-fenil-3H-isobenzofuran-1-ona (22,5 g, 94%). Recristalización: Se disuelve 5-bromo-3-fenil-3H-isobenzofuran-1-ona en acetona caliente (250 ml) y la mezcla se enfría en un baño de hielo-agua durante una noche. El sólido resultante se filtra, se aclara con ACN frío (2 x 15 ml) y después se seca al vacío sobre KOH para producir 5-bromo-3-fenil-3H-isobenzofuran-1-ona (D3) (14,4 g, 61%, p.f.: 189°C).

Etapa 4

Ácido 2-bencil-4-bromo-benzoico (239): La mezcla de 5-bromo-3-fenil-3H-isobenzofuran-1-ona (D3) (14,4 g, 50 mmol), yodo (9 g, 70 mmol), fósforo rojo amorfo (7,8 g, 250 mmol), ácido acético (125 ml) y agua destilada (15 ml) se recogen en este orden en un matraz de 3

bocas con un agitador mecánico y un condensador. Después de agitar durante una noche a 50°C (90% de producto y 10% de material de partida), la reacción se interrumpe por adición a agua (500 ml), se añade éter (200 ml) y el fósforo se retira por filtración. La capa acuosa se extrae con éter (3 x 100 ml) y las capas orgánicas combinadas se lavan con una solución de bisulfito sódico (100 ml) y agua (2 x 100 ml). La fase orgánica se extrae usando una solución acuosa 1 N de NaOH (4 x 100 ml), se lava de nuevo con agua (4 x 100 ml), se seca sobre Na_2SO_4 y se evapora para conseguir la fracción neutra (2 g, p.f. 180°C). La fase básica se acidifica con HCl 5 N (150 ml) y se extrae con DCM (4 x 100 ml). Los extractos combinados se lavan con agua (3 x 100 ml), se secan sobre **Na_2SO_4** y se evaporan para conseguir el producto (12 g, p.f. 137°C). Se recristaliza adicionalmente en ACN en ebullición (50 ml) para producir ácido 2-bencil-4-bromo-benzoico (239) (10 g, 83%, p.f. 145°C).

EJEMPLO 240



<u>Éster etílico del ácido 2-(2-bencil-4-bromo-benzoilamino)-indan-2-carboxílico (240):</u>

Se recogen éster etílico del ácido 2-amino-indan-2-carboxílico (2) (250 mg, 1,2 mmol), ácido 2-bencil-4-bromo-benzoico (239) (354 mg, 1,2 mmol) y HATU (555 mg, 1,46 mmol) en un vial, se evacúa y se carga de nuevo con nitrógeno. Se añade DMF anhidra (2 ml) y se inicia la agitación. Después de unos min, se añade DIPEA (0,302 ml, 1,82 mmol) y la mezcla se agita a TA durante una noche. El análisis por tlc de la mezcla de reacción (sílice, EtOAc al 50%/heptanos) indica el consumo completo de la amina de partida. Se añade agua (10 ml), se extrae con EtOAc (3 x 5 ml), se seca sobre Na_2SO_4, se concentra y el producto en bruto se cromatografía sobre una columna de 25 g de gel de sílice usando EtOAc al 20-50% en heptano como gradiente para producir éster etílico del ácido 2-(2-bencil-4-bromo-benzoilamino)-indan-2-carboxílico (495 mg, 86%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,26 (t, 3H), 3,35 (dd, 4H), 4,14 (s, 3H), 4,24 (c, 2H), 6,12 (s, 1H), 7,05 - 7,39 (m, 12H).

LC/MS m/z = 478,13.

EJEMPLO 241

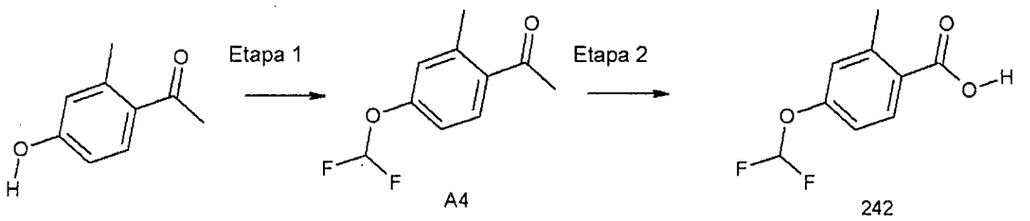
Ácido 2-(2-bencil-4-bromo-benzoilamino)-indan-2-carboxílico (241):

La mezcla de éster etílico del ácido 2-(2-bencil-4-bromo-benzoilamino)-indan-2-carboxílico (240) (339 mg, 0,71 mmol), KOH (solución acuosa al 50%, 1,58 g, 14,14 mmol), EtOH (10 ml) y agua (1 ml) se agita en un vial de 20 ml a 50°C durante 30 min. Después de la concentración al vacío, el residuo se disuelve en agua (5 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. La filtración produce ácido 2-(2-bencil-4-bromo-benzoilamino)-indan-2-carboxílico (241) en forma de un sólido de color blanco (310 mg, 97%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 3,37 (dd, 4H), 4,10 (s, 2H), 6,23 (s, 1H), 7,01 - 7,38 (m, 12H).
LC/MS m/z = 450,06,

EJEMPLO 242

Ácido 4-difluorometoxi-2-metil-benzoico (242):



Etapa 1

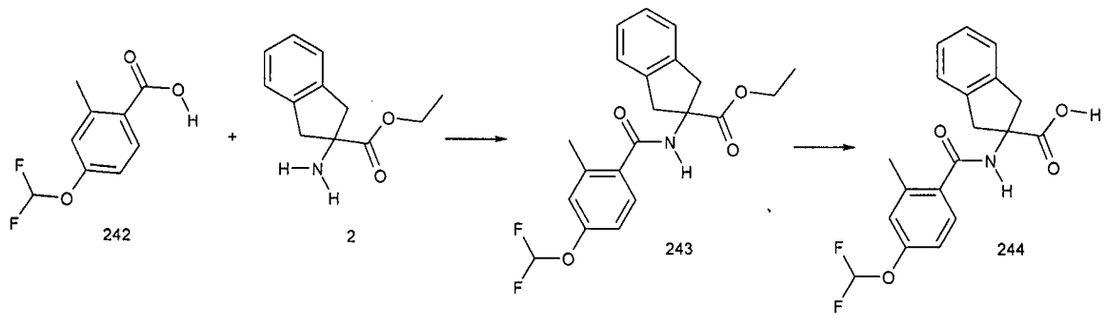
1-(4-Difluorometoxi-2-metil-fenil)-etanona (A4): A una suspensión agitada de 1-(4-hidroxi-2-metil-fenil)-etanona (15 g, 100 mmol) en dioxano (30 ml) se le añade agua (25 ml) seguido de la adición de NaOH (20 g, 500 mmol). La reacción se calienta a 65°C y se pasa clorodifluorometano gaseoso (30 g, 150 mmol) usando un tubo de vidrio sumergido bajo el nivel de la solución durante 75 minutos. Se agita durante 30 min más y se deja a TA durante el fin de semana. Después de la transferencia a un embudo de decantación, se añaden agua (100 ml) y éter (40 ml). Se deposita un material semi-gelatinoso en el fondo de la capa acuosa después de cierto tiempo. La capa acuosa del fondo se retira por drenado y se extrae con éter (2 x 40 ml). Las capas de éter combinadas se lavan con agua (5 x 25 ml), se secan sobre

K_2SO_4 sólido, se evaporan y se destilan (0,04 mm Hg, 61-64°C) para producir 1-(4-difluorometoxi-2-metil-fenil)-etanona (A4) (16,2 g, 81%). R_f en tlc de 0,60 con éter.

Etapa 2

Ácido 4-difluorometoxi-2-metil-benzoico (242): Una solución agitada de hipoclorito sódico (acuoso al 5,25%, 204 ml, 143 mmol) y KOH acuoso 2 N (22 ml, 44 mmol) se calienta a 50°C y se añade 1-(4-difluorometoxi-2-metil-fenil)-etanona (A4) (5,8 g, 29 mmol). Después de mantener la temperatura a 50-70°C durante 3 h y de mantenerla a TA durante una noche, la reacción se calienta de nuevo a 50°C y se añade en 3 porciones metabisulfito sódico (4,5 g). Después, la reacción se acidifica con HCl 12 N y se agita bien. El sólido de color blanco precipitado se retira por filtración, se aclara con un poco de agua y se seca al aire para producir ácido 4-difluorometoxi-2-metil-benzoico (242) (5,4 g, 92%). El producto se recristaliza en una mezcla 1:1 de ACN y agua. p.f.: 117-119°C. Análisis elemental: Actual C (53,23), H (3,88), F (18,66) Teórico C (53,47), H (3,99), F (18,80).

EJEMPLO 243



Éster etílico del ácido 2-(4-difluorometoxi-2-metil-benzoilamino)-indan-2-carboxílico (243):

Se recogen éster etílico del ácido 2-amino-indan-2-carboxílico (2) (250 mg, 1,2 mmol), ácido 4-difluorometoxi-2-metil-benzoico (242) (246 mg, 1,2 mmol) y HATU (555 mg, 1,46 mmol) en un vial, se evacúa y se carga de nuevo con nitrógeno. Se añade DMF anhidra (2 ml) y se inicia la agitación. Después de unos min, se añade DIPEA (0,302 ml, 1,82 mmol) y la mezcla se agita a TA durante una noche. El análisis por tlc de la mezcla de reacción (sílice, EtOAc al 50%/heptanos) indica el consumo completo de la amina de partida. Se añade agua (10 ml), se extrae con EtOAc (3 x 5 ml), se seca sobre Na_2SO_4, se concentra y el producto en bruto se cromatografía sobre una columna de 25 g de gel de sílice usando EtOAc al 20-50% en

heptano como gradiente para producir éster etílico del ácido 2-(4-difluorometoxi-2-metil-benzoilamino)-indan-2-carboxílico (415 mg, 89%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 2,42 (s, 3H), 3,56 (dd, 4H), 4,27 (c, 2H), 6,21 (s, 1H), 6,91 (m, 2H), 7,22 (m, 4H), 7,33 (d, 1H).
LC/MS m/z = 390,16.

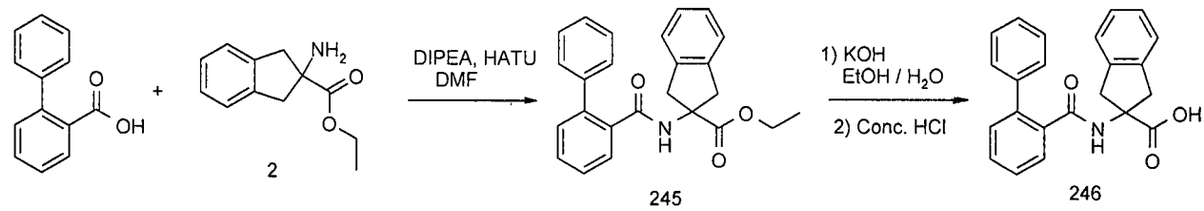
EJEMPLO 244

Ácido 2-(4-difluorometoxi-2-metil-benzoilamino)-indan-2-carboxílico (244):

La mezcla de éster etílico del ácido 2-(4-difluorometoxi-2-metil-benzoilamino)-indan-2-carboxílico (243) (301 mg, 0,77 mmol), KOH (solución acuosa al 50%, 1,73 g, 15,5 mmol), EtOH (10 ml) y agua (1 ml) se agita en un vial de 20 ml a 50°C durante 30 min. Después de la concentración al vacío, el residuo se disuelve en agua (10 ml) y se acidifica con HCl conc. hasta que no surge más cantidad de precipitado del agua. La filtración produce ácido 2-(4-difluorometoxi-2-metil-benzoilamino)-indan-2-carboxílico (244) en forma de un sólido de color blanco (245 mg, 88%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,37 (s, 3H), 3,62 (dd, 4H), 6,23 (s, 1H), 6,92 (m, 2H), 7,24 (m, 5H).
LC/MS m/z = 362,10.

EJEMPLO 245



Éster etílico del ácido 2-[(bifenil-2-carbonil)-amino]-indan-2-carboxílico (245):

A una solución de ácido bifenil-2-carboxílico (289 mg, 1,46 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (300 mg, 1,46 mmol) y HATU (666 mg, 1,75 mmol) en DMF anhidra (1,8 ml) se le añade DIPEA (381 µl, 2,19 mmol). La solución resultante se agita a TA durante una noche. La reacción se vierte en agua (10 ml) y se extrae con EtOAc (3 x 5 ml).

Las capas orgánicas combinadas se concentran al vacío y el residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0-30% en heptano) para dar un producto puro (245) en forma de un sólido de color blanquecino (525 mg, 93%).

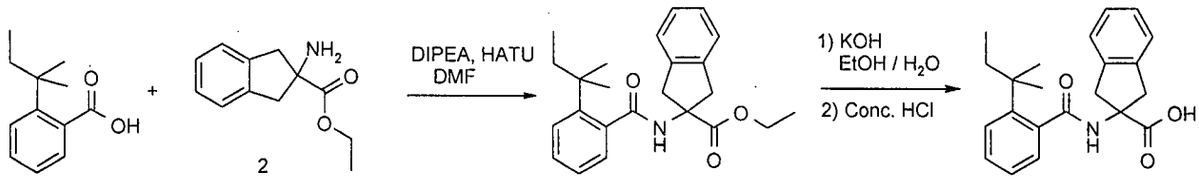
EJEMPLO 246

Ácido 2-[(bifenil-2-carbonil)-amino]-indan-2-carboxílico (246):

Se disuelve éster etílico del ácido 2-[(bifenil-2-carbonil)-amino]-indan-2-carboxílico (525 mg, 1,36 mmol) en EtOH (15 ml) y se añaden KOH sólido (1,42 g, 24,7 mmol) y agua (1,5 ml). La mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en agua (10 ml) y se acidifica con HCl concentrado hasta que no precipita más cantidad de sólido de color blanco. El sólido se recoge por filtración al vacío para dar el producto (246) en forma de un sólido de color blanco (453 mg, 93%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 2,92 (d, 2H), 3,63 (d, 2H), 5,84 (s, 1H), 7,08-7,12 (m, 2H), 7,15-7,19 (m, 2H), 7,24 (s, 4H), 7,30 (dd, 2H), 7,40-7,54 (m, 2H), 7,85 (dd, 1H)
LC/MS (ES+) m/z = 358,14

EJEMPLO 247



Éster etílico del ácido 2-[2-(1,1-dimetil-propil)-benzoilamino]-indan-2-carboxílico (247):

A una solución de ácido 2-(1,1-dimetil-propil)-benzoico (140 mg, 0,73 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (150 mg, 0,73 mmol) y HATU (333 mg, 0,87 mmol) en DMF anhidra (1 ml) se le añade DIPEA (190 µl, 1,1 mmol). La solución resultante se agita a TA durante una noche. Después, se vierte agua (10 ml) en la mezcla de reacción y después la mezcla de reacción se extrae con EtOAc (3 x 5 ml). Las capas orgánicas combinadas se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0-30% en heptano) para dar un producto (247) en forma de un aceite de color amarillo (220 mg, 89%).

EJEMPLO 248

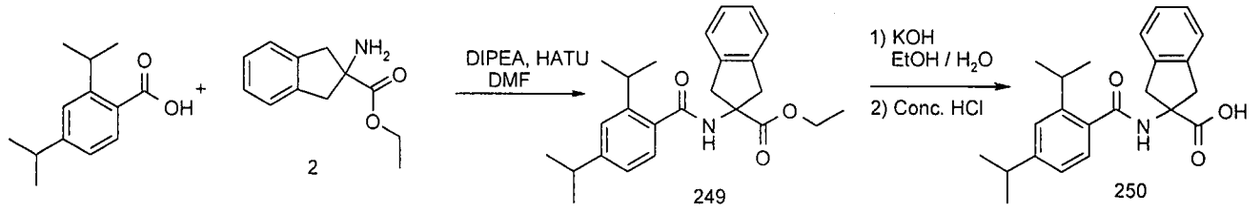
Ácido 2-[2-(1,1-dimetil-propil)-benzoilamino]-indan-2-carboxílico (248):

Se disuelve éster etílico del ácido 2-[2-(1,1-dimetil-propil)-benzoilamino]-indan-2-carboxílico (220 mg, 0,58 mmol) en EtOH (8 ml) y se añaden KOH sólido (600 mg, 10 mmol) y agua (0,8 ml). La mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en agua (10 ml) y se acidifica con HCl concentrado hasta que no precipita más cantidad de sólido de color blanco. El sólido se recoge por filtración al vacío para dar el producto (248) en forma de un sólido de color blanco (158 mg, 78%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 0,53 (t, 3H), 1,29 (s, 6H), 1,66-1,73 (c, 2H), 3,44 (d, 2H), 3,80 (d, 2H), 6,14 (s, 1H), 7,13-7,14 (m, 1H), 7,15 (d, 1H), 7,22 (d, 4H), 7,32 (d, 1H), 7,34 (t, 1H), 7,37 (dd, 1H)

LC/MS (ES+) m/z = 352,17

EJEMPLO 249



Éster de éter del ácido 2-(2,4-diisopropil-benzoilamino)-indan-2-carboxílico (249):

A una solución de ácido 2,4-diisopropil-benzoico (150 mg, 0,73 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (150 mg, 0,73 mmol) y HATU (333 mg, 0,87 mmol) en DMF anhidra (1 ml) se le añade DIPEA (190 µl, 1,10 mmol). La solución resultante se agita a TA durante una noche. La reacción se vierte en agua (10 ml) y se extrae con EtOAc (3 x 5 ml). Las capas orgánicas combinadas se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0-30% en heptano) para dar un producto puro (245) en forma de un sólido de color blanquecino (211 mg, 73%).

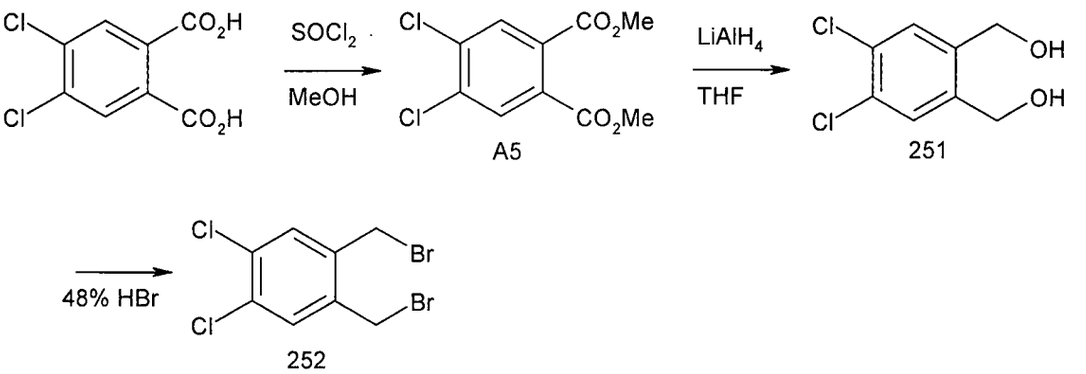
EJEMPLO 250

Ácido 2-(2,4-diisopropil-benzoilamino)-indan-2-carboxílico (250):

Se disuelve éster etílico del ácido 2-(2,4-diisopropil-benzoilamino)-indan-2-carboxílico (211 mg, 0,54 mmol) en EtOH (8 ml) y se añaden KOH sólido (823 mg, 14 mmol) y agua (0,8 ml). La mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en agua (10 ml) y se acidifica con HCl concentrado hasta que no precipita más cantidad de sólido de color blanco. El sólido se recoge por filtración al vacío para dar el producto (250) en forma de un sólido de color blanco (188 mg, 95%).

^{1}H RMN ($CDCl_3$, 300 MHz): 1,12 (d, 6H), 1,21 (d, 6H), 2,83-2,92 (m, 1H), 3,10-3,19 (m, 1H), 3,41 (d, 2H), 3,82 (d, 2H), 6,18 (s, 1H), 7,00-7,10 (m, 2H), 7,16 (s, 1H), 7,22-7,31 (m, 4H)
LC/MS (ES+) m/z = 366,20

EJEMPLO 251



4,5-dicloroftalato de dimetilo (A5):

Se añade gota a gota cloruro de tionilo (150 ml, 2,05 mol) durante 2 h a una solución agitada magnéticamente de ácido 4,5-dicloroftálico (110,43 g, 469,8 mmol) en MeOH (1 l) a TA. Después de agitar durante una noche, el MeOH se retira al vacío en un evaporador rotatorio. El residuo se disuelve en EtOAc (750 ml) y se extrae con agua (1 x 500 ml) y $NaHCO_3$ acuoso saturado (1 x 500 ml). La capa orgánica se separa, se seca sobre $MgSO_4$, se filtra y se concentra al vacío en un evaporador rotatorio para producir el compuesto A5 (122,8 g) en forma de un líquido de color amarillo pálido. [A. Rosowsky, C. M. Vaidya, h. Bader, J. E. Wright, B. A. Teicher, *J. Med. Chem.* 40, 286-299 (1997); E. J. Hennessy, S. L. Buchwald, *J. Org. Chem.*, 70, 7371-7375 (2005)]

^{1}H RMN ($CDCl_3$, 300 MHz): δ 3,92 (s, 3H), 7,82 (s, 1H)

4,5-Dicloro-1,2-bis(hidroximetil)benceno (251):

Una solución del 4,5-dicloroftalato de dimetilo A5 (98,86 g, 375,78 mmol) en tetrahidrofurano (150 ml) se añade gota a gota durante 1 h a una suspensión agitada mecánicamente de LAH (20,8 g, 548,1 mmol) en tetrahidrofurano (1,5 l). Durante la adición, la reacción se enfría en un baño de hielo-agua. Cuando se completa la adición, la reacción se agita durante una noche a TA. El exceso de LAH se descompone mediante la adición cuidadosa de agua (20 ml), NaOH acuoso al 10% (40 ml) y agua (20 ml). Los sólidos se retiran por filtración a través de una capa de celite y se lavan con tetrahidrofurano. El filtrado y el lavado combinados se concentran al vacío en un evaporador rotatorio para producir el compuesto 251 en bruto en forma de un sólido de color blanco que se purifica por cristalización en acetona (150 ml)-heptano (150 ml). Los cristales se recogen por filtración, se lavan con heptano y se secan para dar 4,5-dicloro-1,2-bis(hidroximetil)benceno (37,2 g). El filtrado y el lavado combinados producen una segunda extracción del compuesto 251 (18,8 g, 24,1%). [L. A. Levy, *Synth. Commun.*, 13, 639-648 (1983); O. Farooq, *Synthesis*, 1035-1036 (1994)]

^{1}H RMN (DMSO-d_6, 300 MHz): δ 4,49 (d, 2H), 5,32 (t, 1H), 7,57 (s, 1H)

EI-MS m/z 209, 207

Anál. calc. para $C_8H_8Cl_2O_2$: C, 46,41; H, 3,89. Encontrado: C, 46,50; H, 3,83

EJEMPLO 252

1,2-Bis-(bromometil)-4,5-diclorobenceno (252):

Una mezcla de 4,5-dicloro-1,2-bis(hidroximetil)benceno (251, 32,87 g, 158,75 mmol) y ácido bromhídrico acuoso al 48% (160 ml) se calienta a la temperatura de reflujo durante 6 h. La reacción se enfría y se extrae con éter dietílico (1 x 450 ml + 2 x 200 ml). Los extractos orgánicos combinados se lavan de nuevo con agua (1 x 200 ml) y con salmuera (1 x 200 ml). La capa orgánica se separa, se seca sobre $MgSO_4$, se filtra y se concentra al vacío en un evaporador rotatorio para producir un sólido de color amarillo claro que se disuelve en heptano-EtOAc al 0,5% con calentamiento y se pone en la parte superior de una columna de gel de sílice (7,2 cm x 23 cm) preparada en heptano-EtOAc al 0,5% y se somete a

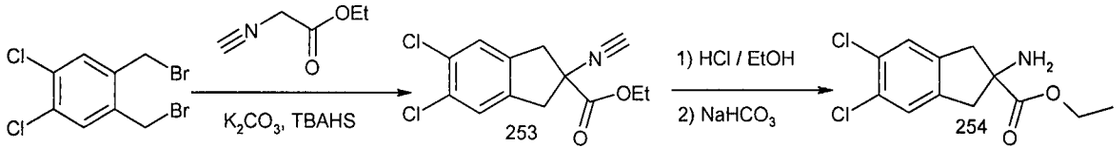
cromatografía ultrarrápida en fracciones de 500 ml y eluyendo con heptano-EtOAc al 0,5% (1,6 l) y heptano-EtOAc al 1% (4 l). Las fracciones que contienen el producto (5-14) se combinan y se concentran al vacío en un evaporador rotatorio para dar 1,2-bis-(bromometil)-4,5-diclorobenceno (252, 50,01 g) en forma de un líquido incoloro. [L. A. Levy, *Synth. Commun.*, 13, 639-648 (1983)]

^{1}H RMN ($CDCl_3$, 300 MHz): δ 4,55 (s, 2H), 7,46 (s, 1H)

EI-MS m/z 330, 332, 334, 336

Anál. calc. para $C_8H_6Br_2Cl_2$: C, 28,87; H, 1,82. Encontrado: C, 28,84; H, 1,68

EJEMPLO 253



Éster etílico del ácido 4,5-dicloro-isociano-indan-2-carboxílico (253):

A una solución de isocianoacetato de etilo (3,85 ml, 35 mmol) en ACN anhidro (300 ml) se le añaden K_2CO_3 anhidro finamente molido (29 g, 210 mmol), TBAHS (hidrogenosulfato de tetrabutilamonio, 2,34 g, 7 mmol) y 1,2-bis-(bromometil)-4,5-diclorobenceno (11,6 g, 35 mmol). La mezcla heterogénea resultante se agita a 80°C durante una noche. La mezcla de reacción se enfría a TA y se filtra para retirar las sales indeseadas. El filtrado se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (200 g de gel de sílice; gradiente de elución: EtOAc al 0-25% en heptano) para dar un producto puro en forma de un polvo de color blanco (6,63 g, 66%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,35 (t, 3H), 3,47 (d, 2H), 3,71 (d, 2H), 4,32 (c, 2H), 7,46 (s, 2H)

LC/MS (ES+) m/z = 286,14

EJEMPLO 254

Éster etílico del ácido 2-amino-4,5-dicloro-indan-2-carboxílico (254):

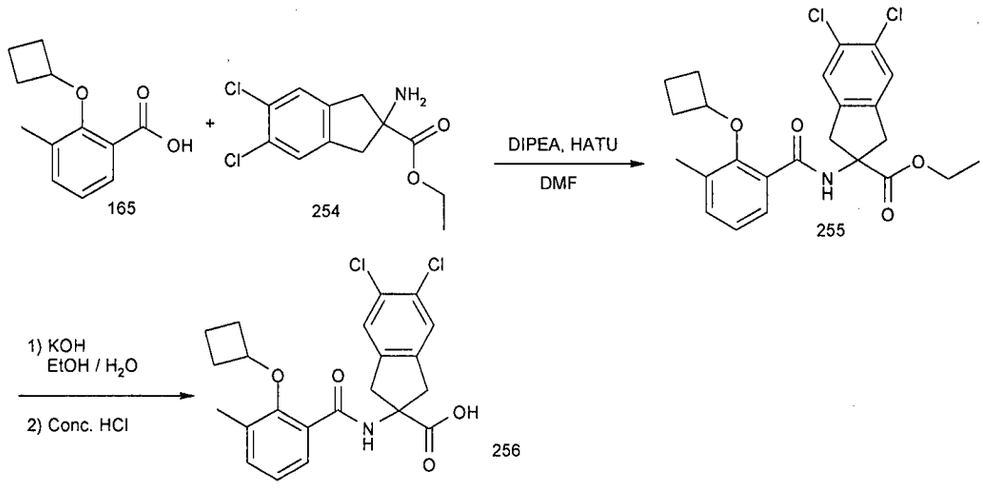
A una solución de éster etílico del ácido 4,5-dicloro-isociano-indan-2-carboxílico (253) (6,63 g, 23,2 mmol) en EtOH absoluto (200 ml) se le añade gota a gota HCl concentrado (10 ml). La

solución resultante se agita a TA durante 24 h. Después de la retirada del EtOH al vacío, la sal hidrocloruro restante se disuelve en agua (100 ml) y se extrae con éter etílico (3 x 50 ml) para retirar las impurezas orgánicas indeseadas. La capa acuosa se lleva a un valor de pH de 9 mediante la adición de una solución saturada de $NaHCO_3$ y después se extrae con EtOAc (3 x 100 ml). La capa de EtOAc combinada se lava con salmuera (100 ml). La capa orgánica se seca sobre Na_2SO_4 y se concentra al vacío para dar un producto puro en forma de un sólido de color blanco (5,2 g, 82%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 2,88 (d, 2H), 3,57 (d, 2H), 4,23 (c, 2H), 7,46 (s, 2H)

LC/MS (EZ+) m/z = 275,18

EJEMPLO 255



<u>Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4,5-dicloro-indan-2-carboxílico (255):</u>

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (225 mg, 1,1 mmol), éster etílico del ácido 2-amino-4,5-dicloro-indan-2-carboxílico (254) (360 mg, 1,31 mmol) y HATU (622 mg, 1,64 mmol) en DMF anhidra (10 ml) se le añade DIPEA (360 µl, 2,20 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío y el residuo se suspende en H_2O (50 ml) y se lava con EtOAc (3 x 50 ml). Los extractos orgánicos se combinan y se lavan sucesivamente con $NaHCO_3$ y salmuera y después la capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0%-20% en

heptano) para dar un producto puro (255) en forma de un polvo de color blanco (460 mg, 90%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,21-1,36 (m, 4H), 1,50-1,56 (m, 1H), 1,96-2,09 (m, 4H), 2,27 (s, 3H), 3,44 (t, 2H), 3,73 (dd, 2H), 4,21- 4,33 (m, 3H), 6,85-6,94 (m, 2H), 7,08 (t, 1H), 7,14-7,19 (m, 1H), 7,27 (d, 1H), 7,85 (dd, 1H), 8,37 (s, 1H)
LC/MS (ES+) m/z = 428,93

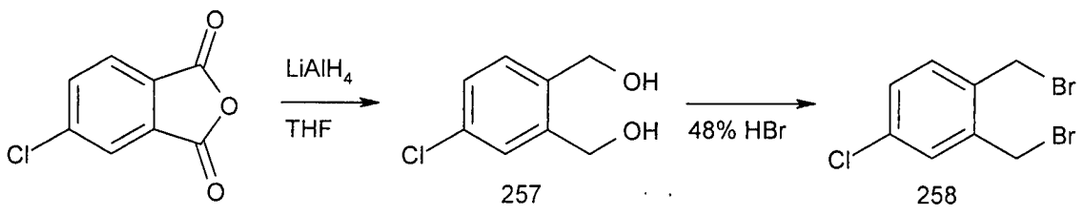
EJEMPLO 256

Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4,5-dicloro-indan-2-carboxílico (256):

Se disuelve éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4,5-dicloro-indan-2-carboxílico (255) (460 mg, 0,99 mmol) en EtOH (50 ml) y la mezcla se deja en agitación a TA. A esta solución se le añade KOH 5 M (3 ml). La mezcla de reacción se agita a TA durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl concentrado hasta alcanzar un valor de pH de 2. La mezcla resultante se lava con EtOAc (3 x 100 ml). Los extractos orgánicos se combinan y se lavan con salmuera, después se secan sobre Na_2SO_4 anhidro y se concentran al vacío. El producto deseado (256) se obtiene en forma de un sólido de color blanco (405 mg, 94%).

^{1}H RMN (d-DMSO-d_6, 300 MHz): δ 1,21-1,36 (m, 1H), 1,50 (m, 1H), 1,92-2,14 (m, 4H), 2,26 (s, 3H), 3,38 (t, 2H), 3,73 (dd, 2H), 4,29 (m, 1H), 6,86-6,95 (m, 2H), 7,11 (t, 1H), 7,15-7,20 (m, 1H), 7,29 (d, 1H), 7,83 (dd, 1H), 8,51 (s, 1H)
LC/MS (ES+) m/z = 434,32

EJEMPLO 257



4-Cloro-1,2-bis(hidroximetil)benceno (257):

Una solución de anhídrido 4-cloroftálico (24,83 g, 136,01 mmol) en tetrahidrofurano (100 ml) se añade gota a gota a una suspensión agitada mecánicamente de LAH (8,72 g, 229,78 mmol) en tetrahidrofurano (500 ml). Después de agitar durante una noche a temperatura ambiente, el exceso de LAH se descompone mediante la adición cuidadosa de agua (8,5 ml), NaOH acuoso al 10% (17 ml) y agua (8,5 ml). La reacción se diluye con tetrahidrofurano (300 ml) y los sólidos se retiran por filtración a través de una capa de celite y se lavan con tetrahidrofurano. El filtrado y el lavado combinados se concentran al vacío en un evaporador rotatorio para producir el diol 257 en forma de un líquido incoloro (22,16 g) que cristaliza después de un periodo de reposo. La cristalización se realiza en benceno. [O. Farooq, *Synthesis*, 1035-1036 (1994); R. F. Bird, E. E. Turner, *J. Chem. Soc.* 5050-5051 (1952); J. Tirouflet, *Compt. rend.*, 238, 2246-2247 (1954)]

^{1}H RMN (DMSO-d_6, 300 MHz): δ 4,48 (t, 2H), 4,52 (t, 2H), 5,15 (t, 1H), 5,24 (t, 1H), 7,27 (dd, 1H), 7,38 (s, 1H), 7,41 (t, 1H)

EJEMPLO 258

1,2-Bis(bromometil)-4-clorobenceno (258):

Una mezcla de 4-cloro-1,2-bis(hidroximetil)benceno (257, 20,57 g, 119,17 mmol) y ácido bromhídrico acuoso al 48% (140 ml) se calienta a 137°C durante 4,5 h. La reacción se enfría a TA, después se diluye con agua fría (250 ml) y se extrae con éter dietílico (1 x 400 ml + 2 x 200 ml). Los extractos orgánicos combinados se lavan con agua (1 x 200 ml) y con salmuera (1 x 200 ml), se secan sobre $MgSO_4$, se filtran y se concentran al vacío en un evaporador rotatorio para producir el dibromuro en bruto 258 en forma de un líquido de color amarillo. Este material se disuelve en heptano-EtOAc al 0,5%, se pone en la parte superior de una columna de gel de sílice (7,2 cm x 22 cm) y se somete a cromatografía ultrarrápida con fracciones de 400 ml eluyendo con heptano-EtOAc al 0,5% (1,6 l) y heptano-EtOAc al 1% (3 l). Las fracciones que contienen el producto (5-9) se combinan y se concentran al vacío en un evaporador rotatorio para producir el dibromuro 258 en forma de un líquido incoloro (34,46 g). [D. R. Lyon, F.G. Mann, G. H.. Cookson, *J. Chem. Soc.*, 662-670 (1947)]

^{1}H RMN ($CDCl_3$, 300 MHz): δ 4,58 + 4,61 (s + s, 4H), 7,28-7,32 (m, 2H), 7,36 (d, 1H)
EI-MS 298, 300

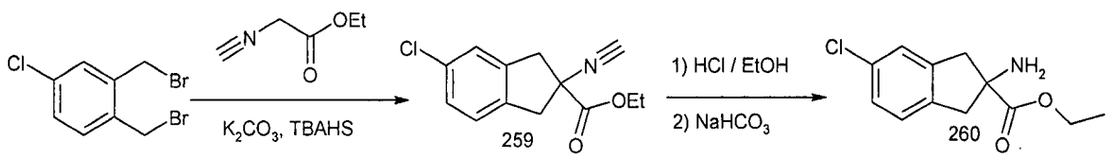
Anál. calc. para $C_8H_7Br_2Cl$: C, 32,20; H, 2,36. Encontrado: C, 32,30; H, 2,22

Ruta Alternativa:

Una mezcla agitada magnéticamente de 4-cloro-*orto*-xileno (5 g, 35,56 mmol), *N*-bromosuccinimida (12,65 g, 71,07 mmol), AIBN (0,55 g) y CCl_4 (150 ml) se calienta a la temperatura de reflujo durante 3,5 h y después se enfría a TA. Los sólidos se retiran por filtración y se lavan con CCl_4. El filtrado y el lavado combinados se concentran al vacío en un evaporador rotatorio para dar el dibromuro 10 en bruto en forma de un líquido incoloro que se disuelve en heptano-EtOAc al 1%, se pone en la parte superior de una columna de gel de sílice (7,2 cm x 18 cm) preparada en heptano-EtOAc al 1% y se somete a cromatografía ultrarrápida con fracciones de 200 ml eluyendo con heptano-EtOAc al 1%. Las fracciones que contienen el producto (7-11) se combinan y se concentran al vacío en un evaporador rotatorio para producir el compuesto impuro 258 en forma de un líquido incoloro.

^{1}H RMN ($CDCl_3$, 300 MHz): δ 4,46 (s, 0, 3H), 4,51 (s, 0,6H), 4,58 + 4,61 (s a, 4H), 7,26-7,29 (m, 2,5H), 7,36 (d, 1,2H).

EJEMPLO 259



Éster etílico del ácido 4-cloro-isociano-indan-2-carboxílico (259):

A una solución de isocianoacetato de etilo (3,85 ml, 35.0 mmol) en ACN anhidro (300 ml) se le añaden K_2CO_3 anhidro finamente molido (29 g, 210 mmol), TBAHS (hidrogenosulfato de tetrabutilamonio, 2,34 g, 7 mmol) y 1,2-bis-(bromometil)-4-clorobenceno (10,4 g, 35 mmol). La mezcla heterogénea resultante se agita a 80°C durante una noche. La mezcla de reacción se enfría a TA y se filtra para retirar las sales indeseadas. El filtrado se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (200 g de gel de sílice; gradiente de elución: EtOAc al 0-25% en heptano) para dar un producto puro en forma de un aceite incoloro (5,06 g, 58%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,35 (t, 3H), 3,47 (d, 2H), 3,71 (d, 2H), 4,32 (c, 2H), 7,28-7,32 (m, 2H), 7,36 (d, 1H)

LC/MS (ES+) m/z = 250,56

EJEMPLO 260

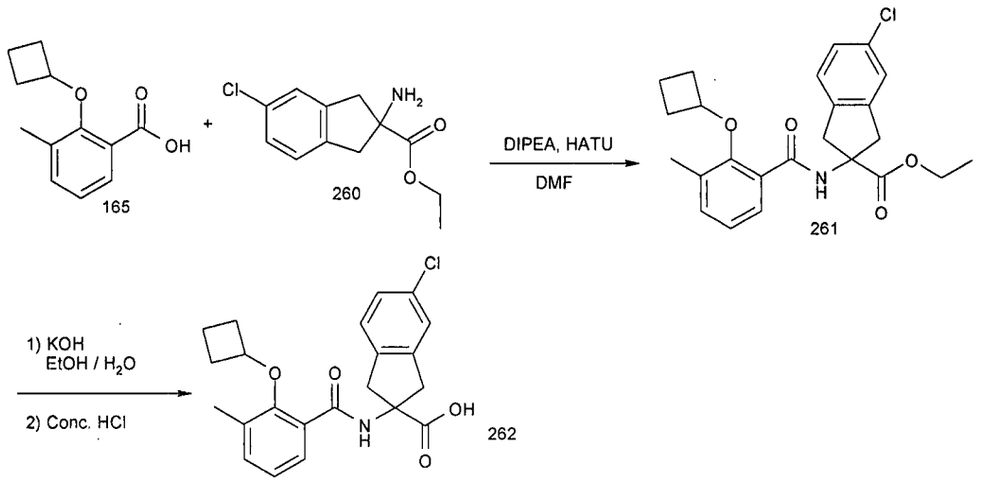
Éster etílico del ácido 2-amino-4-cloro-indan-2-carboxílico (260):

A una solución de éster etílico del ácido 4-cloro-isociano-indan-2-carboxílico (259) (5,06 g, 20,2 mmol) en EtOH absoluto (200 ml) se le añade gota a gota HCl concentrado (10 ml). La solución resultante se agita a TA durante 24 h. Después de la retirada del EtOH al vacío, la sal hidrocloruro restante se disuelve en agua (100 ml) y se extrae con éter etílico (3 x 50 ml) para retirar las impurezas orgánicas indeseadas. La capa acuosa se lleva a un valor de pH de 9 mediante la adición de una solución saturada de $NaHCO_3$ y después se extrae con EtOAc (3 x 100 ml). La capa de EtOAc combinada se lava con salmuera (100 ml). La capa orgánica se seca sobre Na_2SO_4 y se concentra al vacío para dar un producto puro en forma de un sólido de color blanco (4,2 g, 87%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 2,88 (d, 2H), 3,57 (d, 2H), 4,23 (c, 2H), 7,28-7,32 (m, 2H), 7,36 (d, 1H)

LC/MS (EZ+) m/z = 239,58

EJEMPLO 261



Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-cloro-indan-2-carboxílico (261):

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (213 mg, 1,04 mmol), éster etílico del ácido 2-amino-4-cloro-indan-2-carboxílico (260) (298 mg, 1,24 mmol) y HATU (591 mg, 1,55 mmol) en DMF anhidra (10 ml) se le añade DIPEA (345 µl, 2,07 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío y el residuo se suspende en H_2O (50 ml) y se lava con EtOAc (3 x 50 ml). Los extractos orgánicos se combinan y se lavan sucesivamente con $NaHCO_3$ y salmuera y después la capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0%-20% en heptano) para dar un producto puro (261) en forma de un polvo de color blanco (370 mg, 83%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,21-1,36 (m, 4H), 1,50-1,56 (m, 1H), 1,96-2,09 (m, 4H), 2,27 (s, 3H), 3,44 (t, 2H), 3,73 (dd, 2H), 4,21- 4,33 (m, 3H), 6,85-6,94 (m, 2H), 7,08 (t, 1H), 7,14-7,19 (m, 1H), 7,27 (d, 1H), 7,85 (dd, 1H), 8,37 (s, 1H)
LC/MS (ES+) m/z = 428,93

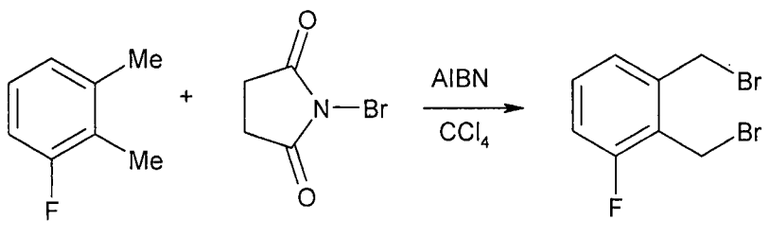
EJEMPLO 262

Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-cloro-indan-2-carboxílico (262):

Se disuelve éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-cloro-indan-2-carboxílico (261) (370 mg, 0,86 mmol) en EtOH (50 ml) y la mezcla se deja en agitación a TA. A esta solución se le añade KOH 5 M (3 ml). La mezcla de reacción se agita a TA durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl conc. hasta alcanzar un valor de pH de 2. La mezcla resultante se lava con EtOAc (3 x 100 ml). Los extractos orgánicos se combinan y se lavan con salmuera, después se secan sobre Na_2SO_4 anhidro y se concentran al vacío. El producto deseado (262) se obtiene en forma de un sólido de color blanco (320 mg, 93%).

^{1}H RMN (d-DMSO-d_6, 300 MHz): δ 1,21-1,36 (m, 1H), 1,50 (m, 1H), 1,92-2,14 (m, 4H), 2,26 (s, 3H), 3,38 (t, 2H), 3,73 (dd, 2H), 4,29 (m, 1H), 6,86-6,95 (m, 2H), 7,11 (t, 1H), 7,15-7,20 (m, 1H), 7,29 (d, 1H), 7,83 (dd, 1H), 8,51 (s, 1H)
LC/MS (ES+) m/z = 399,93

EJEMPLO 263



263

1,2-Bis(bromometil)- 3-fluorobenceno (263):

Una mezcla agitada magnéticamente de 3-fluoro-*orto*-xileno (5,05 g, 40,67 mmol), *N*-bromosuccinimida (15,23 g, 85,56 mmol), AIBN (78 mg) y CCl_4 (75 ml) se calienta a la temperatura de reflujo durante 1,75 h y después se enfría a TA. Los sólidos se retiran por filtración y se lavan con CCl_4. El filtrado y el lavado combinados se concentran al vacío en un evaporador rotatorio para dar el dibromuro 263 en bruto en forma de un líquido de color amarillo que se disuelve en heptano-EtOAc al 1%, se pone en la parte superior de una columna de gel de sílice (7,2 cm x 18 cm) preparada en heptano-EtOAc al 1% y se somete a cromatografía ultrarrápida con fracciones de 200 ml eluyendo con heptano-EtOAc al 1%. Las fracciones que contienen el producto se combinan y se concentran al vacío en un evaporador rotatorio para producir un líquido incoloro. Después de un periodo de reposo, se forman cristales en el líquido. El líquido se separa usando una pipeta. El proceso se repite una vez más. El líquido resultante es 1,2 bis(bromometil)-3-fluorobenceno puro. [J. E. Rice, A. Czech, N, Hussain, E. J. La Voie, *J. Org. Chem.*, 53, 1775-1779 (1988); R. A. Aitken, P. K.g. Hodgson, M. J. Morrison, A. O. Oyewale, *J. Chem. Soc. (Perkin 1)*, 402-415 (2002)]

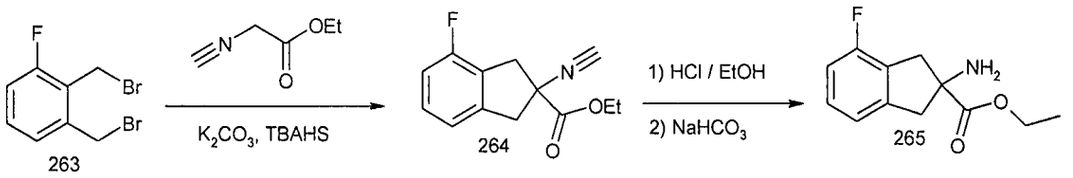
^{1}H RMN ($CDCl_3$, 300 MHz): δ 4,63 (s, 3H), 4,70 (s, 3H), 7,05 (ddd, 1H), 7,17 (d, 1H), 7,29 (ddd, 1H)

F RMN ($CDCl_3$, 300 MHz): δ 115,26 (d)

LC-MS 3,23 (sin ion parental)

Anál. calc. para $C_8H_7Br_2F$: C, 34,08; H, 2,50; F, 6,74. Encontrado: C, 34,11; H, 2,28; F, 6,88

EJEMPLO 264



Éster etílico del ácido 3-fluoro-isociano-indan-2-carboxílico (264):

A una solución de isocianoacetato de etilo (3,85 ml, 35,0 mmol) en ACN anhidro (300 ml) se le añaden K_2CO_3 anhidro finamente molido (K_2SO_4, 29,0 g, 210 mmol), TBAHS (hidrogenosulfato de tetrabutilamonio, 2,34 g, 7,0 mmol) y 1,2-bis(bromometil)-3-fluorobenceno (9,87 g, 35 mmol). La mezcla heterogénea resultante se agita a 80°C durante una noche. La mezcla de reacción se enfría a TA y se filtra para retirar las sales indeseadas. El filtrado se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (200 g de gel de sílice; gradiente de elución: EtOAc al 0-25% en heptano) para dar un producto puro en forma de un aceite incoloro (4,5 g, 55%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,35 (t, 3H), 3,47 (d, 2H), 3,71 (d, 2H), 4,32 (c, 2H), 7,05 (ddd, 1H), 7,17 (d, 1H), 7,29 (ddd, 1H)

LC/MS (ES+) m/z = 234,26

EJEMPLO 265

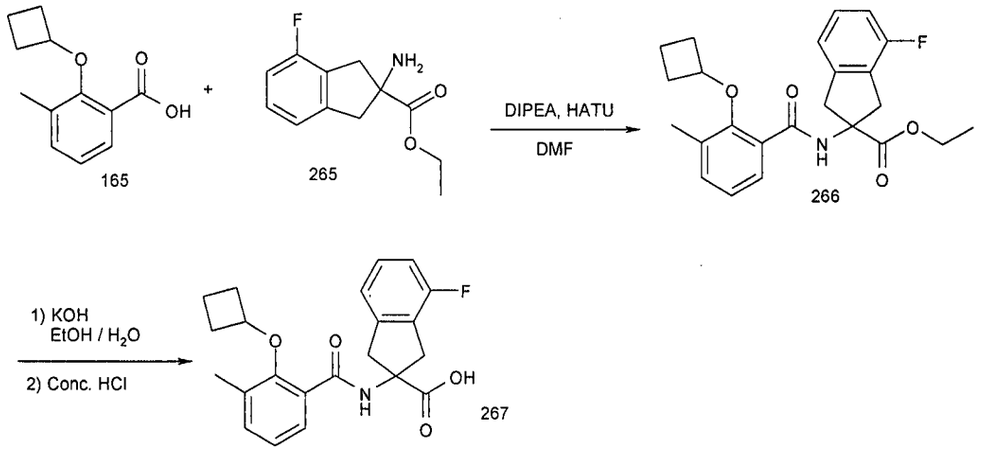
Éster etílico del ácido 2-amino-3-fluoro-indan-2-carboxílico (265):

A una solución de éster etílico del ácido 2-isociano-indan-2-carboxílico (264) (4,5 g, 19,3 mmol) en EtOH absoluto (200 ml) se le añade gota a gota HCl concentrado (10 ml). La solución resultante se agita a TA durante 24 h. Después de la retirada del EtOH al vacío, la sal hidrocloruro restante se disuelve en agua (100 ml) y se extrae con éter etílico (3 x 50 ml) para retirar las impurezas orgánicas indeseadas. La capa acuosa se lleva a un valor de pH de 9 mediante la adición de una solución saturada de $NaHCO_3$ y después se extrae con EtOAc (3 x 100 ml). La capa de EtOAc combinada se lava con salmuera (100 ml). La capa orgánica se seca sobre Na_2SO_4 y se concentra al vacío para dar un producto puro en forma de un sólido de color blanco (2,3 g, 53%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,29 (t, 3H), 2,88 (d, 2H), 3,57 (d, 2H), 4,23 (c, 2H), 7,05 (ddd, 1H), 7,17 (d, 1H), 7,29 (ddd, 1H)

LC/MS (EZ+) m/z = 223,08

EJEMPLO 266



<u>Éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4-fluoro-indan-2-carboxílico (266):</u>

A una solución de ácido 2-ciclobutoxi-3-metil-benzoico (127 mg, 0,61 mmol), éster etílico del ácido 2-amino-3-fluoro-indan-2-carboxílico (265) (165 mg, 0,74 mmol) y HATU (352 mg, 0,93 mmol) en DMF anhidra (10 ml) se le añade DIPEA (204 µl, 1,23 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío y el residuo se suspende en H_2O (50 ml) y se lava con EtOAc (3 x 50 ml). Los extractos orgánicos se combinan y se lavan sucesivamente con $NaHCO_3$ y salmuera y después la capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0%-20% en heptano) para dar un producto puro (266) en forma de un aceite incoloro (210 mg, 84%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,21-1,36 (m, 4H), 1,50-1,56 (m, 1H), 1,96-2,09 (m, 4H), 2,27 (s, 3H), 3,44 (t, 2H), 3,73 (dd, 2H), 4,21- 4,33 (m, 3H), 6,85-6,94 (m, 2H), 7,08 (t, 1H), 7,14-7,19 (m, 1H), 7,27 (d, 1H), 7,85 (dd, 1H), 8,37 (s, 1H)

LC/MS (ES+) m/z = 412,19

EJEMPLO 267

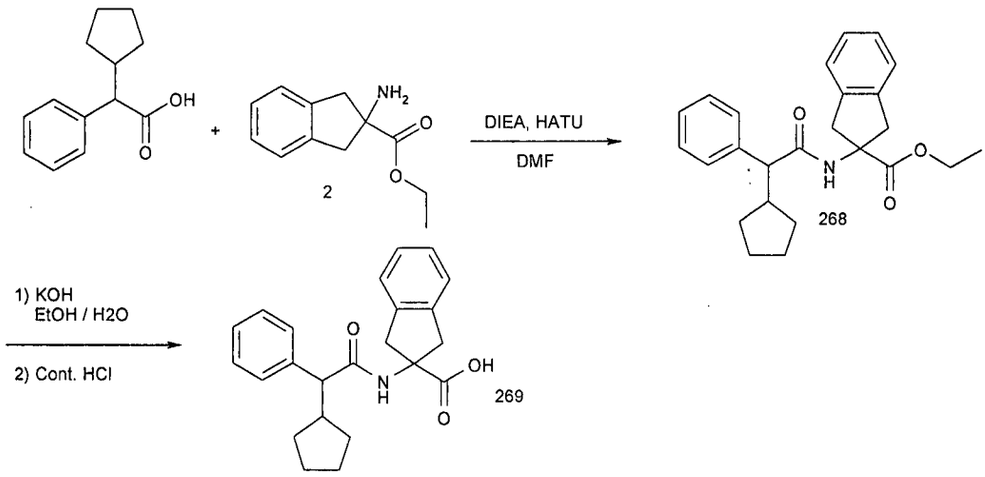
<u>Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4-fluoro-indan-2-carboxílico (267):</u>

Se disuelve éster etílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4-fluoro-indan-2-carboxílico (7) (210 mg, 0,51 mmol) en EtOH (50 ml) y la mezcla se deja en agitación a TA.

A esta solución se le añade KOH 5 M (3 ml). La mezcla de reacción se agita a TA durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se acidifica con HCl concentrado hasta alcanzar un valor de pH de 2. La mezcla resultante se lava con EtOAc (3 x 100 ml). Los extractos orgánicos se combinan y se lavan con salmuera, después se secan sobre Na_2SO_4 anhidro y se concentran al vacío. El producto deseado (267) se obtiene en forma de un sólido de color blanco (168 mg, 86%).

^{1}H RMN (d-DMSO-d_6, 300 MHz): δ 1,21-1,36 (m, 1H), 1,50 (m, 1H), 1,92-2,14 (m, 4H), 2,26 (s, 3H), 3,38 (t, 2H), 3,73 (dd, 2H), 4,29 (m, 1H), 6,86-6,95 (m, 2H), 7,11 (t, 1H), 7,15-7,20 (m, 1H), 7,29 (d, 1H), 7,83 (dd, 1H), 8,51 (s, 1H)
LC/MS (ES+) m/z = 384,15

EJEMPLO 268



<u>Éster etílico del ácido 2-(2-ciclopentil-2-fenil-acetilamino)-indan-2-carboxílico (268):</u>

A una solución de ácido α-fenilciclopenteacético (2,04 g, 10 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (2,05 g, 10 mmol) y HATU (7,60 g, 20 mmol) en DMF anhidra (50 ml) se le añade DIPEA (3,30 ml, 20 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo se disuelve en EtOAc (100 ml) y se lava con $NaHCO_3$ saturado (1 x 100 ml), agua (1 x 100 ml) y salmuera (1 x 100 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: EtOAc al 0%-20% en heptano) para dar un producto puro (268) en forma de un sólido (3,16 g, 82%).

^{1}H RMN (d-DMSO-d_6, 300 MHz): δ 0,91 (m, 1H), 1,23 (m, 2H), 1,29 (t, 3H), 1,35-1,64 (m, 4H), 1,65-1,81 (m, 1H), 2,34-2,49 (m, 1H), 2,78 (d, 2H), 2,89-3,03 (d, 1H), 3,13-3,23 (m, 2H), 3,42-3,52 (m, 2H), 7,1-7,35 (m, 9H)

LC/MS (ES+) m/z = 392,19

EJEMPLO 269

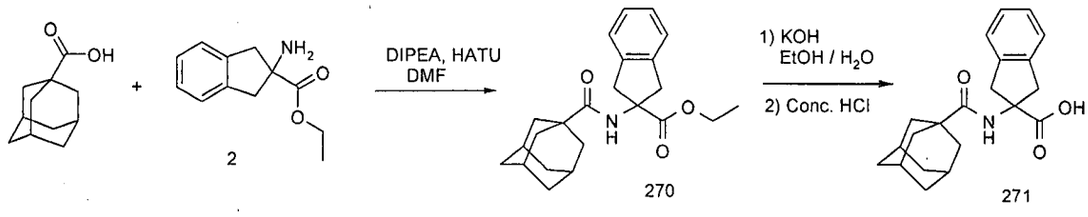
Ácido 2-(2-ciclopentil-2-fenil-acetilamino)-indan-2-carboxílico (269):

Se disuelve éster etílico del ácido 2-(2-ciclopentil-2-fenil-acetilamino)-indan-2-carboxílico (268) (1 g, 2,56 mmol) en EtOH (50 ml) y la mezcla se deja en agitación a TA. A esta solución se le añade KOH 5 M (3 ml). La mezcla de reacción se agita a TA durante una noche. Después de la concentración al vacío, el residuo se disuelve en agua (20 ml) y se lava con EtOAc (20 ml). Las fases se separan y la fase acuosa se acidifica con HCl concentrado hasta alcanzar un valor de pH de 2. El precipitado sólido se recoge por filtración y se seca al vacío. El producto deseado (269) se obtiene en forma de un sólido de color blanco (710 mg, 71%).

^{1}H RMN (d-DMSO-d_6, 300 MHz): δ 0,91 (m, 1H), 1,23 (m, 2H), 1,35-1,64 (m, 4H), 1,65-1,81 (m, 1H), 2,34-2,49 (m, 1H), 2,89-3,03 (d, 1H), 3,13-3,23 (m, 2H), 3,42-3,52 (m, 2H), 7,1-7,35 (m, 9H), 8,57 (s, 1H)

LC/MS (ES+) m/z = 364,46

EJEMPLO 270



Éster de éter del ácido 2-[(adamantano-1-carbonil)-amino]-indan-2-carboxílico (270):

A una solución de ácido adamantano-1-carboxílico (131 mg, 0,73 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (150 mg, 0,73 mmol) y HATU (333 mg, 0,87 mmol) en DMF anhidra (1 ml) se le añade DIPEA (190 µl, 1,1 mmol). La solución resultante se agita a TA durante una noche. La reacción se vierte en agua (10 ml) y se extrae con EtOAc (3 x 5 ml). Las capas orgánicas combinadas se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al

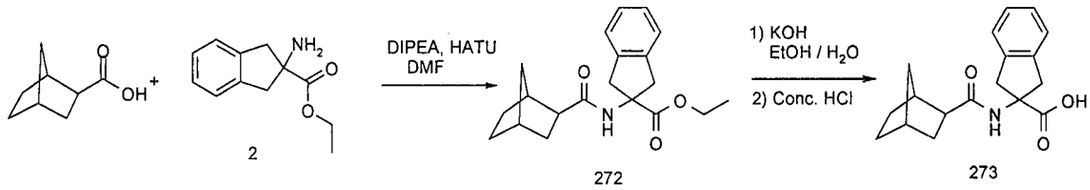
0-30% en heptano) para dar el producto (270) en forma de un sólido de color blanco (261 mg, 97%).

Ácido 2-[(adamantano-1-carbonil)-amino]-indan-2-carboxílico (271):

Se disuelve éster de éter del ácido 2-[(adamantano-1-carbonil)-amino]-indan-2-carboxílico (261 mg, 0,71 mmol) en EtOH (8 ml) y se añaden KOH sólido (823 mg, 14 mmol) y agua (0,8 ml). La mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en agua (10 ml) y se acidifica con HCl concentrado hasta que no precipita más cantidad de sólido de color blanco. El sólido se recoge por filtración al vacío para dar el producto (271) en forma de un sólido de color blanco (159 mg, 66%).

^{1}H RMN ($CDCl_3$, 300 MHz): 1,62-1,76 (c, 6H), 1,76 (d, 6H), 2,02 (s, 3H), 3,25 (d, 2H), 3,79 (d, 2H), 6,04 (s, 1H), 7,15 (d, 1H), 7,21 (s, 4H)
LC/MS (ES+) m/z = 340,18

EJEMPLO 272



Éster etílico del ácido 2-[(biciclo[2.2.1]heptano-2-carbonil)-amino]-indan-2-carboxílico (272):

A una solución de ácido biciclo[2.2.1]heptano-2-carboxílico (102 mg, 0,73 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (150 mg, 0,73 mmol) y HATU (333 mg, 0,87 mmol) en DMF anhidra (1 ml) se le añade DIPEA (190 µl, 1,10 mmol). La solución resultante se agita a TA durante una noche. Se vierte agua (10 ml) en la mezcla de reacción y después se extrae con EtOAc (3 x 5 ml). Las capas orgánicas combinadas se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0-30% en heptano) para dar un producto (272) en forma de un aceite de color amarillo (148 mg, 62%).

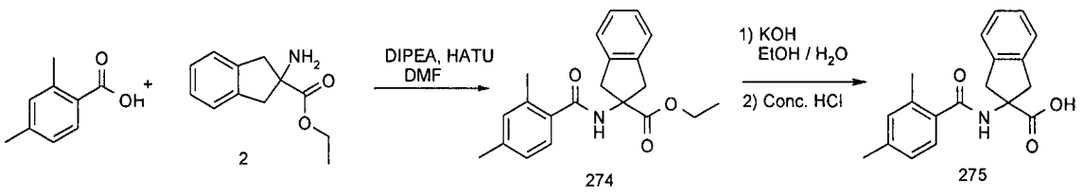
EJEMPLO 273

Ácido 2-[(biciclo[2.2.1]heptano-2-carbonil)-amino]-indan-2-carboxílico (273):

Se disuelve éster etílico del ácido 2-[(biciclo[2.2.1]heptano-2-carbonil)-amino]-indan-2-carboxílico (148 mg, 0,45 mmol) en EtOH (8 ml) y se añaden KOH sólido (600 mg, 10 mmol) y agua (0,8 ml). La mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en agua (10 ml) y se acidifica con HCl concentrado hasta que no precipita más cantidad de sólido de color blanco. El sólido se recoge por filtración al vacío para dar el producto (273) en forma de un sólido de color blanco (105 mg, 77%).

^{1}H RMN ($CDCl_3$, 300 MHz): 1,14 (d, 1H), 1,26-1,40 (m, 4H), 1,44-1,54 (c, 2H), 1,57-1,67 (m, 1H), 2,27 (d, 2H), 2,58-2,64 (m, 1H) 3,27 (t, 2H), 3,75 (d, 2H), 5,97 (s, 1H), 7,20 (s, 4H)
LC/MS (ES+) m/z = 300,13

EJEMPLO 274



Éster etílico del ácido 2-(2,4-dimetil-benzoilamino)-indan-2-carboxílico (274):

A una solución de ácido 2,4-dimetil-benzoico (219 mg, 1,46 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (300 mg, 1,46 mmol) y HATU (666 mg, 1,75 mmol) en DMF anhidra (1,8 ml) se le añade DIPEA (381 µl, 2,19 mmol). La solución resultante se agita a TA durante una noche. Se vierte agua (10 ml) en la mezcla de reacción y después se extrae con EtOAc (3 x 5 ml). Las capas orgánicas combinadas se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0-30% en heptano) para dar el producto (274) en forma de un sólido de color blanco (414 mg, 84%).

EJEMPLO 275

Ácido 2-(2,4-dimetil-benzoilamino)-indan-2-carboxílico (275):

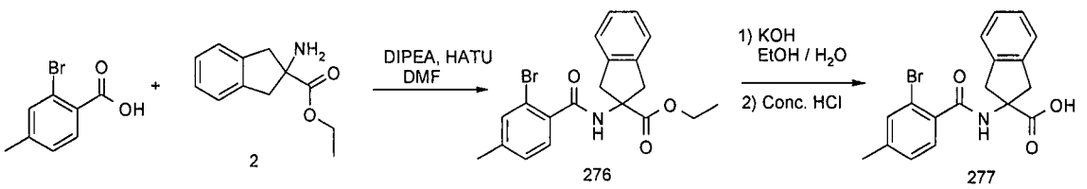
Se disuelve éster etílico del ácido 2-(2,4-dimetil-benzoilamino)-indan-2-carboxílico (414 mg, 1,23 mmol) en EtOH (15 ml) y se añaden KOH sólido (1,42 g, 24,7 mmol) y agua (1,5 ml). La

mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en agua (10 ml) y se acidifica con HCl concentrado hasta que no precipita más cantidad de sólido de color blanco. El sólido se recoge por filtración al vacío para dar el producto (275) en forma de un sólido de color blanco (350 mg, 92%).

^{1}H RMN ($CDCl_3$, 300 MHz): 2,30 (s, 6H), 3,41 (d, 2H), 3,84 (d, 2H), 6,20 (s, 1H), 6,96 (d, 1H), 7,00 (s, 1H), 7,13 (d, 1H), 7,24 (d, 4H)

LC/MS (ES+) m/z = 310,14

EJEMPLO 276



Éster etílico del ácido 2-(2-bromo-4-metil-benzoilamino)-indan-2-carboxílico (276):

A una solución de ácido 2-bromo-4-metil-benzoico (314 mg, 1,46 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (300 mg, 1,46 mmol) y HATU (666 mg, 1,75 mmol) en DMF anhidra (1,8 ml) se le añade DIPEA (381 µl, 2,19 mmol). La solución resultante se agita a TA durante una noche. La reacción se vierte en agua (10 ml) y se extrae con EtOAc (3 x 5 ml). Las capas orgánicas combinadas se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0-30% en heptano) para dar un producto puro (245) en forma de un sólido de color blanquecino (445 mg, 76%).

EJEMPLO 277

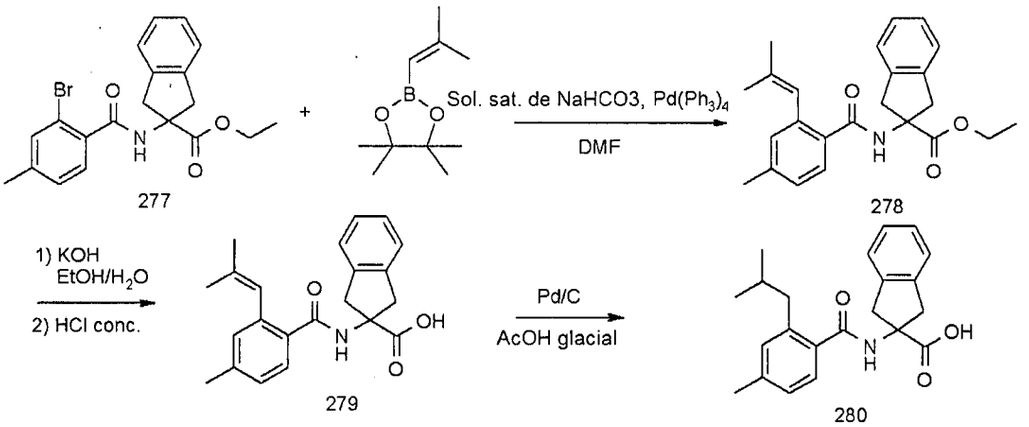
Ácido 2-(2-bromo-4-metil-benzoilamino)-indan-2-carboxílico (277):

Se disuelve éster etílico del ácido 2-(2-bromo-4-metil-benzoilamino)-indan-2-carboxílico (445 mg, 1,11 mmol) en EtOH (15 ml) y se añaden KOH sólido (1,42 g, 24,7 mmol) y agua (1,5 ml). La mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en agua (10 ml) y se acidifica con HCl conc. hasta que no precipita más cantidad de sólido de color blanco. El sólido se recoge por filtración al vacío para dar el producto (277) en forma de un sólido de color blanco (415 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz): 2,33 (s, 3H), 3,45 (d, 2H), 3,83 (d, 2H), 6,70 (s, 1H), 7,15 (d, 1H), 7,19-7,25 (m, 4H), 7,35 (s, 1H), 7,51 (d, 1H)

LC/MS (ES+) m/z = 374,04, 376,04

EJEMPLO 278



Éster etílico del ácido 2-[4-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (278):

Una mezcla de éster etílico del ácido 2-(2-bromo-4-metil-benzoilamino)-indan-2-carboxílico (880 mg, 2,2 mmol), 4,4,5,5-tetrametil-2-(2-metil-propenil)-[1,3,2]dioxaborolano (903 µl, 4,4 mmol) y una solución saturada de $NaHCO_3$ (4,4 ml) en DMF anhidra (20 ml) se desgasifica con N_2. Mientras permanece en una atmósfera de N_2, se añade tetraquis(trifenilfosfina)paladio (196 mg, al 10% en mol) y la reacción se calienta en un baño de aceite a 110°C durante 2 h. La reacción se enfría a temperatura ambiente, se vierte en agua (40 ml) y se extrae con EtOAc (2 x 30 ml). Las capas orgánicas combinadas se lavan con agua (15 ml) y salmuera (20 ml) y después se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (24 g de gel de sílice, gradiente de elución: EtOAc al 0-50% en heptano) para dar el producto (278) en forma de un aceite viscoso de color rojizo-pardo (764 mg, 92%).

EJEMPLO 279

Ácido 2-[4-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (279):

Se disuelve éster etílico del ácido 2-[4-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (764 mg, 2,02 mmol) en EtOH (25 ml) y se añaden KOH sólido (2,32 g, 40 mmol)

y agua (2,5 ml). La mezcla se agita a TA durante 30 minutos y después se concentra al vacío. El residuo se disuelve en una mezcla de agua (40 ml) y EtOAc (20 ml) y la capa orgánica se separa. La capa acuosa se ajusta a un valor de pH de aproximadamente 7 con HCl conc. y después se extrae EtOAc (2 x 15 ml). Las capas orgánicas combinadas se concentran al vacío para producir el producto (279) en forma de un sólido de color blanquecino (544 mg, 78%).

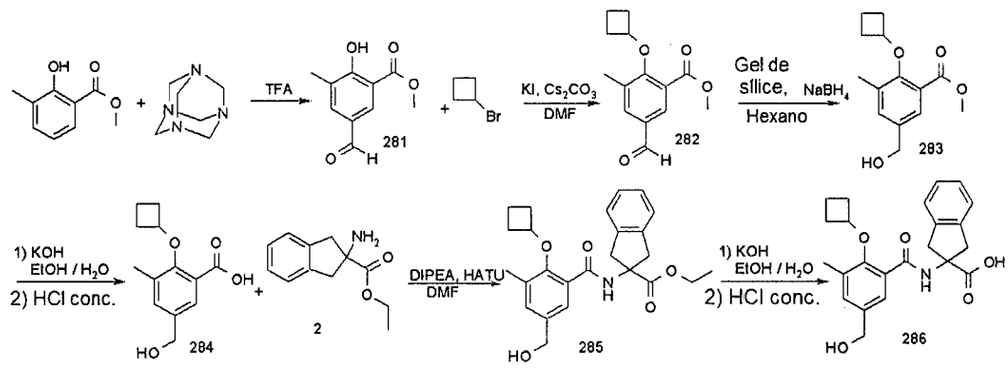
^{1}H RMN ($CDCl_3$, 300 MHz): 1,49 (s, 3H), 1,70 (s, 3H), 2,34 (s, 3H), 3,34 (d, 2H), 3,82 (d, 2H), 6,01 (s, 1H), 6,87 (s, 1H), 7,14 (d, 1H), 7,22 (s, 4H), 7,31 (d, 1H), 7,91 (d, 1H)
LC/MS (ES+) m/z = 350,17

Ácido 2-(2-isobutil-4-metil-benzoilamino)-indan-2-carboxílico (280):

A una solución de ácido 2-[4-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (510 mg, 1,45 mmol) en ácido acético glacial (65 ml) en una atmósfera de N_2 se le añade Pd/C (Pd al 10%, 138 mg, al 10% en mol). La reacción se hidrogena a 413,68 kPa (60 psi) de H_2 y 90°C durante una noche. La reacción se enfría a TA y se filtra a través de Celite, lavando la torta de filtro con agua (2 x 15 ml) y MeOH (2 x 15 ml); y el filtrado se concentra al vacío. El residuo se disuelve en agua (75 ml) y se extrae con EtOAc (2 x 30 ml). Las capas orgánicas combinadas se lavan con una solución al 5% de $NaHCO_3$ (3 x 20 ml), agua (20 ml) y salmuera (20 ml) y después se secan sobre Na_2SO_4 anhidro. La capa orgánica se concentra al vacío para dar el producto (280) en forma de un sólido de color blanco (350 mg, 69%).

^{1}H RMN ($CDCl_3$, 300 MHz): 0,78 (d, 6H), 1,72-1,81 (m, 1H), 2,30 (s, 3H), 2,55 (d, 2H), 3,38 (d, 2H), 3,77 (d, 2H), 6,30 (s, 1H), 6,94 (d, 1H), 6,95 (s, 1H), 7,16 (d, 1H), 7,20 (s, 4H)
LC/MS (ES+) m/z = 352,22

EJEMPLO 281



Éster metílico del ácido 5-formil-2-hidroxi-3-metil-benzoico (281):

A una solución de HMTA (1,3,5,7-tetraaza-triciclo[3.3.1.1^{3,7}]decano, 8,43 g, 60,2 mmol) en TFA (100 ml) se le añade éster metílico del ácido 2-hidroxi-3-metil-benzoico (5 g, 30,1 mmol) y la reacción se calienta a reflujo (78°C) durante una noche. La reacción se enfría a 50°C y se añade agua (400 ml) con agitación. La mezcla se agita a 50°C durante 2 h, después se enfría a TA y se extrae con EtOAc (2 x 200 ml). Las capas orgánicas combinadas se lavan con salmuera (75 ml), se secan sobre $MgSO_4$ anhidro y se concentran al vacío. El residuo se purifica por cromatografía en columna ultrarrápida (120 g de gel de sílice, gradiente de elución: EtOAc al 0-50% en heptano) para dar un producto puro (245) en forma de un sólido de color blanquecino (5.05 g, 86%).

EJEMPLO 282

Éster metílico del ácido 2-ciclobutoxi-5-formil-3-metil-benzoico (282):

A una mezcla de bromociclobutano (1,39 g, 10,3 mmol), yoduro potásico (43 mg, al 5% en mol) y $CsCO_3$ (3,84 g, 11,84 mmol) en DMF (18 ml) se le añade éster metílico del ácido 5-formil-2-hidroxi-3-metil-benzoico (1,0 g, 5,15 mmol). La reacción se pone en el reactor de microondas y se calienta a 110°C durante 6 h. A la reacción se le añade agua (50 ml) y la solución se extrae con EtOAc (3 x 40 ml). Las capas orgánicas combinadas se secan sobre $MgSO_4$ anhidro y se concentran al vacío para dar el producto (282) en forma de un aceite de color naranja-amarillo (1,20 g, 94%).

EJEMPLO 283

Éster metílico del ácido 2-ciclobutoxi-5-hidroximetil-3-metil-benzoico (283):

Una mezcla de éster metílico del ácido 2-ciclobutoxi-5-formil-3-metil-benzoico (676 mg, 2,7 mmol), gel de sílice (5,15 g) y $NaBH_4$ (103 mg, 2,7 mmol) en hexano (30 ml) se calienta a 40°C durante una noche. La mezcla se enfría a TA y se filtra, lavando los sólidos con EtOAc (15 ml) y éter dietílico (15 ml). El filtrado se concentra al vacío para dar el producto (283) en forma de un aceite viscoso de color amarillo (566 mg, 84%).

EJEMPLO 284

Ácido 2-ciclobutoxi-5-hidroximetil-3-metil-benzoico (284):

Se disuelve éster metílico del ácido 2-ciclobutoxi-5-hidroximetil-3-metil-benzoico (410 mg, 1,64 mmol) en EtOH (15 ml) y se añaden KOH sólido (1,90 g, 32,8 mmol) y agua (1,5 ml). La mezcla se agita a TA durante 1 h y después se concentra al vacío. El residuo se disuelve en agua (10 ml), se acidifica con HCl conc. y después se extrae con EtOAc (3 x 10 ml). Las capas orgánicas combinadas se secan sobre $MgSO_4$ anhidro y se concentran al vacío para dar el producto (284) en forma de un aceite viscoso de color amarillo (387 mg, 100%).

EJEMPLO 285

Éster etílico del ácido 2-(2-ciclobutoxi-5-hidroximetil-3-metil-benzoilamino)-indan-2-carboxílico (285):

A una solución de ácido 2-ciclobutoxi-5-hidroximetil-3-metil-benzoico (410 mg, 1,7 mmol), éster etílico del ácido 2-amino-indan-2-carboxílico (425 mg, 1,7 mmol) y HATU (760 mg, 2 mmol) en DMF anhidra (5 ml) se le añade DIPEA (435 µl, 2,5 mmol). La solución resultante se agita a TA durante una noche. Se vierte agua (10 ml) en la mezcla de reacción y después se extrae con EtOAc (3 x 7 ml). Las capas orgánicas combinadas se concentran al vacío. El residuo se purifica por cromatografía de fase inversa (gradiente de elución: ACN al 20-100% en agua) para dar el producto (285) en forma de un aceite incoloro (70 mg, 10%).

^{1}H RMN ($CDCl_3$, 300 MHz): 1,14-1,24 (m, 1H), 1,34-1,44 (c, 1H), 1,80-1,86 (m, 2H), 1,90-1,99 (m, 2H), 2,20 (s, 3H), 3,37 (d, 2H), 3,81 (d, 2H), 4,13-4,24 (m, 1H), 4,55 (s, 2H) 7,17-7,24 (m, 4H), 7,26 (d, 1H), 7,78 (d, 1H), 8,45 (s, 1H)

LC/MS (ES+) m/z = 396,16

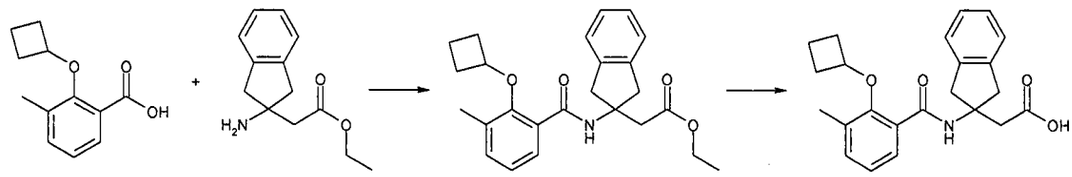
EJEMPLO 286

Ácido 2-(2-ciclobutoxi-5-hidroximetil-3-metil-benzoilamino)-indan-2-carboxílico (286):

Se disuelve éster etílico del ácido 2-(2-ciclobutoxi-5-hidroximetil-3-metil-benzoilamino)-indan-2-carboxílico (70 mg, 0,16 mmol) en etanol (1,5 ml) y se añaden KOH sólido (191 mg, 3,3 mmol) y agua (150 µl). La mezcla se agita a temperatura ambiente durante 30 min y después se concentra al vacío. El residuo se disuelve en agua (1,5 ml) y se acidifica con HCl conc. hasta que no precipita más cantidad de sólido de color blanco. La mezcla se extrae con acetato de etilo (2 x 8 ml) y las capas orgánicas combinadas se concentran al vacío para dar el producto (286) en forma de un sólido de color blanco (60 mg, 95%).

^{1}H RMN ($CDCl_3$, 300 MHz): δ 1,14-1,24 (m, 1H), 1,34-1,44 (c, 1H), 1,80-1,86 (m, 2H), 1,90-1,99 (m, 2H), 2,20 (s, 3H), 3,37 (d, 2H), 3,81 (d, 2H), 4,13-4,24 (m, 1H), 4,55 (s, 2H) 7,17-7,24 (m, 4H), 7,26 (d, 1H), 7,78 (d, 1H), 8,45 (s, 1H)
LC/MS (ES+) m/z = 396,16

EJEMPLO 287



165 A6 287 288

Éster etílico del ácido 2-aminoindan-2-acético (A6)

Este compuesto se prepara de acuerdo con la Patente de Estados Unidos WDF2006/134111.

Éster etílico del ácido 2-(2-ciclobutiloxi-3-metilbenzoilamino)indan-2-acético (287)

A una solución de ácido 2-ciclobutiloxi-3-metilbenzoico (210 mg, 1,02 mmol), éster etílico del ácido 2-aminoindan-2-acético (A6) (260 mg, 1,02 mmol) y HATU (470 mg, 1,224 mmol, 1,2 equiv.) en DMF seca (10 ml) se le añade diisopropiletilamina (0,36 ml, 2,24 mmol, 2,2 equiv.) y la solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo se disuelve en EtOAc (60 ml) y se lava con agua (2 x 20 ml) y salmuera (2 x 20 ml). La capa orgánica se seca sobre $MgSO_4$ y se concentra al vacío. El

residuo se purifica por cromatografía ultrarrápida (120 g de gel de sílice, EtOAc al 15% en heptano) para dar el producto puro en forma de un aceite incoloro (400 mg, 96%).

LC/MS (ES+) m/z 408

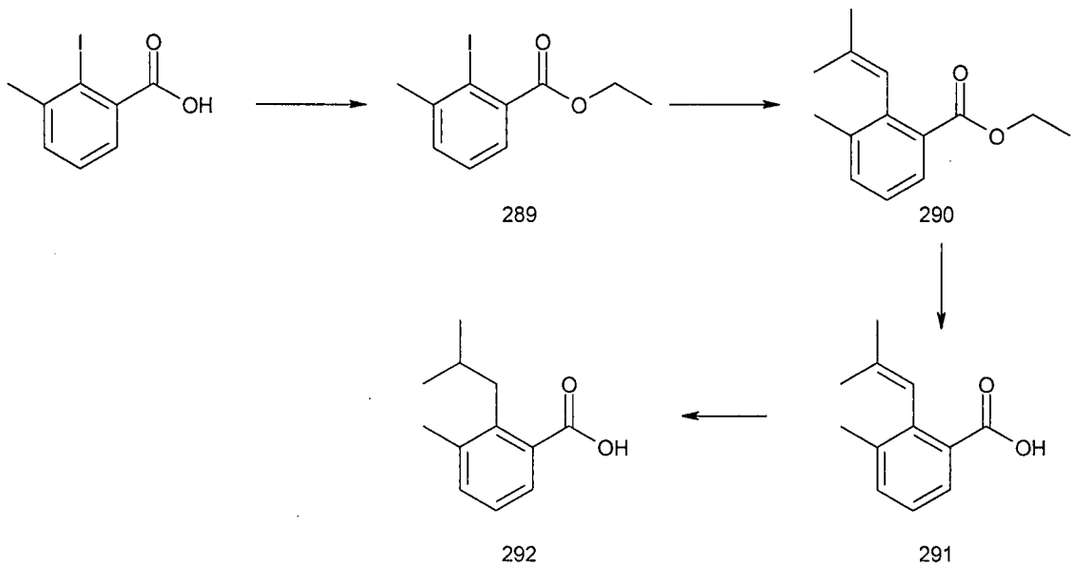
EJEMPLO 288

Ácido 2-(2-ciclobutiloxi-3-metilbenzoilamino)indan-2-acético (288)

Una solución del éster etílico del ácido 2-(2-ciclobutiloxi-3-metilbenzoilamino)indan-2-acético (288) (400 mg, 1 mmol) en EtOH (15 ml)/agua (1 ml) se trata con gránulos de NaOH (800 mg, 20 mmol) y se agita a TA durante 24 h. Después de la concentración al vacío, el residuo se disuelve en agua (30 ml) y se acidifica con HCl hasta alcanzar un valor de pH de 2-3. El producto se extrae en EtOAc (3 x 20 ml) y los extractos combinados se lavan con agua (2 x 10 ml) y salmuera (2 x 15 ml). La capa orgánica se seca sobre $MgSO_4$ y se concentra al vacío. El residuo se tritura con heptano y el producto puro se aísla por filtración para dar un sólido de color blanco (350 mg, 92%).

LC/MS (ES+) m/z 380

Ejemplo 289



289 290 291 292

Éster etílico del ácido 2-yodo-3-metilbenzoico (289)

Una solución del ácido 2-yodo-3-metilbenzoico (6 g, 0,023 mol) en EtOH (150 ml) se trata con HCl concentrado (20 ml) y se calienta a reflujo durante 48 h. Después de la retirada del EtOH al vacío, el residuo se diluye con agua (125 ml) y se enfría a 0°C en un baño de hielo. El valor del pH se ajusta a 10 con gránulos sólidos de NaOH y se extrae con EtOAc (3 x 75 ml). Los extractos orgánicos se lavan con agua (2 x 50 ml) y salmuera (2 x 50 ml) y se secan sobre $MgSO_4$. Se concentran al vacío para dar el producto en forma de un aceite de color amarillo pálido. (6 g, 90%).

LC/MS (ES+) m/z 291

Ejemplo 290

Éster etílico del ácido 3-metil-2-(2-metil-1-propenil)benzoico (290)

Una suspensión del éster etílico del ácido 2-yodo-3-metilbenzoico (289) (2,9 g, 0,01 mol) y pinacol éster del ácido 2-metil-1-propenilborónico (3,64 g, 0,02 mol, 2 equiv.) en DMF seca (50 ml) y $NaHCO_3$ saturado (10 ml) se desgasifica durante 10 minutos y después se trata con tetraquis(trifenilfosfina)paladio (0) (400 mg). La mezcla se agita a 110°C durante una noche. La reacción se enfría, la DMF se retira al vacío y el residuo se diluye con agua (120 ml). La fase acuosa se filtra a través de hyflo y se extrae con EtOAc (3 x 75 ml). Los extractos orgánicos se lavan con agua (2 x 50 ml) y salmuera (2 x 50 ml) y se secan sobre $MgSO_4$. Los extractos orgánicos se concentran al vacío y se purifican por cromatografía ultrarrápida (400 g de gel de sílice, EtOAc al 5% en heptano) para dar el producto en forma de un aceite de color amarillo pálido (1,85 g, 85%).

LC/MS (ES+) m/z 218

Ejemplo 291

Ácido 3-metil-2-(2-metil-1-propenil)benzoico (291)

Una solución del éster etílico del ácido 3-metil-2-(2-metil-1-propenil)benzoico (290) (3 g, 0,014 mol) en MeOH (50 ml) se trata con NaOH 2 N (10 ml) y se calienta a reflujo durante 6 h. El disolvente se retira al vacío y el residuo se diluye con agua (75 ml). La fase acuosa se extrae con EtOAc (30 ml) y después se separa y se acidifica a un valor de pH de 2-3 con HCl

concentrado. El sólido precipitado se extrae en EtOAc (3 x 50 ml). Los extractos se lavan con agua (2 x 30 ml) y salmuera (2 x 30 ml), se secan sobre $MgSO_4$ y se concentran al vacío para dar el producto en forma de un sólido de color blanco (2,0 g, 75%).

^{1}H RMN ($CDCl_3$, 300 MHz): 1,43 (s, 3H), 1,91 (s, 3H), 2,24 (s, 3H), 6,35 (s, 1H), 7,2-7,27 (t, 1H), 7,37-7,44 (m, 1H), 7,79-7,81 (d, 1H).
LC/MS (ES+) m/z 191

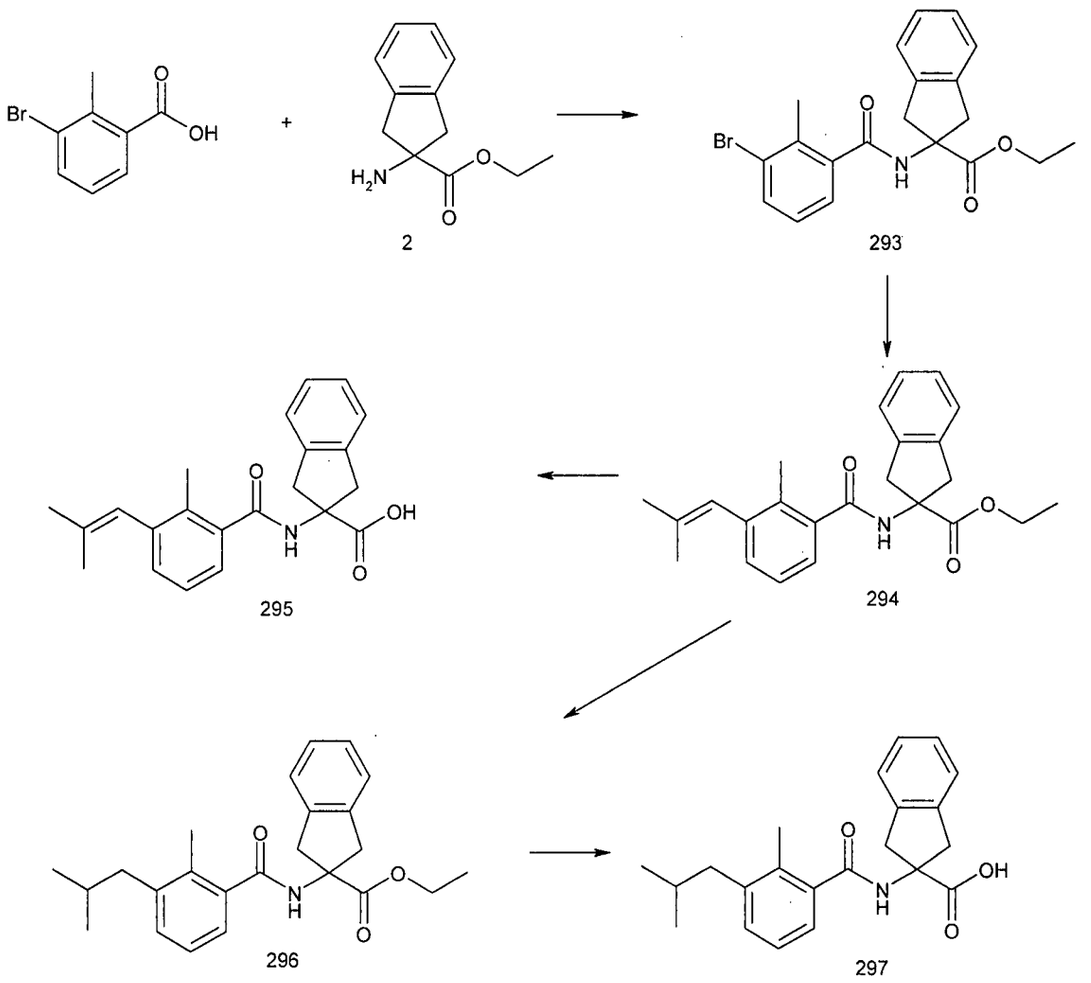
Ejemplo 292

Ácido 2-isobutil-3-metilbenzoico (292)

Una solución del ácido 3-metil-2-(2-metil-1-propenil)benzoico (291) (2 g, 10,5 mmol) en MeOH (40 ml) se hidrogena usando catalizador de paladio al 10%/carbón a 40 bar/30°C usando el H-cube de Thales Nanotechnology durante 48 h. El MeOH se concentra al vacío para dar el producto en forma de un aceite incoloro (1,85 g, 90%).

^{1}H RMN ($CDCl_3$, 300 MHz): 0,92 (d, 6H), 1,78-1,90 (m, 1H), 2,38 (s, 3H), 7,1-7,2 (t, 1H), 7,35-7,38 (d, 1H), 7,75-7,80 (d, 1H).
LC/MS (E/S+) m/z 193

Ejemplo 293



Éster etílico del ácido 2-(3-bromo-2-metilbenzoilamino)indan-2-carboxílico (293)

Este compuesto se prepara de una manera similar al ejemplo 287. El producto en bruto obtenido se purifica por cromatografía ultrarrápida (120 g de gel de sílice, EtOAc al 20% en heptano) para dar el producto puro en forma de un sólido de color blanco (1,9 g, 91%).

^{1}H RMN ($CDCl_3$, 300 MHz): 1,20-1,25 (t, 3H), 3,30-3,40 (d, 2H), 3,40 (s, 3H), 3,70-3,80 (d,2H), 4,25-4,40 (m, 2H), 6,30-6,40 (s, 1H), 6,95-7,05 (t, 1H), 7,20-7,30 (m,2H), 7,55-7,60 (d, 1H).

LC/MS (ES+) m/z 403

Ejemplo 294

Éster etílico del ácido 2-[2-metil-3-(2-metil-1-propenil)benzoilamino]indan-2-carboxílico (294)

Una suspensión de éster etílico del ácido 2-(3-bromo-2-metilbenzoilamino)indan-2-carboxílico (293) (402 mg, 1 mmol) y ácido 2-metil-1-propenilborónico (200 mg, 2 mmol, 2 equiv.) en DMF seca (20 ml) y $NaHCO_3$ saturado (5 ml) se desgasifica durante 10 min y después se trata con tetraquis(trifenilfosfina)paladio (0) (400 mg). La mezcla se agita a 110°C durante 5 h. La reacción se enfría, la DMF se retira al vacío y el residuo se diluye con agua (80 ml). La fase acuosa se filtra a través de celite y se extrae con EtOAc (3 x 50 ml). Los extractos orgánicos se lavan con agua (2 x 30 ml) y salmuera (2 x 30 ml) y se secan sobre $MgSO_4$. Después, la fase orgánica se concentra al vacío y se purifica por cromatografía ultrarrápida (120 g de gel de sílice, EtOAc al 30% en heptano) para dar un aceite de color amarillo pálido (350 mg, 92%).

LC/MS (E/S+) m/z 378

Ejemplo 295

Ácido 2-[2-metil-3-(2-metil-1-propenil)benzoilamino]indan-2-carboxílico (295)

Este compuesto se prepara de una manera similar al ejemplo 288. La purificación por cromatografía ultrarrápida (120 g de gel de sílice, EtOAc al 20% en heptano) da un sólido de color blanco. (20 mg, 6%)

LC/MS (E/S+) m/z 350

Ejemplo 296

Éster etílico del ácido 2-(2-metil-3-isobutilbenzoilamino)indan-2-carboxílico (296)

Una solución de éster etílico del ácido 2-[2-metil-3-(2-metil-1-propenil)benzoilamino]indan-2-carboxílico (294) (700 mg, 1,86 mmol) en AcOH glacial (125 ml) se trata con el catalizador, Pd-C (Pd al 10% en peso, 360 mg) en una atmósfera de nitrógeno. Después, la mezcla de reacción resultante se hidrogena en un aparato Parr a 379,21 kPa (55 psi) a 75°C durante una noche. El catalizador se retira por filtración a través de una pre-columna (10 g de gel de sílice) y se lava con EtOH. La solución orgánica combinada se concentra al vacío. El residuo se

disuelve en EtOAc (75 ml), se lava con agua (30 ml) y salmuera (30 ml), se seca sobre $MgSO_4$ y se concentra al vacío para dejar el producto en forma de un sólido de color blanco (660 mg, 94%).

LC/MS (E/S+) m/z 380

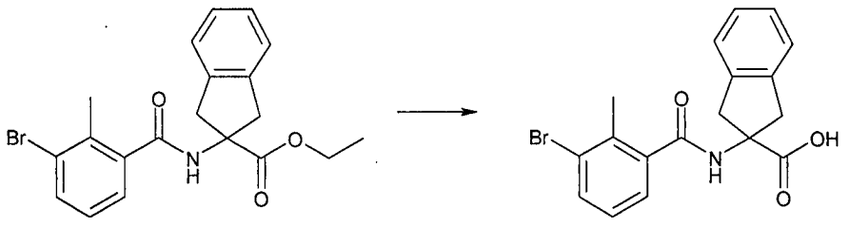
Ejemplo 297

Ácido 2-(2-metil-3-isobutilbenzoilamino)indan-2-carboxílico (297)

Este compuesto se prepara de una manera similar al ejemplo 288. La purificación por cromatografía ultrarrápida (120 g de gel de sílice, EtOAc al 50% en heptano) da el producto en forma de un sólido de color blanco. (130 mg, 21%)

^{1}H RMN (DMSO-d_6, 300 MHz): 0,87-0,89 (d, 6H), 1,73-1,82 (m, 1H), 2,21 (s, 3H), 2,40-2,45 (m, 2H), 3,32-3,36 (d, 2H), 3,53-3,59 (d, 2H), 7,00-7,23 (m, 7H), 8,83 (s, 1H), 11,0 (s, 1H).
LC/MS (E/S+) m/z 353

Ejemplo 298

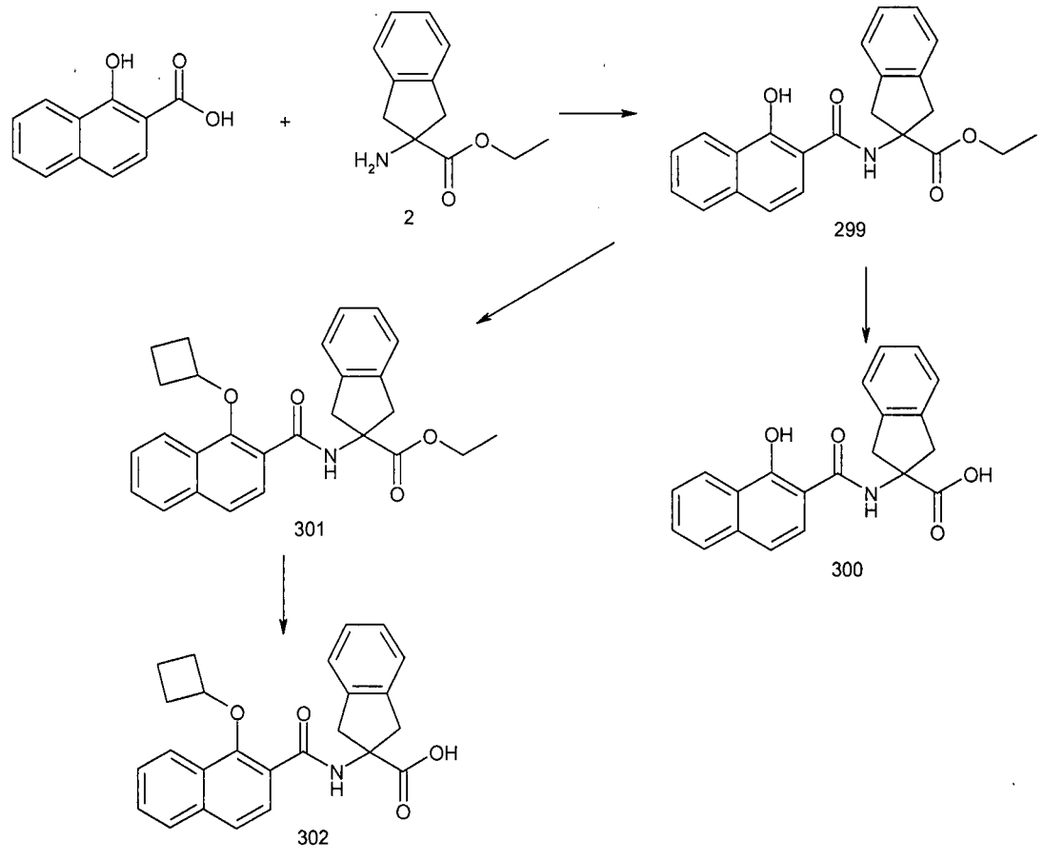


293 298

Ácido 2-(3-bromo-2-metilbenzoilamino)indan-2-carboxílico (298)

Este compuesto se prepara de una manera similar al ejemplo 288. El extracto orgánico se evapora al vacío para dar el producto en forma de un sólido de color blanco (270 mg, 96%)

^{1}H RMN (DMSO-d_6, 300 MHz): 2,33 (s, 3H), 2,29-3,35 (d, 2H), 3,54-3,60 (d, 2H), 7,13-7,24 (m, 6H), 7,63-7,66 (d, 1H), 8,99 (s, 1H), 12,55-12,60 (s, 1H).
LC/MS (E/S+) m/z 376



Ejemplo 299

Éster etílico del ácido 2-[(1-hidroxinaftaleno-2-carbonil)amino]indan-2-carboxílico (299)

Este compuesto se prepara de una manera similar al ejemplo 287. La purificación por cromatografía ultrarrápida (400 g de gel de sílice, EtOAc al 30% en heptano) da un aceite de color naranja (1,75 g, 93%).

LC/MS (E/S+) m/z 376

Ejemplo 300

Ácido 2-[(1-hidroxinaftaleno-2-carbonil)amino]indan-2-carboxílico (300)

Este compuesto se prepara de una manera similar al ejemplo 288. El extracto orgánico se evapora al vacío para dar un sólido de color blanco (280 mg, 99%).

^{1}H RMN (DMSO-d_6, 300 MHz): 3,48-3,53 (d, 2H), 3,63-3,69 (d, 2H), 7,17-7,28 (m, 5H), 7,34-7,37 (d, 1H), 7,53-7,66 (m, 2H), 7,85-7,88 (d, 1H), 7,96-7,99 (d, 1H), 8,26-8,28 (d, 1H), 9,22 (s, 1H).

LC/MS (E/S+) m/z 376

Ejemplo 301

Éster etílico del ácido 2-[(1-ciclobutiloxinaftaleno-2-carbonil)amino]indan-2-carboxílico (301)

Una solución de éster etílico del ácido 2-[(1-hidroxinaftaleno-2-carbonil)amino]indan-2-carboxílico (289) (560 mg, 1,5 mmol) en DMF seca se trata con una dispersión en aceite de NaH (al 60%, 100 mg, 2,25 mmol, 1,5 equiv.) y la mezcla se agita durante 10 min. Se añade bromuro de ciclobutilo (405 mg, 3 mmol, 2 equiv.) y la reacción se calienta y se agita en el microondas a 150°C durante 3 horas. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (75 ml) y se lava con agua (2 x 30 ml) y salmuera (30 ml). La capa orgánica se seca sobre $MgSO_4$ y se concentra al vacío. El residuo se purifica por cromatografía ultrarrápida (200 g de gel de sílice, EtOAc al 10% en heptano) para dar un sólido de color blanco. (290 mg, 45%)

LC/MS (E/S+) m/z 430

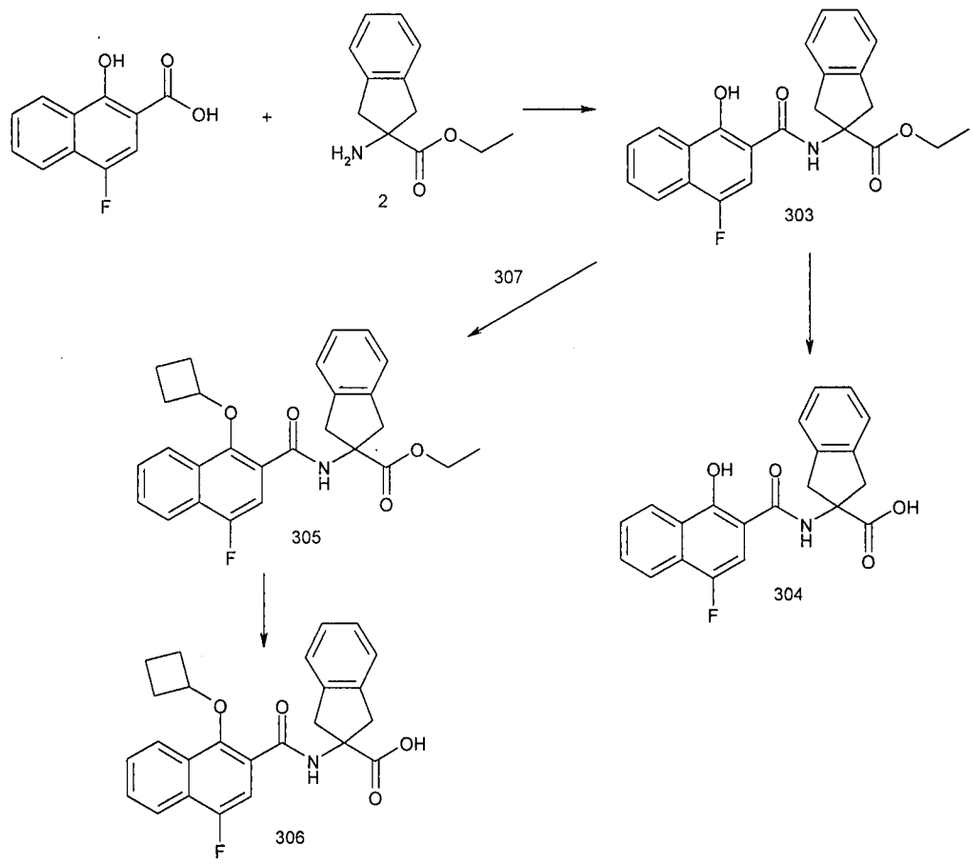
Ejemplo 302

Ácido 2-[(1-ciclobutiloxinaftaleno-2-carbonil)amino]indan-2-carboxílico (302)

Este compuesto se prepara de una manera similar al ejemplo 288. La purificación por cromatografía ultrarrápida (400 g de gel de sílice, gradiente de elución: EtOAc al 25-60% en heptano) da el producto en forma de un sólido de color blanco. (20 mg, 9%)

LC/MS (E/S+) m/z 402

Ejemplo 303



Éster etílico del ácido 2-[(4-fluoro-1-hidroxinaftaleno-2-carbonil)amino]indan-2-carboxílico (303)

Este compuesto se prepara de una manera similar al ejemplo 287. La purificación por cromatografía ultrarrápida (400 g de gel de sílice, EtOAc al 30% en heptano) da un aceite de color naranja (1,67 g, 85%).

^{1}H RMN (DMSO-d_6, 300 MHz): 1,13-1,16 (t, 3H), 3,46-3,52 (d,2H), 3,64-3,69 (d, 2H), 4,11-4,18 (c, 2H), 7,19-7,29 (m, 4H), 7,69-7,72 (t, 1H), 7,76-7,81 (t, 1H), 7,93-8,01 (m,2H), 8,31-8,34 (d, 1H), 9,26 (s, 1H), 13,90 (s, 1H).
LC/MS (E/S+) m/z 394

Ejemplo 304

Ácido 2-[(4-fluoro-1-hidroxinaftaleno-2-carbonil)amino]indan-2-carboxílico (304) Este compuesto se prepara de una manera similar al ejemplo 288. El extracto orgánico se evapora al vacío para dar el producto en forma de un sólido de color blanco (270 mg, 97%).

^{1}H RMN (DMSO-d_6, 300 MHz): 3,47-3,58 (d, 2H), 3,64-3,75 (d, 2H), 7,18-7,29 (m, 5H), 7,66-7,75 (m, 1H), 7,77-7,85 (m, 1H), 7,95-8,8,01 (m, 1H), 8,31-8,34 (d, 1H), 9,16 (s, 1H),12,75 (s, 1H).

LC/MS (E/S-) m/z 364

Ejemplo 305

Éster etílico del ácido 2-[(1-ciclobutiloxi-4-fluoronaftaleno-2-carbonil)amino]indan-2-carboxílico (305)

Una solución de éster etílico del ácido 2-[(4-fluoro-1-hidroxinaftaleno-2-carbonil)amino]indan-2-carboxílico (303) (197 mg, 0,5 mmol) y 1,1-dióxido de 3,3-dimetil-1,2,5-tiadiazolidina-5 trifenilfosfina (ejemplo 307, 245 mg, 0,6 mmol, 1,2 equiv.) en DCM (6 ml) se trata con ciclobutanol (44 mg, 0,6 mmol, 1,2 equiv.) y se agita a TA durante 6 días. La mezcla de reacción bruta se purifica por cromatografía ultrarrápida (100 g de gel de sílice, DCM al 100%) para dar un aceite incoloro (120 mg, 54%).

LC/MS (E/S+) m/z 448

Ejemplo 306

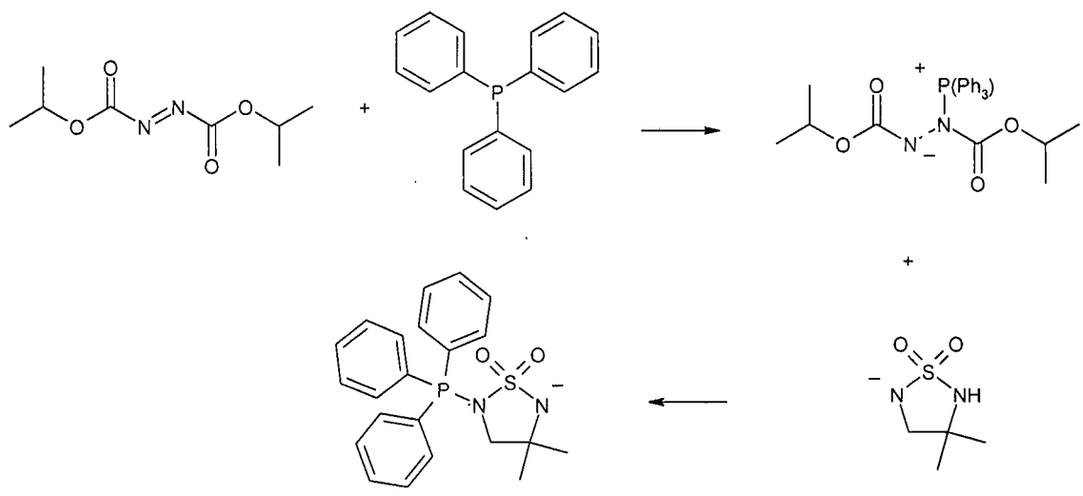
Ácido 2-[(1-ciclobutiloxi-4-fluoronaftaleno-2-carbonil)amino]indan-2-carboxílico (306)

Este compuesto se prepara de una manera similar al ejemplo 288. El extracto orgánico se evapora al vacío para dar un sólido de color blanco (95 mg, 84%).

^{1}H RMN (DMSO-d_6, 300 MHz): 1,20-1,33 (m, 1H), 1,44-1,54 (m, 1H), 3,42-3,47 (d, 2H), 3,58-3,63 (d, 2H), 4,49-4,57 (m, 1H), 7,17-7,36 (m, 6H), 7,69-7,75 (m, 2H), 8,03-8,06 (m, 1H), 8,17-8,19 (m, 1H), 8,88 (s, 1H), 12,70 (s, 1H).

LC/MS (E/S+) m/z 420

Ejemplo 307

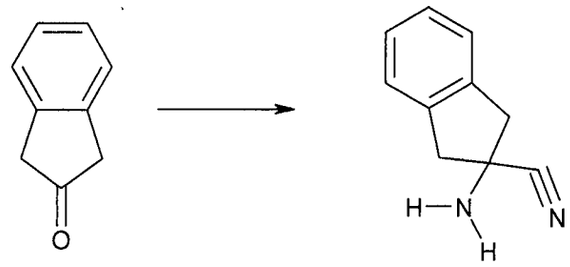


307

1,1-Dióxido de 3,3-dimetil-1,2,5-tiadiazolidina-5 trifenilfosfina (307)

Una solución de trifenilfosfina (4,4 g, 0,016 mol) y 1,1-dióxido de 3,3-dimetil-1,2,5-tiadiazolidina (2,5 g, 0,016 mol) en THF seco (50 ml) se trata gota a gota con diazodicarboxilato de diisopropilo (3,3 g, 0,016 mol). El sólido blanco precipitado se agita a TA durante 4 h más. Después, el producto se recoge por filtración y se lava con éter dietílico (5,7 g, 86%).

Ejemplo 308



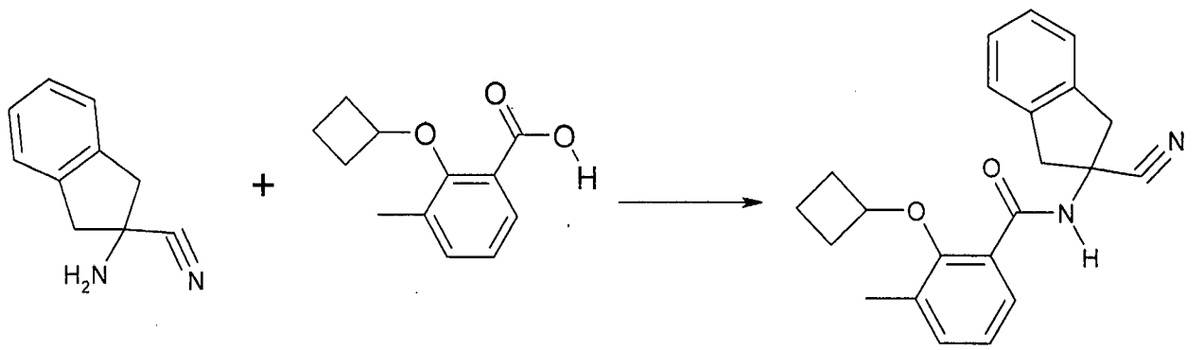
(308)

2-Amino-indan-2-carbonitrilo (308)

Un matraz de fondo redondo de 250 ml se carga con 2-indanona (2,64 g, 19,98 mmol) e iPrOH (40 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade una solución acuosa de hidróxido de amonio (al 29%, 8,3 M, 16 ml, 132,3 mmol). Se añaden cloruro de amonio (2,14 g, 39,96 mmol) y NaCN (1,96 g, 39,96 mmol). Después de 11 días, el análisis por tlc (sílice, 2:1 de heptanos:EtOAc) indica que la

indona de partida se ha consumido. El disolvente orgánico se retira al vacío. El material resultante se transfiere a un embudo de decantación y se reparte entre DCM (200 ml) y agua (100 ml). Las fases se separan. La fase acuosa se extrae con DCM (100 ml). Los extractos orgánicos se combinan, se lavan con salmuera (100 ml), se secan sobre $MgSO_4$, se filtran y se evaporan por bombeo hasta alcanzar un peso constante, produciendo 2,6 g de un sólido de color pardo oscuro. Este material se disuelve en DCM (15 ml). Esta solución se aplica a una columna (sílice, 40 g) que se equipa en un ISCO Companion. El gradiente es iPrOH al 1% en DCM durante 4 volúmenes de columna seguido de un gradiente lineal hasta iPrOH al 20% en DCM durante 10 volúmenes de columna. El eluyente se recoge en fracciones de 17 ml. Las fracciones 15 a 32 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color beige claro (0,82 g, 26%).

Ejemplo 309



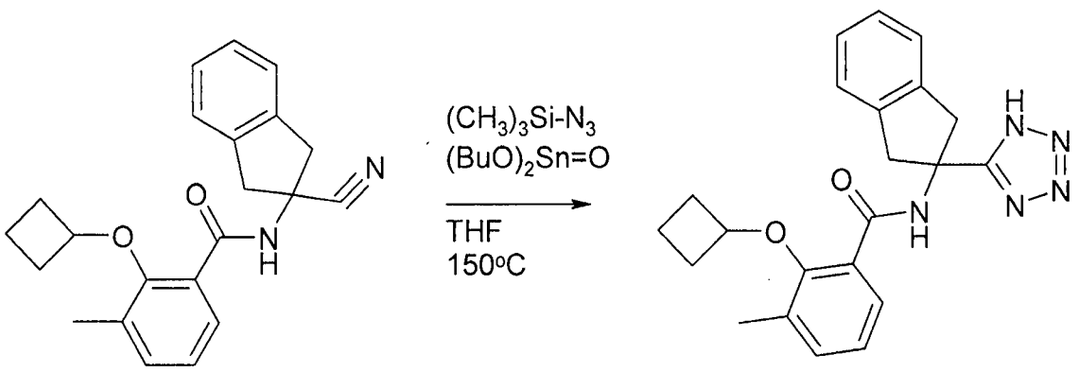
308 309

N-(2-ciano-indan-2-il)-2-ciclobutoxi-3-metil-benzamida (309)

Un vial de 30 ml se carga con ácido 2-ciclobutoxi-3-metil-benzoico (734 mg, 3,56 mmol) y DCM seco (10 ml). Se añade una barra de agitación y se inicia la agitación. Después de 5 min, se añade HTBU (1,35 g, 3,56 mmol). Después de 5 min, se añade 2-amino-indan-2-carbonitrilo (308, 563 mg, 3,56 mmol) seguido de DIPEA (1,5 ml, 8,95 mmol). La reacción se deja en agitación durante 38 h. El análisis de la mezcla de reacción por tlc (sílice, iPrOH al 15%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (60 ml). Se lava con $NaHCO_3$ acuoso saturado (2 x 20 ml) y salmuera (20 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,2 g de un aceite pegajoso de color negro. Este material se

disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta acetato de etilo al 50% durante 8 volúmenes de columna y después EtOAc al 90% en heptanos durante 2 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente activo por UV. Las fracciones 27 a 30 se combinan y se evaporan al vacío para dar un sólido de color blanco (0,51 g, 41%).

Ejemplo 310



309 310

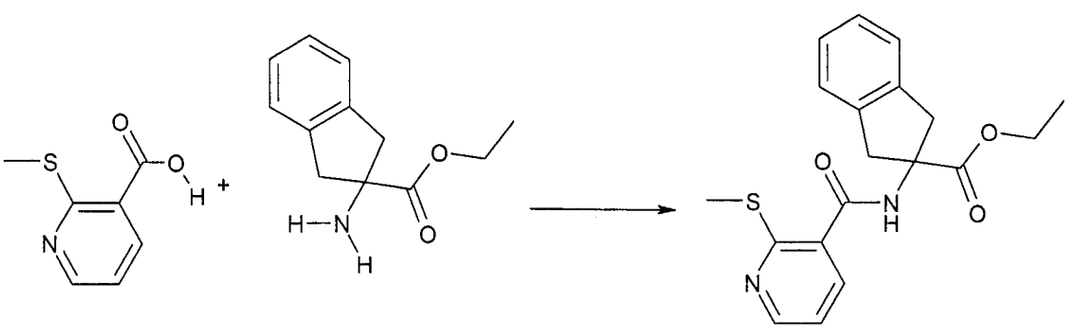
2-Ciclobutoxi-3-metil-N-[2-(1H-tetrazol-5-il)-indan-2-il]-benzamida (310)

Un vial de reacción para microondas de 10 ml se carga con N-2-(ciano-indan-2-il)-2-ciclobutoxi-3-metil-benzamida (309, 300 mg, 0,87 mmol) y tetrahidrofurano seco (THF, 4 ml). Se añade una barra de agitación y se inicia la agitación. Después de 1 minuto, al vial de reacción se le añaden trimetilsililazida (228 µl, 1,73 mmol) y óxido de di-n-butilestaño (22 mg, 0,087 mmol). El vial de reacción se cubre y se introduce en un aparato de microondas Emyrs Optimizer. El vial de reacción se agita previamente durante 10 segundos. La temperatura se fija a 150°C durante 10 min. Al final de este proceso, al vial de reacción se le añaden alícuotas adicionales de trimetilsililazida (228 µl, 1,73 mmol) y óxido de di-n-butilestaño (22 mg, 0,087 mmol). El vial de reacción se cubre y se introduce en un aparato de microondas Emyrs Optimizer. El vial de reacción se agita previamente durante 10 segundos. La temperatura se fija a 150°C durante 10 min. El análisis por tlc (sílice, MeOH al 10% en DCM) indica que el material de partida se ha consumido completamente. El contenido del vial de reacción se reconstituye en DCM (8 ml) e iPrOH (4 ml). Esta solución se agita durante 10 min y se filtra a

través de una capa de celite. El filtrado se evapora a presión reducida, bombeando hasta alcanzar un peso constante, para dar 0,4 g de una espuma de color amarillo claro. La espuma se disuelve en DCM (10 ml) y se aplica a una columna ISCO Companion (sílice, 40 g). Se aplica el siguiente gradiente: iPrOH al 1% en DCM durante 4 volúmenes de columna, seguido de un gradiente lineal hasta iso-propanol al 50% en DCM durante 10 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 2 a 6 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,31 g, 92%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,08-1,25 (m, 2H), 1,38-1,51 (m, 1H), 1,71-1,96 (m, 4H), 2,22 (s, 3H), 3,79-3,93 (m, 4H), 4,35 (m, 1H), 7,03 (dd, 1H), 7,1-7,37 (m, 6H), 8,98 (s, 1H). LC/MS (ES+) m/z = 390,16.

Ejemplo 311



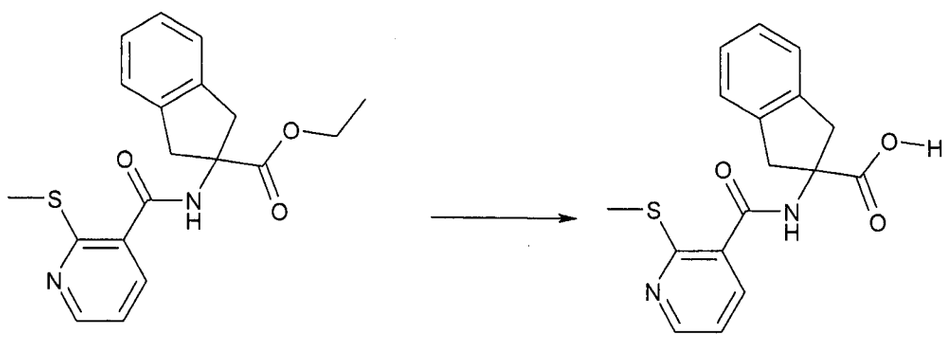
311

Éster etílico del ácido 2-[(2-metilsulfanil-piridina-3-carbonil)-amino]-indan-2-carboxílico (311)

Un vial de 40 ml se carga con ácido 2-(metiltio)-nicotínico (0,37 g, 2,19 mmol) y DCM seco (8 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, 5 min, se añade HTBU (831 mg, 2,19 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino)-indan-2-carboxílico (450 mg, 2,19 mmol) seguido de DIPEA (0,96 ml, 5,48 mmol). La reacción se deja en agitación durante 14 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 15%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). La fase orgánica se lava con salmuera (20 ml), se seca sobre $MgSO_4$, se filtra

y se evapora al vacío para proporcionar 1,23 g de una espuma de color amarillo claro. La espuma se disuelve en 10 ml de DCM. Esta solución se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente activo por UV. Las fracciones 8 a 12 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,47 g, 60%).

Ejemplo 312



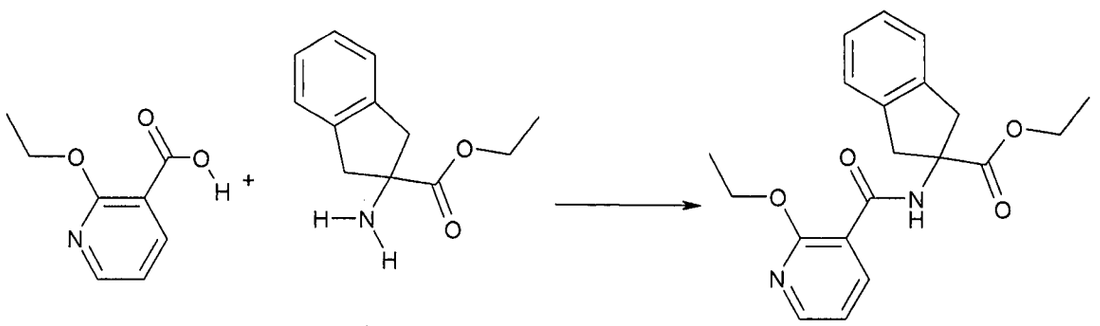
311 312

Ácido 2-[(2-metilsulfanil-piridina-3-carbonil)-amino]-indan-2-carboxílico (312)

A un matraz de 100 ml que contiene éster etílico del ácido 2-[(2-metilsulfanil-piridina-3-carbonil)-amino]-indan-2-carboxílico (311, 490 mg, 1,38 mmol) se le añaden 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH (146 mg, 3,5 mmol). Después de 40 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El contenido del matraz se diluye con iPrOH (30 ml). Se añade Resina de Intercambio Iónico Dowex Muy Ácida (10 g). El matraz de reacción se cubre y se deja en agitación a temperatura ambiente. Después de 7 días, al matraz de reacción se le añade más cantidad de iPrOH (35 ml). El contenido del matraz de reacción se filtra a través de una capa de celite y se concentra a presión reducida, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,44 g, 97%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 2,41 (s, 3H), 3,26-3,48 (m, 4H), 7,16-7,25 (m, 5H), 7,71 (dd, 1H), 8,51 (dd, 1H), 9,01 (s, 1H).
LC/MS (ES+) m/z = 329,14.

Ejemplo 313

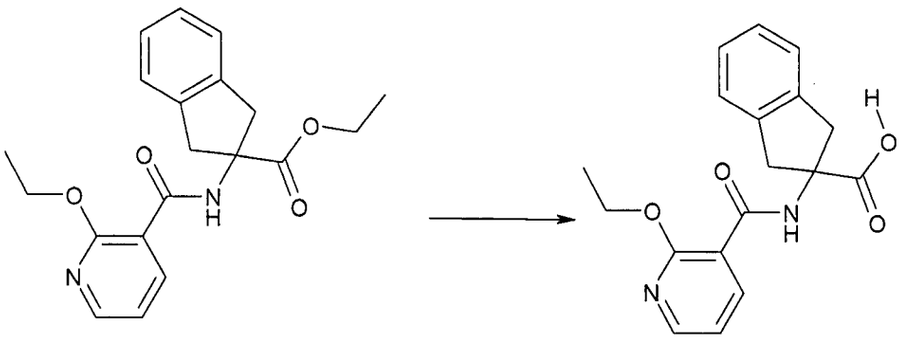


313

Éster etílico del ácido 2-[(2-etoxi-piridina-3-carbonil)-amino]-indan-2-carboxílico (313)

Un vial de 40 ml se carga con ácido 2-etoxinicotínico (366 mg, 2,19 mmol) y DCM seco (7 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, 5 min, se añade HTBU (831 mg, 2,19 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (450 mg, 2,19 mmol) seguido de DIPEA (0,96 ml, 5,48 mmol). La reacción se deja en agitación durante 17 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 15%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). La fase orgánica se lava con salmuera (20 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 2,38 g de un jarabe de color amarillo claro. El jarabe se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es iPrOH al 1%/DCM durante 4 volúmenes de columna seguido de un gradiente lineal hasta iPrOH al 30% en DCM durante 10 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente activo por UV. Las fracciones 5 a 10 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para producir un sólido de color blanco (0,34 g, 44%).

Ejemplo 314



313 314

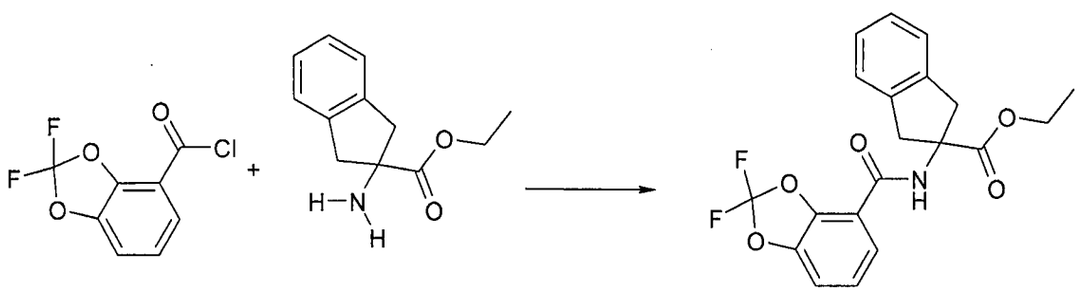
Ácido 2-[(2-etoxi-piridina-3-carbonil)-amino]-indan-2-carboxílico (314)

Un matraz de 100 ml que contiene éster etílico del ácido 2-[(2-etoxi-piridina-3-carbonil)-amino]-indan-2-carboxílico ([313], 340 mg, 0,96 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH monohidrato (102 mg, 2,42 mmol). Después de 13 días, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El contenido del matraz se diluye con iPrOH (30 ml). Se añade Resina de Intercambio Iónico Dowex Muy Ácida (2 g). El matraz de reacción se cubre y se deja en agitación a temperatura ambiente. Después de 18 días, al matraz de reacción se le añade más cantidad de iPrOH (35 ml). El contenido del matraz de reacción se filtra a través de una capa de celite y se concentra a presión reducida, bombeando hasta alcanzar un peso constante, para producir 0,44 g de un sólido de color blanco. Este material se disuelve en una mezcla de DCM (10 ml) e iPrOH (3 ml). Al matraz se le añade celite (15 g). El disolvente se retira a presión reducida. El material restante se transfiere a una jeringa de plástico de 40 ml que se equipa con un disco vitrificado. La jeringa se equipa en un ISCO Companion que tiene una columna de 40 g (sílice). Se aplica el siguiente gradiente: iPrOH al 1%/DCM durante 4 volúmenes de columna. Después, un gradiente lineal hasta iPrOH al 50%/DCM durante 10 volúmenes de columna. Mantenido en iPrOH al 50%/DCM durante 2 volúmenes de columna. Se recogen fracciones de 14 ml. Las fracciones 39 a 41 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para producir un sólido de color blanco (0,28 g, 89%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,22 (t, 3H), 3,26-3,63 (m, 4H), 4,36 (c, 2H), 7,14-7,25 (m, 5H), 8,13 (dd, 1H), 8,28 (dd, 1H), 8,76 (s, 1H).

LC/MS (ES+) m/z = 327,11.

Ejemplo 315

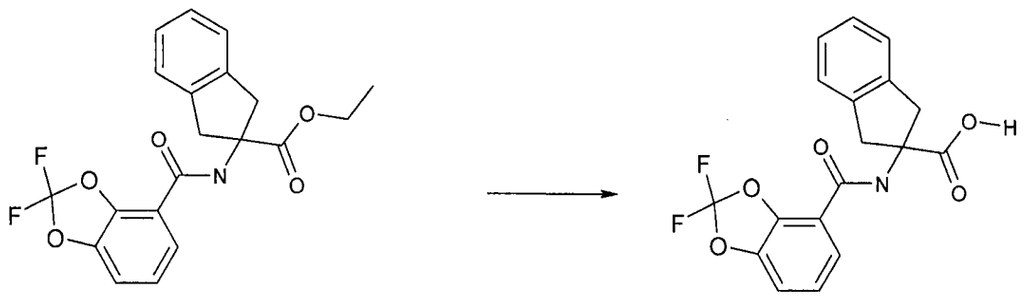


315

Éster etílico del ácido 2-[(2,2-difluoro-benzo[1,3]dioxol-4-carbonil)-amino]-indan-2-carboxílico (315)

Un matraz de fondo redondo de 100 ml se carga con ácido 2-aminoindan-2-carboxílico (340 mg, 1,66 mmol) y DCM seco (6 ml). Se añade una barra de agitación y se inicia la agitación. Se añade DIPEA (0,46 ml, 2,65 mmol). Se añade cloruro de 2-[(2,2-difluoro-benzo[1,3]dioxol-4-carbonilo (438 mg, 1,99 mmol). Se añade 4-dimetilaminopiridina ([MFCD0006418], 2 mg, cat.). La reacción se cubre. Después de 18 días, el análisis por tlc (sílice, iPrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (60 ml). Se lava con HCl acuoso diluido (2 x 25 ml), $NaHCO_3$ acuoso saturado (2 x 25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para producir 0,73 g de una espuma de color pardo oscuro. Se diluye con DCM y se aplica a una columna de sílice (40 g) en un ISCO Companion. La columna se eluye con 3 volúmenes de columna de EtOAc al 10%-heptanos seguido de un gradiente lineal hasta EtOAc al 50%/heptanos durante 10 volúmenes de columna. Y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente positivo por UV. Las fracciones 8 -10 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color naranja claro (0,57 g, 88%).

Ejemplo 316



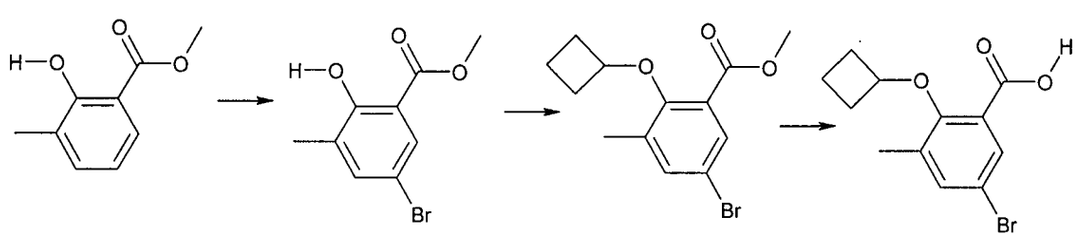
315 316

Ácido 2-[(2,2-difluoro-benzo[1,3]dioxol-4-carbonil)-amino]-indan-2-carboxílico (316)

Un matraz de 100 ml que contiene éster etílico del ácido 2-[(2,2-diflouro-1,3-benzodioxol-4-carbonil)-amino]-indan-2-carboxílico (0,38 g, 0,98 mmol) se carga con 1,4-dioxano (6 ml) y MeOH (6 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (3 ml) seguido del LiOH monohidrato (103 mg, 2,46 mmol). Después de 70 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~6 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanquecino (0,33 g, 94%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 3,26-3,63 (m, 4H), 7,13-7,32 (m, 5H), 7,48 (dd, 1H), 7,55 (dd, 1H), 8,97 (s, 1H), 12,63 (s a, 1H).
LC/MS (ES+) m/z = 362,05.

Ejemplo 317



317

Ácido 5-bromo-2-ciclobutoxi-3-metil-benzoico (317)

Un matraz de fondo redondo de 3 bocas y de 250 ml está equipado con un embudo de adición, una entrada de N_2 y un condensador. El matraz se carga con bromo (3,6 ml, 70,11 mmol) y DCM (40 ml). Se añade una barra de agitación y se inicia la agitación. El matraz de reacción se sumerge en un baño de hielo-agua. Después de agitar durante 15 min, el embudo de adición se carga con una solución de 2-hidroxi-3-metilbenzoato de metilo (10 g, 60,18 mmol) en 1,4-dioxano (40 ml). Esta solución se añade gota a gota a la mezcla de reacción agitada durante 30 min. Después, el embudo de adición se lava con 1,4-dioxano (10 ml). Todo esto se añade a la mezcla de reacción. Después, la mezcla de reacción se deja calentar lentamente a temperatura ambiente. Después de 18 días, el contenido del matraz de reacción se transfiere a un matraz de fondo redondo. El disolvente se retira a presión reducida, bombeando hasta alcanzar un peso constante, para dar 17,66 g de un sólido de color amarillo claro. Este sólido se tritura con MeOH enfriado con hielo (75 ml). Los cristales resultantes se recogen mediante filtración por succión. El secado al aire proporciona un sólido de color blanco (14,26 g, 97%).

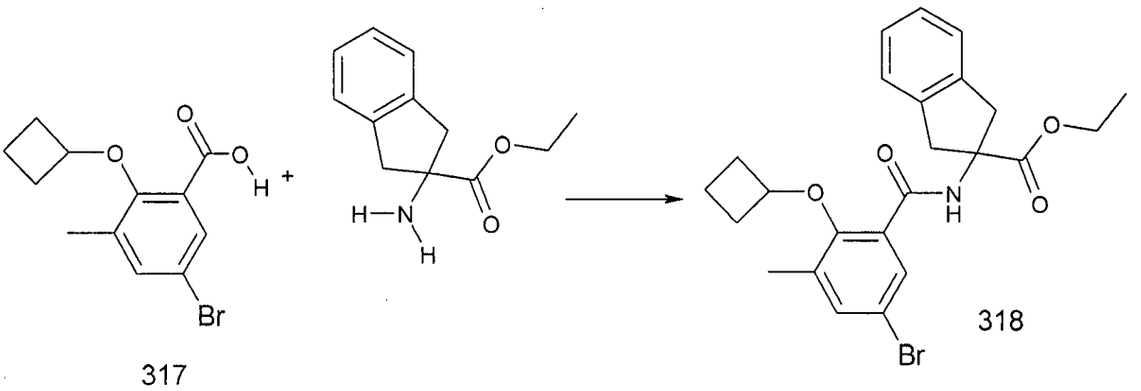
Un matraz de fondo redondo de 100 ml se carga con éster metílico del ácido 5-bromo-2-hidroxi-3-metil-bezoico (4,05 g, 16,53 mmol) como se ha preparado anteriormente. Se añaden DMF seca (20 ml) y una barra de agitación. Se inicia la agitación. Después de la disolución, se añaden K_2SO_4 (6,85 g, 49,59 mmol) y bromociclobutano (2,35 ml, 24,8 mmol). El matraz de reacción se equipa con un manto de calentamiento. La temperatura del manto se fija a 35°C. Después de 8 días, el análisis por tlc (sílice, EtOAc al 25%/heptanos) indica un ligero consumo del material de partida y la aparición de una mancha positiva por UV con un valor de R_f ligeramente mayor. La reacción se equipa con un manto de calentamiento y se calienta a 37°C. Después de 3 días más, el análisis por tlc (sílice, EtOAc al 25%/heptanos) indica el consumo del material de partida y la conversión completa en una mancha positiva por UV con un valor de R_f ligeramente mayor. La mezcla de reacción se filtra a través de una capa de Celite. El filtrado se diluye con EtOAc y (100 ml) y se transfiere a un embudo de decantación. La solución de EtOAc se lava con $NaHCO_3$ saturado (2 x 25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar un material semi-sólido (2,09 g, 42%). Este material se utiliza .en la siguiente etapa.

Un matraz de 100 ml que contiene éster metílico del ácido 5-bromo-2-ciclobutoxi-3-metil-benzoico (2,07 g, 7,25 mmol), como se ha preparado anteriormente, se carga con 1,4-dioxano (12 ml) y MeOH (12 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (6 ml) seguido de LiOH (768 mg, 18,31 mmol). Después de 18 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~11 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (50 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (40 ml). Las fases orgánicas combinadas se lavan con agua (40 ml) y salmuera (40 ml), se secan sobre $MgSO_4$, se filtran y se concentran, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (1,82 g, 88%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,16-1,25 (m, 2H), 1,38-1,51 (m, 1H), 1,71-2,12 (m, 3H), 2,23 (s, 3H), 4,37 (m, 1H), 7,53-7,62 (m, 2H).

LC/MS (ES+) m/z = 390,16.

Ejemplo 318



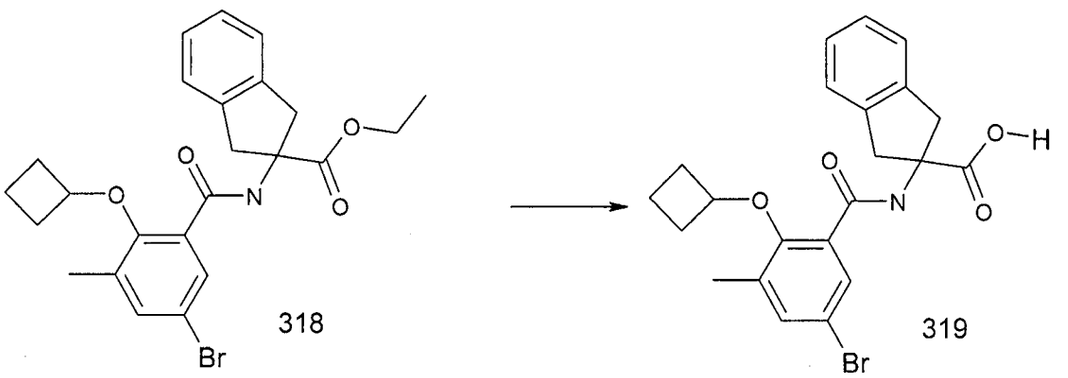
317 318

Éster etílico del ácido 2-(5-bromo-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (318)

Un matraz de fondo redondo de 100 ml que contiene una barra de agitación se carga con ácido 2-ciclobutoxil-3-metil-5-bromo-benzoico 317 (695 mg, 2,44 mmol) y DCM seco (8 ml). Se inicia la agitación. Después de que se complete la disolución, se añade HTBU (924 mg, 2,44 mmol). Después de 5 min, se añade éster etílico del ácido 2-amino-indan-2-carboxílico (500 mg, 2,44 mmol) seguido de DIPEA (1,1 ml, 6,1 mmol). La reacción se deja en agitación

durante 15 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). La fase orgánica se lava consecutivamente con HCl acuoso diluido (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml) y después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para dar 1,42 g de un sólido de color naranja claro. Este sólido se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 60% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente activo por UV. Las fracciones 4 a 9 se combinan y se evaporan al vacío. Esto produce un material sólido de color blanco (0,8 g, 70%).

Ejemplo 319



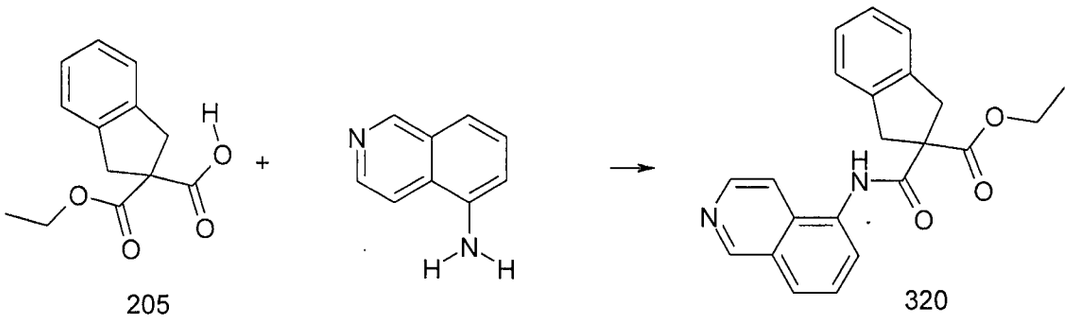
Ácido 2-(5-bromo-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (319)

Un vial de reacción de 30 ml se carga con éster etílico del ácido 2-(5-bromo-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico (0,29 g, 0,61 mmol), con 1,4-dioxano (4 ml) y con MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH monohidrato (65 mg, 1,55 mmol). Después de 38 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~6 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Las fases orgánicas combinadas se lavan con agua (20 ml) y salmuera (20 ml), se secan sobre $MgSO_4$, se filtran y se concentran,

bombeando hasta alcanzar un peso constante, para dar un sólido de color blanquecino (0,26 g, 95%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,11-1,27 (m, 2H), 1,43-1,57 (m, 1H), 1,79-1,99 (m, 4H), 2,21 (s, 3H), 3,55-3,84 (m, 4H), 4,37 (m, 1H), 7,18-7,33 (m, 4H), 7,35 (d, 1H), 7,51 (d, 1H), 8,78 (s, 1H) 12,62 (s, 1H).
LC/MS (ES+) m/z = 446,11.

Ejemplo 320

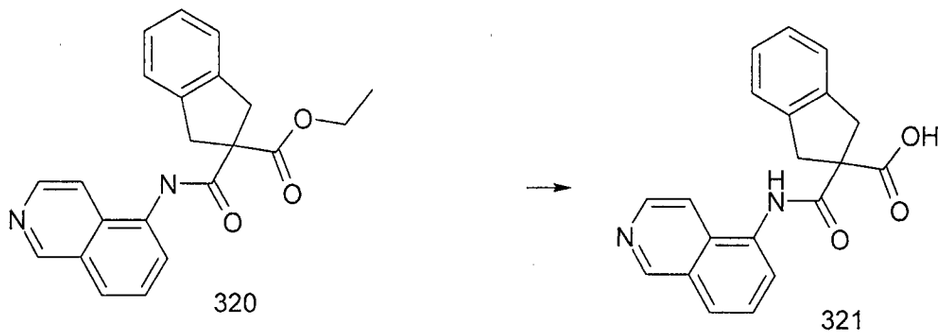


205 320

Éster etílico del ácido 2-(isoquinolin-5-ilcarbamoil)-indan-2-carboxílico (320)

Un vial de reacción de 25 ml que contiene una barra de agitación se carga con éster etílico del ácido indan-2-carboxílico (205, 1,0g, 4,27 mmol) y DCM seco (15 ml). Se inicia la agitación. Después de que se complete la disolución, se añade el HTBU (1,62 g, 4,27 mmol). Después de 5 min, se añade 5-aminoisoquinolina (616 mg, 4,27 mmol) seguido de DIPEA (1,72 ml, 9,8 mmol). La reacción se deja en agitación durante 63 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo del ácido de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (40 ml). La fase orgánica se lava consecutivamente con HCl acuoso diluido (al 3%, 20 ml), $NaHCO_3$ acuoso saturado (20 ml) y salmuera (20 ml) y después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 3,13 g de un sólido de color naranja claro. Este material se disuelve en 15 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 90% durante 12 volúmenes de columna. Se recogen fracciones de 17 ml de eluyente. Las fracciones 17 a 31 se combinan y se evaporan al vacío. Esto da un sólido de color blanco (1,39 g, 90%).

Ejemplo 321

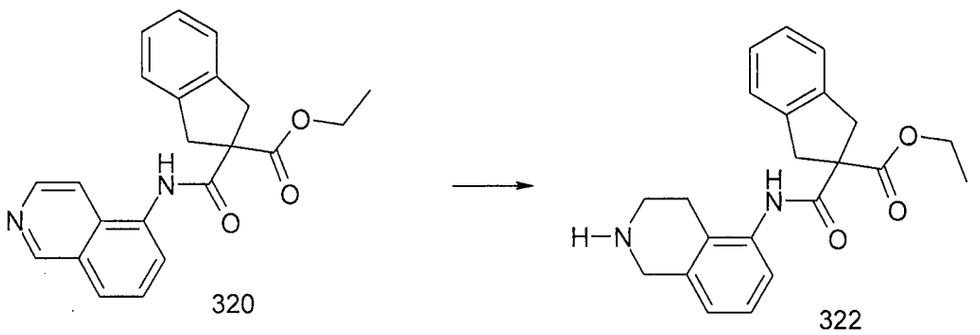


Ácido 2-(isoquinolin-5-ilcarbamoil)-indan-2-carboxílico (321)

Un vial de reacción de 30 ml se carga con éster etílico del ácido 2-(isoquinolin-5-ilcarbamoil)-indan-2-carboxílico (320, 354 mg, 0,98 mmol), con 1,4-dioxano (6 ml) y con MeOH (6 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (3 ml) seguido de LiOH monohidrato (104 mg, 252 mmol). Después de 20 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (1 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 64 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado, bombeando hasta alcanzar un peso constante, para dar 0,29 g de un sólido de color blanquecino. Este material se tritura con DCM (15 ml). Los sólidos se recogen mediante filtración por succión y se lavan con DCM (20 ml). El secado por succión proporciona un sólido de color blanquecino (280 mg, 86%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 3,55-3,76 (m, 4H), 4,37 (m, 1H), 7,02-7,19 (m, 4H), 7,61 (dd, 1H), 7,78 (d, 1H), 8,06 (d, 1H), 8,46 (d, 1H), 8,57 (d, 1H), 9,30 (s, 1H) 13,77 (s, 1H).
LC/MS (ES+) m/z = 333,11.

Ejemplo 322

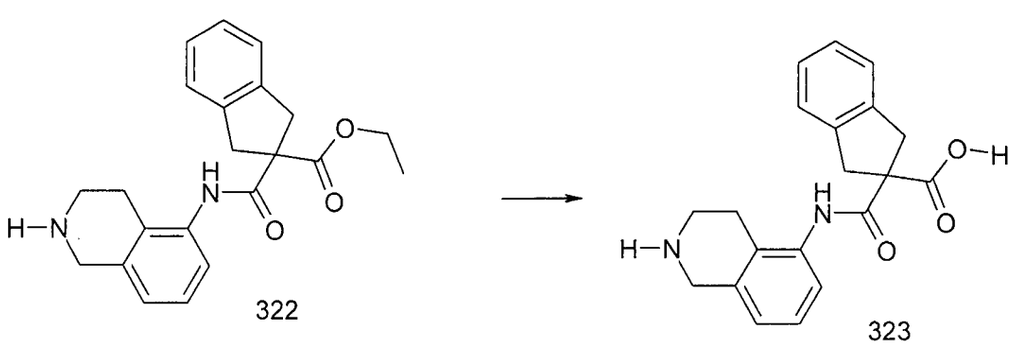


320 322

Éster etílico del ácido 2-(1,2,3,4-tetrahidro-isoquinolin-5-ilcarbamoil)-indan-2-carboxílico (322)

Un recipiente de reacción Parr de 100 ml se carga con éster etílico del ácido 2-(isoquinolin-5-ilcarbamoil)-indan-2-carboxílico (320, 500 mg, 1,39 mmol) y EtOH (10 ml). El recipiente de reacción se agita por rotación hasta que se produce la disolución. Se añaden ácido acético (10 ml) y óxido de platino (IV) (117 mg, 0,52 mmol). El recipiente se equipa en un aparato de hidrogenación Parr, se lava abundantemente con N_2 y después se evacúa. El recipiente se carga con hidrógeno a 344,74 kPa (50 psi). El aparato se deja en agitación. Después de 4 h, la agitación se interrumpe. El recipiente de reacción se evacúa y se lava abundantemente con nitrógeno. Este proceso se repite. El contenido del recipiente de reacción se diluye con iPrOH (50 ml) y se filtra a través de una capa de celite. El disolvente se retira del filtrado a presión reducida. El residuo resultante se reconstituye en iPrOH (15 ml) y tolueno (15 ml). El disolvente se retira a presión reducida. Este proceso se repite. Después de bombear hasta alcanzar un peso constante, se produce un sólido de color beige claro (0,5 g, 99%).

Ejemplo 323



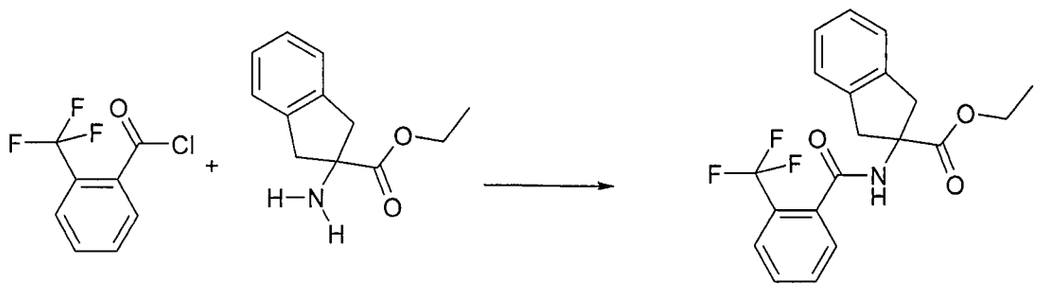
322 323

Ácido 2-(1,2,3,4-tetrahidro-isoquinolin-5-ilcarbamoil)-indan-2-carboxílico (323)

Un matraz de fondo redondo de 250 ml que contiene éster etílico del ácido 2-(1,2,3,4-tetrahidro-isoquinolin-5-ilcarbamoil)-indan-2-carboxílico (322, 440 mg, 1,21 mmol) se carga con 1,4-dioxano (7 ml) y MeOH (7 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (3,5 ml) seguido de LiOH monohidrato (128 mg, 3,05 mmol). Después de 18 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. Al matraz de reacción se le añade resina de intercambio Amberlyst muy ácida (1 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 24 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo resultante se reconstituye con iPrOH/tolueno (1:1, 25 ml). El disolvente se separa a vacío. Este proceso se repite dos veces. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanquecino (400 mg, 99%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 2,58 (m, 1H), 2,99 (m, 1H), 3,43-3,71 (m, 4H), 3,81 (m, 1H), 6,72 (d, 1H), 7,01 (dd, 1H), 7,04-7,18 (m, 4H), 7,84 (d, 1H), 11,82 (s, 1H).
LC/MS (ES+) m/z = 337,15.

Ejemplo 324



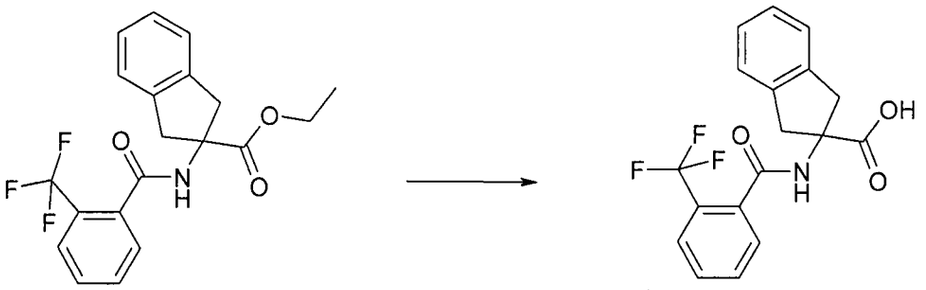
324

Éster etílico del ácido 2-(2-trifluorometil-benzoilamino)-indan-2-carboxílico (324)

Un vial de 30 ml se carga con ácido 2-aminoindan-2-carboxílico (450 mg, 2,19 mmol) y DCM seco (5 ml). Se añade una barra de agitación y se inicia la agitación. Se añade DIPEA (0,61 ml, 3,51 mmol). Se añaden cloruro de 2-(trifluorometil)-benzoílo (388 µl, 2,63 mmol) y DMAP (3 mg, cat.). La reacción se cubre. Después de 38 días, el análisis por tlc (sílice, iPrOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (60

ml). La fase orgánica se lava con HCl acuoso diluido (2 x 25 ml), $NaHCO_3$ acuoso saturado (2 x 25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para producir 0,84 g de un sólido de color naranja claro. Se diluye con DCM y se aplica a una columna de sílice (24 g) en un ISCO Companion. Se recogen fracciones de 14 ml del eluyente positivo por UV. Las fracciones 4-10 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color amarillo claro (0,76 g, 92%).

Ejemplo 325



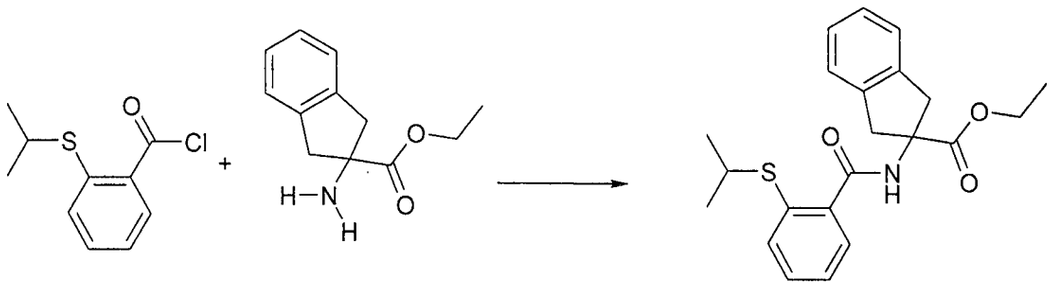
324 325

Ácido 2 2-(2-trifluorometil-benzoilamino)-indan-2-carboxílico (325)

Un matraz de 100 ml que contiene éster etílico del ácido 2-(2-trifluorometil-benzoilamino)-indan-2-carboxílico (324, 0,57 g, 1,51 mmol) se carga con 1,4-dioxano (9 ml) y MeOH (9 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (4,5 ml) seguido de LiOH monohidrato (160 mg, 3,81 mmol). Después de 110 h, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~9 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (40 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Las fases orgánicas combinadas se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran, bombeando hasta alcanzar un peso constante, para producir un sólido de color blanquecino (0,51 g, 97%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 3,23-3,63 (m, 4H), 7,11-7,23 (m, 4H), 7,47 (d, 1H), 7,60-7,76 (m, 3H), 9,12 (s, 1H), 12,55 (s, 1H).
LC/MS (ES+) m/z = 350,11.

Ejemplo 326

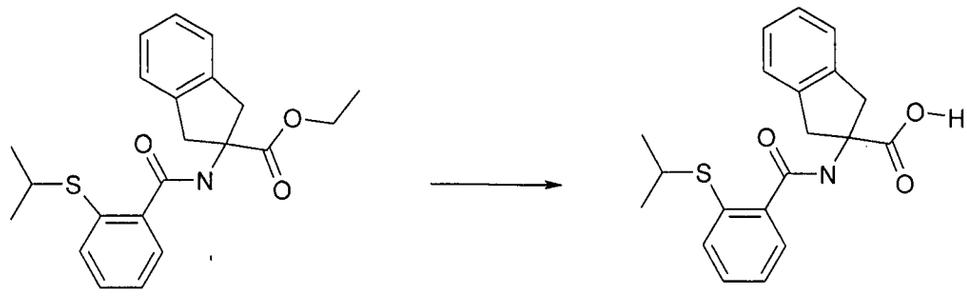


326

Éster etílico del ácido 2-(2-isopropilsulfanil-benzoilamino)-indan-2-carboxílico (326)

Un vial de reacción de 30 ml se carga con ácido 2-isopropilsulfanilbenzoico (430 mg, 2,19 mmol) y DCM seco (7 ml). Se añade una barra de agitación. Se inicia la agitación. Después de que se complete la disolución, se añade el HTBU (831 mg, 2,19 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (450 mg, 2,19 mmol) seguido de DIPEA (0,96 ml, 5,48 mmol). La reacción se deja en agitación durante 3 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). Se lava consecutivamente con HCl acuoso diluido (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml), después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 0,87 g de un sólido de color amarillo claro. Este material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 17 ml de eluyente. Las fracciones 32 a 40 se combinan y se evaporan al vacío. Esto produce un material sólido de color blanco (0,69 g, 82%).

Ejemplo 327



326 327

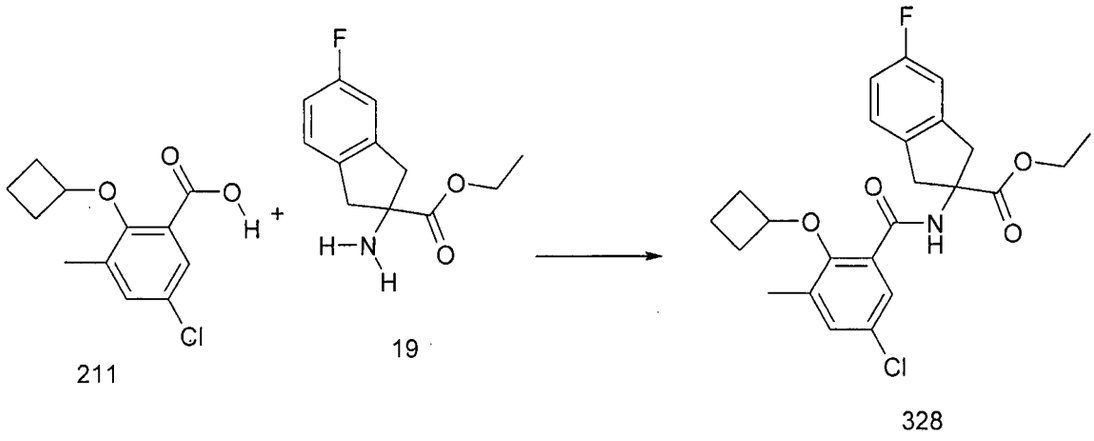
Ácido 2-(2-isopropilsulfanil-benzoilamino)-indan-2-carboxílico (327)

Un matraz de 100 ml que contiene éster etílico del ácido 2-(2-isopropilsulfanil-benzoilamino)-indan-2-carboxílico (326, 0,52 g, 1,45 mmol) se carga con 1,4-dioxano (8 ml) y MeOH (8 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (4 ml) seguido de LiOH monohidrato (145 mg, 3,46 mmol). Después de 20 días, el análisis por tlc (sílice, iPrOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~9 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (40 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Las fases orgánicas combinadas se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanquecino (0,45 g, 93%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,14 (d, 6H), 3,24-3,623 (m, 5H), 7,12-7,44 (m, 8H), 8,85 (s, 1H), 12,92 (s, 1H).

LC/MS (ES+) m/z = 356,15.

Ejemplo 328

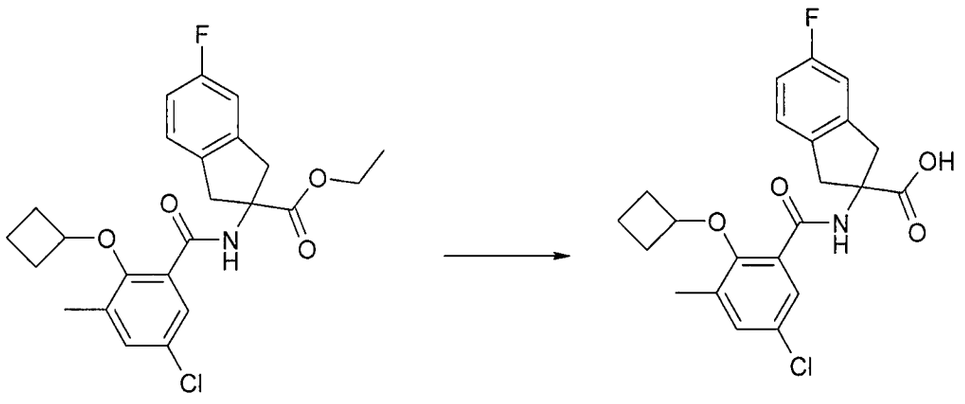


211 19 328

Éster etílico del ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (328)

Un vial de reacción de 40 ml se carga con ácido 2-ciclobutoxil-3-metil-5-cloro-benzoico (221, 0,40 g, 1,62 mmol) y DCM seco (5 ml). Se añade una barra de agitación. Se inicia la agitación. Después de que se complete la disolución, se añade el HBTU (630 mg, 1,66 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-5-fluoro-indan-2-carboxílico (19, 371 mg, 1,66 mmol) seguido de DIPEA (0,74 ml, 4,16 mmol). La reacción se deja en agitación durante 5 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). Se lava consecutivamente con HCl acuoso diluido (al 3%, 20 ml), $NaHCO_3$ acuoso saturado (20 ml) y salmuera (20 ml), después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1 g de un aceite de color amarillo claro. Este material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 24 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 70% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 17 ml. Las fracciones 22 a 28 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,65 g, 88%).

Ejemplo 329



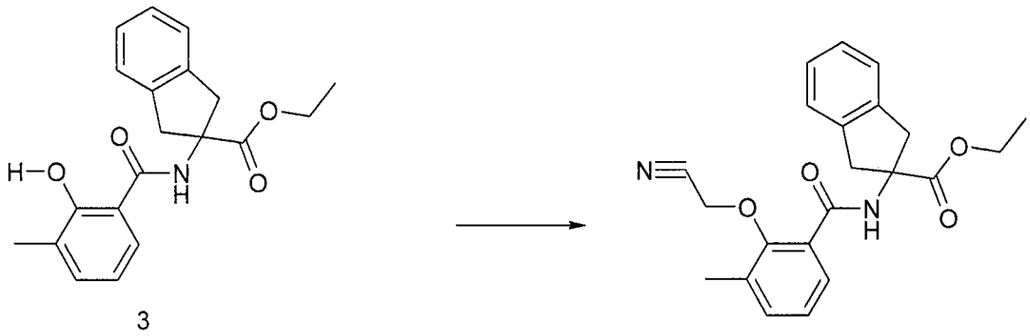
328 329

Ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (329)

Un matraz de 100 ml que contiene éster etílico del ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico (328, 0,49 g, 1,09 mmol) se carga con 1,4-dioxano (3 ml) y MeOH (3 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH (117 mg, 2,78 mmol). Después de 1 día, el análisis por tlc (sílice, MeOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~8 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (25 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Las fases orgánicas combinadas se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,45 g, 98%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,22-1,37 (m, 1H), 1,43-1,57 (m, 1H), 1,78-1,95 (m, 4H), 2,03 (s, 3H), 3,285-3,63 (m, 5H), 4,37 (m, 1H), 6,98 (m, 1H), 7,06-7,11 (m, 1H), 7,20-7,27 (m, 2H), 7,385 (d, 1H), 8,82 (s, 1H) 12,67 (s, 1H).
LC/MS (ES+) m/z = 418,18

Ejemplo 330

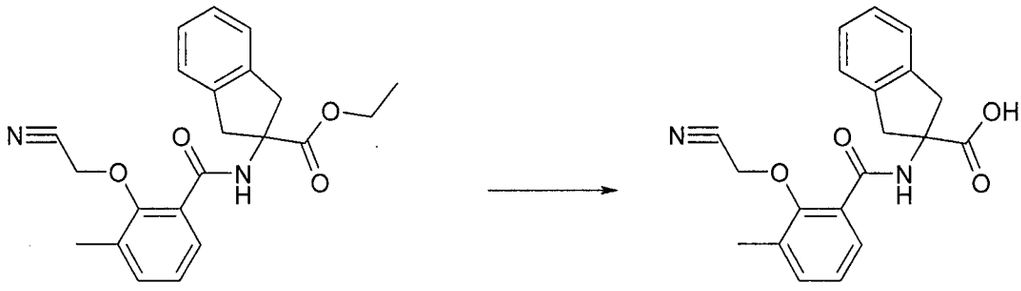


3 330

Éster etílico del ácido 2-(2-cianometoxi-3-metil-benzoilamino)-indan-2-carboxílico (330)

Un vial de reacción de 30 ml se carga con éster etílico del ácido 2-(2-hidroxi-3-metil-benzoilamino)-indan-2-carboxílico (3, 400 mg, 1,18 mmol) y DMF seca (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añaden sucesivamente K_2SO_4 (326 mg, 2,36 mmol) y bromoacetonitrilo (164 µl, 2,36 mmol). El vial de reacción se cubre y se pone en un bloque de calentamiento que se sitúa sobre un agitador orbital. El bloque de calentamiento se fija a 55°C. Después de 16 h, el análisis por tlc (sílice, 1:1 de EtOAc en heptanos) indica que el material de partida se ha consumido completamente. El calentamiento se termina. Después de agitar a temperatura ambiente durante 1 día, el contenido del matraz se filtra a través de una capa de celite. El filtrado se transfiere a un embudo de decantación que contiene EtOAc (40 ml). Las capas se separan. La fase orgánica se lava con agua (20 ml), $NaHCO_3$ acuoso saturado y salmuera (20 ml) y después se seca sobre $MgSO_4$, se filtra y se concentra, bombeando hasta alcanzar un peso constante, para dar un sólido de color pardo oscuro (0,42 g). Este material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 25 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 17 ml de eluyente. Las fracciones 4 a 6 se combinan y se evaporan al vacío. Esto proporciona un sólido de color blanco (0,26 g, 58%).

Ejemplo 331



330 331

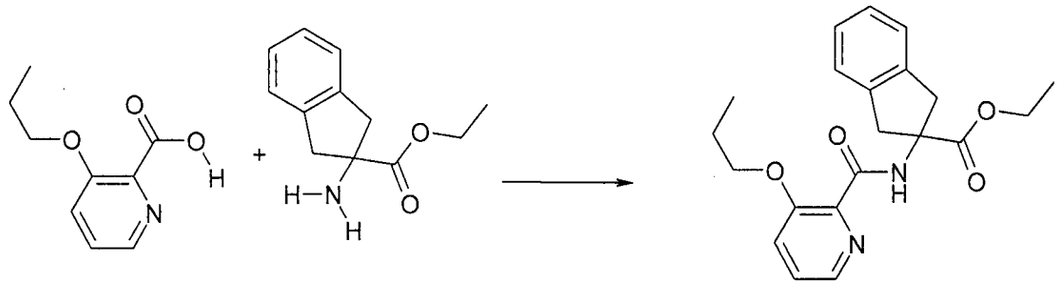
Ácido 2-(2-cianometoxi-3-metil-benzoilamino)-indan-2-carboxílico (331)

Un matraz de 100 ml que contiene éster etílico del ácido 2-(2-cianometoxi-3-metil-benzoilamino)-indan-2-carboxílico (330, 0,25 g, 0,66 mmol) se carga con 1,4-dioxano (2 ml) y MeOH (2 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1 ml) seguido de LiOH monohidrato (71 mg, 1,67 mmol). Después de 18 h, el análisis por tlc (sílice, MeOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~8 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (25 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,23 g, 99%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 3,26-3,63 (m, 4H), 3,43 (s, 3H), 4,56 (s, 2H), 7,07 (dd, 1H), 7,14-7,23 (m, 5H), 7,29 (dd, 1H), 8,81 (s, 1H), 12,55 (s a, 1H).

LC/MS (ES+) m/z = 351,14.

Ejemplo 332

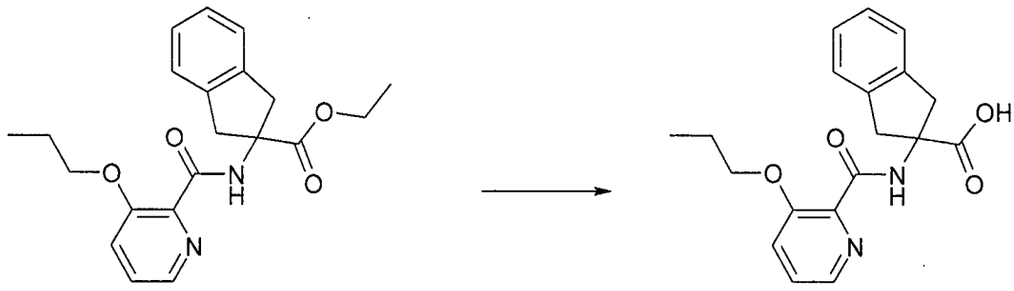


332

Éster etílico del ácido 2-[(3-propoxi-piridina-2-carbonil)-amino]-indan-2-carboxílico (332)

Un vial de reacción de 40 ml que contiene una barra de agitación se carga con ácido 3-*n*-propoxipicolínico (397 mg, 2,19 mmol) y DCM seco (6 ml). Se inicia la agitación. Después de 2 min, se añade el HTBU (831 mg, 2,195 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (450 mg, 2,19 mmol) seguido de DIPEA (0,96 ml, 5,48 mmol). La reacción se deja en agitación a temperatura ambiente. Después de 20 días, el análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). Se lava consecutivamente con HCl acuoso diluido (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para dar 1,23 g de un sólido de color naranja claro. Este material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 60% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de eluyente de 17 ml. Las fracciones 57 a 67 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,8 g, 99%).

Ejemplo 333



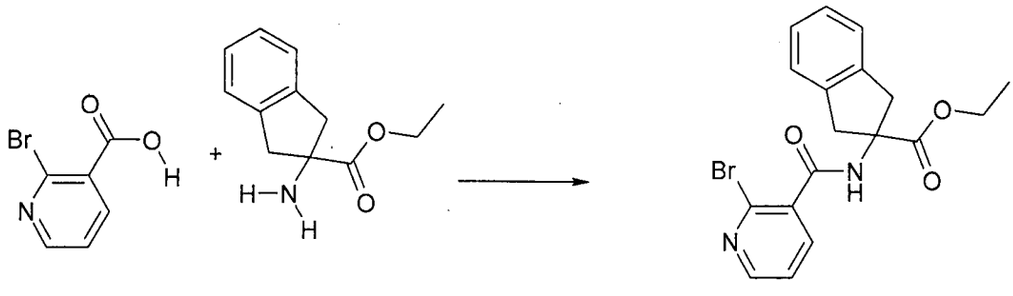
332 333

Ácido 2-[(3-propoxi-piridina-2-carbonil)-amino]-indan-2-carboxílico (333)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-[(3-propoxi-piridina-2-carbonil)-amino]-indan-2-carboxílico (332, 620 mg, 1,68 mmol) se carga con 1,4-dioxano (6 ml) y MeOH (6 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (3 ml) seguido de LiOH monohidrato (178 mg, 4,25 mmol). Después de 22 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al matraz de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 125 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 10 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporcionan 0,58 g de un sólido de color blanco.

^{1}H RMN (DMSO-d_6, 300 MHz): δ 0,76 (t, 3H), 1,71 (dt, 2H), 3,17-3,53 (m, 4H), 3,98 (t, 2H), 7,03-7,12 (m, 4H), 7,43 (dd, 1H), 7,55 (dd, 1H), 7,43 (dd, 1H), 8,12 (dd, 1H), 8,86 (s, 1H).
LC/MS (ES+) m/z = 341,14

Ejemplo 334

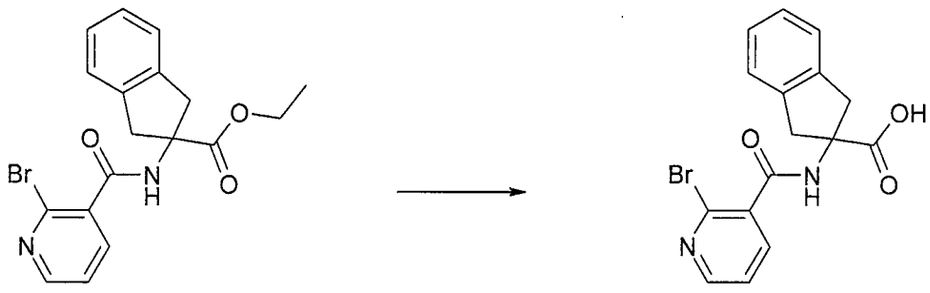


334

Éster etílico del ácido 2-[(2-bromo-piridinil-3-carbonil)-amino]-indan-2-carboxílico (334)

Un vial de reacción de 40 ml que contiene una barra de agitación se carga con ácido 2-bromonicotínico (1,18 g, 5,85 mmol) y DCM seco (15 ml). Se inicia la agitación. Después de 2 min, se añade el HTBU (2,22 g, 5,85 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (1,2 g, 5,25 mmol) seguido de DIPEA (2,55 ml, 14,62 mmol). La reacción se deja en agitación durante 32 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). Se lava consecutivamente con agua (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (2 25 ml) y salmuera (25 ml), después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 3,1 g de un sólido de color naranja claro. Este material se disuelve en 15 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 5% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 60% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 17 ml de eluyente. Las fracciones 30 a 43 se combinan y se evaporan al vacío para producir un sólido de color blanco (1,62 g, 72%).

Ejemplo 335



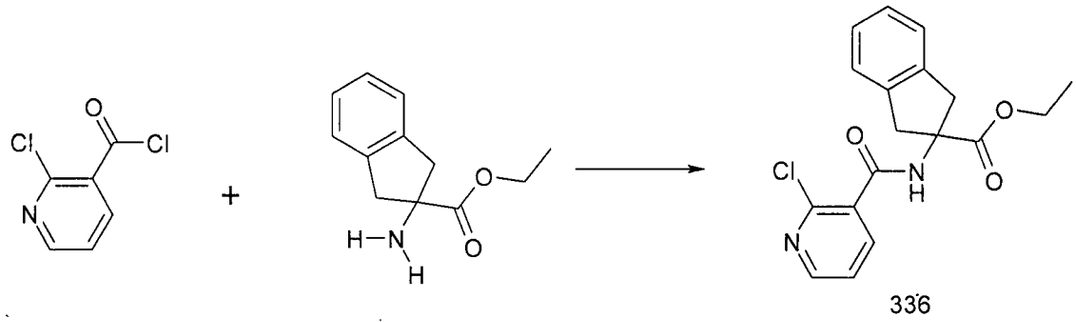
Ácido 2-[(2-bromo-piridinil-3-carbonil)-amino]-indan-2-carboxílico (335)

Un matraz de fondo redondo de 50 ml que contiene éster etílico del ácido 2-[(2-bromo-piridina-3-carbonil)-amino]-indan-2-carboxílico (335, 356 mg, 0,92 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH (97 mg, 2,31 mmol).

Después de 18 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 6 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,32 g, 97%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 3,23-3,53 (m, 4H), 7,03-7,18 (m, 4H), 7,49 (dd, 1H), 7,86 (dd, 1H), 8,40-8,51 (m, 2H).
LC/MS (ES+) m/z = 361,02.

Ejemplo 336



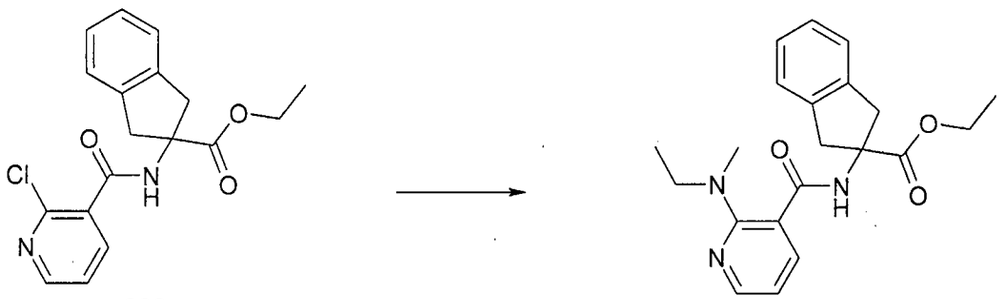
336

Éster etílico del ácido 2-[(2-cloro-piridina-3-carbonil)-amino]-indan-2-carboxílico (336)

Un matraz de fondo redondo de 100 ml se carga con ácido 2-amino-indan-2-carboxílico (1,5 g, 7,31 mmol) y DCM seco (15 ml). Se añade una barra de agitación y se inicia la agitación. Se añade DIPEA (2 ml, 11,69 mmol). Se añaden cloruro de 2-[cloronicotinoílo (1,54 g, 8,77 mmol) y DMAP (8 mg, cat.). La reacción se cubre. Después de 2 días, el análisis por tlc (sílice, iPrOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (60 ml). Se lava con agua (2 x 25 ml), $NaHCO_3$ acuoso saturado (2 x 25 ml) y salmuera (25 ml) y después se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para dar 2,15 g de un sólido de color blanquecino. Éste se disuelve con DCM (20 ml) y se aplica a una columna de sílice (80 g) en un ISCO Companion. La columna se eluye con EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 75% en heptanos durante 12 volúmenes de columna. Se

recogen fracciones de 17 ml del eluyente positivo por UV. Las fracciones 14 - 20 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color amarillo claro (2 g, 79%).

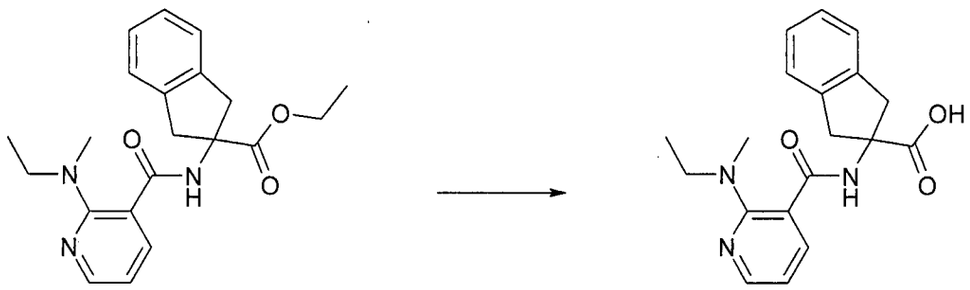
Ejemplo 337



Éster etílico del ácido 2-{[2-(etil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (337)

Un recipiente de reacción para microondas de 25 ml se carga con éster etílico del ácido 2-[2-(cloro-piridina-3-carbonil]-amino]-indan-2-carboxílico (336, 400 mg, 1,16 mmol) y 1,4-dioxano seco (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de 30 segundos, se añaden DIPEA (2,1 ml, 11,6 mmol) y N-metilisopropilamina (1,2 ml, 11,6, mmol). El recipiente de reacción se cierra herméticamente con una tapa corrugada. El recipiente de reacción se pone en un baño de aceite que se calienta a 80°C. Después de 6 días, el análisis por TLC (sílice, 2:1 de EtOAc:heptanos) indica que el material de partida se ha consumido tal como se visualiza por UV. El contenido del matraz de reacción se transfiere a un matraz de fondo redondo y el disolvente se retira al vacío, bombeando hasta alcanzar un peso constante, para dar 0,78 g de un aceite viscoso de color amarillo. El material se disuelve en DCM (10 ml) y se aplica a una columna de cromatografía ISCO (sílice, 40 g). Se aplica un gradiente de EtOAc al 5% en heptanos durante 3 volúmenes de columna seguido de una rampa lineal hasta EtOAc al 60% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 4 a 13 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanquecino (0,41 g, 93%).

Ejemplo 338



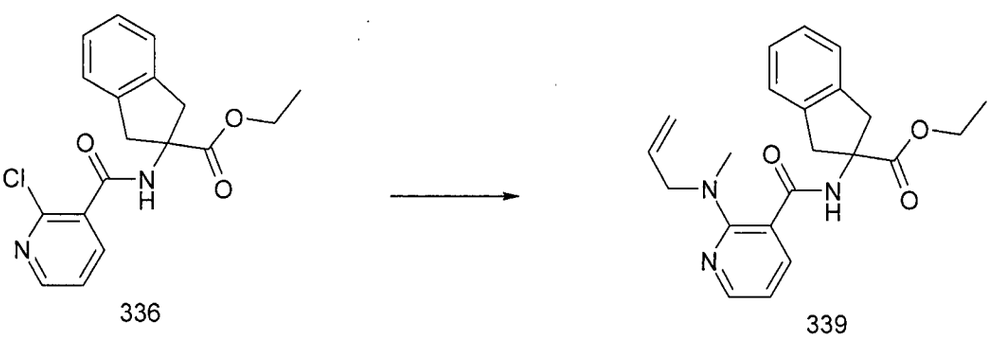
337 338

Ácido 2-{[2-(etil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (338)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-{[2-(etil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (337, 650 mg, 1,77 mmol) se carga con 1,4-dioxano (10 ml) y MeOH (10 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (5 ml) seguido de LiOH monohidrato (187 mg, 4,46 mmol). Después de 18 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (1 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 18 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira a presión reducida. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se da un sólido de color beige (0,58 g, 97%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,07 (t, 3H), 3,18-3,48 (m,4H), 3,37 (c, 2H), 6,75 (dd, 1H), 7,03-7,13 (m, 4H), 7,63 (dd, 1H), 8,15 (dd, 1H), 8,77 (s, 1H).
LC/MS (ES+) m/z = 340,17.

Ejemplo 339

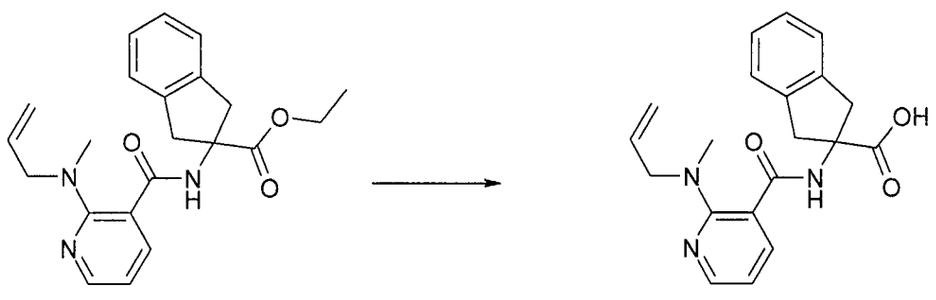


336 339

Éster etílico del ácido 2-{[2-(alilmetil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (339)

Un recipiente de reacción para microondas de 25 ml se carga con éster etílico del ácido 2-[2-(cloro-piridina-3-carbonil]-amino]-indan-2-carboxílico (336, 400 mg, 1,16 mmol) y 1,4-dioxano seco (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de 30 segundos, se añaden DIPEA (2,1 ml, 11,6 mmol) y N-alilmetilamina (1,1 ml, 11,6, mmol). El recipiente de reacción se cierra herméticamente con una tapa corrugada. El recipiente de reacción se pone en un baño de aceite que se calienta a 80°C. Después de 21 días, el análisis por TLC sobre sílice (2:1 de EtOAc:heptanos) indica que el material de partida se ha consumido tal como se visualiza por UV. El contenido del matraz de reacción se transfiere a un matraz de fondo redondo y el disolvente se retira al vacío, bombeando hasta alcanzar un peso constante, para dar 0,85 mg de un material de color pardo oscuro. El material se disuelve en DCM y se aplica a una columna de cromatografía ISCO (sílice, 25 g). Se aplica un gradiente de EtOAc al 5% en heptanos durante 3 volúmenes de columna seguido de una rampa lineal hasta EtOAc al 60% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 2 a 8 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanquecino (0,43 g, 98%).

Ejemplo 340



339 340

Ácido 2-{[2-(alil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (340)

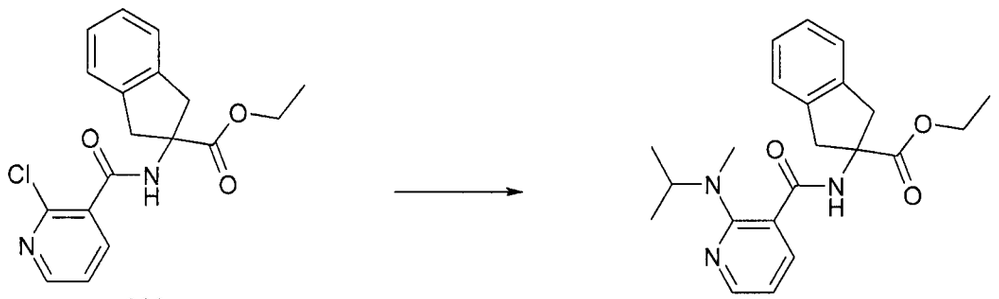
Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-{[2-(alil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (339, 280 mg, 0,74 mmol) se carga

con 1,4-dioxano (2 ml) y MeOH (2 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1 ml) seguido de LiOH monohidrato (78 mg, 1,86 mmol). Después de 38 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 15 días, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,26 g, 100%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 2,82 (s, 3H), 3,18-3,48 (m,4H), 3,92 (dd,2H), 5,04-5,22 (m, 2H), 5,86-6,02 (m, 1H), 6,79 (dd, 1H), 7,04-7,11 (m, 4H), 7,67 (dd, 1H), 8,16 (dd, 1H), 8,77 (s, 1H).

LC/MS (ES+) m/z = 352,20.

Ejemplo 341

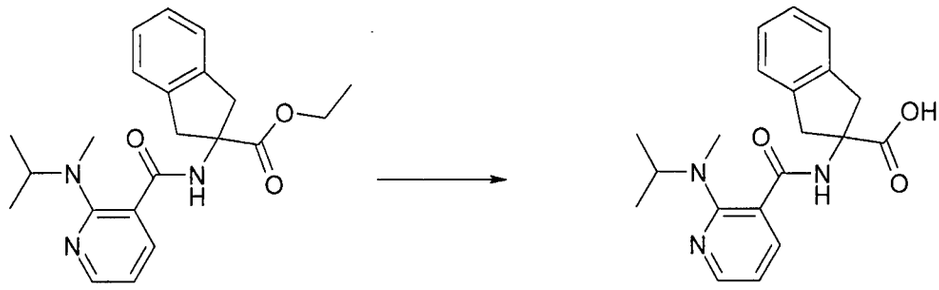


Éster etílico del ácido 2-{[2-(isopropil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (341)

Un recipiente de reacción para microondas de 25 ml se carga con éster etílico del ácido 2-[2-(cloro-piridina-3-carbonil]-amino]-indan-2-carboxílico (341, 400 mg, 1,16 mmol) y 1,4-dioxano seco (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de 30 segundos, se añaden DIPEA (2,1 ml, 11,6 mmol) y N-metiletilamina (1,2 ml, 11,6, mmol). El recipiente de reacción se cierra herméticamente con una tapa corrugada. El recipiente de

reacción se pone en un baño de aceite que se calienta a 80°C. Después de 6 días, el análisis por TLC (sílice, 2:1 de EtOAc:heptanos) indica que el material de partida se ha consumido tal como se visualiza por UV. El contenido del matraz de reacción se transfiere a un matraz de fondo redondo y el disolvente se retira al vacío, bombeando hasta alcanzar un peso constante, para proporcionar 0,78 g de un aceite viscoso de color amarillo. El material se disuelve en DCM y se aplica a una columna de cromatografía ISCO (sílice, 40 g). Se aplica un gradiente de EtOAc al 5% en heptanos durante 3 volúmenes de columna seguido de una rampa lineal hasta EtOAc al 60% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 4 a 13 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para producir 0,41 g de un sólido de color blanquecino.

Ejemplo 342



341 342

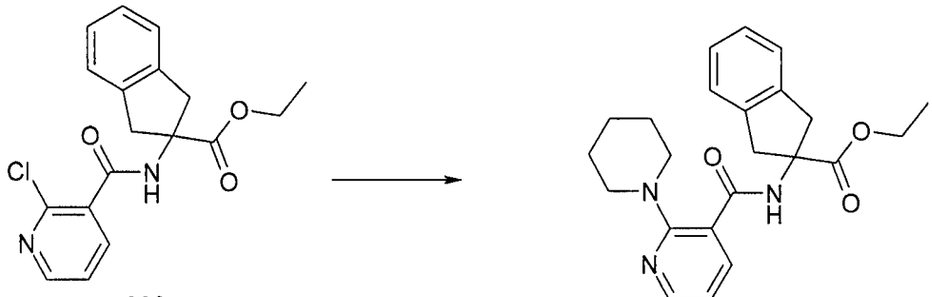
Ácido 2-{[2-(isopropil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (342)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-{[2-(isopropil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico (341, 220 mg, 0,58 mmol) se carga con 1,4-dioxano (2 ml) y MeOH (2 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1 ml) seguido de LiOH monohidrato (61 mg, 1,46 mmol). Después de 16 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 4 días, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de

bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,2 g, 98%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,15 (d,6H), 2,48 (s, 3H), 3,18-3,42 (m,4H), 4,18 (septuplete, 1H), 6,78 (dd, 1H), 7,05-7,12 (m, 4H), 7,67 (dd, 1H), 8,16 (dd, 1H), 8,81 (s, 1H). LC/MS (ES+) m/z = 354,17

Ejemplo 343



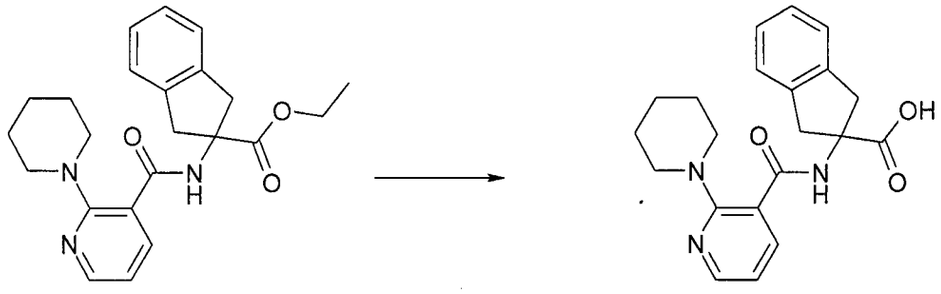
336 343

Éster etílico del ácido 2-[(3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-3'-carbonil)-amino]-indan-2-carboxílico (343)

Un recipiente de reacción para microondas de 25 ml se carga con éster etílico del ácido 2-[2-(cloro-piridina-3-carbonil)-amino]-indan-2-carboxílico (336, 400 mg, 1,16 mmol) y 1,4-dioxano seco (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de 30 segundos, se añaden DIPEA (2,1 ml, 11,6 mmol) y N-metilisopropilamina (1,2 ml, 11,6, mmol). El recipiente de reacción se cierra herméticamente con una tapa corrugada. El recipiente de reacción se pone en un baño de aceite que se calienta a 80°C. Después de 6 días, el análisis por TLC (sílice, 2:1 de EtOAc:heptanos) indica que el material de partida se ha consumido tal como se visualiza por UV. El contenido del matraz de reacción se transfiere a un matraz de fondo redondo y el disolvente se retira al vacío, bombeando hasta alcanzar un peso constante, para proporcionar 0,78 g de un aceite viscoso de color amarillo. El material se disuelve en DCM y se aplica a una columna de cromatografía ISCO (sílice, 40 g). Se aplica un gradiente de EtOAc al 5% en heptanos durante 3 volúmenes de columna seguido de una rampa lineal hasta EtOAc al 60% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 4 a 13 se combinan y se

evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanquecino (0,41 g, 90%).

Ejemplo 344



343 344

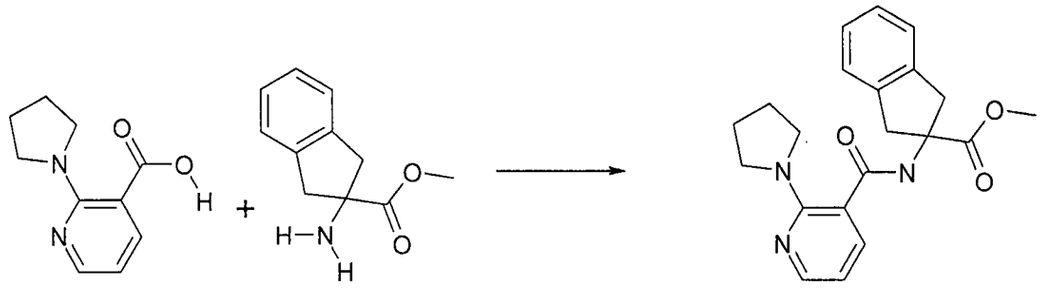
Ácido 2-[(3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-3'-carbonil)-amino]-indan-2-carboxílico (344)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-[(3,4,5,6-tetrahidro-2H-[1,2']bipiridinil-3'-carbonil)-amino]-indan-2-carboxílico (343, 330 mg, 0,84 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH monohidrato (89 mg, 2,12 mmol). Después de 62 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al matraz de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 38 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporcionan 0,3 g de un sólido de color blanco.

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,52 (m,2H), 1,76 (m, 4H), 3,13 (m, 4H), 3,18-3,43 (m, 4H), 3,92 (dd, 2H), 6,94 (dd, 1H), 7,05-7,12 (m, 4H), 7,81 (dd, 1H), 8,24 (dd, 1H), 9,35 (s, 1H).

LC/MS (ES+) m/z = 366,17.

Ejemplo 345



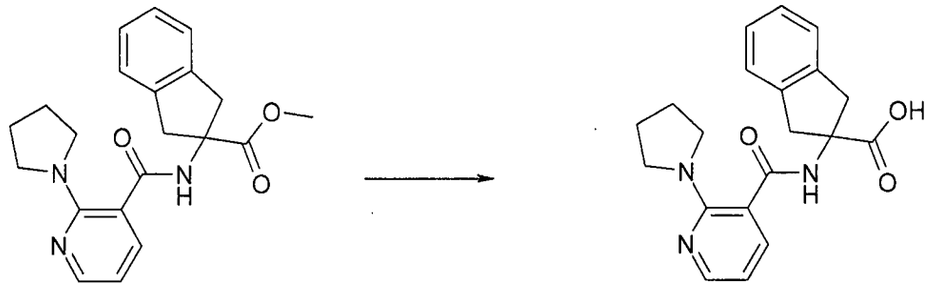
HCl

345

Éster metílico del ácido 2-[(2-pirrolidin-1-il-3-carbonil)-amino]-indan-2-carboxílico (345)

Un vial de reacción de 40 ml que contiene una barra de agitación se carga con ácido 2-(1-pirrolidinil)-nicotínico (422 mg, 2,2 mmol) y DCM seco (6 ml). Se inicia la agitación. Después de 2 min, se añade el HTBU (833 mg, 2,2 mmol). Después de 5 min, se añade sal HCl de éster metílico el ácido 2-amino-indan-2-carboxílico (0,5 g, 2,2 mmol) seguido de DIPEA (1,17 ml, 6,7 mmol). El vial de reacción se cubre y se deja en agitación a temperatura ambiente. Después de 18 h, el análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). Se lava consecutivamente con agua (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (2 x 25 ml) y salmuera (25 ml) y después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,05 g de un sólido de color amarillo claro. Este material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 24 g de sílice. El gradiente es EtOAc al 5% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 60% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 6 a 12 se combinan y se evaporan al vacío para dar un sólido de color blanco (0,73 g, 91%).

Ejemplo 346



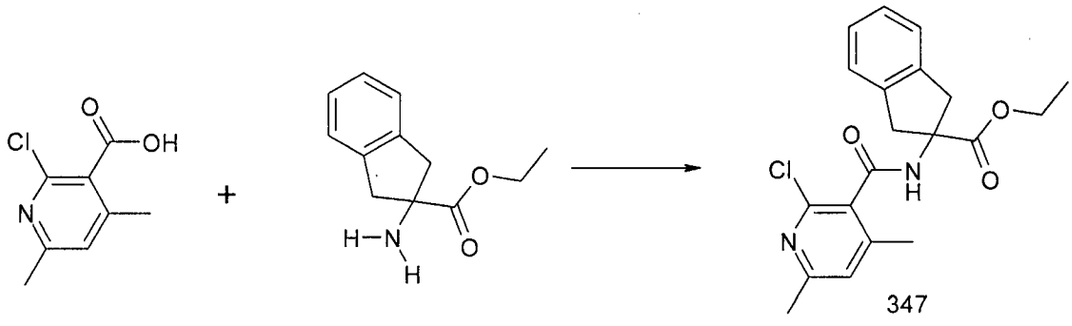
345 346

Ácido 2-[(2-pirrolidin-1-il-3-carbonil)-amino]-indan-2-carboxílico (346)

Un matraz de fondo redondo de 100 ml que contiene éster metílico del ácido 2-[(2-pirrolidin-1-il-3-carbonil)-amino]-indan-2-carboxílico (345, 440 mg, 1,20 mmol) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH monohidrato (128 mg, 3,05 mmol). Después de 30 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al matraz de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 18 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporcionan 0,38 g de un sólido de color blanco.

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,82 (m, 4H), 3,21-3,48 (m, 8H), 3,92 (dd, 2H), 6,59 (dd, 1H), 7,04-7,11 (m, 4H), 7,46 (dd, 1H), 8,08 (dd, 1H), 8,22 (s a, 1H).
LC/MS (ES+) m/z = 352,14.

Ejemplo 347

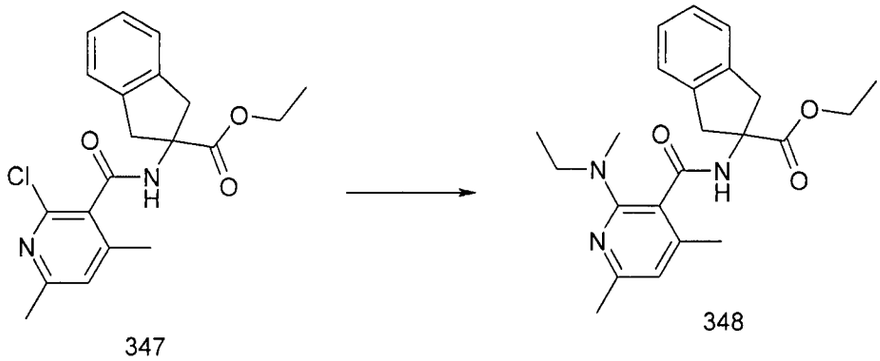


347

Éster etílico del ácido 2-[(2-cloro-4,6-dimetil-piridina-3-carbonil)-amino]-indan-2-carboxílico (347)

Un vial de 40 ml se carga con ácido 2-cloro-4,6-dimetilnicotínico (497 mg, 2,68 mmol) y DCM seco (9 ml). Se añade una barra de agitación y se inicia la agitación. Después de 2 min, se añade el HTBU (1,02 g, 2,68 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino)-indan-2-carboxílico (550 mg, 2,68 mmol) seguido de DIPEA (1,2 ml, 6,74 mmol). La reacción se deja en agitación durante 14 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 15%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (70 ml). Se lava con HCl acuoso diluido (al 3%, 2 x 30 ml), $NaHCO_3$ acuoso saturado (2 x 30 ml) y salmuera (30 ml) y después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,6 g de una espuma de color amarillo. Este material se disuelve en 15 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50% durante 10 volúmenes de columna. Se recogen fracciones de 27 ml del eluyente activo por UV. Las fracciones 32 a 40 se combinan y se evaporan al vacío para dar un material semi-sólido de color amarillo (0,67 g, 67%).

Ejemplo 348

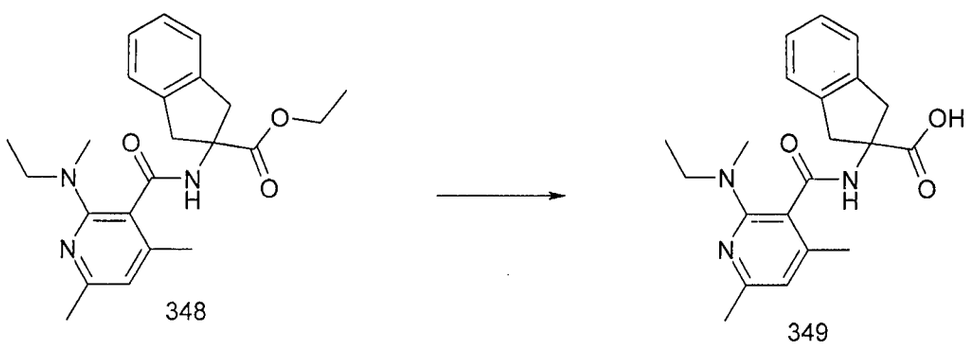


347 348

Éster etílico del ácido 2-{[2-(etil-metil-amino)-4,6-dimetil-piridina-3-carbonil]-amino}-indan-2-carboxílico (348)

Un recipiente de reacción para microondas de 25 ml se carga con éster etílico del ácido 2-[2-(cloro-4,6-dimetil-piridina-3-carbonil]-amino]-indan-2-carboxílico (347, 480 mg, 1,29 mmol) y 1,4-dioxano seco (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de 30 segundos, se añade N-etilmetilamina (2 ml, 23,28 mmol). El recipiente de reacción se cierra herméticamente con una tapa corrugada. El recipiente de reacción se pone en un aparato de microondas Smith Optimizer. La pre-agitación se fija a 20 segundos seguido de calentamiento a 100°C. El tiempo de mantenimiento se fija a 18 min. El análisis por TLC (sílice, 2:1 de EtOAc:heptanos) indica la aparición de una nueva mancha con un valor de R_f mayor tal como se visualiza por UV. El material de partida aún está presente. Se añade N-etilmetilamina (506 µl, 5,89, mmol). El recipiente de reacción se cierra herméticamente con una tapa corrugada. El vial de reacción se sumerge en un baño de aceite que se calienta a 80°C. Después de 5 días, el análisis por tlc (sílice, 2:1 de EtOAc:heptanos) indica que el material de partida se ha convertido en una mancha de mayor movimiento como se visualiza por UV. El contenido del matraz de reacción se transfiere a un matraz de fondo redondo y el disolvente se retira al vacío, bombeando hasta alcanzar un peso constante, para proporcionar 1,3 g de un aceite viscoso de color amarillo. El material se disuelve en DCM (10 ml) y se aplica a una columna de cromatografía ISCO (sílice, 40 g). Se aplica un gradiente de EtOAc al 5% en heptanos durante 3 volúmenes de columna seguido de una rampa lineal hasta EtOAc al 60% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 4 a 9 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,41 g, 83%).

Ejemplo 349

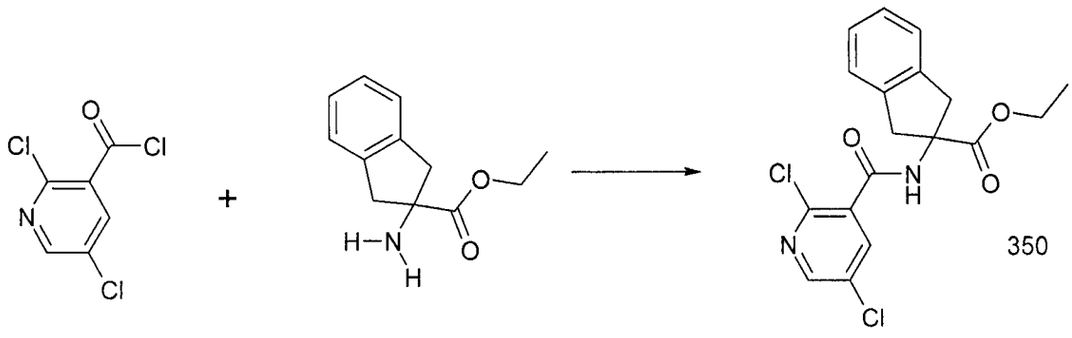


Ácido 2-{[2-(etil-metil-amino)-4,6-dimetil-piridina-3-carbonil]-amino}-indan-2-carboxílico (349)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-{[2-(etil-metil-amino)-4,6-dimetil-piridina-3-carbonil]-amino}-indan-2-carboxílico (348, 260 mg, 0,66 mmol) se carga con 1,4-dioxano (3 ml) y MeOH (3 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH monohidrato (70 mg, 1,66 mmol). Después de 18 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 38 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,18 g, 75%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,03 (t, 3H), 3,17-3,53 (m, 6H), 6,41 (s, 1H), 7,05-7,12 (m, 4H), 8,05 (s, 1H).
LC/MS (ES+) m/z = 368,25.

Ejemplo 350

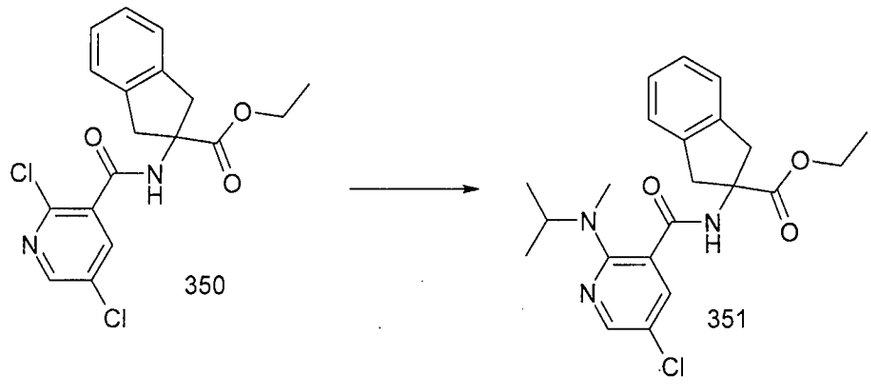


Éster etílico del ácido 2-[(2,5-dicloro-piridina-3-carbonil)-amino]-indan-2-carboxílico (350)

Un vial de reacción de 30 ml se carga con éster etílico del ácido 2-aminoindan-2-carboxílico (1 g, 4,87 mmol) y DCM seco (5 ml). Se añade una barra de agitación y se inicia la agitación. Se añade DIPEA (1,35 ml, 7,8 mmol). Se añaden cloruro de 2,5-dicloro-piridina-3-carbonil

(1,23 g, 5,85 mmol) y DMAP (8 mg, cat.). La reacción se cubre. Después de 57 días, el análisis por tlc (sílice, iPrOH al 10%/DCM) indica que el material de partida se ha consumido completamente. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (60 ml). Se lava con agua (2 x 25 ml), $NaHCO_3$ acuoso saturado (2 x 25 ml) y salmuera (25 ml) y después se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para producir 1,99 g de un sólido de color blanquecino. Éste se diluye con DCM (20 ml) y se aplica a una columna de sílice (80 g) en un ISCO Companion. La columna se eluye con EtOAc al 5% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 75% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente positivo por UV. Las fracciones 12 - 16 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color amarillo claro (1,39 g, 75%).

Ejemplo 351

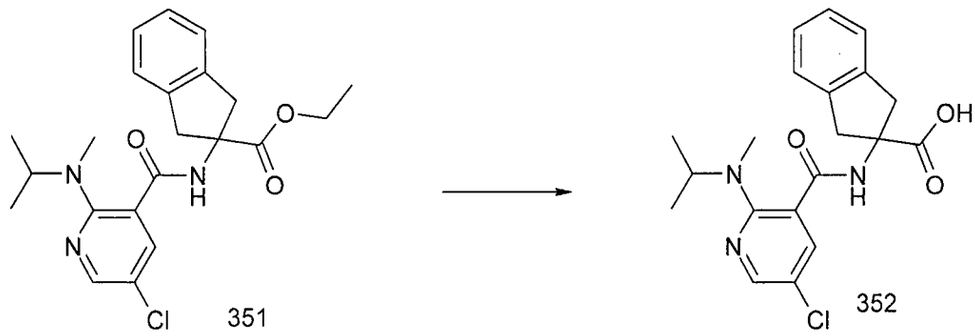


Éster etílico del ácido 2-{[5-cloro-2-(isopropil-metil-amino)-piridina-3-carbonil)-amino]-indan-2-carboxílico (351)

Un vial de reacción de 40 ml se carga con éster etílico del ácido 2-[2-(cloro-piridina-3-carbonil]-amino]-indan-2-carboxílico (350, 400 mg, 1,16 mmol) y 1,4-dioxano seco (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de 30 segundos, se añaden DIPEA (2,1 ml, 11,6 mmol) y N-metilisopropilamina (1,2 ml, 11,6, mmol). El vial de reacción se cierra herméticamente con una tapa recubierta de teflón. El recipiente de reacción se pone en un baño de aceite que se calienta a 80°C. Después de 7 días, el análisis por TLC (sílice, 2:1 de EtOAc:heptanos) indica que el material de partida se ha consumido tal como se visualiza

por UV. El contenido del matraz de reacción se transfiere a un matraz de fondo redondo y el disolvente se retira al vacío, bombeando hasta alcanzar un peso constante, para proporcionar 0,84 g de un aceite viscoso de color amarillo. El material se disuelve en DCM y se aplica a una columna de cromatografía ISCO (sílice, 40 g). Se aplica un gradiente de EtOAc al 5% en heptanos durante 3 volúmenes de columna seguido de una rampa lineal hasta EtOAc al 60% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 2 a 5 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color amarillo claro (0,42 g, 85%).

Ejemplo 352

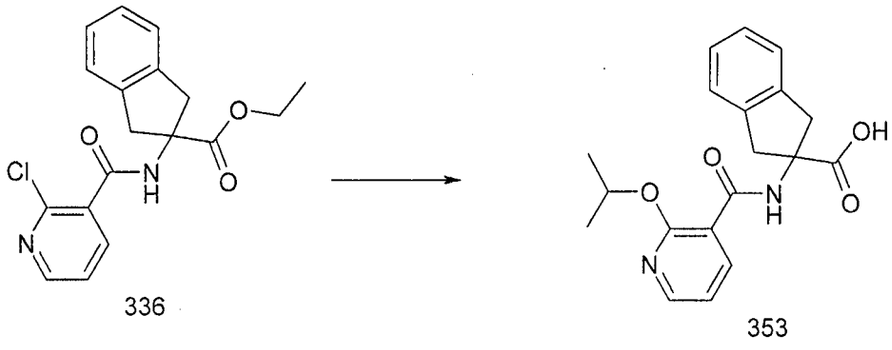


Ácido 2-{[5-cloro-2-(isopropil-metil-amino)-piridina-3-carbonil)-amino]-indan-2-carboxílico (352)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-{[5-cloro-2-(isopropil-metil-amino)-piridina-3-carbonil)-amino]-indan-2-carboxílico (351, 270 mg, 0,58 mmol) se carga con 1,4-dioxano (3 ml) y MeOH (3 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH (62 mg, 1,48 mmol). Después de 18 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 20 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,21 g, 94%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,09 (t, 3H), 2,71 (s, 3H), 3,22-3,48 (m, 4H), 4,18 (septuplete, 1H), 7,04-7,11 (m, 4H), 7,65 (s, 1H), 8,17 (s, 1H), 8,48 (s, 1H), 8,72 (s a, 1H). LC/MS (ES+) m/z = 390,10.

Ejemplo 353



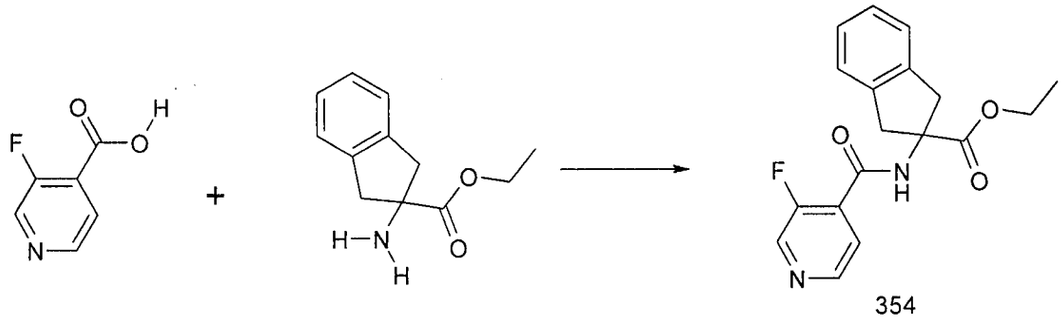
Ácido 2- [2-(isopropoxi-piridina-3-carbonil)-amino]-indan-2-carboxílico (353)

Un vial de reacción para microondas de 10 ml se carga con iPrOH (4 ml, 51,9 mmol). Se añade una barra de agitación y se inicia la agitación. Se añade una suspensión de NaH en aceite (104 mg, 2,61 mmol). Después de 2 min, se añade éster etílico del ácido 2-[(2-cloro-piridina-3-carbonil)-amino]-indan-2-carboxílico (336, 450 mg, 1,31 mmol). El matraz de reacción se cubre ligeramente y se deja en agitación a temperatura ambiente. Después de 7 días, el análisis por tlc (sílice, 2:1 de EtOAc/heptanos) indica que el material de partida se ha consumido. Al matraz de reacción se le añade Resina de Intercambio Iónico Dowex Muy Ácida (0,5 g). El matraz se deja en agitación a temperatura ambiente. Después de 1 semana, la mezcla de reacción se diluye con iPrOH (20 ml) y se filtra a través de una capa de celite. El filtrado se transfiere a un matraz de fondo redondo y se evapora a presión reducida. El residuo se reconstituye con iPrOH (10 ml) y tolueno (10 ml). El disolvente se retira a presión reducida. Las etapas de reconstitución y evaporación se repiten. Después de bombear hasta alcanzar un peso constante, se produce un sólido amorfo de color blanco (0,40 g). Este material se disuelve en DCM (5 ml). Esta solución se aplica a un ISCO Companion que está equipado con una columna de 12 g (sílice). La columna se eluye con ACN al 5% en DCM durante 5 volúmenes de columna seguido de un gradiente lineal hasta ACN al 90% en DCM durante 10 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las

fracciones 6 - 9 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,1 g, 12%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,21 (d, 6H), 3,23-3,58 (m, 4H), 5,33 (septuplete, 1H), 7,13 (dd, 1H), 7,20-7,26 (m, 4H), 8,17 (dd, 1H), 8,29 (dd, 1H), 8,77 (s, 1H) 13,77 (s a, 1H). LC/MS (ES+) m/z = 341,10.

Ejemplo 354

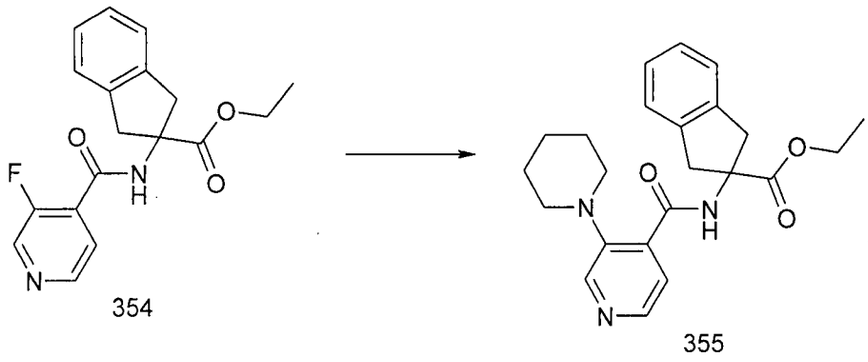


354

Éster etílico del ácido 2-[(2-fluoro-piridina-4-carbonil)-amino]-indan-2-carboxílico (354)

Un vial de reacción de 40 ml que contiene una barra de agitación se carga con ácido 3-fluoroisonicotínico (825 mg, 5,85 mmol) y DCM seco (15 ml). Se inicia la agitación. Después de 2 min, se añade el HTBU (2,22 g, 5,85 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (1,2 g, 5,25 mmol) seguido de DIPEA (2,55 ml, 14,62 mmol). La reacción se deja en agitación durante 7 días. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (75 ml). Se lava consecutivamente con salmuera (25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml) y después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 3,93 g de un sólido de color amarillo claro. Este material se disuelve en 15 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 5% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 65% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 4 a 9 se combinan y se evaporan al vacío. Esto produce un sólido de color blanco (1,5 g, 94%).

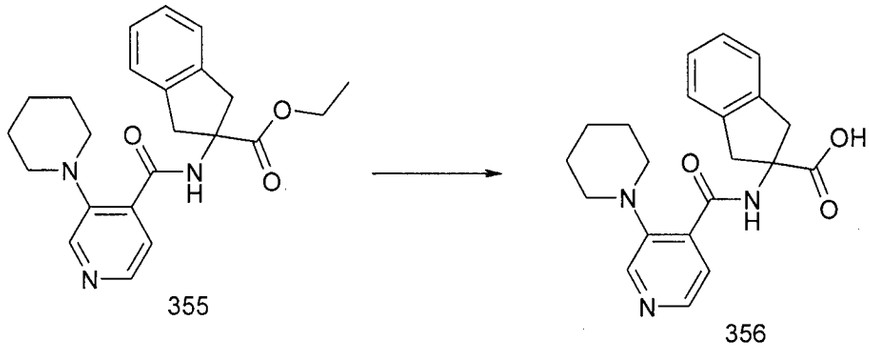
Ejemplo 355



Éster etílico del ácido 2-[(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-4'-carbonil)-amino]-indan-2-carboxílico (355)

Un vial de reacción para microondas de 10 ml se carga con éster etílico del ácido 2-[(3-fluoro-piridina-4-carbonil)-amino]-indan-2-carboxílico (354, 500 mg, 1,52 mmol), 1,4-dioxano (1,5 ml) y piperidina (1,51 ml, 15,23 mmol). Se añade una barra de agitación. El vial de reacción se cierra herméticamente con una tapa corrugada. El vial de reacción se pone en un aparato de reacción de microondas Smith. La temperatura se fija a 150°C con un tiempo de mantenimiento fijado de 10 min. El tiempo de pre-agitación se fija en 20 segundos. El vial de reacción se retira del aparato. La barra de agitación se extrae. El contenido del matraz se transfiere a un matraz de fondo redondo y el disolvente se retira a presión reducida. Después de bombear hasta alcanzar un peso constante, se dan 1,2 g de un semi-sólido de color amarillo. El residuo se disuelve en DCM (10 ml) y se aplica a un ISCO Companion que está equipado con una columna de 40 g (sílice). La columna se eluye con EtOAc/heptanos (al 5%) durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 65%/heptanos durante 10 volúmenes de columna y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 14 ml. Las fracciones 42 - 50 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,56 g, 93%).

Ejemplo 356



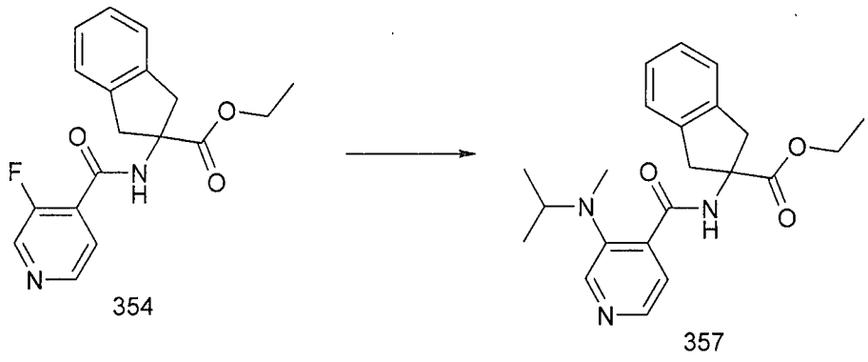
355 356

Ácido 2-[(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-4'-carbonil)-amino]-indan-2-carboxílico (356)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-[(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-4'-carbonil)-amino]-indan-2-carboxílico (355, 370 mg, 0,94 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH monohidrato (100 mg, 2,38 mmol). Después de 68 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 20 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,35 g, 96%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,43 (m, 2H), 1,78 (m, 4H) 2,96 (m, 4H), 3,22-3,46 (m, 4H), 7,05-7,12 (m, 4H), 7,46 (d, 1H), 8,28 (d, 1H), 8,40 (s, 1H), 9,83 (s a, 1H).
LC/MS (ES+) m/z = 366,16.

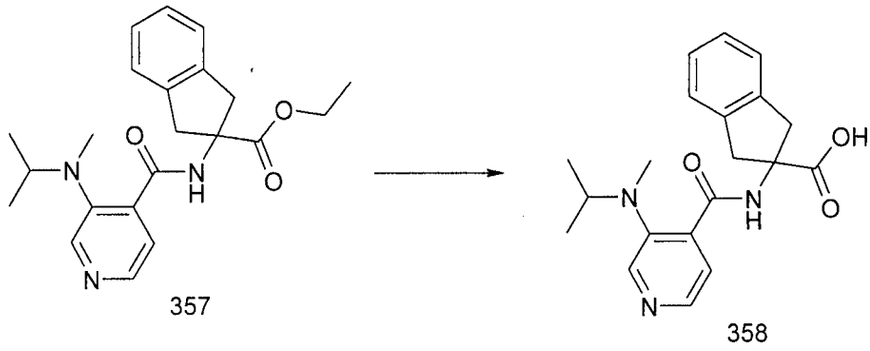
Ejemplo 357



éster etílico del ácido 2-{[3-(isopropil-metil-amino)-piridina-4-carbonil]-amino}-indan-2-carboxílico (357)

Un recipiente de reacción para microondas de 10 ml se carga con éster etílico del ácido 2-[(3-fluoro-piridina-4-carbonil)-amino]-indan-2-carboxílico (354, 500 mg, 1,52 mmol), 1,4-dioxano (2 ml) y piperidina (2 ml, 29,5 mmol). Se añade una barra de agitación. El vial de reacción se cierra herméticamente con una tapa corrugada. El vial de reacción se pone en un aparato de reacción de microondas Smith. La temperatura se fija a 150°C con un tiempo de mantenimiento fijado de 10 min. El tiempo de pre-agitación se fija en 20 segundos. Después de que se complete esta secuencia, el vial de reacción se retira del aparato. La barra de agitación se extrae. El contenido del matraz se transfiere a un matraz de fondo redondo y el disolvente se retira a presión reducida. Después de bombear hasta alcanzar un peso constante, se dan 0,71 g de un jarabe de color pardo. Se disuelve en DCM (10 ml) y se aplica a un ISCO Companion que está equipado con una columna de 40 g (sílice). La columna se eluye con EtOAc/heptanos (al 5%) durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 65%/heptanos durante 10 volúmenes de columna y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 5 -11 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar un 0,29 g de un sólido amorfo de color blanco (0,29 g, 51%).

Ejemplo 358



357 358

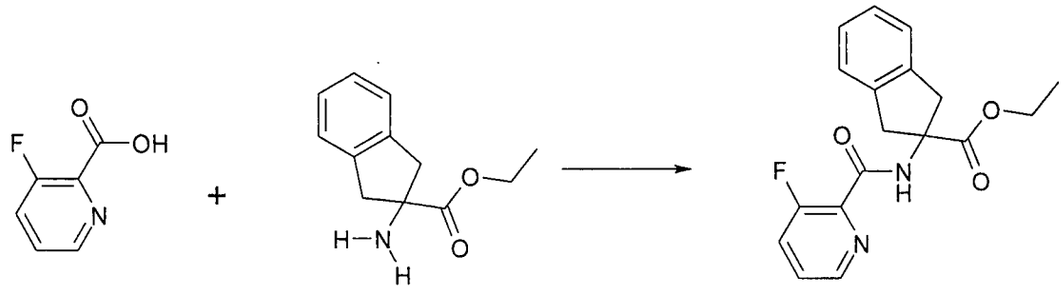
Ácido 2-{[3-(isopropil-metil-amino)-piridina-4-carbonil]-amino}-indan-2-carboxílico (358)

Se carga éster etílico del ácido 2-{[3-(isopropil-metil-amino)-piridina-4'-carbonil]-amino}-indan-2-carboxílico (357, 270 mg, 0,71 mmol) con 1,4-dioxano (3 ml) y MeOH (3 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH monohidrato (75 mg, 1,94 mmol). Después de 4 días, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 3 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,22 g, 88%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,03 (d, 6H), 2,69 (s, 3H), 3,77 (septuplete, 1H), 7,05-7,12 (m, 4H), 7,43 (d, 1H), 8,21 (d, 1H), 8,39 (s, 1H).

LC/MS (ES+) m/z = 354,19.

Ejemplo 359

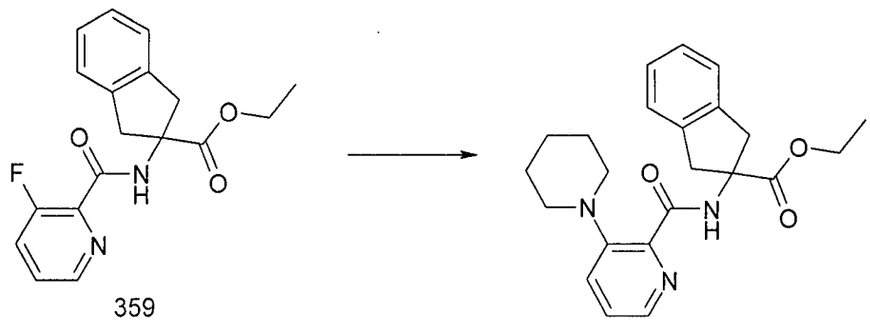


359

Éster etílico del ácido 2-[(3-fluoro-piridina-2-carbonil)-amino]-indan-2-carboxílico (359)

Un vial de reacción de 40 ml que contiene una barra de agitación se carga con ácido 3-fluoropiridina-2-carboxílico (997 mg, 7,07 mmol) y DCM seco (15 ml). Se inicia la agitación. Después de 2 min, se añade el HTBU (2,7 g, 7,07 mmol). Después de 5 min, se añade el éster etílico del ácido 2-amino-indan-2-carboxílico (1,45 g, 7,07 mmol) seguido de DIPEA (2,50 ml, 14,5 mmol). La reacción se deja en agitación durante 18 h. El análisis por tlc de la mezcla de reacción (sílice, iPrOH al 5%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se transfiere a un embudo de decantación y se diluye con EtOAc (50 ml). Se lava consecutivamente con agua (al 3%, 25 ml), $NaHCO_3$ acuoso saturado (2 ml) y salmuera (25 ml), después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 4,15 g de un sólido de color naranja claro. Este material se disuelve en 20 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 80 g de sílice. El gradiente es EtOAc al 5% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 60% en heptanos durante 10 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 6 a 14 se combinan y se evaporan al vacío. Esto produce 2,04 g de un sólido de color blanco (2,04 g, 88%).

Ejemplo 360



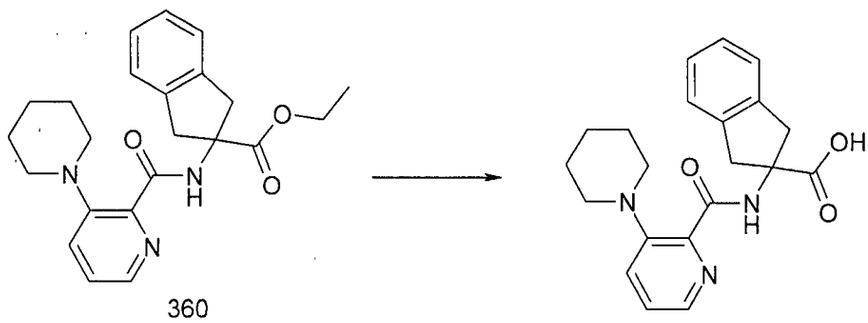
359

360

Éster etílico del ácido 2-[(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-2'-carbonil)-amino]-indan-2-carboxílico (360)

Un vial de reacción para microondas de 10 ml se carga con éster etílico del ácido 2-[(3-fluoro-piridina-2-carbonil)-amino]-indan-2-carboxílico (359, 488 mg, 1,49 mmol), 1,4-dioxano (1,5 ml) y piperidina (1,51 ml, 15,23 mmol). Se añade una barra de agitación. El vial de reacción se cierra herméticamente con una tapa corrugada. El vial de reacción se pone en un aparato de reacción de microondas Smith. La temperatura se fija a 150°C con un tiempo de mantenimiento fijado de 10 min. El tiempo de pre-agitación se fija en 20 segundos. El vial de reacción se retira del aparato. La barra de agitación se extrae. El contenido del matraz se transfiere a un matraz de fondo redondo y el disolvente se retira a presión reducida. Después de bombear hasta alcanzar un peso constante, se dan 1,02 g de un sólido de color blanquecino. Se disuelve en DCM (10 ml) y se aplica a un ISCO Companion que está equipado con una columna de 40 g (sílice). La columna se eluye con EtOAc/heptanos (al 5%) durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 65%/heptanos durante 10 volúmenes de columna y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 2 - 10 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido de color blanco (0,5 g, 86%).

Ejemplo 361



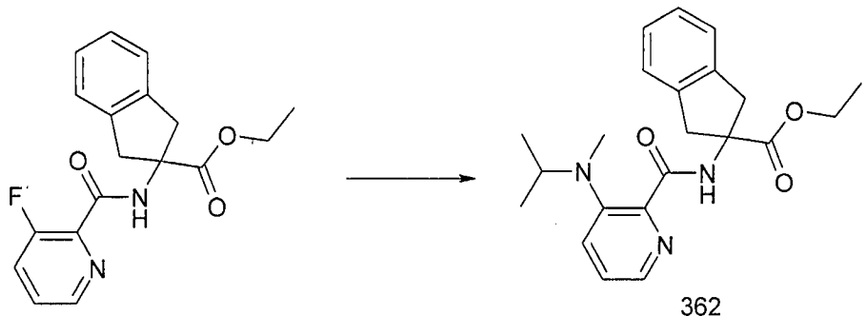
360 361

Ácido 2-[(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-2'-carbonil)-amino]-indan-2-carboxílico (361)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-[(3,4,5,6-tetrahidro-2H-[1,3']bipiridinil-2'-carbonil)-amino]-indan-2-carboxílico (360, 370 mg, 0,94 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH monohidrato (100 mg, 2,38 mmol). Después de 38 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 4 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,29 g, 84%).

^{1}H RMN (300 MHz): δ 1,43 (m, 2H), 1,78 (m, 4H), 2,96 (m, 4H), 3,22-3,46 (m, 4H), 7,05-7,12 (m, 4H), 7,46 (d, 1H), 8,28 (d, 1H), 8,40 (s, 1H), 9,83 (s a, 1H).
LC/MS (ES+) m/z = 366,16.

Ejemplo 362

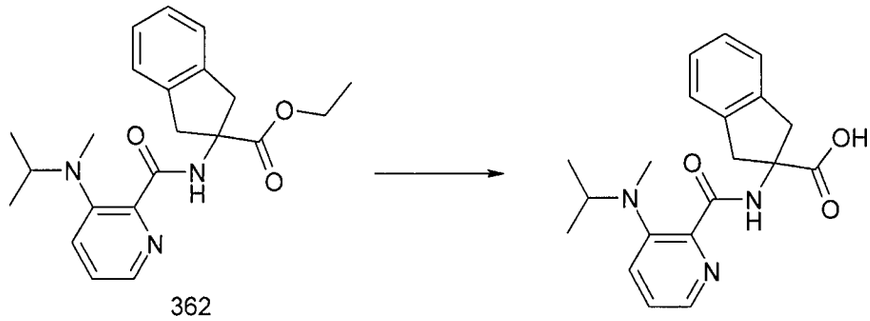


Éster etílico del ácido 2-{[[3-isopropilmetil-amino)-piridina-2-carbonil]-amino}-indan-2-carboxílico (362)

Un recipiente de reacción para microondas de 10 ml se carga con éster etílico del ácido 2-[(3-fluoro-piridina-2-carbonil)-amino]-indan-2-carboxílico (359, 492 mg, 1,5 mmol) y 1,4-dioxano (1,5 ml) y se añaden N-metilisopropilamina (2 ml, 19,25 mmol) y DIPEA (2 ml, 11,48 mmol). Se añade una barra de agitación. El vial de reacción se cierra herméticamente

con una tapa corrugada. El vial de reacción se pone en un aparato de reacción de microondas Smith. La temperatura se fija a 155°C con un tiempo de mantenimiento fijado de 10 min. El tiempo de pre-agitación se fija en 20 segundos. El vial de reacción se retira del aparato. La barra de agitación se extrae. El contenido del matraz se transfiere a un matraz de fondo redondo y el disolvente se retira a presión reducida. Después de bombear hasta alcanzar un peso constante, se dan 0,75 g de un jarabe de color pardo. Se disuelve en DCM (10 ml) y se aplica a un ISCO Companion que se ha equipado con una columna de 40 g (sílice). La columna se eluye con EtOAc/heptanos (al 5%) durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 65%/heptanos durante 10 volúmenes de columna y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 7 - 15 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un sólido amorfo de color blanco (0,38 g, 67%).

Ejemplo 363



362 363

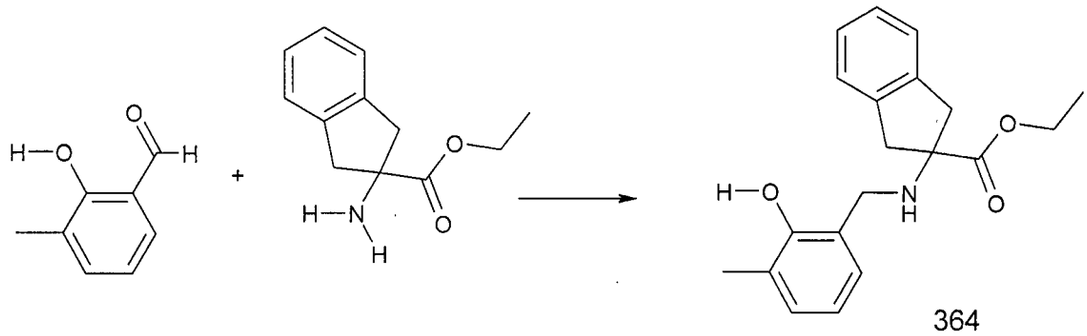
Ácido 2-{[3-isopropilmetil-amino)-piridina-2-carbonil]-amino}-indan-2-carboxílico (363)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-{[[3-isopropilmetil-amino)-piridina-2-carbonil]-amino}-indan-2-carboxílico (362, 370 mg, 0,97 mmol) se carga con 1,4-dioxano (4 ml) y MeOH (4 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2 ml) seguido de LiOH monohidrato (103 mg, 2,46 mmol). Después de 62 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,7 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 4 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se

reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,33 g, 96%).

^{1}H RMN (300 MHz): δ 1,04 (d, 6H), 2,39 (s, 3H), 3,18-3,53 (m, 4H), 3,64 (septuplete, 1H), 7,02-7,12 (m, 4H), 7,28 (dd, 1H), 7,36 (dd, 1H), 7,98 (dd, 1H), 8,84 (s, 1H).
LC/MS (ES+) m/z = 354,17.

Ejemplo 364



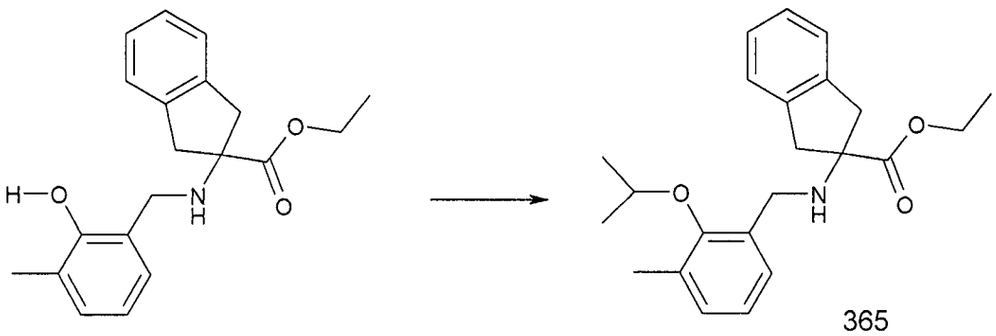
364

Éster etílico del ácido 2-(2-hidroxi-3-metil-bencilamino)-indan-2-carboxílico (364)

Un recipiente de reacción para microondas de 10 ml se carga con éster etílico del ácido 2-amino-indan-2-carboxílico (500 mg, 2,44 mmol) y tetrahidrofurano seco (THF, 5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade 2-hidroxi-3-metil-benzaldehído (0,3 ml, 2,43 mmol). Se continua la agitación. Se añaden fenilsilano (0,61 ml, 4,87 mmol) y dicloruro de dibutilestaño (53 µl, 244 µM). El vial de reacción se cierra herméticamente con una tapa corrugada y se pone en un aparato de microondas Smith. El tiempo de pre-agitación se fija en 10 segundos. El calentamiento se fija a 100°C durante 10 min. El contenido del vial de reacción se transfiere a un matraz de fondo redondo y se evapora, bombeando hasta alcanzar un peso constante, para producir 1,67 g de un sólido de color amarillo claro. Este material se disuelve en DCM (10 ml) y se aplica a un ISCO Companion que está equipado con un cartucho de 40 g (sílice). La columna se eluye con EtOAc al 5%/heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50%/heptanos durante 10 volúmenes de columna y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV.

Las fracciones 5 a 8 se combinan y se evapora, bombeando hasta alcanzar un peso constante, para dar 0,59 g de un material sólido de color blanco (0,59 g, 74%).

Ejemplo 365



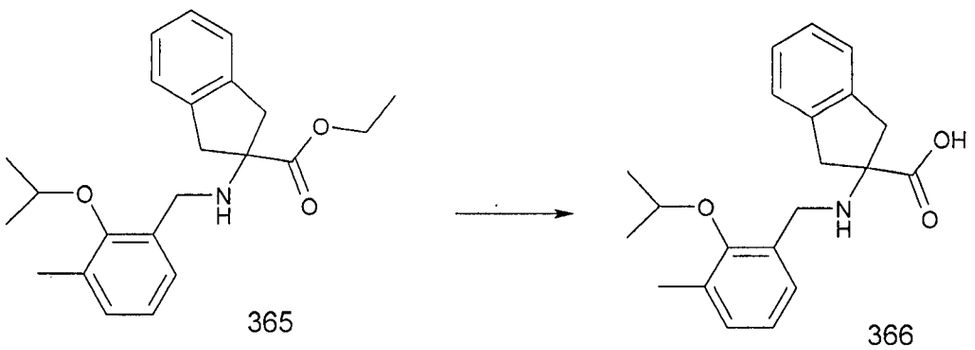
364 365

Éster etílico del ácido 2-(2-isopropoxi-3-metil-bencilamino)-indan-2-carboxílico (365)

Un matraz de fondo redondo de 100 ml que contiene el éster etílico del ácido 2-(2-hidroxi-3-metil-bencilamino)-indan-2-carboxílico (364, 1,01 g, 3,10 mmol) se carga con tetrahidrofurano seco (THF, 10 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añaden sucesivamente iPrOH ([67-63-0], 0,47 ml, 6,21 mmol) y trifenilfosfina ([603-35-0], 1,63 g, 6,21 mmol). Después de la disolución de la trifenilfosfina, se añade azodicarboxilato de diisopropilo (1,20 ml, 6,21 mmol). El matraz de reacción se cubre y se deja en agitación a temperatura ambiente durante una noche. Después de 24 h, el análisis por tlc (sílice, 1:2 de EtOAc:heptanos) indica que el material de partida se ha consumido completamente y se ha convertido en una mancha de mayor movimiento tal como se visualiza por UV. La barra de agitación se retira del matraz de reacción y el disolvente se retira a presión reducida. Después de bombear hasta alcanzar un peso constante, se dan 2,06 g de un aceite viscoso de color amarillo. Se disuelve en DCM (10 ml) y se aplica a un ISCO Companion que se ha equipado con una columna de 40 g (sílice). La columna se eluye con EtOAc/heptanos (al 5%) durante 4 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 60%/heptanos durante 10 volúmenes de columna y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 17 ml del eluyente activo por UV. Las fracciones 5 - 14 se combinan y se evaporan, bombeando hasta alcanzar un peso constante, para dar un residuo viscoso (0,42 g, 37%).

^{1}H RMN (300 MHz): δ 1,18 (d, 6H), 1,22 (t, 3H), 2,18 (s, 3H), 2,98-3,41 (m, 4H), 3,61 (d, 2H), 4,16 (c, 1H), 6,90 (dd, 1H), 7,04 (dd, 1H), 7,11-7,20 (m, 4H)
LC/MS (ES+) m/z = 368,24.

Ejemplo 366

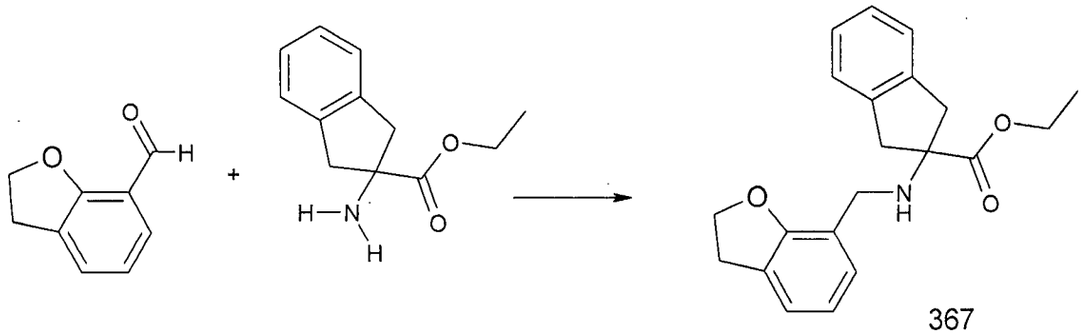


Ácido 2-(2-isopropoxi-3-metil-bencilamino)-indan-2-carboxílico (366)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-(2-isopropoxi-3-metil-bencilamino)-indan-2-carboxílico (365, 360 mg, 0,98 mmol) se carga con 1,4-dioxano (3 ml) y MeOH (3 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH monohidrato (104 mg, 2,47 mmol). Después de 39 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 15 días, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,24 g, 72%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,12 (d, 6H), 2,17 (s, 3H), 2,77-3,68 (m, 6H), 4,16 (septuplete, 1H), 6,84 (dd, 1H), 6,97-7,22 (m, 6H).
LC/MS (ES+) m/z = 340,20.

Ejemplo 367

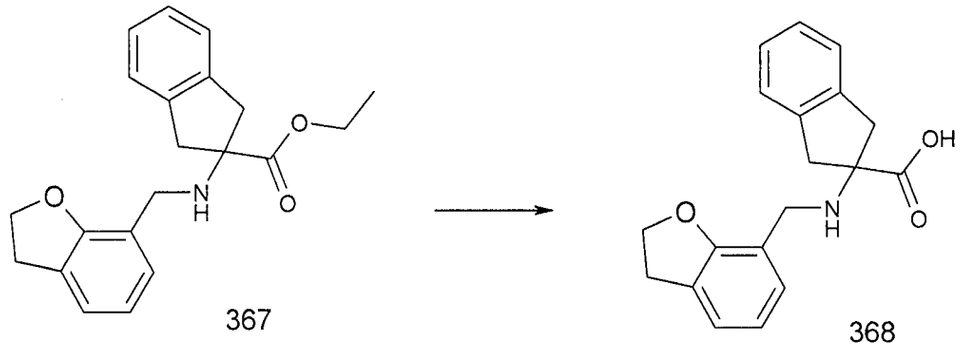


367

Éster etílico del ácido 2-[(2,3-dihidro-benzofuran-7-ilmetil)-amino]-indan-2-carboxílico (367)

Un recipiente de reacción para microondas de 10 ml se carga con éster etílico del ácido 2-amino-indan-2-carboxílico (500 mg, 2,44 mmol) y tetrahidrofurano seco (THF, 5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade 2,3-dihidro-1-benzofuran-7-carbaldehído (361 mg, 2,43 mmol). Se continua la agitación. Se añaden fenilsilano ([694-18-1], 0,61 ml, 4,87 mmol) y dicloruro de dibutilestaño (53 µl, 244 µM). El vial de reacción se cierra herméticamente con una tapa corrugada y se pone en un aparato de microondas Smith. El tiempo de pre-agitación se fija en 10 segundos. El calentamiento se fija a 100°C durante 10 min. El contenido del vial de reacción se transfiere a un matraz de fondo redondo y se evapora, bombeando hasta alcanzar un peso constante, para producir 1,56 g de un aceite de color amarillo claro. Este material se disuelve en DCM (10 ml) y se aplica a un ISCO Companion que está equipado con un cartucho de 40 g (sílice). La columna se eluye con EtOAc al 5%/heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta EtOAc al 50%/heptanos durante 10 volúmenes de columna y después EtOAc al 90%/heptanos durante 2 volúmenes de columna. Se recogen fracciones de 14 ml del eluyente activo por UV. Las fracciones 7 a 11 se combinan y se evapora, bombeando hasta alcanzar un peso constante, para producir 0,59 g de un material sólido de color blanco (0,52 g, 63%).

Ejemplo 368



367 368

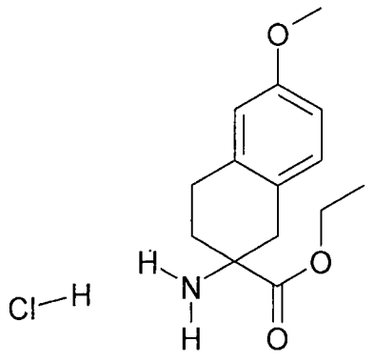
Ácido 2-[(2,3-dihidro-benzofuran-7-ilmetil)-amino]-indan-2-carboxílico (368)

Un matraz de fondo redondo de 100 ml que contiene éster etílico del ácido 2-[(2,3-dihidro-benzofuran-7-ilmetil)-amino]-indan-2-carboxílico (367, 350 mg, 1,037 mmol) se carga con 1,4-dioxano (3 ml) y MeOH (3 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (1,5 ml) seguido de LiOH monohidrato (110 mg, 2,52 mmol). Después de 16 h, el análisis por tlc (sílice, EtOAc al 50%/heptanos) indica que el material de partida se ha consumido completamente. Al vial de reacción se le añade resina de intercambio Amberlyst muy ácida (0,5 g). La reacción se cubre y se deja en agitación a temperatura ambiente. Después de 6 h, el contenido del matraz se filtra a través de una capa de celite. El disolvente se retira del filtrado. El residuo se reconstituye con iPrOH/tolueno (20 + 20 ml) y el disolvente se retira. Este proceso se repite 1 vez. Después de bombear hasta alcanzar un peso constante, se proporciona un sólido de color blanco (0,31 g, 99%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 2,77-3,58 (m, 6H), 3,11 (t, 2H), 4,45 (t, 2H), 6,70 (dd, 1H), 7,02-7,11 (m, 6H).
LC/MS (ES+) m/z = 310,14.

Se sintetizan los ésteres etílicos del ácido 2-amino-1,2,3,4-tetrahidro-naftaleno-2-carboxílico 369, 370, 371, 372 y 373 de acuerdo con el método de Michael Cox en la Solicitud de Patente Europea EP 82-304382.

Ejemplo 369

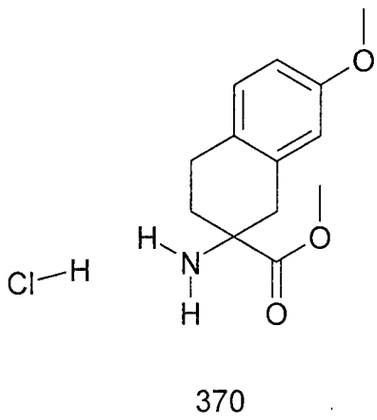


369

Sal hidrocloruro de éster etílico del ácido 2-amino-6-metoxi-1,2,3,4-tetrahidro-naftaleno-2-carboxílico (369)

LC/MS (ES+) m/z = 250,18.

Ejemplo 370



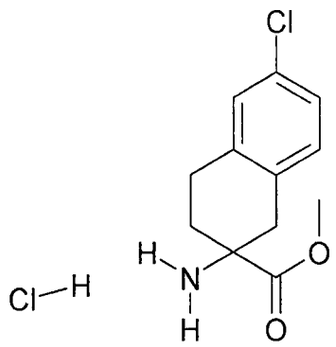
370

Ejemplo 370

Éster metílico del ácido 2-amino-7-metoxi-1,2,3,4-tetrahidro-naftaleno-2-carboxílico; hidrocloruro (370)

LC/MS (ES+) m/z = 336,16.

Ejemplo 371

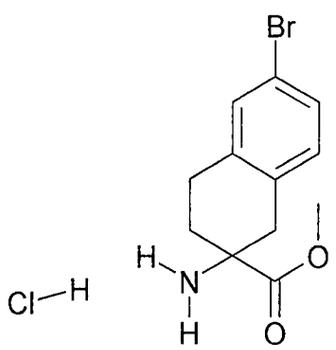


371

Sal hidrocloruro de éster metílico del ácido 2-amino-6-cloro-1,2,3,4-tetrahidro-naftaleno-2-carboxílico (371)

LC/MS (ES+) m/z = 340,11.

Ejemplo 372

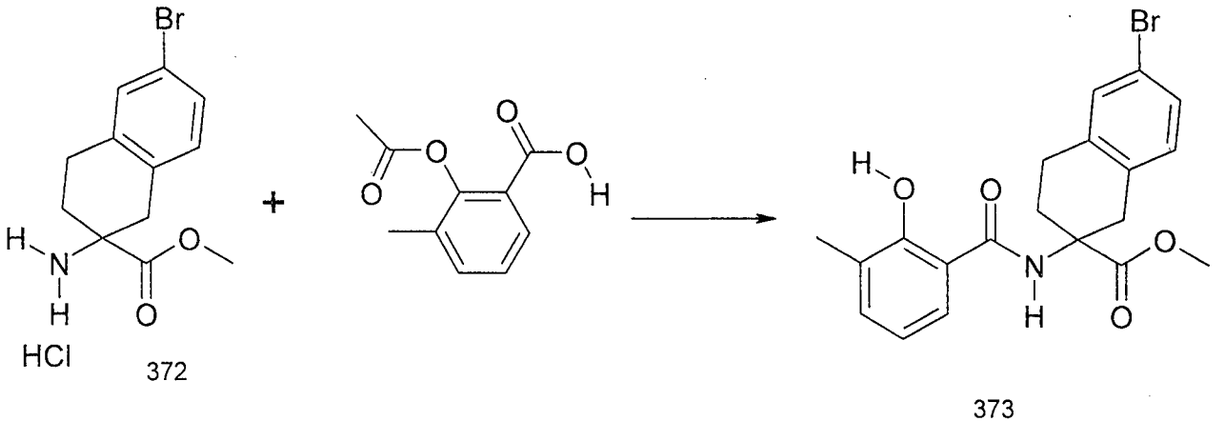


372

Sal hidrocloruro de éster metílico del ácido 2-amino-6-bromo-1,2,3,4-tetrahidro-naftaleno-2-carboxílico (372)

LC/MS (ES+) m/z = 340,11.

Ejemplo 373



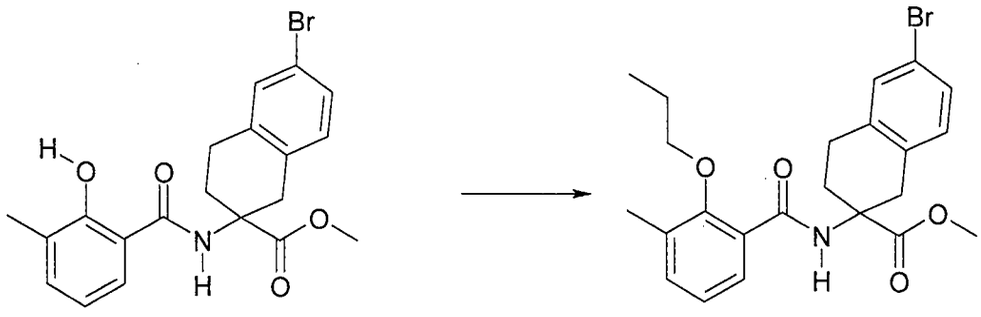
372

373

Éster metílico del ácido 2-(2-hidroxi-3-metil-benzoil)-6-bromo-1,2,3,4-tetrahidroisoquinolina-3-carboxílico (373)

Un vial de 40 ml que contiene una barra de agitación se carga con ácido 2-acetoxil-3-metil-benzoico ([2386-93-4], 1,69 g, 8,7 mmol) y DCM seco (10 ml). Se inicia la agitación. Después de que se complete la disolución, se añade el HTBU (3,29 g, 8,7 mmol). Después de 5 min, se añade la sal hidrocloruro del ácido 2-amino-6-bromo-1,2,3,4-tetrahidro-naftaleno-2-carboxílico (372, 1,25 g, 3,9 mmol) seguido de DIPEA (3,4 ml, 19,5 mmol). Se añade una alícuota de DCM seco (4 ml). La reacción se deja en agitación durante 36 h. El análisis por tlc de la mezcla de reacción (sílice, EtOAc al 50%/heptanos) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (100 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con $NaHCO_3$ acuoso diluido (50 ml) y salmuera (50 ml), se seca sobre $Na2SO_4$, se filtra y se evapora al vacío para proporcionar 5,2 g de una goma espesa de color parduzco. Este material se purifica utilizando un ISCO Companion con un cartucho de 120 g de sílice. El gradiente es EtOAc al 2% en heptanos durante 4 volúmenes de columna seguido de un gradiente lineal hasta acetato de etilo al 30% durante 10 volúmenes de columna y después EtOAc al 100% en heptanos durante 12 volúmenes de columna. Se recogen fracciones de 170 ml del eluyente activo por UV. Las fracciones 13 a 23 se combinan y se evaporan al vacío. Esto produce un material espumoso (0,42 g, 26%).

Ejemplo 374

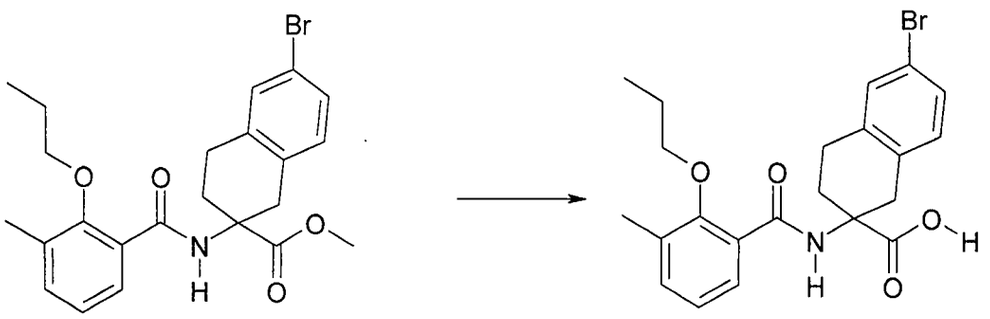


373 374

Éster metílico del ácido 2-(2-propoxi-3-metil-benzoil)-6-bromo-1,2,3,4-tetrahidroisoquinolina-3-carboxílico (374)

Un matraz de fondo redondo de 100 ml que contiene éster metílico del ácido 6-bromo-(2-hidroxoxi-3-metil-benzoilamino)-1,2,3,4-tetrahidronaftaleno-2-carboxílico (373, 0,39 g, 0,932 mmol) y una barra de agitación se carga con DMF seca (10 ml). Se inicia la agitación. Se añaden sucesivamente K_2SO_4 (0,258 g, 1,86 mmol), KI (1 mg, 6 μM) y 1-bromopropano (0,2 ml, 2,24 mmol). El matraz de reacción se sumerge en un baño de aceite y se equipa con un condensador de reflujo. El baño de aceite se calienta a 79°C. La reacción se agita durante 2 h a esta temperatura y después el baño de aceite se retira. Después de 16 h a temperatura ambiente, el calentamiento se reinicia a 53°C durante una hora más. El análisis por tlc (sílice, 1:1 de EtOAc:Heptanos) indica el consumo del material de partida y la aparición de una mancha con un valor de R_f ligeramente inferior. La reacción se deja enfriar de nuevo a temperatura ambiente y se filtra a través de un lecho de celite. La solución resultante se diluye con EtOAc (60 ml) y se lava repetidamente con salmuera (4 x 40 ml), después se seca sobre $MgSO_4$, se filtra y se evapora, bombeando hasta alcanzar un peso constante, para producir un aceite de color amarillo claro (0,42 g, 98%).

Ejemplo 375



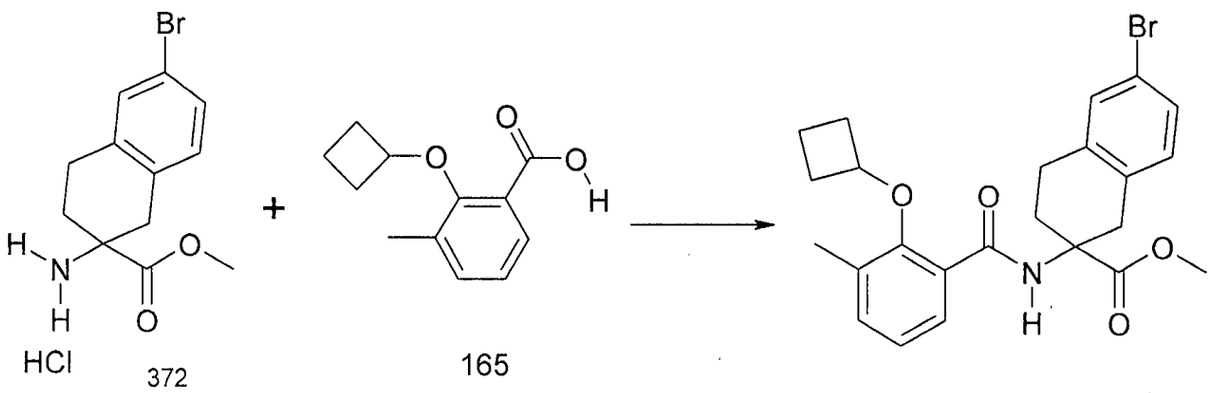
374 375

Ácido 2-(2-propoxi-3-metil-benzoil)-6-bromo-1,2,3,4-tetrahidroisoquinolina-3-carboxílico (375)

Un matraz de 50 ml que contiene el éster etílico del ácido 6-bromo-2-(2-propoxi-3-metil-benzoilamino)-1,2,3,4-tetrahidro-naftaleno-2-carboxílico (374, 0,34 g, 0,74 mmol) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH monohidrato (77 mg, 1,44 mmol). Después de 16 horas, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~12 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se da un sólido de color blanquecino (0,30 g, 91%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 0,82 (t, 3H), 1,43 (m, 1H), 1,96-2,08 (m, 1H), 2,19 (s, 3H), 2,38-2,91 (m, 1H), 2,73-2,91 (m, 2H), 3,02-3,38 (m, 5H), 3,58-3,64 (m, 3H), 7,03 - 7,09 (m, 2H), 7,27 - 7,36 (m, 3H), 8,36 (s, 1H), 12,56 (s a, 1H).
LC/MS m/z = 448,10.

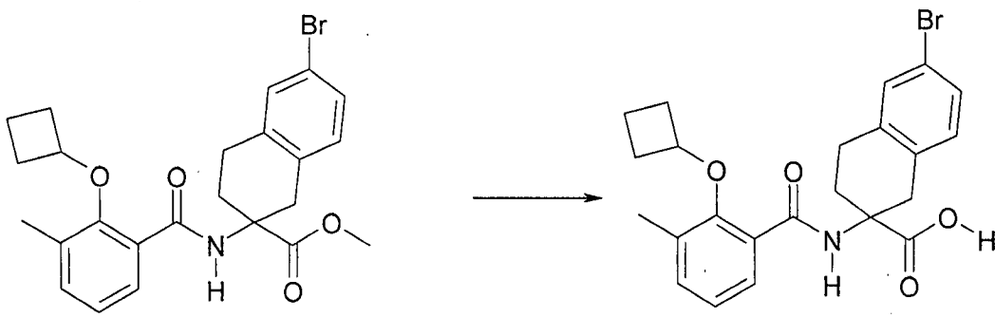
Ejemplo 376



Éster metílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-bromo-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (376)

Un vial de 40 ml que contiene una barra de agitación y el ácido 2-ciclobutoxi-3-metilbenzoico (165, 447 mg, 2,17 mmol) se carga con DCM seco (6,5 ml). Se inicia la agitación. Se añade HTBU (824 mg, 2,17 mmol). Se añade éster metílico del ácido 2-amino-6-bromo-1,2,3,4-tertrahidronaftaleno-2-carboxílico; sal hidrocloruro (372, 590 mg, 2,17 mmol) seguido del DIPEA (1,1 ml, 6,35 mmol). La reacción se deja en agitación durante 18 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con HCl acuoso diluido (1 N, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,18 g de un sólido de color blanquecino. El material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 10 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml. Las fracciones 9 a 15 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar un sólido amorfo de color blanco (0,81 g, 79%).

Ejemplo 377



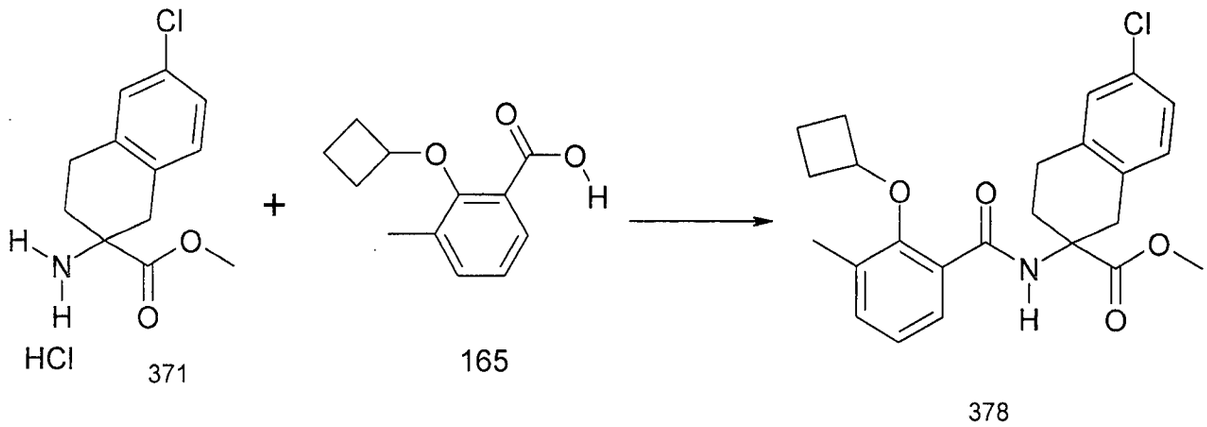
376 377

Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-bromo-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (377)

Un matraz de 50 ml que contiene el éster metílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-bromo-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (376, 0,44 g, 0,93 mmol) se carga con 1,4-dioxano (9 ml) y MeOH (9 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (4,5 ml) seguido de LiOH monohidrato (173 mg, 4,12 mmol). Después de 64 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se da un sólido de color blanquecino (0,40 g, 98%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,17-1,34 (m, 1H), 1,39-1,57 (m, 1H), 1,78-2,16 (m, 4H), 2,21 (s, 3H), 2,37-2,42 (m, 1H), 2,74-2,98 (m, 2H), 3,15-3,27 (m, 3H), 4,34 (m, 1H), 7,01 - 7,11 (m, 2H), 7,25 - 7,35 (m, 3H), 8,34 (s, 1H), 12,53 (s a, 1H).
LC/MS m/z = 460,05

Ejemplo 378

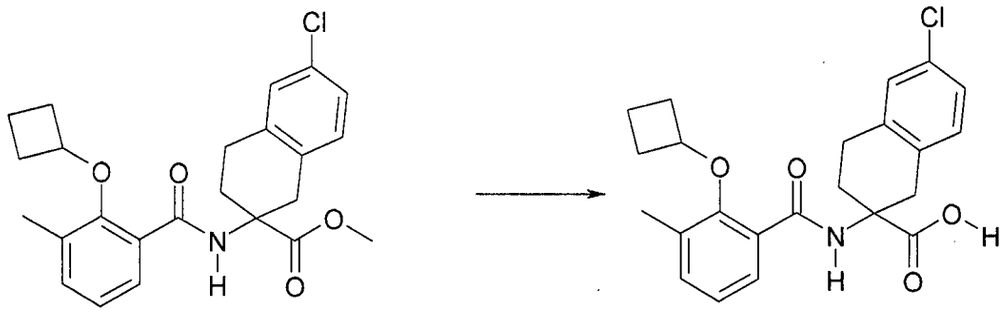


371 165 378

Éster metílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-cloro-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (375)

Un vial de 40 ml que contiene una barra de agitación y el ácido 2-ciclobutoxi-3-metilbenzoico (165, 447 mg, 2,17 mmol) se carga con DCM seco (6,5 ml). Se inicia la agitación. Se añade HTBU (824 mg, 2,17 mmol). Se añade éster metílico del ácido 2-amino-6-cloro-1,2,3,4-tertrahidronaftaleno-2-carboxílico; sal hidrocloruro (371, 590 mg, 2,17 mmol) seguido del DIPEA (1,1 ml, 6,35 mmol). La reacción se deja en agitación durante 18 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con HCl acuoso diluido (1 N, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml), después se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,18 g de un sólido de color blanquecino. El material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 10 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml del eluyente activo por UV. Las fracciones 2 a 11 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar un sólido amorfo de color blanco (0,65 g, 70%).

Ejemplo 379



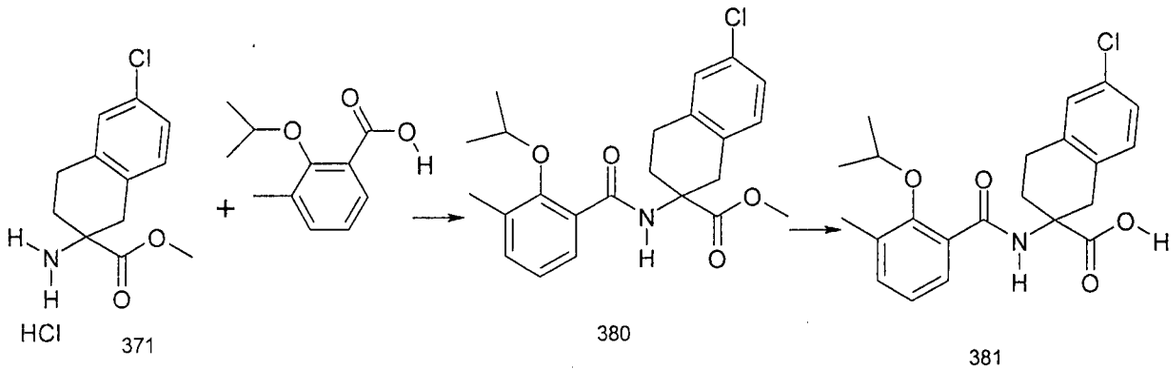
378 379

Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-cloro-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (379)

Un matraz de 50 ml que contiene el éster metílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-cloro-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (378, 0,42 g, 0,98 mmol/g) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH monohidrato (103 mg, 2,45 mmol). Después de 260 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se da un sólido de color blanquecino (0,38 g, 93%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,08-1,17 (m, 1H), 1,21-1,36 (m, 1H), 1,78-2,13 (m, 4H), 2,21 (s, 3H), 2,37-2,43 (m, 1H), 2,77-2,98 (m, 2H), 3,17-3,37 (m, 3H), 4,34 (m, 1H), 7,02 (dd, 1H), 7,10 - 7,35 (m, 5H), 8,35 (s, 1H), 12,57 (s a, 1H).
LC/MS m/z = 414,15

Ejemplos 380 y 381



371 380 381

Éster metílico del ácido 2-(2-isopropoxi-3-metil-benzoilamino)-6-cloro-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (380)

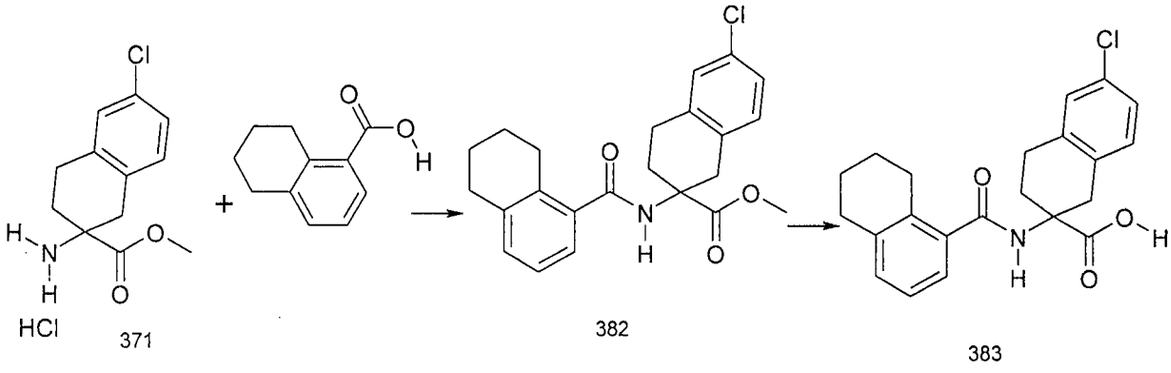
Ácido 2-(2-isopropoxi-3-metil-benzoilamino)-6-cloro-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (381)

Se sintetiza ácido 2-(2-isopropoxi-3-metil-benzoilamino)-6-cloro-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (381) de acuerdo con el procedimiento del producto 379 anterior, con la excepción de que se usan ácido 2-isopropoxi-3-metilbenzoico y ácido 2-ciclobutoxi-3-metilbenzoico en vez de ácido 2-ciclobutoxi-3-metilbenzoico en la etapa de formación del enlace amida. Rendimiento = 94% para la etapa uno. La etapa 2 produce un material sólido de color blanco (0,43 g, 81%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 0,98 (d, 3H), 1,03 (d, 3H), 1,97-2,07 (m, 1H), 2,21 (s, 3H), 2,38-2,42 (m, 1H), 2,76-2,93 (m, 2H), 3,08-3,41 (m, 3H), 4,19 (m, 1H), 7,03 (dd, 1H), 7,11 - 7,20 (m, 3H), 7,27 - 7,35 (m, 2H), 8,35 (s, 1H), 12,52 (s a, 1H).

LC/MS m/z = 414,15

Ejemplos 382 y 383



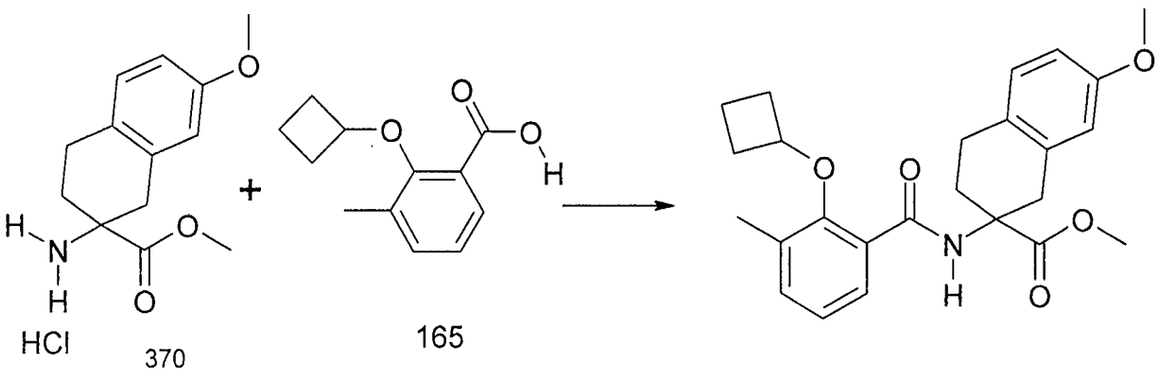
371 382 383

Ácido 6-cloro-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-1,2,3,4-tetrahidro-naftaleno-2-carboxílico (383)

Se sintetiza ácido 6-cloro-2-[(5,6,7,8-tetrahidronaftaleno-1-carbonil)-amino]-1,2,3,4-tetrahidronaftaleno-2-carboxílico (383) de acuerdo con el procedimiento del producto 379 anterior, con la excepción de que se usa ácido 5,6,7,8-tertrahidro-1-naftaleno carboxílico en vez de ácido 2-ciclobutoxi-3-metilbenzoico en la etapa de formación del enlace amida. Rendimiento = 83% para la etapa uno. La etapa 2 produce un material sólido de color blanco (0,42 g, 99%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,56-1,78 (m, 4H), 1,88-2,08 (m, 1H), 2,33-2,41 (m, 1H), 2,48-3,07 (m, 8H), 6,92 (dd, 1H), 7,03 - 7,18 (m, 5H), 8,72 (s, 1H), 12,49 (s a, 1H).
LC/MS m/z = 384,11

Ejemplo 384

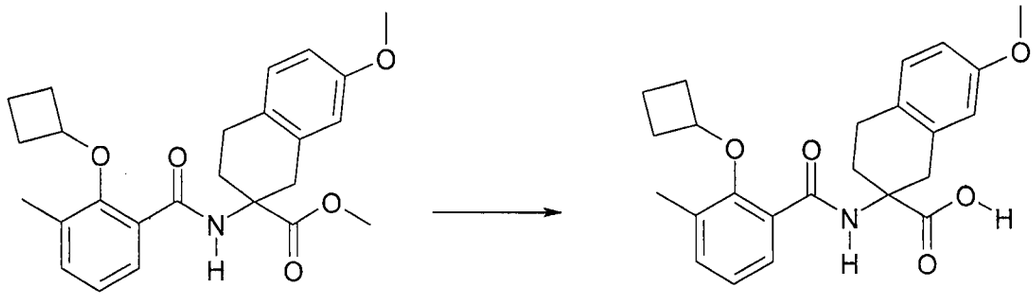


Éster metílico del ácido 6-metoxi-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-1,2,3,4-tetrahidro-naftaleno-2-carboxílico (384)

Un vial de 40 ml que contiene una barra de agitación y el ácido 2-ciclobutoxi-3-metilbenzoico (165, 447 mg, 2,17 mmol) se carga con DCM seco (6,5 ml). Se inicia la agitación. Se añade HTBU (824 mg, 2,17 mmol). Se añaden sal hidrocloruro de éster metílico del ácido 2-amino-7-metoxi-1,2,3,4-tertrahidronaftaleno-2-carboxílico (370, 590 mg, 2,17 mmol) seguido del DIPEA (1,1 ml, 6,35 mmol). La reacción se deja en agitación durante 18 h. El análisis por tlc de la mezcla de reacción (sílice, MeOH al 10%/DCM) indica el consumo completo de la amina de partida. El contenido del matraz de reacción se diluye con EtOAc (50 ml) y se transfiere a un embudo de decantación. Se lava consecutivamente con HCl acuoso diluido (1

N, 25 ml), $NaHCO_3$ acuoso saturado (25 ml) y salmuera (25 ml), se seca sobre $MgSO_4$, se filtra y se evapora al vacío para proporcionar 1,2 g de un sólido de color blanquecino. El material se disuelve en 10 ml de DCM. Este material se purifica utilizando un ISCO Companion con un cartucho de 40 g de sílice. El gradiente es EtOAc al 10% en heptanos durante 3 volúmenes de columna seguido de un gradiente lineal hasta 50% durante 10 volúmenes de columna y después EtOAc al 90% durante 2 volúmenes de columna con una rampa de 1 volumen de columna. Se recogen fracciones de 25 ml del eluyente activo por UV. Las fracciones 9 a 15 se combinan y se evaporan al vacío, bombeando hasta alcanzar un peso constante, para dar un sólido amorfo de color blanco (0,86 g, 83%).

Ejemplo 385



384 385

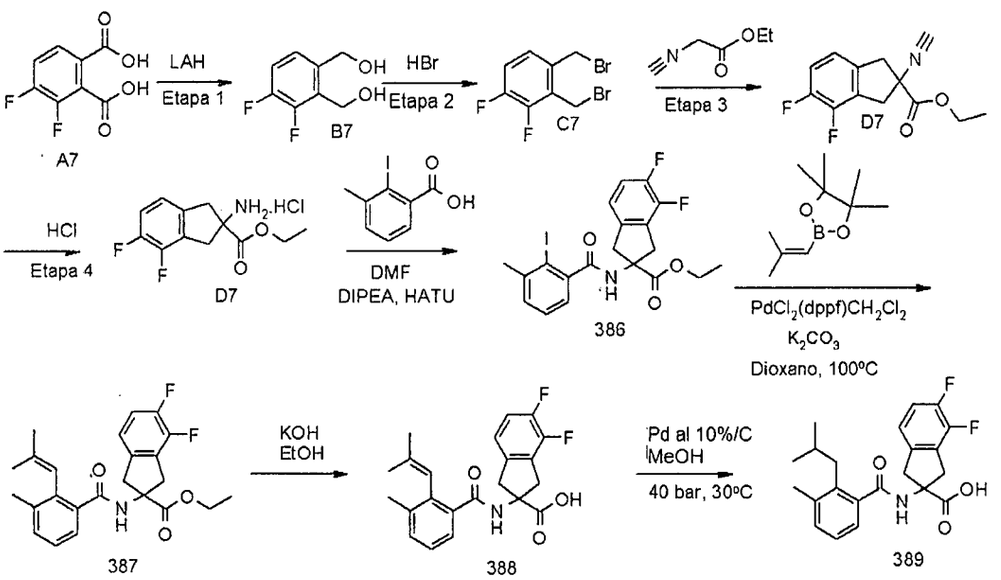
Ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-metoxi-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (385)

Un matraz de 50 ml que contiene el éster metílico del ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-6-metoxi-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-2-carboxílico (384, 0,45 g, 1,06 mmol) se carga con 1,4-dioxano (5 ml) y MeOH (5 ml). Se añade una barra de agitación y se inicia la agitación. Después de la disolución, se añade agua (2,5 ml) seguido de LiOH monohidrato (111 mg, 2,65 mmol). Después de 37 h, el análisis por tlc (sílice, i-PrOH al 5%/DCM) indica que el material de partida se ha consumido completamente. El valor del pH de la mezcla de reacción se ajusta cuidadosamente a pH 2 mediante la adición lenta de HCl acuoso diluido (al 3%, ~10 ml). El contenido del matraz se vierte en un embudo de decantación que contiene EtOAc (30 ml). Las capas se separan. La capa acuosa se extrae con EtOAc (20 ml). Los extractos orgánicos combinados se lavan con agua (20 ml) y salmuera (20 ml), después se secan sobre $MgSO_4$, se filtran y se concentran. Después de bombear hasta alcanzar un peso constante, se da un sólido de color blanquecino (0,43 g, 99%).

^{1}H RMN (300 MHz, DMSO-d_6): δ 1,18-1,33 (m, 1H), 1,41-1,57 (m, 1H), 1,79-2,11 (m, 4H), 2,21 (s, 3H), 2,37-2,43 (m, 1H), 2,63-2,91 (m, 2H), 3,07-3,37 (m, 3H), 3,41 (s, 3H), 4,37 (m, 1H), 6,69-6,72 (m, 2H), 7,00-7,05 (m, 2H), 7,26 - 7,35 (m, 2H), 8,31 (s, 1H), 12,49 (s a, 1H).

LC/MS m/z = 410,15

Ejemplos 386 - 389:



(2,3-difluoro-6-hidroximetil-fenil)-metanol (A7)

A una suspensión de LAH (6,2 g, 0,163 mol) en THF seco (100 ml) se le añade una solución del compuesto ácido 3,4-difluoro-ftálico (15 g, 0,074 mol) en THF (75 ml), gota a gota a 0°C. la mezcla resultante se calienta a reflujo durante 3 h. Después de 3 h, la mezcla de reacción se enfría y se inactiva con una solución saturada de Na_2SO_4. Después, la masa de reacción se filtra a través de una capa de celite y el lecho se lava minuciosamente con MeOH. El filtrado combinado se concentra para producir un producto en bruto que se purifica por cromatografía en columna (sílice, MeOH al 5% en DCM). La combinación de las fracciones apropiadas, seguido de la retirada del disolvente, produce un sólido de color blanco (7 g, 54,2%).

1,2-Bis-bromometil-3,4-difluoro-benceno (B7)

Una suspensión de (2,3-difluoro-6-hidroximetil-fenil)-metanol (8 g, 0,046 mol) en 80 ml de HBr ac. (al 47%) se agita a 80°C durante 3 h. Después de que se complete el consumo del material de partida, la mezcla de reacción se enfría a TA y se extrae con EtOAc. La capa

orgánica combinada se lava con salmuera, se seca y se concentra para dar un sólido de color pardo (13 g, 94,2%) que se usa sin purificación adicional.

Éster etílico del ácido 4,5-difluoro-2-isociano-indan-2-carboxílico: (C7)

Una mezcla del compuesto 1,2-bis-bromometil-3,4-difluoro-benceno (8 g, 0,027 mol), isocianoacetato de etilo (3,01 g, 0,0266 mol), K_2CO_3 (22,07 g, 0,159 mol) e hidrogenosulfato de tetrabutilamonio (5,45 g, 0,016 mol) en ACN (200 ml) se calienta a reflujo durante una noche. Después de que se complete el consumo del material de partida, la mezcla de reacción se enfría a TA y el ACN se retira a presión reducida. A la masa en bruto se le añade agua (300 ml) y después se extrae con EtOAc (3 x 250 ml). Los extractos orgánicos combinados se lavan con agua, se secan y se concentran para dar un producto en bruto. El producto en bruto se purifica por cromatografía en columna (sílice, EtOAc al 3% en hexano) y el disolvente se retira para dar un líquido viscoso (1,6 g, 23,7%).

Sal hidrocloruro de éster etílico del ácido 4,5-difluoro-2-amino-indan-2-carboxílico (D7)

Una solución agitada de éster etílico del ácido 4,5-difluoro-2-isociano-indan-2-carboxílico (6 g, 0,0237 mol) en EtOH (100 ml) se sumerge en un baño de hielo-agua y se deja enfriar. Después de la refrigeración, se añade HCl concentrado (5 ml). La mezcla de reacción se retira del baño de hielo-agua, se deja volver a la temperatura ambiente y se agita durante 3 h. Después, la mezcla de reacción se concentra, se diluye con agua y se extrae con éter (2 x 50 ml). La capa orgánica se desecha, la capa acuosa se enfría y el valor del pH se ajusta a 9-10 usando una solución ac. de amoniaco. La solución resultante se extrae con EtOAc (3 x 100 ml). Los extractos combinados se lavan con agua, se secan y se concentran para dar una masa viscosa (4,5 g, 78%). Esta masa en bruto se enfría inmediatamente a 5°C, se acidifica con HCl metanólico y se concentra para dar sal hidrocloruro de éster etílico del ácido 4,5-difluoro-2-amino-indan-2-carboxílico.

Éster etílico del ácido 4,5-difluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (386):

A una solución de ácido 2-yodo-3-metil-benzoico (1,31 g, 5 mmol), sal HCl de éster etílico del ácido 2-amino-4,5-difluoro-indan-2-carboxílico (D7, 1,38 g, 5 mmol) y HATU [O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio PF6, 3,8 g, 10 mmol) en DMF anhidra (20 ml) se le añade DIPEA (N,N-diisopropiletilamina, 3,3 ml, 15 mmol). La solución resultante se

agita a temperatura ambiente durante dos días. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en acetato de etilo (200 ml) y se lava con $NaHCO_3$ saturado (1 x 100 ml) y salmuera (2 x 100 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo obtenido se purifica por cromatografía en columna ultrarrápida (24 g de gel de sílice, gradiente de elución: EtOAc al 0%-50% en heptano) para dar un producto puro (386) en forma de un sólido de color blanco (1,93 g, 79%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,15 (t, 3H), 1,20 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 4,25 (m, 2H), 7,13-7,30 (m, 3H), 7,52 (m, 2H)
LC/MS (ES+) m/z = 486,1

Éster etílico del ácido 4,5-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (387):

A una solución de éster etílico del ácido 6-(4,5-difluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (386) (2,55 g, 5,25 mmol) y pinacol éster del ácido 2-metil-1-propenil borónico (364 mg, 10,5 mmol) en dioxano (100 ml) se le añaden aducto de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) y diclorometano (350 mg, al 8,2% en mmol) y una solución acuosa 2 M de K_2CO_3 (7,87 ml, 15,75 mmol). La mezcla de reacción resultante se carga con N_2, se calienta a 100°C y se agita continuamente durante 6 h. La mezcla de reacción se filtra y se concentra al vacío y el residuo resultante se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0%-50% en heptano) para dar un producto puro (387) en forma de un sólido de color pardo claro (1,24 g, 57%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,10 (t, 3H), 1,16 (s, 3H), 1,66 (s, 3H), 2,12 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 4,25 (m, 2H), 6,06 (s, 1H), 7,13-7,30 (m, 3H), 7,52 (m, 2H)
LC/MS (ES+) m/z = 414,47

Ácido 4,5-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (388):

Se disuelve éster etílico del ácido 4,5-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (387) (650 mg, 1,57 mmol) en EtOH (50 ml) y la mezcla se deja en agitación a TA. A esta solución se le añade KOH 5 M (4 ml). La mezcla de reacción se agita

a TA durante una noche. Después de la concentración al vacío, el residuo obtenido se disuelve en agua (20 ml) y se lava con EtOAc (20 ml). Las fases se separan y la fase acuosa se acidifica con HCl concentrado hasta alcanzar un valor de pH de 2. El precipitado sólido se recoge por filtración, se seca al vacío y después se purifica en una HPLC. El producto deseado (388) se obtiene en forma de un sólido de color blanco (440,0 mg, 73%).

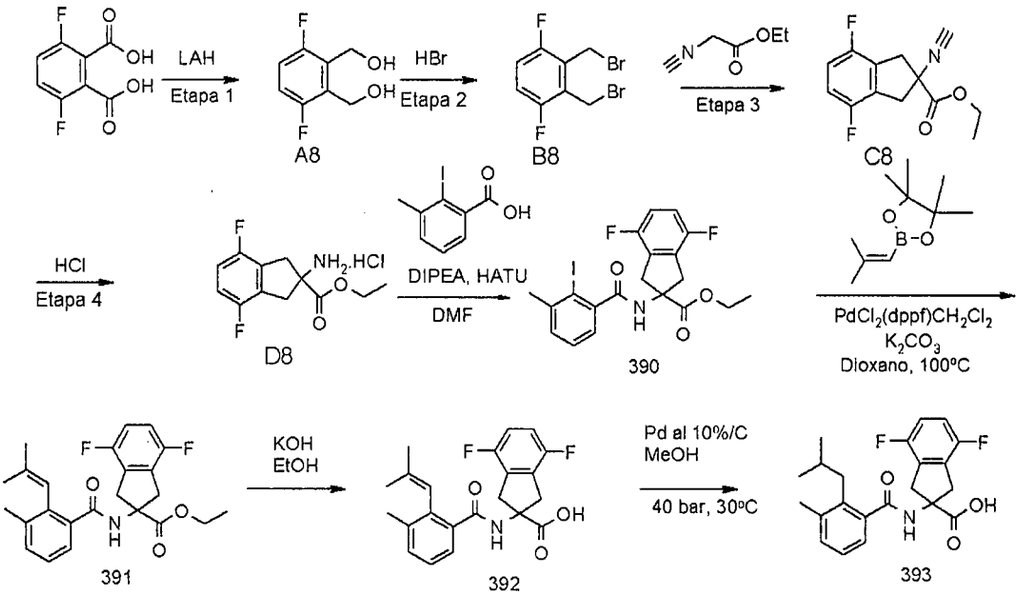
^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,16 (s, 3H), 1,66 (s, 3H), 2,12 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 6,06 (s, 1H), 7,08-7,36 (m, 5H)
LC/MS (ES+) m/z = 386,3

Ácido 4,5-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico (389)

Una solución de ácido 4,5-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (388) (220 mg, 0,57 mmol) en metanol (40 ml) se hidrogena usando catalizador de paladio al 10%/carbono a 40 bar y 30°C usando el H-Cube de Thales Nanotechnology durante 24 horas. El metanol se concentra a sequedad al vacío para dar el producto (389) en forma de un polvo sólido de color blanco.

^{1}H RMN (DMSO-d_6, 300 MHz): δ 0,77 (d, 6H), 1,74 (m, 1H), 2,27 (s, 3H), 2,62 (d, 2H), 3,31 (d, 2H), 3,48 (d, 2H), 7,00-7,39 (m, 5H)
LC/MS (ES+) m/z = 388,3

EJEMPLOS 390-393



Se prepara sal HCl de éster etílico del ácido 2-amino-4,7-difluoro-indan-2-carboxílico a partir de

ácido 3,6-difluoro-ftálico como se indica por el esquema anterior con respecto a A7-D7 utilizando los mismos procedimientos que para la síntesis de sal HCl de éster etílico del ácido 2-amino-4,5-difluoro-indan-2-carboxílico.

<u>Éster etílico del ácido 4,7-difluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (390):</u>

A una solución de ácido 2-yodo-3-metil-benzoico (1,31 g, 5 mmol), sal HCl de éster etílico del ácido 2-amino-4,7-difluoro-indan-2-carboxílico (1,38 g, 5 mmol) y HATU [O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio PF6, 3,80 g, 10 mmol) en DMF anhidra (20 ml) se le añade DIPEA (N, N-diisopropiletilamina, 3,3 ml, 15 mmol). La solución resultante se agita a TA durante 2 días. Después de la retirada de la DMF al vacío, el residuo obtenido se disuelve en EtOAc (200 ml) y se lava con $NaHCO_3$ saturado (1 x 100 ml) y salmuera (2 x 100 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo obtenido se purifica por cromatografía en columna ultrarrápida (40 g de gel de sílice, gradiente de elución: EtOAc al 0%-80% en heptano) para dar un producto puro (390) en forma de un sólido de color blanco (1,83 g, 75%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,15 (t, 3H), 1,20 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 4,25 (m, 2H), 7,13-7,30 (m, 5H)

LC/MS (ES+) m/z = 486,1

Éster etílico del ácido 4,7-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (391):

A una solución de éster etílico del ácido 4,7-difluoro-2-(2-yodo-3-metil-benzoilamino)-indan-2-carboxílico (390) (451 mg, 1 mmol) y pinacol éster del ácido 2-metil-1-propenil borónico (364 mg, 2 mmol) en dioxano (20 ml) se le añaden aducto de dicloro[1,1'-bis(difenilfosfino)-ferroceno]paladio (II) y diclorometano (65 mg, al 8,2% en mmol) y una solución acuosa 2 M de K_2CO_3 (1,5 ml, 3 mmol). La mezcla de reacción resultante se carga con N_2, se calienta a 100°C y se agita continuamente durante 4 h. La mezcla de reacción se filtra y se concentra al vacío y el residuo resultante se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0%-50% en heptano) para dar un producto puro (391) en forma de un aceite de color pardo claro (150 mg, 36%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,10 (t, 3H), 1,16 (s, 3H), 1,66 (s, 3H), 2,12 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 4,25 (m, 2H), 6,06 (s, 1H), 7,13-7,30 (m, 5H)
LC/MS (ES+) m/z = 414,47

Ácido 4,7-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (392):

Se disuelve éster etílico del ácido 4,7-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (391) (133 mg, 0,32 mmol) en EtOH (20 ml) y la mezcla se deja en agitación a TA. A esta solución se le añade KOH 5 M (2 ml). La mezcla de reacción se agita a TA. Después de la concentración al vacío, el residuo obtenido se disuelve en agua (20 ml) y se lava con EtOAc (20 ml). Las fases se separan y la fase acuosa se acidifica con HCl concentrado hasta alcanzar un valor de pH de 2. La fase acuosa se lava con 100 ml de EtOAc. Las fases orgánicas se recogen y se concentran a sequedad y después el residuo resultante se purifica en una HPLC. El producto deseado (392) se obtiene en forma de un sólido de color blanco (38 mg, 28%).

^{1}H RMN (DMSO-d_6, 300 MHz): δ 1,21 (s, 3H), 1,66 (s, 3H), 2,12 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 6,06 (s, 1H), 7,08-7,36 (m, 5H)
LC/MS (ES+) m/z = 386,3

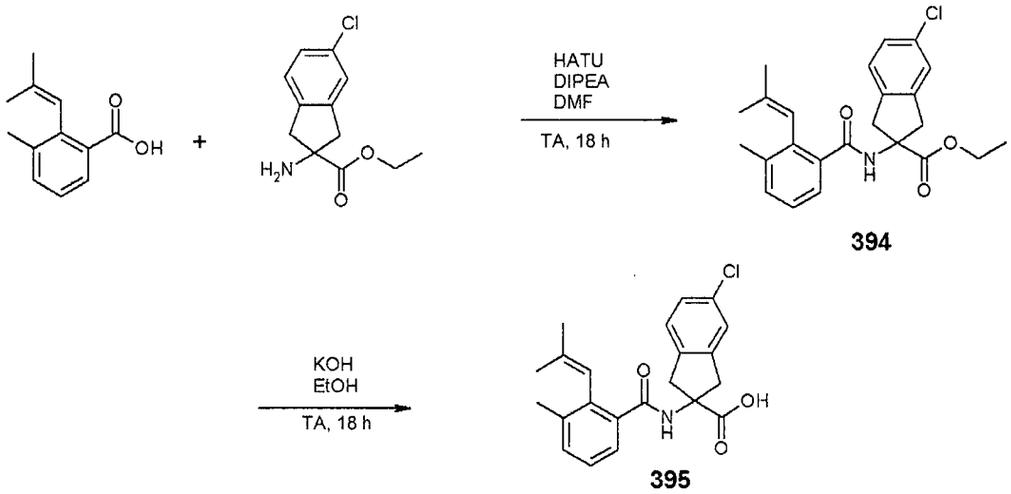
Ácido 4,7-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico (393)

Una solución de ácido 4,7-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (392) (82 mg, 0,21 mmol) en MeOH (40 ml) se hidrogena usando catalizador de paladio al 10%/carbono a 40 bar y 30°C usando el H-Cube de Thales Nanotechnology durante 5 h. El MeOH se concentra a sequedad al vacío para dar el producto (393) en forma de un polvo sólido de color blanco.

^{1}H RMN (DMSO-d_6, 300 MHz): δ 0,76 (d, 6H), 1,72 (m, 1H), 2,28 (s, 3H), 2,61 (d, 2H), 3,42 (d, 2H), 3,51 (d, 2H), 6,93-7,30 (m, 5H)

LC/MS (ES+) m/z = 388,3

EJEMPLOS 394-395



Éster etílico del ácido 5-cloro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (394):

A una solución de ácido 3-metil-2-(2-metil-propenil)-benzoico (95 mg, 0,50 mmol), éster etílico del ácido 5-cloro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (120 mg, 0,5 mmol) y HATU [O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio PF6, 380 mg, 1 mmol) en DMF anhidra (10 ml) se le añade DIPEA (N, N-diisopropiletilamina, 0,25 ml, 1,5 mmol). La solución resultante se agita a TA durante 18 h. Después de la retirada de la DMF al vacío, el residuo resultante se disuelve en EtOAc (200 ml) y se lava con $NaHCO_3$ saturado (1 x 100 ml) y salmuera (2 x 100 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo resultante se purifica por cromatografía en

columna ultrarrápida (40 g de gel de sílice, gradiente de elución: EtOAc al 0%-50% en heptano) para dar un producto puro (394) en forma de un sólido de color blanco (120 mg, 58%).

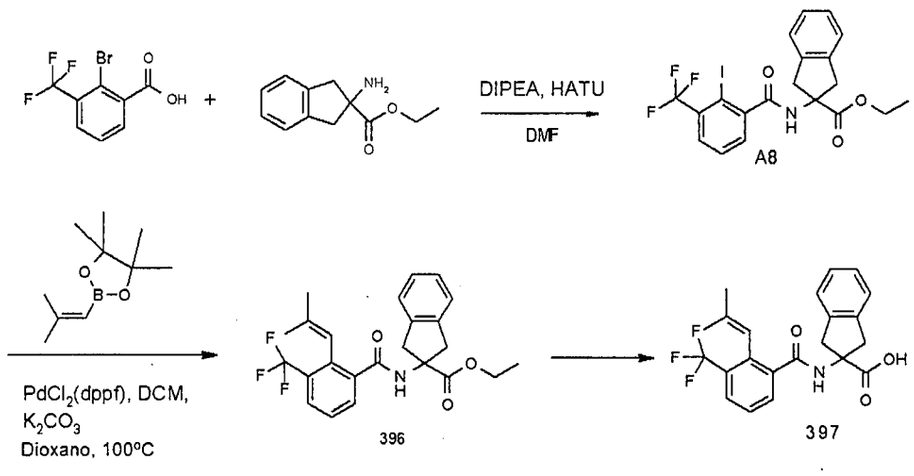
^{1}H RMN (d-DMSO, 300 MHz): δ 1,10 (t, 3H), 1,16 (s, 3H), 1,66 (s, 3H), 2,12 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 4,25 (m, 2H), 6,06 (s, 1H), 7,13-7,30 (m, 6H)
LC/MS (ES+) m/z = 411,93

Ácido 5-cloro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (395):

Se disuelve éster etílico del ácido 5-cloro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico (394) (120 mg, 0,3 mmol) en EtOH (20 ml) y la mezcla se deja en agitación a TA. A esta solución se le añade KOH 5 M (2 ml). La mezcla de reacción se agita a TA durante una noche. Después de la concentración al vacío, el residuo resultante se disuelve en agua (20 ml) y se lava con EtOAc (20 ml). Las fases se separan y la fase acuosa se acidifica con HCl concentrado hasta alcanzar un valor de pH de 2. La fase acuosa se lava con 100 ml de EtOAc. Las fases orgánicas se recogen y se concentran a sequedad y después el residuo resultante se purifica en una HPLC. El producto deseado (395) se obtiene en forma de un sólido de color blanco (73 mg, 63%).

^{1}H RMN (d-DMSO, 300 MHz): δ 1,21 (s, 3H), 1,66 (s, 3H), 2,12 (s, 3H), 3,24 (d, 2H), 3,48 (d, 2H), 6,06 (s, 1H), 7,08-7,36 (m, 6H)
LC/MS (ES+) m/z = 383,88

EJEMPLOS 394-395



Éster etílico del ácido 2-(2-yodo-3-trifluorometil-benzoilamino)-indan-2-carboxílico (A8):

A una solución de ácido 2-bromo-3-(trifluorometil) benzoico (5 g, 18,59 mmol),éster etílico del ácido 2-amino-indan-2-carboxílico (3,82 g, 18,59 mmol), HATU (14,14 g, 37,19 mmol) en DMF anhidra (75 ml) se le añade DIPEA (6,15 ml, 37,19 mmol). La solución resultante se agita a TA durante una noche. Después de la retirada de la DMF al vacío, el residuo resultante se disuelve en EtOAc (100 ml) y se lava con $NaHCO_3$ saturado (1 x 100 ml) y salmuera (2 x 100 ml). La capa orgánica se seca sobre Na_2SO_4 anhidro y se concentra al vacío. El residuo obtenido se purifica por cromatografía en columna ultrarrápida (115 g de gel de sílice, gradiente de elución: acetato de etilo al 0%-50% en heptano) para dar un producto puro (A8) en forma de un sólido de color pardo claro (4,9 g, 58%).

^{1}H RMN (d-DMSO, 300 MHz): 1,15 (t, 3H), 1,20(s, 3H), 3,24(d, 2H), 3,48(d, 2H), 4,25 (m, 2H), ,12-7,28(m, 4H), 7,55(m, 2H), 7,75 (d, 1H)
LC/MS (ES+) m/z = 455,1

Éster etílico del ácido 2-[2-(2-metil-propenil)-3-trifluorometil-benzoilamino]-indan-2-carboxílico (396):

A una solución de éster etílico del ácido 42-(2-yodo-3-trifluorometil-benzoilamino)-indan-2-carboxílico (A8) (500 mg, 1,10 mmol) y pinacol éster del ácido 2-metil-1-propenil borónico (400 mg, 2,20 mmol) en dioxano (20 ml) se le añaden aducto de dicloro[1,1'-bis(difenilfosfino)-ferroceno]paladio (II) (71,8mg, 8,2% en mmol) y una solución acuosa 2 M de K_2CO_3 (1,65 ml, 3,30 mmol). La mezcla de reacción resultante se carga con N_2, se calienta

a 100°C y se agita continuamente durante la noche. La mezcla de reacción se filtra y se concentra al vacío y el residuo resultante se purifica por cromatografía en columna ultrarrápida (12 g de gel de sílice, gradiente de elución: EtOAc al 0%-50% en heptano) para dar un producto puro (396) en forma de un aceite de color pardo claro (100 mg, 21%).

^{1}H RMN (d-DMSO, 300 MHz): 1,10 (t, 3H), 1,66(s, 3H), 2,12(s, 3H), 3,24(d, 2H), 3,48(d, 2H), 4,25 (m, 2H), 6,06 (s, 1H), ,12-7,28(m, 4H), 7,55(m, 2H), 7,75 (d, 1H)
LC/MS (ES+) m/z = 431,27

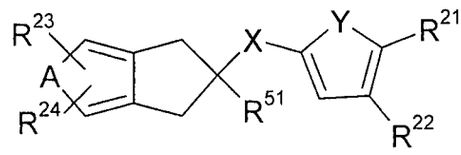
Ácido 2-[2-(2-metil-propenil)-3-trifluorometil-benzoilamino]-indan-2-carboxílico (397):

Se disuelve éster etílico del ácido 2-[2-(2-metil-propenil)-3-trifluorometil-benzoilamino]-indan-2-carboxílico (2) (100 mg, 0,32 mmol) en EtOH (20 ml) y la mezcla se deja en agitación a TA. A esta solución se le añade KOH 5 M (2 ml). La mezcla de reacción se calienta a reflujo y se agita durante 1 h. Después de la concentración al vacío, el residuo resultante se disuelve en agua (10 ml) y se lava con EtOAc (20 ml). Las fases se separan y la fase acuosa se acidifica con HCl concentrado hasta alcanzar un valor de pH de 2. La fase acuosa se lava con 50 ml de éter (3X). Las fases orgánicas se recogen, se concentran a sequedad, después el residuo resultante se purifica en una HPLC. El producto deseado (397) se obtiene en forma de un sólido de color blanco (40,0 mg, 43%).

^{1}H RMN (d-DMSO, 300 MHz): 1,21(s, 3H), 1,66(s, 3H), 2,12(s, 3H), 3,24(d, 2H), 3,48(d, 2H), 6,06 (s, 1H), 7,12-7,28(m, 4H), 7,55(m, 2H), 7,75 (d, 1H)
LC/MS (ES+) m/z = 403,13

Reivindicaciones:

1. Un compuesto de la fórmula Ia



en la que:

A es CH=CH o S;

R^{23} es hidrógeno, halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-S- o nitro;

R^{24} es hidrógeno o halógeno cuando A es CH=CH, o es hidrógeno, halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-S-, o nitro cuando A es S;

X es N(H)C=O, N(H)S(O)$_2$, C=ON(H) o S(O)$_2$N(H);

Y es N(R^{11}), S, O, C(R^{12})=C(R^{13}), N=C(R^{14}) o C(R^{15})=N, o carbociclilo condensado de 5-7 miembros opcionalmente sustituido;

R^{11} es hidrógeno, alquilo (C_1-C_{10}), hidroxi-alquil (C_1-C_{10})-, alquiloxi (C_1-C_{10}), alquil (C_1-C_{10})-S(O)$_m$-, alquilcarbonil (C_1-C_{10})-, fenilo, amino, alquilamino (C_1-C_{10}) o di(alquil (C_1-C_{10}))amino;

R^{12} es hidrógeno, halógeno, alquilo (C_1-C_{10}), alquenilo (C_2-C_{10}), cicloalquiloxi (C_3-C_6), cicloalqueniloxi (C_3-C_{10}), cicloalquilo (C_3-C_6), cicloalquenilo (C_3-C_{10}), cicloalquil (C_3-C_6)-alquilo[(C_1-C_4) o alquenilo (C_2-C_4)], cicloalquil (C_3-C_6)-alquiloxi(C_1-C_4), hidroxialquilo(C_1-C_{10}), alquiloxi (C_1-C_{10}), alqueniloxi (C_2-C_{10}), alquil (C_1-C_{10})-S-, ciano, alquilcarbonilo (C_1-C_{10}), fenilo o nitro;

R^{13} es hidrógeno, halógeno o alquilo (C_1);

R^{14} es hidrógeno, halógeno, alquilo (C_1-C_4), hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{14} no supere 4;

R^{15} es hidrógeno, halógeno, alquilo (C_1-C_{10}), alquenilo (C_2-C_{10}), cicloalquilo (C_3-C_6), cicloalquenilo (C_3-C_6), cicloalquil (C_3-C_6)-[alquilo (C_1-C_4) o alquenilo (C_2-C_4)], hidroxi-alquil (C_1-C_{10})-, ciano, alquilcarbonil (C_1-C_{10})-, fenilo, amino, [alquil (C_1-C_{10}) o alquenil (C_2-C_{10})-]amino, [alquil (C_1-C_{10}) o alquenil (C_2-C_{10})](alquil (C_1-C_{10}))amino o nitro;

R^{21} es hidrógeno cuando Y es $C(R^{12})=C(R^{13})$, $N=C(R^{14})$ o $C(R^{15})=N$, y es hidrógeno, halógeno, alquilo (C_1-C_4), hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro cuando Y es $N(R^{11})$, S o O, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{21} no supere 4;

R^{22} es hidrógeno, halógeno, alquilo (C_1) cuando Y es $C(R^{12})=C(R^{13})$, $N=C(R^{14})$ o $C(R^{15})=N$, o es hidrógeno, hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-$S(O)_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro cuando Y es $N(R^{11})$, S o O, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{22} no supere 4;

R^{51} es COOH o $CONH(R^{53})$;

R^{53} es R^{55}-SO_2- o tetrazolilo;

R^{55} es alquilo (C_1-C_4) o fenilo opcionalmente sustituido con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-sulfonilo y ciano; y

m es 0, 1 ó 2;

donde todos los grupos fenilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_{1-4}), alquiloxi (C_{1-4}), alquilsulfonilo (C_{1-4}) y ciano;

donde todos los grupos alquilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más átomos de flúor; o

una forma estereoisomérica del mismo, una mezcla de formas estereoisoméricas del mismo en cualquier proporción o una sal fisiológicamente aceptable del mismo.

2. El compuesto de acuerdo con la reivindicación 1, en el que

R^{23} es hidrógeno, halógeno, alquilo (C_1-C_4) o alquiloxi (C_1-C_4);

R^{24} es hidrógeno o halógeno cuando A es CH=CH, o es hidrógeno, halógeno o alquilo (C_1-C_4) cuando A es S;

X es N(H)C=O, N(H)S(O)$_2$ o C=ON(H);

Y es C(R^{12})=C(R^{13}) o C(R^{15})=N, o carbociclo de 5-6 miembros, opcionalmente sustituido y condensado;

R^{12} es alquilo (C_1-C_6), alquenilo (C_3-C_6), cicloalquiloxi (C_4-C_6), cicloalquilo (C_5-C_6), cicloalquenilo (C_5-C_6), cicloalquil (C_3)-[alquilo (C_2) o alquenilo (C_2)], cicloalquil (C_3)-alquiloxi (C_1), alquiloxi (C_3-C_4), alqueniloxi (C_3), alquil (C_1-C_3)-S-, alquilcarbonilo (C_3), fenilo;

R^{13} es hidrógeno, halógeno o alquilo (C_1);

R^{15} es alquilo (C_1-C_6), alquenilo (C_2-C_6) o [alquil (C_2-C_3) o alquenil (C_3)](alquil (C_1))amino;

R^{21} es hidrógeno cuando Y es $C(R^{12})=C(R^{13})$ o $C(R^{15})=N$;

R^{22} es hidrógeno o halógeno, alquilo (C_1) cuando Y es $C(R^{12})=C(R^{13})$ o $C(R^{15})=N$;

R^{51} es COOH;

donde todos los grupos fenilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_{1-4}), alquiloxi (C_{1-4}), alquilsulfonilo (C_{1-4}) y ciano;

donde todos los grupos alquilo de esta memoria pueden estar independientemente entre sí opcionalmente sustituidos con uno o más átomos de flúor; o

una forma estereoisomérica del mismo, una mezcla de formas estereoisoméricas del mismo en cualquier proporción o una sal fisiológicamente aceptable del mismo.

3. El compuesto de acuerdo con la reivindicación 1, en el que

A es CH=CH.

4. El compuesto de acuerdo con la reivindicación 1, en el que

R^{23} es hidrógeno o halógeno.

5. El compuesto de acuerdo con la reivindicación 1, en el que

R^{24} es hidrógeno o halógeno cuando A es CH=CH;

6. El compuesto de acuerdo con la reivindicación 1, en el que

X es N(H)C=O.

7. El compuesto de acuerdo con la reivindicación 1, en el que

Y es $C(R^{12})=C(R^{13})$.

8. El compuesto de acuerdo con la reivindicación 1, en el que

Y es $C(R^{15})=N$.

9. El compuesto de acuerdo con la reivindicación 1, en el que

Y es carbociclilo de 5-6 miembros, opcionalmente sustituido y condensado.

10. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es alquilo (C_4-C_6).

11. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es alquenilo (C_4).

12. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es cicloalquiloxi (C_4).

13. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es cicloalquilo (C_5-C_6).

14. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es cicloalquenilo (C_5-C_6).

15. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es cicloalquil (C_3)-[alquilo (C_2) o alquenilo (C_2)].

16. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es cicloalquil (C_3)-alquiloxi (C_1).

17. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es alquiloxi (C_3-C_4).

18. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es alqueniloxi (C_3).

19. El compuesto de acuerdo con la reivindicación 1, en el que

R^{12} es fenilo.

20. El compuesto de acuerdo con la reivindicación 1, en el que

R^{13} es halógeno o alquilo (C_1).

21. El compuesto de acuerdo con la reivindicación 1, en el que

R^{13} es alquilo (C_1), donde el alquilo está opcionalmente sustituido con 1-3 átomos de flúor.

22. El compuesto de acuerdo con la reivindicación 1, en el que

R^{13} es alquilo (C_1).

23. El compuesto de acuerdo con la reivindicación 1, en el que

R^{13} es alquilo (C_1) que está sustituido con 2-3 átomos de flúor.

24. El compuesto de acuerdo con la reivindicación 1, en el que

R^{13} es halógeno.

25. El compuesto de acuerdo con la reivindicación 1, en el que

R^{15} es [alquil (C_2-C_3) o alquenil (C_3)](alquil (C_1-C_{10}))amino.

26. El compuesto de acuerdo con la reivindicación 1, en el que

R^{15} es alquil (C_2-C_3)-(alquil (C_1))amino.

27. El compuesto de acuerdo con la reivindicación 1, en el que

R^{21} es hidrógeno.

28. El compuesto de acuerdo con la reivindicación 1, en el que

R^{22} es hidrógeno o halógeno o alquilo (C_1) cuando Y es $C(R^{12})=C(R^{13})$.

29. El compuesto de acuerdo con la reivindicación 1, en el que

R^{51} es COOH.

30. El compuesto de acuerdo con la reivindicación 1 seleccionado entre:
ácido 2-(2-aliloxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,

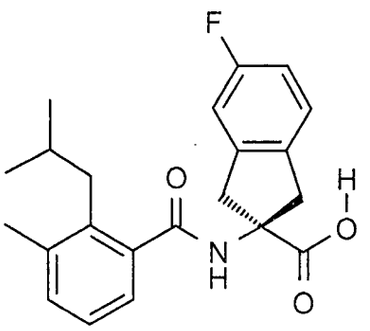
ácido 2-(2-ciclopropilmetoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-sec-butoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(3-cloro-2-isopropoxi-benzoilamino)-indan-2-carboxílico
ácido 2-(2-aliloxi-3-cloro-benzoilamino)-indan-2-carboxílico,
ácido 2-(3,5-dicloro-2-ciclobutoxi-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 2-(3,5-dicloro-2-isopropoxi-bencenosulfonilamino)-indan-2-carboxílico,
ácido 2-(2-aliloxi-3,5-dicloro-bencenosulfonilamino)-indan-2-carboxílico,
ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico,
ácido 1,3-dimetil-5-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico,
ácido 5-metoxi-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico,
ácido 2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-5-trifluorometil-indan-2-carboxílico
ácido 5-fluoro-2-[(5,6,7,8-tetrahidro-naftaleno-1-carbonil)-amino]-indan-2-carboxílico,
ácido 5-(2-isopropoxi-3-metil-benzoilamino)-1,3-dimetil-5,6-dihidro-4H-ciclopenta[c]tiofeno-5-carboxílico,
ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-metoxi-indan-2-carboxílico,
ácido 2-(2-isopropoxi-3-metil-benzoilamino)-5-trifluorometil-indan-2-carboxílico,
ácido 5-fluoro-2-(2-isopropoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-trifluoro-indan-2-carboxílico,
ácido 5-bromo-2-(2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5,6-difluoro-indan-2-carboxílico,
ácido 2-[3-metil-2-((Z)-pent-1-enil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(3-metil-2-pentil-benzoilamino)-indan-2-carboxílico,
ácido 2-[2-(1-etil-but-1-enil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-[2-(1-etil-butil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclopentil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-[2-(-2-ciclopropil-vinil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-[2-(2-ciclopropil-etil)-3-metil-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-ciclohex-1-enil-3-metil-benzoilamino)-indan-2-carboxílico,

ácido 2-[3-metil-2-(1-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(3-metil-2-propil-benzoilamino)-indan-2-carboxílico,
ácido 2-[3-metil-2-((E)-pent-1-enil)-benzoilamino]-indan-2-carboxílico,
ácido 5-fluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 5-fluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-ciclopent-1-enil-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 5-fluoro-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 5-fluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5,6-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 5,6-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5,6-difluoro-2-(3-metil-2-propenil-benzoilamino)-indan-2-carboxílico,
ácido 5,6-difluoro-2-(3-metil-2-propil-benzoilamino)-indan-2-carboxílico,
ácido 5-bromo-2-[3-metil-2-((E)-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-[(2-cloro-6-metil-benzoil)-amino]-indan-2-carboxílico,
ácido 2-[(2-metiltiolbencen-1-carbonil)-amino]-indan-2-carboxílico,
ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-isobutiril-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2,3-dimetil-benzoilamino)-indan-2-carboxílico,
ácido 2-(3-ciano-2-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-[(bifenil-2-carbonil)-amino]-indan-2-carboxílico,
ácido 2-[2-(1,1-dimetil-propil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4,5-dicloro-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-5-cloro-indan-2-carboxílico,
ácido 2-(2-ciclobutoxi-3-metil-benzoilamino)-4-fluoro-indan-2-carboxílico,
ácido 2-(2-ciclobutiloxi-3-metilbenzoilamino)indan-2-acético,
ácido 2-(3-bromo-2-metilbenzoilamino)indan-2-carboxílico,
ácido 2-(5-bromo-2-ciclobutoxi-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 2-(2-isopropilsulfanil-benzoilamino)-indan-2-carboxílico,
ácido 2-(5-cloro-2-ciclobutoxi-3-metil-benzoilamino)-5-fluoro-indan-2-carboxílico,
ácido 2-{[2-(etil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,
ácido 2-{[2-(alil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,
ácido 2-{[2-(isopropil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,
ácido 2-{[5-cloro-2-(isopropil-metil-amino)-piridina-3-carbonil]-amino}-indan-2-carboxílico,

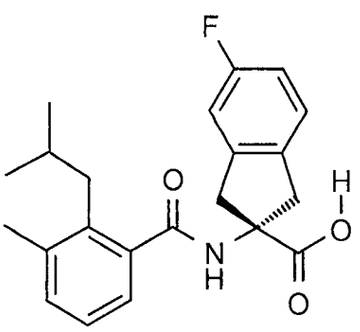
ácido 4,5-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 4,5-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 4,7-difluoro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 4,7-difluoro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5-cloro-2-(2-isobutil-3-metil-benzoilamino)-indan-2-carboxílico,
ácido 5-cloro-2-[3-metil-2-(2-metil-propenil)-benzoilamino]-indan-2-carboxílico,
ácido 2-(5,6,7,8-tetrahidro-naftalen-1-ilcarbamoil)-indan-2-carboxílico,
2-ciclobutoxi-N-(2-metanosulfonilaminocarbonil-indan-2-il)-3-metil-benzamida,
2-ciclobutoxi-3-metil-N-(2-trifluorometanosulfonilaminocarbonil-indan-2-il)-benzamida,
2-ciclopent-1-enil-3-metil-N-(2-trifluorometanosulfonilaminocarbonil-indan-2-il)-benzamida,
2-ciclobutoxi-3-metil-N-[2-(1H-tetrazol-5-il)-indan-2-il]-benzamida, y
ácido 2-[2-(2-Metil-propenil)-3-trifluorometil-benzoilamino]-indan-2-carboxílico, o

una forma estereoisomérica del mismo, una mezcla de formas estereoisoméricas del mismo en cualquier proporción o una sal fisiológicamente aceptable del mismo.

31. El compuesto según la reivindicación 1 de la siguiente estructura.



32. El compuesto según la reivindicación 1 de la siguiente estructura.



33. Una composición farmacéutica que comprende una cantidad farmacéuticamente aceptable de un compuesto de acuerdo con la reivindicación 1 y al menos uno de un excipiente farmacéuticamente aceptable y un vehículo farmacéuticamente aceptable.

34. Un método para el tratamiento de un paciente que padece de, o que es propenso a, una afección fisiológica que puede mejorarse por la administración de una cantidad farmacéuticamente eficaz de un inhibidor del receptor CXCR5 al paciente, que comprende administrar el compuesto de acuerdo con la reivindicación 1 a dicho paciente.

35. El método de acuerdo con la reivindicación 34 en el que la afección fisiológica es una enfermedad inflamatoria.

36. El método de acuerdo con la reivindicación 34 en el que la afección fisiológica es artritis reumatoide.

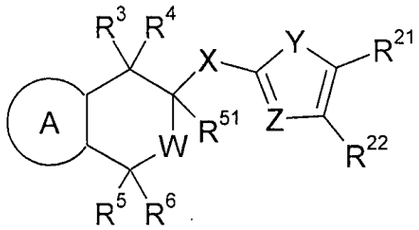
37. El método de acuerdo con la reivindicación 34 en el que la afección fisiológica es asma.

38. El método de la reivindicación 4 en el que con el compuesto de la reivindicación 1 se administra otro agente terapéutico al mismo tiempo o secuencialmente.

39. Un proceso para producir un compuesto de acuerdo con la reivindicación 1 como se describe en la presente memoria.

RESUMEN

La presente invención se refiere a nuevos compuestos de la fórmula I:



en cualquiera de sus formas estereoisoméricas o una mezcla de formas estereoisoméricas en cualquier proporción, o una sal fisiológicamente aceptable de los mismos, donde los sustituyentes son como se han descrito en la presente memoria. Los compuestos de la presente invención tienen actividad inhibidora de CXCR5 y son particularmente útiles en el tratamiento o prevención de diversas enfermedades inflamatorias, tales como artritis reumatoide, esclerosis múltiple, lupus o enfermedad de Crohn, asociadas con la modulación del receptor CXCR5 humano.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/065711

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D333/68 C07D333/78 C07C233/63 C07C235/54 C07C235/84
C07C311/15 C07C317/14 C07C323/62 A61K31/33 A61K31/16
A61P11/06 A61P19/02 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 701 480 A1 (ELF SANOFI SA, FR.) 19 August 1994 (1994-08-19) page 11, lines 24,25	1-32,39
X	LOHMAR, RAINALD ET AL: ".alpha.-Amino acids as nucleophilic acyl equivalents. IV. Synthesis of symmetrical ketones by means of 2-phenyl-2-oxazolin-5-one" CHEMISCHE BERICHTE , 113(12), 3706-15 CODEN: CHBEAM; ISSN: 0009-2940, 1980, XP002150545 page 3714, lines 3-7; compound 4J	1-32,39
A	WO 98/53818 A1 (MERCK & CO., INC., USA) 3 December 1998 (1998-12-03) page 15, lines 3-6; claims 5,9,10	1,33,34

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 August 2008	03/09/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	van Laren, Martijn

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/065711

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2701480 A1	19-08-1994	AT 179430 T	15-05-1999
		AU 673398 B2	07-11-1996
		AU 5516594 A	18-08-1994
		CA 2115631 A1	16-08-1994
		CN 1104634 A	05-07-1995
		DE 69418083 D1	02-06-1999
		DE 69418083 T2	25-11-1999
		DK 614911 T3	08-11-1999
		EP 0614911 A1	14-09-1994
		ES 2132351 T3	16-08-1999
		FI 940680 A	16-08-1994
		GR 3030243 T3	31-08-1999
		HU 66960 A2	30-01-1995
		IL 108649 A	24-09-1998
		JP 2994546 B2	27-12-1999
		JP 6293794 A	21-10-1994
		MX 9401191 A1	31-08-1994
		NO 940503 A	16-08-1994
		NZ 250878 A	27-02-1996
		PH 30887 A	23-12-1997
		RU 2126382 C1	20-02-1999
		US 5506258 A	09-04-1996
		ZA 9401029 A	15-08-1995
WO 9853818 A1	03-12-1998	AU 728435 B2	11-01-2001
		AU 7703298 A	30-12-1998
		CA 2291708 A1	03-12-1998
		EP 0998282 A1	10-05-2000
		JP 2002501537 T	15-01-2002

PATENT COOPERATION TREATY PCT/US2008/065711

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

LIN, Jiang
Sanofi-Aventis U.S. Inc.
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
07 July 2008 (07.07.2008)

Applicant's or agent's file reference
US2006/126WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/065711

International filing date *(day/month/year)*
04 June 2008 (04.06.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
CAUFIELD, Thomas J. 55 Corporate Drive Bridgewater, New Jersey 08807 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
CAULFIELD, Thomas, J. 55 Corporate Drive Bridgewater, New Jersey 08807 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Samuels Frederick
Facsimile No. +41 22 338 89 65	e-mail pt02.pct@wipo.int Telephone No. +41 22 338 74 02

65A

PATENT COOPERATION TREATY PCT/US2008/065711

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

LIN, Jiang
Sanofi-Aventis U.S. Inc.
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
07 July 2008 (07.07.2008)

Applicant's or agent's file reference
US2006/126WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/065711

International filing date *(day/month/year)*
04 June 2008 (04.06.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
SMRCINA, Martin
55 Corporate Drive
Bridgewater, New Jersey 08807
United States of America

State of Nationality: CZ
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
SMRCINA, Martin
1580 E. Hanley Blvd.
Tucson, Arizona 85737
United States of America

State of Nationality: CZ
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 65

Authorized officer
Samuels Frederick
e-mail pt02.pct@wipo.int
Telephone No. +41 22 338 74 02

659

PATENT COOPERATION TREATY PCT/US2008/065711

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

LIN, Jiang
Sanofi-Aventis U.S. Inc.
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
07 July 2008 (07.07.2008)

Applicant's or agent's file reference
US2006/126WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/065711

International filing date *(day/month/year)*
04 June 2008 (04.06.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
THORPE, David S.
55 Corporate Drive
Bridgewater, New Jersey 08807
United States of America

State of Nationality	State of Residence
US	US

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
THORPE, David S.
1580 E. Hanley Blvd.
Tucson, Arizona 85737
United States of America

State of Nationality	State of Residence
US	US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 65

Authorized officer
Samuels Frederick
e-mail pt02.pct@wipo.int
Telephone No. +41 22 338 74 02

Form PCT/IB/306 (October 2005) 1/DPQYWMU10

660

PATENT COOPERATION TREATY

PCT/US2008/065711

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

LIN, Jiang
Sanofi-Aventis U.S. Inc.
Route 202-206
P.O. Box 6800
Bridgewater, NJ 08807-0800
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
07 July 2008 (07.07.2008)

Applicant's or agent's file reference
US2006/126WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2008/065711

International filing date *(day/month/year)*
04 June 2008 (04.06.2008)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address
WIRE, William
55 Corporate Drive
Bridgewater, New Jersey 08807
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
WIRE, William
1580 E. Hanley Blvd.
Tucson, Arizona 85737
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 65

Authorized officer
Samuels Frederick
e-mail pt02.pct@wipo.int
Telephone No. +41 22 338 74 02

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad (31) ***Prioridad*** (32) ***Fecha*** (33) ***País***
60/942,169 **05/06/2007** **US**

(51) Int Cl: **C07D 333/068**

(71)Solicitante(s) **SANOFI–AVENTIS**

(72) Inventor(es) **THOMAS J. CAULFIELD Y OTROS**

(74) Apoderado: **LUZ CLEMENCIA DE PÁEZ**

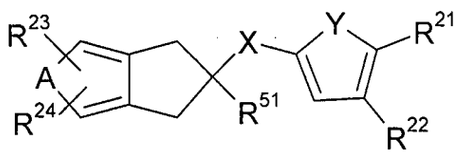
(85) Fecha limite inicio fase nacional: 05/01/2010
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 04/06/2008
No. de solicitud PCT/US2008/065711

(87) Publicación internacional
Fecha: 11/12/2008
N° publicación: ***WO 2008/151211 A1***

(54) Titulo: **ÁCIDOS BENZOILAMINO-INDAN-2-CARBOXÍLICOS SUSTITUIDOS Y COMPUESTOS RELACIONADOS**

Reivindicación(es):

1. Un compuesto de la fórmula Ia



en la que:

A es CH=CH o S;

R^{23} es hidrógeno, halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-S- o nitro;

R^{24} es hidrógeno o halógeno cuando A es CH=CH, o es hidrógeno, halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-S-, o nitro cuando A es S;

X es N(H)C=O, N(H)S(O)$_2$, C=ON(H) o S(O)$_2$N(H);

Y es N(R^{11}), S, O, C(R^{12})=C(R^{13}), N=C(R^{14}) o C(R^{15})=N, o carbociclilo condensado de 5-7 miembros opcionalmente sustituido;

R^{11} es hidrógeno, alquilo (C_1-C_{10}), hidroxi-alquil (C_1-C_{10})-, alquiloxi (C_1-C_{10}), alquil (C_1-C_{10})-S(O)$_m$-, alquilcarbonil (C_1-C_{10})-, fenilo, amino, alquilamino (C_1-C_{10}) o di(alquil (C_1-C_{10}))amino;

R^{12} es hidrógeno, halógeno, alquilo (C_1-C_{10}), alquenilo (C_2-C_{10}), cicloalquiloxi (C_3-C_6), cicloalqueniloxi (C_3-C_{10}), cicloalquilo (C_3-C_6), cicloalquenilo (C_3-C_{10}), cicloalquil (C_3-C_6)-alquilo[(C_1-C_4) o alquenilo (C_2-C_4)], cicloalquil (C_3-C_6)-alquiloxi(C_1-C_4), hidroxialquilo(C_1-C_{10}), alquiloxi (C_1-C_{10}), alqueniloxi (C_2-C_{10}), alquil (C_1-C_{10})-S-, ciano, alquilcarbonilo (C_1-C_{10}), fenilo o nitro;

R^{13} es hidrógeno, halógeno o alquilo (C_1);

R^{14} es hidrógeno, halógeno, alquilo (C_1-C_4), hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-S(O)$_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{14} no supere 4;

R^{15} es hidrógeno, halógeno, alquilo (C_1-C_{10}), alquenilo (C_2-C_{10}), cicloalquilo (C_3-C_6), cicloalquenilo (C_3-C_6), cicloalquil (C_3-C_6)-[alquilo (C_1-C_4) o alquenilo (C_2-C_4)], hidroxi-alquil (C_1-C_{10})-, ciano, alquilcarbonil (C_1-C_{10})-, fenilo, amino, [alquil (C_1-C_{10}) o alquenil (C_2-C_{10})-]amino, [alquil (C_1-C_{10}) o alquenil (C_2-C_{10})](alquil (C_1-C_{10}))amino o nitro;

R^{21} es hidrógeno cuando Y es C(R^{12})=C(R^{13}), N=C(R^{14}) o C(R^{15})=N, y es hidrógeno, halógeno, alquilo (C_1-C_4), hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-S(O)$_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro cuando Y es N(R^{11}), S o O, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{21} no supere 4;

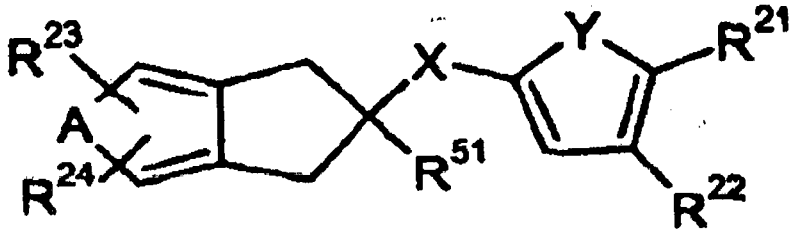
R^{22} es hidrógeno, halógeno, alquilo (C_1) cuando Y es C(R^{12})=C(R^{13}), N=C(R^{14}) o C(R^{15})=N, o es hidrógeno, hidroxi-alquil (C_1-C_3)-, alquiloxi (C_1-C_3), alquil (C_1-C_3)-S(O)$_m$-, ciano, alquilcarbonil (C_1-C_2)-, amino, alquilamino (C_1-C_3), di(alquil (C_1-C_3))amino o nitro cuando Y es N(R^{11}), S o O, con la condición de que el número total de átomos de C, N, O y S que están presentes en R^{22} no supere 4;

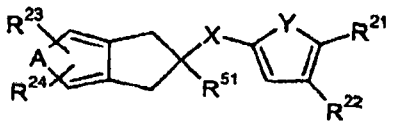
R^{51} es COOH o CONH(R^{53});

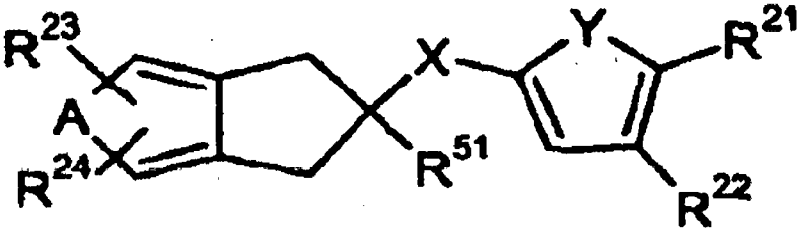
R^{53} es R^{55}-SO$_2$- o tetrazolilo;

R^{55} es alquilo (C_1-C_4) o fenilo opcionalmente sustituido con uno o más sustituyentes iguales o diferentes elegidos entre el grupo que consiste en halógeno, alquilo (C_1-C_4), alquiloxi (C_1-C_4), alquil (C_1-C_4)-sulfonilo y ciano; y

m es 0, 1 ó 2;


R23
A
R24
X
R51
Y
R21
R22


R23
A
R24
X
R51
Y
R21
R22


R23
A
R24
X
R51
Y
R21
R22

63

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 75,153
FECHA : OCTUBRE 5 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-123805- -00000-0000
Fecha: 2009-11-03 16:25:13 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 664

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	130928173	05/10/2009	40,246,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	*** TASA ANUAL A#OS 17 a 20 PARA MANT	872,000.00

****

TOTAL : $ 872,000.00

SON: OCHOCIENTOS SETENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 14775-841-106-9

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 70,532
FECHA : SEPTIEMBRE 21 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-123805- -00000-0000

Fecha: 2009-11-03 16:25:13 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 664

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
VELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	17854550	21/09/2009	45,108,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-06 REGISTRO DE CESION, CAMBIO NOM	13 NOMBRES Y ENSENAS COMERCIALES,MAR		273,000.00
		TOTAL :	$	273,000.00

SON: DOSCIENTOS SETENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

COLO: 14775-841-906-9.

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha_

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-123805- -00000-0000
Fecha: 2009-11-03 16:25:13 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 664

rrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: Info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

Bogotá,
2020

Doctor(a)
SUAREZ DE PAEZ LUZ CLEMENCIA
Apoderado(a) y/o Representante de
SANOFI-AVENTIS

REFERENCIA	Radicación No.	9 123805
	Solicitud internacional	PCT/US2008/065711
	Fecha inicio fase nacional	05/01/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1288

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 05 FEB. 2010
adpall